ICAR: endoscopic skull-base surgery

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Background: Endoscopic skull-base surgery (ESBS) is employed in the management of diverse skull-base pathologies. Paralleling the increased utilization of ESBS, the literature in this field has expanded rapidly. However, the rarity of these diseases, the inherent challenges of surgical studies, and the continued learning curve in ESBS have resulted in significant variability in the quality of the literature. To consolidate and critically appraise the available literature, experts in skull-base surgery have produced the International Consensus Statement on Endoscopic Skull-Base Surgery (ICAR:ESBS).

Methods: Using previously described methodology, topics spanning the breadth of ESBS were identified and assigned a literature review, evidence-based review or evidence-based review with recommendations format. Subsequently, each topic was written and then reviewed by skull-base surgeons in both neurosurgery and otolaryngology. Following this iterative review process, the ICAR:ESBS document was synthesized and reviewed by all authors for consensus.

Results: The ICAR:ESBS document addresses the role of ESBS in primary cerebrospinal fluid (CSF) rhinorrhea, intradural tumors, benign skull-base and orbital pathology, sinonasal malignancies, and clival lesions. Additionally, specific challenges in ESBS including endoscopic reconstruction and complication management were evaluated.

Conclusion: A critical review of the literature in ESBS demonstrates at least the equivalency of ESBS with alternative approaches in pathologies such as CSF rhinorrhea and pituitary adenoma as well as improved reconstructive techniques in reducing CSF leaks. Evidence-based recommendations are limited in other pathologies and these significant knowledge gaps call upon the skull-base community to embrace these opportunities and collaboratively address these shortcomings.

Key Words:
endoscopic endonasal approach; endoscopic endonasal skull-base surgery; CSF rhinorrhea; pituitary adenoma; craniopharyngioma; meningioma; angiofibroma; olfactory neuroblastoma; esthesioneuroblastoma; squamous cell carcinoma; clival chordoma; nasoseptal flap reconstruction; evidence-based medicine

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I. Introduction

The utilization of endoscopic skull-base surgery (ESBS) continues to expand as both surgical techniques and experience with more complex pathologies concurrently increase. From the initial experience using endoscopic visualization to manage pituitary macroadenomas[1] and cerebrospinal fluid fistulas into the paranasal sinuses,[2] ESBS is now selectively employed in pathology from the frontal sinus to the clivus and involving the anterior, middle, and posterior intracranial fossae. Paralleling the increased application of this surgical corridor, the literature in the field has similarly grown. Because this intervention now has widespread adoption in both otolaryngology and neurological surgery, the opportunity to evaluate the current published evidence on the effectiveness, complications, and limitations of ESBS across multiple pathologies exists. With this systematic evaluation, knowledge gaps and potential new lines of investigation can also be identified.

Similar to the other International Consensus Statement on Allergy and Rhinology (ICAR) documents on rhinosinusitis (ICAR:RS) and allergic rhinitis (ICAR:AR),[3,4] the overarching goal is to promote the practice of evidence-based medicine (EBM) by summarizing the best external evidence. With the volume of publications, the variability in publication quality, and the multidisciplinary nature of skull-base pathologies themselves, clinicians face significant obstacles in determining the best external evidence and practicing EBM in this area.

The ICAR: Endoscopic Skull-Base Surgery (ICAR:ESBS) is the result of a joint effort from both otolaryngologists and neurosurgeons who are actively involved in skull-base surgery to summarize the best external evidence in this burgeoning field. Using the structured review process of the prior ICAR statements, the authors first gathered, then critically appraised and summarized the available evidence on the use of ESBS for the treatment of specific pathologies, the reconstructive challenges of ESBS, specific perioperative care, and management of complications. Subsequently, an iterative review process was then undertaken for each topic. Because of the multidisciplinary nature of skull-base pathology and to take advantage of the differing expertise between each discipline, at least 1 otolaryngology and 1 neurosurgery author reviewed every section. The culmination of this endeavor is a robust multidisciplinary review of the current evidence pertaining to the benefits, shortcomings, and limitations of ESBS.

Importantly, ICAR:ESBS focuses specifically on the efficacy and challenges of ESBS and is not intended to

summarize all of the available evidence on each specific skull-base pathology and/or the role of alternative approaches in the surgical management of these pathologies. It cannot be overemphasized that alternative surgical approaches such as a craniotomy or transorbital approach have a critical role in the management of many tumors. This document is intended to assist the surgeon in the practice of EBM by summarizing the best evidence available to determine if ESBS is a viable option. By combining this with individual expertise and experience as well as patient-specific factors, the best treatment strategy can then be employed.

As noted in the prior ICAR documents,[3,4] this is neither a meta-analysis nor a clinical practice guideline (CPG). When available, meta-analyses and systematic reviews were identified to support the recommendations proposed on a specific topic because these are higher levels of evidence. Additionally, the significant variability in the outcome measures and disease heterogeneity often do not support the use of meta-analysis. This document also does not represent a clinical practice guideline that requires both strong evidence and vetting by critical stakeholders.

Despite the increased number of publications on ESBS, there is tremendous variability in the quality of the literature. Although some areas have strong evidence, the majority of the topics demonstrate relatively lower levels of evidence. In many situations, this is secondary to the relative rarity of the disease process. Additionally, randomized controlled trials (RCTs) can be exceptionally difficult in surgical interventions, which adds more challenges in identifying strong evidence. In some areas, the lack of high-quality evidence allows for only a literature review on the topic. This calls to the skull-base community to strive to overcome this disadvantage through multi-institutional collaboration and to actively seek to address these areas of limitation.

Although treatment recommendations are included in ICAR:ESBS, this document has limitations. As noted, many topics simply lack adequate evidence to support a recommendation. Regardless of the strength of the evidence, these recommendations do not define the standard of care. As noted by Wise et al.[4] in ICAR:AR, recommendations within this document do not dictate the specific care of an individual patient because numerous other factors, including the tumor characteristics, patient comorbidities, symptomatology, and surgical experience, will undoubtedly impact treatment recommendations. This is particularly true in ICAR:ESBS because surgical procedures can vary tremendously despite being categorized as the same surgery. Individual surgical technique, goals of surgery, and surgeon experience all factor into the decision-making for the care of specific patients. Finally, the recommendations proposed in this document should be interpreted in light of the strength of the evidence supporting those recommendations. It is anticipated that with emerging evidence, technology, and collaboration, these recommendations will change over time and continue to result in improved patient outcomes and minimization of complications.

II. Methods

II.A. Topic development

The ICAR:ESBS document was undertaken with an expressed commitment to focus on the published literature rather than expert opinion and is purposely consistent with the ICAR:RS and ICAR:AR documents.[3,4] Similar to these prior statements, the process of systematically evaluating the literature, grading the evidence, and providing evidence-based recommendations was adapted from Rudmik and Smith.[5]

ICAR:ESBS differs from the prior statements that centered on the diagnosis of either rhinosinusitis or allergic rhinitis because this statement focuses on the role of a surgical intervention in the management of numerous pathologies and the specific challenges and benefits of these procedures. Topic generation spanned from the use of ESBS for the treatment of tumor pathologies such as pituitary adenoma or esthesioneuroblastoma, to the reconstruction of skull-base defects, to complications and perioperative considerations. The topic generation was first undertaken by a group of experts that included both otolaryngology and neurosurgery. This was then vetted by a second, larger group of experts in skull-base surgery until the final topic sections were established to cover the current breadth of the field. As expected, the evidence available varied greatly. Topics with modest evidence were assigned as literature reviews. In areas where literature existed, but was limited, such as a relatively rare condition, an evidence-based review without recommendations (EBR) was conducted. Subject matter with sufficient evidence to produce recommendations were assigned an evidence-based review with recommendations (EBRR).

Subsequently, a senior author who is a recognized expert in skull-base surgery and the specific subject matter was assigned a topic area to perform a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standardized guidelines.[6] The search for each topic was conducted using Ovid MEDLINE (1947 to September 2017), EMBASE (1947 to September 2017), and Cochrane review database. Consistent with PRISMA guidelines and the prior ICAR statements, the systematic review of each topic began with the identification of prior published systematic reviews or guidelines. High-quality evidence such as RCTs and meta-analyses were first identified if available. When these did not exist, as is common in surgical studies, observational studies were then identified. Reference lists of all identified studies were subsequently evaluated to ensure all relevant studies were captured.

In the EBR and EBRR sections, all included studies were presented in a standardized table format and the quality of the study was graded using the Oxford Level of Evidence (LOE) (Level 1a to 5).[7] Once the systematic review and assessment of quality was completed for each topic, an aggregate grade of evidence (A to D) was determined based upon the guidelines from the American Academy

TABLE II.A. Aggregate grade of evidence

Grade	Research quality
A	Well-designed randomized controlled trials
B	Randomized controlled trials with minor limitations; overwhelming consistent evidence from observational studies
C	Observational studies (case control and cohort design)
D	Expert opinion; case report; reasoning from first principles

of Pediatrics Steering Committee on Quality Improvement and Managements (AAP SCQIM)[8] (see Table II.A). When appropriate, an evidence-based recommendation was produced using the AAP SCQIM. The recommendation was based upon the aggregate grade of evidence as well as the balance of benefit, harm, and costs.

II.B. Iterative review

After the initial development of each section including the associated evidence-based grades and/or recommendations, the manuscript was then evaluated by a 2-stage iterative review process using at least 2 independent reviewers. This process was undertaken to ensure the completeness of the literature identification, the accuracy of the aggregate grade of evidence, and the appropriateness of the EBRR recommendation. Because of the multidisciplinary nature of skull-base surgery and the expertise of both specialties, each section was reviewed by both a neurosurgeon and otolaryngology–head and neck surgeon. At the completion of the review process, the initial author and the assigned reviewers all agreed upon any changes prior to proceeding with the final ICAR statement stage.

II.C. ICAR:ESBS statement development

Following the completion of the review process and consensus by the senior author and reviewers, the principal editor (E.W.W.) assembled all sections into a single ICAR:ESBS statement. The draft of the document was reviewed by all contributing authors to ensure consensus among the authors. Once all of the authors agreed upon the literature completeness and final recommendations, the final ICAR:SB statement was then produced and underwent the external review.

III. Primary CSF rhinorrhea

III.A. Traumatic and iatrogenic CSF leaks

Primary CSF rhinorrhea results from an osseous defect in the skull base with an associated dural fistula. Traumatic leaks are the most common type of CSF leak and include non-iatrogenic (blunt or penetrating injuries) or iatrogenic injuries (usually unintentional violation of the skull base during rhinologic or neurosurgical procedures). Other CSF leak etiologies include spontaneous, congenital, and neoplastic origins. Although open transcranial approaches continue to have a role in the management of traumatic and iatrogenic CSF leaks, endoscopic endonasal approaches (EEAs) are increasingly utilized in the management of these condition. The role of EEA in the repair of both iatrogenic and traumatic CSF rhinorrhea varies by anatomical subsite. This role, as well as nonsurgical options including CSF diversion are evaluated.

III.A.1. *Endoscopic repair of the ethmoid roof and sphenoid*

Due to the heterogeneity of the traumatic etiology definition in the literature and data reported with no distinction between etiologies and locations, the ability to extract data related only to traumatic and iatrogenic CSF leaks involving the sphenoid and ethmoid region is compromised in many studies. However, endoscopic repair of traumatic CSF leaks is a well-accepted treatment with a low complication rate.{Banks, 2009 #3115}[9–20]

There is general acceptance in the literature that non-iatrogenic traumatic leaks are likely to spontaneously resolve. Therefore, an initial conservative approach is typically recommended, including bed rest, head of bed at 30 degrees, and Valsalva precautions (see Section III.A.3. Nonsurgical management options in traumatic and iatrogenic CSF leaks).[21–23] In contrast, iatrogenic injuries are unlikely to spontaneously heal and require initial surgical repair. Repair philosophies and techniques were generally similar in all studies and included multilayer (sandwich grafting) reconstruction according to the size, site, and etiology of the defect. Although various materials were utilized for the repair, this did not appear to impact the successful repair of the CSF leak. Mucoperiosteum was removed around the defects and grafts were stabilized in position with fibrin glue. Nasal packing was used in all cases to support the repair. In a retrospective cohort of 42 patients with confirmed posttraumatic persistent CSF rhinorrhea, the majority of leaks occurred at the cribriform plate and anterior skull base. Multiple defects were identified in 6 of 10 cases of accidental trauma, 2 of 12 following endoscopic sinus surgery, and 1 of 5 cases following anterior skull-base surgery. The primary success rate was 97%, with only 1 case requiring secondary repair.[11] Virk et al.[20] reported a series of 54 patients with CSF rhinorrhea with 18 traumatic leaks and documented location (10 ethmoid, 6 sphenoid, 2 frontal). The frequency of traumatic CSF leak sites endoscopically repaired generally reflected those of other series.[9,13,15,16] Traumatic leaks were repaired with 100% success in the Virk et al.[20] series with the only failures in the spontaneous CSF leak group. Lindstrom et al.[13] also reported a 100% success rate for traumatic CSF leaks in their cohort of 43 patients (23 iatrogenic and 20 traumatic). The predominant location of the CSF leaks was ethmoidal. Lee et al.[14] successfully closed all traumatic CSF leaks in the ethmoid (n = 9) and sphenoid (n = 10) sinuses, but had 4 failures in the frontal sinus (n = 9). Bumm et al.[15] reported

TABLE III.A.1. Traumatic and iatrogenic CSF leaks: endoscopic repair of the ethmoid roof and sphenoid

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Sharma[9]	2016	2a	Systematic review	Review of 67 previously published studies	Outcomes Success rate transnasal endoscopic repair of CSF rhinorrhea is 90.1%	Endoscopic repair is safe and effective with a low complication rate. It has almost completely replaced older open techniques.
Psaltis[10]	2012	2a	Systematic review	Review of 55 previously published studies	Outcomes Repair success 90.6% primary and 96.6% for revision repair	Endoscopic repair is safe and effective and should be considered standard of care for most cases.
Ibrahim[11]	2016	4	Retrospective	n = 42 Posttraumatic CSF leaks 1. Cribiform plate and anterior skull base 32/42 2. Sphenoid 19/42 9 cases >1 defect	Outcomes Success endoscopic repair 97% with 1 case needing 2nd repair	Posttraumatic CSF leaks can be managed successfully using endoscopic techniques.
Virk[20]	2013	4	Retrospective	n = 54 1. Traumatic 18/54 Location 1. Cribiform 33.3% 2. Sphenoid 33.3% 3. Ethmoid 22.2% 4. Frontal 11.1%	Outcomes Repair success 50/54 (93%) and following second operation the repair rate was 100%	Safe and effective.
Lindstrom[13]	2004	4	Retrospective	n = 43 Traumatic Iatrogenic 27/43 1. Traumatic 16/43 Location 1. Ethmoid region 28 2. Sphenoid 11 3. Frontal 4	Outcomes 100% success rate in select patients with traumatic injuries	In select cases endoscopic repair is safe and effective.
Lee[14]	2011	4	Retrospective	n = 28 1. Traumatic 27 2. Spontaneous 1 Sites 1. Frontal sinus 9 2. Ethmoid 9 3. Sphenoid/sella/clivus 10	Outcomes 1. Success 86% 1st attempt 2. Success rate 93% 2nd attempt Frontal sinus and frontal recess had higher failure rates 4/9 (44%)	Endoscopic techniques are effective with a success rate of 93%. Open endoscopic approach may play role to assist with failures of frontal CSF leaks.
Bumm[15]	2009	4	Retrospective	n = 144 CSF leaks identified 1. Iatrogenic 52/144 2. Non-iatrogenic 92/144 Location - iatrogenic 1. Ethmoid (43.7%) 2. Ethmoid sphenoid (21.9%) 3. Frontal (18.7%) Medial ethmoid/cribiform 9.4%	Outcomes 1. Repair success 87.5% and 95% after revision surgery 2. Incidence of iatrogenic CSF leaks Location of the leaks	The incidence of iatrogenic CSF leaks at a teaching hospital is not higher than at specialized rhinology departments.
Kirtane[12]	2005	4	Retrospective	n = 267 1. 267 Transnasal endoscopic technique	Outcomes: efficacy of endoscopic closure success 1. 258/267 (96.6%) Success 2. 264/267 (98.9%) on Revision	Transnasal endoscopic approach is recommended in both primary and secondary cases. Note included spontaneous CSF leaks in group.

(*Continued*)

TABLE III.A.1. Continued

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Banks[24]	2009	4	Retrospective	n = 193 1. Traumatic 109/193 (56%) 2. Other 86/193 Site 1. Ethmoidal/cribiform 52/109 2. Sphenoid 30/109 3. Frontal 12/109 4. Frontoethmoid 3/109 5. Unknown in 9 cases	Recurrent leak 9% Traumatic leaks site recurrence 1. Sphenoid 1 (16.7%) 2. Ethmoid 1 (50%) 3. Cribiform 1 (100%) Iatrogenic 1. Sphenoid 0 2. Ethmoid 3 (9.7%) 3. Cribiform 1 11.1%)	The overall success rate (98%) and low morbidity in this large series support endoscopic approach as standard of care for CSF leak closure.
Singh[16]	2009	4	Retrospective	n = 11 1. 4 Traumatic 2. 7 Spontaneous Sites 1. Ethmoid roof/cribiform 3/4 2. Sphenoid 1/4	Outcomes Success rate 90%	Endoscopic approach safe and effective.
Lee[17]	2004	4	Retrospective	n = 39 1. Traumatic 20/39 2. Iatrogenic 13/39 3. Spontaneous 6/39 Sites 1. Cribiform plate 33.3% 2. Anterior ethmoid sinus 28.2% 3. Sphenoid sinus 18% 4. Posterior ethmoid 12.8% 5. Frontal sinus 7.7%	Outcomes 1. Success 36/39 (92.3%) during first attempt	Endoscopic repair is considered effective.
Bhatti[18]	2011	4	Retrospective	n = 21 1. Traumatic 16/21 (76.2%) 2. Spontaneous in 4/21 (19.0%) 3. Iatrogenic 1/21 (4.7%) Location 1. Cribiform 10/21 (47.7%) 2. Sphenoid 5/21 (23.8%) 3. Frontal 4/21 (19%) 4. Ethmoid 2/21 (9.5%)	Outcomes Success in 17/21 (81%) Reexploration in 2/21 (9.5%) Overall success rate was 95%	Highly successful safe and less traumatic.
Liu[19]	2010	4	Retrospective	n = 132 1. Transnasal endoscopic approach in 98/132 2. Transcranial intradural approach in 34/132	Outcomes 1. Repair success 124/132 (94%) 2. Failed in 8 cases	Type of procedure dependent on location, a transcranial approach should be considered in difficult cases.

CSF = cerebrospinal fluid; LOE = level of evidence.

outcomes on 52 iatrogenic CSF leaks from endoscopic sinus surgery. Distribution was predominantly right sided. The majority (68.7%) were identified during initial surgery and 31.3% presented after surgery. The most common defect location was the ethmoidal region, specifically the anterior ethmoid location at the attachment of the medial concha base (43.7%), but also the medial ethmoid region (9.4%) followed by the junction between the ethmoid and sphenoid sinus (21.9%), and the frontal aditus (18.7%). The success rate of primary repair was 87.5% and 95% with secondary endoscopic repair. Although numerous other studies report high success rates and low complications with endoscopic repair of sphenoid and ethmoid CSF leaks, most authors cluster spontaneous etiology with traumatic and iatrogenic, and therefore cases cannot be extracted. The success rate across all studies was 81% to 100%[10,12,16–19,24] (see Table III.A.1).

- Aggregate Grade of Evidence: B (Level 2a: 2 studies; Level 4: 11 studies)

- Benefit: Endoscopic repair of ethmoid and sphenoid CSF leaks has no external scar and low morbidity. The success rate is 81% to 100% reported across the literature.
- Harm: CSF leak recurrence, general anesthetic, bleeding, anosmia, pain/discomfort, intranasal scarring.
- Cost: Minimal
- Benefit-Harm Assessment: Preponderance of benefit over harm
- Value Judgments: Endoscopic repair of traumatic CSF leaks of the ethmoid and sphenoid has a high success rate with low morbidity with low, reasonable cost.
- Policy Level: Option
- Intervention: Non-iatrogenic (after conservative measures fail) and iatrogenic traumatic CSF (generally not treated conservatively) leaks can be repaired endoscopically with high success rates.

III.A.2. *Endoscopic repair of traumatic frontal sinus CSF leaks*

Management of frontal sinus fractures with CSF leak and significant posterior table displacement has historically been managed with cranialization of the sinus.[25–29] Surgical techniques have recently evolved to incorporate endoscopic approaches into the treatment algorithm.[30–34]

The endoscopic approach to frontal sinus CSF leaks is supported by several case series with high success rates and low morbidity. In a prospective case series regarding transnasal endoscopic management of 46 frontal sinus traumatic fractures,[33] 40 patients with active CSF leaks from comminuted posterior table fractures as large as 5 cm (average 17 mm × 9 mm) were successfully sealed using the endoscopic approach. Repairs were tailored to the type of skull-base defect. Overlay grafts or nasoseptal flaps (NSFs) were used without underlay grafts for simple cracks or when an isolated telescoped segment of posterior table had been manually reduced. If fragments were removed and defects were larger than approximately 5 mm, an underlay epidural repair with porcine small intestine submucosal graft (Biodesign®; Cook Medical, Bloomington, IN) was included prior to overlay graft or flap placement. Supportive packing was utilized in all cases, including gelfoam and rolled 0.5 mm silastic stents. If a Draf III was completed, mucosal grafts were placed on the drilled-out nasofrontal area, as described.[35,36] A polyvinyl alcohol sponge inside a sterile non-latex glove finger was positioned within the middle meatus in apposition to the frontal recess and sutured via a 2-0 Prolene suture to the anterior septum. There was a very low rate of complications. Because the frontal sinus drainage pathway is kept patent, advantages of the endoscopic approach include preservation of a functional frontal sinus and less reliance on computed tomography (CT) scans for postoperative follow-up. Shi et al.[34] categorized their series of frontal sinus CSF leaks into 3 groups: (1) type A (9 patients) defects were located in the frontal recess at the posterior wall of the frontal sinus, <1 cm in diameter, and visualized successfully with a transnasal endoscopic approach; (2) type B (4 patients) defects were in the posterior table and partly obscured by a well-pneumatized agger nasi cell so that a Draf IIa or IIb was required for access; and (3) type C (2 patients) defects were >1 cm in diameter with a small frontal ostium (anteroposterior <6 mm) or located on the posterolateral wall of the frontal sinus and required a combined transnasal and transfrontal endoscopic approach for repair. The complication rate was 20% (1 recurrent leak, 1 sinus abscess, and 1 mucocele), but the 1 recurrence was successfully repaired with a second endoscopic approach. Lee et al.[14] highlighted that frontal sinus CSF leaks can be the most challenging sinus to successfully manage. Although they had an initial success rate of 92.3% in 39 patients (20 traumatic, 13 iatrogenic, 6 spontaneous) only 3 involved the frontal sinus. Of these 3 patients, 2 patients underwent endoscopic fat obliteration and 1 patient was successfully repaired with a mucosal graft. All frontal sinus CSF leaks were preselected to have CSF diversion with a lumbar drain. They concluded the use of lumbar drainage (LD) was appropriate when attempting repair in the frontal sinus, as it is an anatomically difficult location and LD can facilitate graft adherence. Lindstrom et al.[13] reviewed 53 patients with CSF leaks with 6 documented frontal sinus CSF leaks (2 iatrogenic, 2 traumatic, and 2 spontaneous) where 4 leaks were spontaneous or traumatic etiologies.

In contrast, Lee et al.[14] successfully repaired 24 of 28 traumatic or iatrogenic CSF leaks. The failures in this series all occurred in the frontal sinus (44%, 4/9 patients). They recommended against an endoscopic approach to frontal sinus CSF leaks due to the high failure rate in this location.

The advantages of the endoscopic approach to frontal sinus CSF leaks include intraoperative assessment of mucosal injuries, repair of bony disruptions with preservation of functional sinus drainage, and potentially shorter operating times, with no visible incisions.[37] However, there are considerable limitations to interpreting the current studies. The lack of data standardization makes it difficult to provide meaningful collective information. Some individual case series document an almost perfect endoscopic repair success rate, and the majority reported success rates greater than 90%. However, a high failure rate was acknowledged in 1 study. More long-term prospective studies are needed (Table III.A.2).

- Aggregate Grade of Evidence: C (Level 4: 9 studies)
- Benefit: The transnasal endoscopic approach to frontal sinus CSF leaks permits maintenance of normal sinus function, intraoperative assessment of mucosal injuries, and endoscopic surveillance of the frontal sinus drainage pathway. No external incisions are required. Success rates vary in the literature.
- Harm: A high failure rate was documented in 1 series, and this was attributed to the technical difficulty with repair, unlike CSF leaks in the ethmoid and sphenoid sinuses. Limitations of this approach include access to superior and lateral defects in several studies. Difficulty

TABLE III.A.2. Traumatic and iatrogenic CSF leaks: endoscopic repair of traumatic frontal sinus CSF leaks

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Woodworth[32]	2005	4	Retrospective	7 Frontal sinus CSF leaks in 6 patients. 1. Iatrogenic trauma n = 2 2. Accidental trauma n = 1 3. Others n = 4. Endoscopic repair alone n = 5 4. Combined endoscopic approach without obliteration n = 1	CSF leaks endoscopic repair and patent sinus. All repairs successful on first attempt. LD used in all patients.	Endoscopic repair in select patients is effective. Limitations include extreme extension superiorly or laterally and require an open approach. Close follow up is essential in all patients to prevent complications
Chaaban[30]	2012	4	Prospective	13 Patients with posterior table fractures and CSF leak; 4 of these patients had failed previous cranialization/craniotomy	Posterior table CSF repair. All CSF leaks were successfully repaired.	Transnasal endoscopic approach for posterior table fractures can successfully repair CSF leaks with excellent outcomes. Postcranialization CSF leaks can also be repaired by this approach. Lateral defects may require trephination to assist with placement of the graft.
Jones[31]	2012	4	Prospective	37 patients with frontal sinus CSF leaks; 11 traumatic	Successful repair in 97.3%	Endoscopic repair of frontal sinus CSF leaks well supported.
Grayson[33]	2017	4	Prospective	Endoscopic repair of frontal sinus fractures in 46 patients. 41 patients had posterior table fractures with active CSF leaks.	Outcome: all CSF leaks in posterior table fractures repaired and all except 1 retained normal sinus function. The 1 patient underwent a revision Draf IIb successfully.	Endoscopic repair of frontal sinus fractures is effective and safe. In select patients is the preferred treatment as it maintains normal sinus structure and function, minimizing both early and late complications.
Shi[34]	2010	4	Retrospective	n = 15 1. Endoscopic 13/15 2. Combination 2/15	Outcomes Successful repair 14/15 (93%). Second attempt successful repair 1/15.	Most frontal sinus CSF leaks can be repaired by the transnasal endoscopic approach alone or combined with external endoscopic transfrontal approach. A high success rate and low complication rate is obtainable.
Virgin[38]	2011	4	Prospective	n = 16 1. Traumatic 1 2. Spontaneous 8 3. Tumor resection 7	Outcomes CSF repair of 15/16 (93.8%) patients adequately covered Transnasal endoscopic approach.	The pedicled nasoseptal flap can be successfully used for closure of frontal sinus CSF leaks.
Lee[14]	2011	4	Retrospective	n = 28 with 9 frontal CSF leaks 1. Traumatic 5 2. Iatrogenic 4	All of the 4/28 failures occurred in patients with frontal sinus CSF leaks when using transnasal endoscopic approach.	Frontal CSF leaks likely to fail at repair, unlike CSF leaks in the ethmoid and sphenoid.
Lindstrom[13]	2004	4	Retrospective	n = 6 Frontal CSF leaks 1. Iatrogenic 2 2. Traumatic 2 3. Spontaneous 2	Frontal sinus - outcomes Endoscopic: success 3/3 on initial attempt	In select cases endoscopic repair is safe and effective.

(*Continued*)

TABLE III.A.2. Continued

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Lee[17]	2004	4	Retrospective	n = 39 Patients with CSF rhinorrhea and 3 frontal sinus CSF leaks 1. Traumatic 20 2. Iatrogenic 13 3. Spontaneous 6 Sites 1. Frontal sinus 3/39.	Frontal sinus outcomes 2 Failed initial repair and needed obliteration 1 Was effectiveness of endoscopic repair of the CSF leaks and role of LD	Endoscopic frontal sinus CSF repair is difficult and patients may benefit from a lumbar drain to facilitate flap adherence.

CSF = cerebrospinal fluid; LD = lumbar drainage; LOE = level of evidence.

with the techniques may increase failure rate requiring a second surgery for the patient.

- Cost: Reduced perioperative cost is possible with less reliance on imaging postoperatively. If the endoscopic repair is unsuccessful, a second surgery, either repeat endoscopic or open surgical approach may be required.
- Benefit-Harm Assessment: The benefit of the transnasal endoscopic approach for frontal sinus CSF leaks includes maintenance of normal sinus function, low rate of complications, and cosmesis.
- Value Judgments: This technique appears safe and effective in appropriately selected patients, but surgeon experience with endoscopic frontal sinus procedures and adequate equipment and support is necessary. Furthermore, only a few authors have reported their experience with varying success. Success rates are less than other locations.
- Policy Level: Option
- Intervention: The transnasal endoscopic approach to frontal sinus CSF leaks is safe and effective in select patients, but may have higher rates of failure than other locations.

III.A.3. *Nonsurgical management options in traumatic and iatrogenic CSF leaks*

Traumatic leaks are the most common type of CSF leak and include non-iatrogenic (blunt or penetrating injuries) or iatrogenic injuries (usually unintentional violation of the skull base during rhinologic or neurosurgical procedures). Other CSF leak etiologies include spontaneous, congenital, and neoplastic origins. Due to an overrepresentation of traumatic CSF leaks and conservative management in the literature, the ability to extract data related to nonsurgical management options in iatrogenic CSF leaks was insufficient.

The timing and duration of conservative management in traumatic CSF leaks are controversial. Immediate CSF leak closure has been proposed in an effort to minimize the infection risk,[39,40] but many other studies favor conservative management because of a high rate of CSF leak resolution.[22,23,41] Conservative management consists of strict bed rest, and elevation of the head of the bed to 30 degrees. Patients refrain from coughing, nose blowing, and Valsalva maneuvers. Stool softeners and anti-emetics are routinely prescribed. The underlying goal is to prevent surgical intervention. Approximately 50% of CSF leaks are apparent within the first 2 days, 70% within the first week, and almost 100% present within 3 months.[42]

The success rate for conservative management increases with duration of treatment. In 81 patients with traumatic CSF leak, Yilmazlar et al.[22] demonstrated that the overall rate of cessation with conservative treatment for 3 days is 39.5%. In a study of 51 patients by Friedman et al.,[43] there was spontaneous resolution of the CSF leak in 53% at an average of 4.8 days. Dalgic et al.[23] reported a leak cessation rate of 60.4%, whereas Bell et al.[21] observed a resolution in 84.6% of patients with CSF leaks at 7 days (9 with rhinorrhea, 25 with otorrhea). A persistent CSF leak (greater than 7 days) was identified in 6 patients who were treated with LD. Two of these patients were treated with LD successfully; the remaining 4 patients required surgery.[21] However, the high success rate in this cohort may be attributed to the inclusion of otorrhea patients. Dalgic et al.[23] noted that CSF leakage related to temporal bone fractures will resolve in 80% to 95% of cases.

Although CSF diversion by LD is invasive, it is considered part of conservative management by some authors, because it is an attempt to circumvent surgical intervention and avoids general anesthesia. Albu et al.[41] performed the first prospective RCT in 2015 to ascertain the benefit of early LD placement in reducing the length of CSF leakage in patients with traumatic head injury. Sixty patients with 2 days of persistent rhinorrhea despite conservative management with bed rest were randomized to either LD or continued conservative management. The maximum treatment duration was 10 days. When the CSF rhinorrhea stopped, the LD was immediately removed. Cessation of CSF leaks within the 10-day time frame occurred at 4.83 ± 1.88 days in the LD group, compared to 7.03 ± 2.02 days in the conservative management cohort. Although no endoscopic repair was necessary in the LD cohort, 2 patients in the conservative management group required surgical intervention. Recurrent leaks were comparative in each group, with meningitis occurring in 3% of the LD group and 4%

of the conservative group. Complications related to the LD in this study consisted of headaches in 12 of 30 (40%) and fluid collection around the LD site in 1 patient. Dalgic et al.[23] had spontaneous resolution of leakage in 60.4% of patients by 3 days with noninvasive conservative management, but started CSF diversion in the remaining patients, which raised the success rate to 88.2%. Meningitis incidence was 15.3% in the conservative group and 11.7% in the LD cohort.

Because acetazolamide decreases CSF production and hence intracranial pressure, it has also been used as an adjunct to conservative management of CSF rhinorrhea. Gosal et al.[45] conducted a prospective randomized clinical trial where 20 subjects with traumatic CSF leaks undergoing conservative management (bed rest, elevated head of bed, avoidance of Valsalva) were randomized to acetazolamide (250 mg 4 times per day in adults and 8 to 30 mg/kg/day in children) and 23 subjects received no medication. Three of the 20 patients (15%) in the experimental group had a CSF leak after 10 days of treatment, whereas no subjects in the control group had a persistent leak. The mean duration of the CSF leak was 5 days in the acetazolamide group and 4 days in the control group. Acetazolamide caused asymptomatic, but physiological, side effects such as metabolic acidosis and hypokalemia. This study, like prior opinions,[44] concluded that acetazolamide did not decrease CSF leak duration and can cause acidosis and electrolyte imbalance.[45] However, Abrishamkar et al.[46] performed an RCT where subjects were provided acetazolamide, at 25 mg/kg/day, either within the first 48 hours after admission, or after the first 48 hours. Early use of acetazolamide was associated with a significant decrease in the duration of CSF leak. There were no persistent leaks in the early group within 14 days compared to 6 of 27 (22%) patients who had persistent leaks in the control group.[46] Significant limitations are represented within this study, including small sample size, difficulty ascertaining the exact site of the CSF leak, and data extraction relevant for the anterior skull base.

Although conservative management to avoid surgical intervention is prevalent within many centers, it should be noted that patients with traumatic CSF leaks lasting more than 7 days have an estimated 8-fold to 10-fold increase in the risk of meningitis.[47] Bernal-Sprekelsen identified a high incidence of meningitis in patients treated conservatively[48] and recommend closure of a CSF defect because it prevents meningitis.[40] Therefore, many authors recommend closure within 7 days.[49]

There are limitations interpreting the current studies due to a lack of standardization of data, and an overrepresentation of traumatic CSF leaks in 10 of the 12 case series. Nonsurgical management options in iatrogenic CSF leaks were represented by 2 papers with a small sample size. Long-term prospective studies with standardized reporting are needed (see Table III.A.3).

- Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 4 evidence: 9 studies).
- Benefit: Minimization of exposure to surgical intervention risks with increased chance of spontaneous repair in select traumatic CSF leaks.
- Harm: Increased risk of meningitis if delayed closure, exposure to other complications, LD-related complications, deep vein thrombosis from bed rest, extended antibiotic use delay in mobilization.
- Cost:
  - Direct: Time spent in a hospital bed, LD care facility, appropriately trained staff.
  - Indirect: Patient time off work. Surgical intervention may be required if conservative management fails and LD fails.
- Benefit-Harm A ssessment: Increased spontaneous repair with traumatic nonsurgical approach vs increase risk of meningitis and complications of nonsurgical interventions.
- Value Judgments: Current conclusions are based on limitation of high-quality studies. Larger studies are needed.
- Policy Level: Option
- Intervention: Consideration for nonsurgical management within the first 7 days is feasible in traumatic skull base injuries. Lumbar drains may shorten the interval to traumatic CSF leak cessation during conservative management. The evidence for acetazolamide in traumatic or iatrogenic CSF leaks is lacking.

III.A.4. *The role of prophylaxis with antibiotics*

Prophylactic antibiotics in CSF leaks are commonly employed with the cited rationale of exposure of the sterile central nervous system to a contaminated nasal cavity. This exposure may predispose the patients to septic complications or meningitis. No studies have assessed the role of prophylactic antibiotics in iatrogenic CSF leaks, so this section discusses the role of prophylactic antibiotics in traumatic CSF leaks only. The incidence of meningitis in patients with basilar skull fractures and a CSF leak is reported as 7% to 37%,[40,50–53] and this rate is thought to increase with increasing duration of the CSF leak.[43] Postrepair, this rate decreases to 0.3% to 7%.[17,54] However, antibiotic prophylaxis to prevent meningitis in patients with basilar skull fractures is controversial. Antibiotic resistance, allergic and adverse reactions, increased costs, alteration of normal flora,[55] and studies suggesting that antibiotics are ineffective in this setting have warranted further investigation.

Ratilal et al.[56] conducted a meta-analysis in 2015. Five RCTs were included. The aim was to compare prophylactic antibiotics with no antibiotics or placebo in patients with basilar skull fractures. A total of 208 patients were included. One-hundred-and-nine patients received prophylactic antibiotics, with 99 in the control group. No difference was demonstrated in the frequency of meningitis in patients receiving antibiotics compared to those not receiving antibiotics. In addition, a subgroup analysis identified no difference in the meningitis rate in patients with and without CSF leakage. In the same meta-analysis by

TABLE III.A.3. Traumatic and iatrogenic CSF leaks: nonsurgical management options

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Albu[41]	2016	1b	RCT	n = 60 Traumatic CSF leak <24 hours 1. 30 patients CSF diversion group A 2. 30 patients Conservative Group B	Outcomes 1. Length CSF leak A <10 days B >10 days 2/30 patients 2. Recurrent CSF leak A 3/30 (23%) B 4/30 (27%) 3. Meningitis A 3/30 (10%) B 4/30 (13%)	LD within 2 days of traumatic CSF leak, in highly selected patients, results in statistically significant decrease in CSF leak length of time.
Bell[21]	2004	4	Retrospective	n = 735 1. 701 (95.3%), no CSF leak 2. 34 (4.6%), CSF leak (9/34 rhinorrhea) CSF leak divided duration of leak 1. <7 days 2. >7 days CSF diversion	Outcomes: CSF leak resolution 1. Conservative only 28/34 (84.6%) 2. Persistent (>7 days) 6/34 (17.6%) 3. CSF diversion 5/6 2/5 success 3/5 failed	Majority of posttraumatic CSF leaks resolve with conservative measures.
Yilmazlar[22]	2006	4	Retrospective	n = 81 CSF leaks (53 anterior skull base) lasting >24 hours each 3 group divided into 2 groups GCS <8 and >8. 1. Spontaneous resolution (14/53 nasal CSF leaks) 2. Lumbar drainage (7/24 eventually needed surgery) Emergent surgery (all non-endoscopic approaches)	Outcomes CSF leak 1. Spontaneous resolution: (a) GCS >8 17/50. (b) GCS <8 15/31 2. Lumbar drainage (a) GCS >8 15/50. (b) Failed 5/15 (c) GCS <8 9/31 (d) Failed 2/9 3. Surgery (non-endoscopic) (a) GCS >8 18/50. (b) Failed 1/18 (c) GCS <8 7/31 (d) Failed 2/7	Patients with rhinorrhea should be placed into 1 or 2 groups based on the GCS score and presence or absence of intracranial lesions. Results suggest that if conscious at admission and treated conservatively or surgically the prognosis is more likely to be favourable and meningitis risk is low.
Dalgic[23]	2008	4	Retrospective	n = 43 1. Conservative 3 days 26/40 (60.4%) 2. CSF diversion 17/40 (42.5%)	Outcomes 1. CSF diversion success 15/17 (88.2%) 2. CSF diversion failed 2/17 (11.7%)	LD is a less invasive technique to treat patients who failed conservative approach. No increased risk of meningitis.
Bernal-Sprekelsen[40]	2005	4	Retrospective	n = 39 pts CSF leak repair 41 Repairs with 40/41 closures 1. Pre-repair meningitis 2. Post-repair meningitis Of these 39 patients, there were 14 traumatic and 4 iatrogenic injuries	Meningitis pre/post CSF leak repair. Pre-repair 15/39 Post-repair 0/39 No individualized data to separate traumatic and iatrogenic outcomes	Conservative management of CSF leak may lead to meningitis; therefore, surgery is the treatment of choice to prevent ascending meningitis.
Bernal-Sprekelsen[48]	2000	4	Retrospective	n = 27 Patients with CSF leak 1. 10 patients CSF repair 2. 17 patients Conservative	Meningitis 1. 4/10 CSF repair meningitis 2. 5/10 Conservative meningitis	High incidence of meningitis unacceptable and neither the conservative approach nor the transcranial repair was able to prevent this considerable incidence of ascending meningitis.

(*Continued*)

TABLE III.A.3. Continued

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Friedman[43]	2001	4	Retrospective chart review	n = 101 51 Traumatic CSF leaks >24 hours. CSF leak patient developed meningitis 50 traumatic CSF leaks <24 hours 1. 10% with antibiotic prophylaxis 2. 21% without antibiotic prophylaxis.	Outcomes 1. CSF leaks that persist >24 hours are at risk for meningitis, and many will require surgical intervention.	Prophylactic antibiotics may be effective and should be considered in this group of patients.
Schoentgen[39]	2013	4	Retrospective	n = 40 1. Conservative 11/40 2. Surgery 29/40	Outcomes 1. Conservative 4/11 recurrent leak 2. Surgery recurrence leak 5/29 (17%)	Conservative approach lead to a higher risk of meningitis compared to surgical repair.
Sherif[49]	2012	4	Retrospective	n = 138 1. 104/138 Surgical 2. 34/138 Conservative for >5 days Lumbar drain insertion 1. Persistent CSF leak >48 hours	Outcomes 1. Surgical: 2/104 persistent CSF leak and 2/104 (1.9%) meningitis 2. Conservative 1/34 (2.9%) meningitis LD with meningitis 2.9%	Clinical outcome excellent with low morbidity, prophylactic antibiotic and LD use may play role in management approach to traumatic CSF leaks.
Gosal[45]	2015	1b	RCT	n = 42 1. Acetazolamide n = 21 2. Control n = 23	CSF leak duration post 10 days 1. Acetazolamide n = 3 2. Control n = 0	No change in length of hospital stay between the 2 groups. Unwanted metabolic and electrolyte effects in acetazolamide group.
Abrishamkar[46]	2013	1b	RCT	n = 57 1. Acetazolamide in first 48 hours 2. Acetazolamide after 48 hours	Acetazolamide in first 48 hours 1. CSF leak cessation after 14 days = 0 patients 2. Surgical intervention 1/28 (3.6%) 3. LP and LD 2/28 (7.1%) Acetazolamide after 48 hours 1. CSF leak cessation after 14 days = 6/27 (22%) 2. Surgical intervention 3/29 (10.3%) 3. LP and LD 9/29 (31%)	This study showed that early acetazolamide usage in patients with skull-base fracture can help both to prevent CSF leakage and to shorten the period of leak in those with active leakage after trauma.
Stankiewicz[44]	1991	4	Retrospective	n = 8 Iatrogenic injuries 1. 6 Surgery (1 patient added diuretic) 2. 2 Conservative management (1 patient lumbar tap)	Conservative management 1 of 2 patients successful	Early paper with 1 patient treated with diuretic which the author felt was not necessary in traumatic cases.

CSF = cerebrospinal fluid; GCS = Glasgow Coma Scale; LD = lumbar drainage; LOE = level of evidence; LP = lumbar puncture RCT = randomized controlled trial.

Ratilal et al.,[56] they included 17 non-RCTs in 2168 patients. A group of 1141 patients were treated with prophylactic antibiotics and 1027 received no antibiotics. These results were compared to the previous data using the 5 RCTs. The frequency of meningitis in the treatment group was 6.92%, and 6.52% in the control group. Although these results were comparable to the analyses using the 5 RCTs, another subgroup analysis within the non-RCT trials identified a possible small benefit with antibiotic prophylaxis in patients with CSF leakage.[56] However, interpretation is

cautioned within this group because of limitations of the nonrandomized, retrospective nature and variable reporting within the studies. Limitations also include the wide confidence interval and small sample size. Overall, the data was unable to support the use of antibiotic prophylaxis in basilar skull fractures because no proven benefit could be established.

Previous studies also upheld this finding. Eftekhar et al.[50] performed a prospective randomized controlled trial of 109 patients with traumatic pneumocephalus. Fifty-three patients received prophylactic antibiotics and 56 patients did not with comparable incidence of meningitis (18.9% and 21.5% respectively). Interestingly, the meningitis incidence was higher in this study compared to other studies. The authors suggest that a CSF leak is an associated risk factor for meningitis, but concluded that prophylactic antibiotics do not reduce the incidence. Villalobos et al.[57] conducted a meta-analysis of 14 studies over 26 years, involving 1241 patients with basilar skull fractures. Meningitis developed in 5.3% of patients receiving antibiotics and 7.1% of patients not receiving antibiotics. They also conducted a subgroup analysis of 547 patients with associated CSF leakage. Of the 297 patients that received prophylactic antibiotics, 10% developed meningitis compared to 14% who received no antibiotics. Although there was a lower meningitis risk among patients receiving antibiotics, this finding was not statistically significant and was independent of the presence of a CSF leak.[57] Rathore[58] conducted a meta-analysis of 848 basilar skull fractures, of which 519 had antibiotics and 329 did not. Meningitis occurred in 4% in those treated with antibiotics compared to 3% without antibiotics. The subgroup with CSF leak showed that 2% with antibiotics and 6% without antibiotics developed meningitis. Although a higher incidence, there was again no statistical difference between groups. Numerous retrospective trials have also found that no statistically significant conclusion can be drawn regarding the use of antibiotics in basilar skull fractures to prevent meningitis.[21,55,59]

In contrast, Brodie et al.[60] concluded in their meta-analysis that antibiotics do reduce meningitis risk. This study analyzed 324 patients with basilar skull fractures and found 6 of 237 (2.5%) patients who received antibiotics developed meningitis, while 9 of 87 (10%) patients developed meningitis when not administered antibiotics ($p = 0.006$). Demetriades et al.[61] also concluded that antibiotic prophylaxis has a role in open and basilar fractures in their randomized control trial. In their series of 157 patients, the incidence of meningitis was similar in the antibiotics (0.9% of 111 patients) and non-antibiotic groups, (2.1% of 46 patients); however, overall infection rate was higher in the non-antibiotic group, with 8.7% of patients developing septic complications, compared to 0.9% of the antibiotic group.[61] Friedman et al.[43] identified a subset of patients with persistent leaks beyond 24 hours that may benefit from antibiotics, yet patients in this cohort have been included in many of the meta-analyses.

Choi and Spann[62] studied 1 retrospective cohort that identified a higher incidence of meningitis in patients with basilar skull fractures who received prophylactic antibiotics (12/197) vs those who did not have antibiotics (0/73). Although Rimmer et al.[63] acknowledged that there is a lack of evidence to support prophylactic antibiotics in patients with a CSF leak, they proposed that all patients with an anterior skull base CSF leak at least be immunized against pneumococcus, meningococcus, and haemophilus.

In summary, conflicting data exists regarding use of prophylactic antibiotics in traumatic CSF leaks. Because there is a low incidence of meningitis in traumatic skull-base fractures and CSF leaks, large patient numbers are required to have adequate power to detect a difference (see Table III.A.4).

- Aggregate Grade of Evidence: B (Level 1a and 3a: 1 study; Level 1b: 2 studies; Level 3a: 4 studies; Level 4: 10 studies).
- Benefit: Possible reduction in the risk of meningitis in traumatic CSF leaks
- Harm: Antibiotic resistance leading to more pathogenic bacteria, increased susceptibility to infection, and adverse drug reactions.
- Cost: Moderate
- Benefit-Harm Assessment: The majority of studies recommend against using prophylactic antibiotic in basilar skull fractures and CSF leaks, but acknowledge the limitations of their studies.
- Value Judgments: Current conclusions are based on limitations regarding interpretation of data and low-level evidence studies. Larger studies are required.
- Policy Level: Option
- Intervention: There is a lack of evidence to support prophylactic antibiotics administration in patients with a traumatic CSF leak.

III.B. Spontaneous CSF leaks

Spontaneous sinonasal CSF leaks appear to have distinct clinical features from other etiologies of CSF leaks.[69,70] Over the past 3 decades, there has been increased attention toward characterization of this pathology as well as endoscopic endonasal repair.[70,71] As the reported incidence of spontaneous CSF leaks continues to increase, our understanding of the underlying pathophysiology and the nuances of clinical management is critical for the modern skull-base surgeon.[72–74]

Spontaneous CSF leaks classically present with unilateral clear rhinorrhea in obese, middle-aged women,[10,69,70] but can occur at any age, in males and non-obese individuals. Upon initial presentation with suspected CSF rhinorrhea, the first step in evaluation beyond physical exam and confirmed or provoked rhinorrhea is confirmation of a CSF leak. Laboratory testing for beta-2 transferrin or beta trace protein is the initial preferred method of detection.[64,70,75–78] Following laboratory confirmation, an

TABLE III.A.4. Traumatic CSF leaks: role of antibiotic prophylaxis

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Ratilal[56]	2015	1a 3a	Systematic review RCT and a non-RCT meta-analysis	RCTs comparing 1. Antibiotic 2. Control (placebo or no intervention) 17 Non-RCTs meta-analysis to compare results 1. Antibiotic 2. Control (placebo or no intervention) Subgroup analysis: CSF leaks	1. Frequency of meningitis. 2. All-cause mortality. 3. Meningitis-related mortality. 4. Need for surgical correction of CSF leakage. 5. Non-CNS infection.	The RCTs does not support prophylactic antibiotic use in patients with basilar skull fractures, with or without CSF leak. A possible adverse effect of increased susceptibility to infection with more pathogenic (disease-causing) organisms.
Oakley[64]	2016	1/3/4	Systematic review 10 Studies included	10 Studies reviewed including 4 meta-analysis	Prophylaxis and meningitis rate	No benefit in traumatic leaks.
Eftekhar[50]	2004	1b	Prospective RCT	109 Patients traumatic pneumocephalus 1. 53 Antibiotic 2. 56 Control	Meningitis rate 1. 18.9% With antibiotics 2. 21.5% No antibiotics	Prophylactic antibiotics do not decrease incidence meningitis. CSF leak may be considered primary risk factors meningitis.
Villalobos[57]	1998	3a	Meta-analysis	n = 1241 1. 719 Antibiotics 2. 522 No antibiotics Subgroup analysis CSF leak: n = 5471) 1. 297 Antibiotics2) 2. 250 No antibiotics	Meningitis rate 1. 38/719 (5.3%) With antibiotic 2. 37/522 (7.1%) No antibiotic Subgroup analysis CSF leak 1. 10% Meningitis 2. 14% Meningitis	Lower meningitis risk among patients receiving antibiotics but not statistically significant.
Rathore[58]	1991	3a	Meta-analysis	n = 848 Basal skull fracture 1. 519 Antibiotics 2. 329 No antibiotics Subgroup analysis CSF leak 1. 70 Antibiotics 2. 47 No antibiotics	Meningitis rate 1. 19/519 (4%) With antibiotic 2. 10/329 (3%) No antibiotic Subgroup analysis CSF leak 1. 2% Antibiotics 2. 6% No antibiotics	Antibiotics not useful in preventing meningitis. Antibiotics does not provide protection against development of meningitis in patients with CSF leak.
Brodie[60]	1997	3a	Meta-analysis	n = 324 Basal skull fracture 1. 237 = Antibiotics 2. 87 = No antibiotics	Meningitis rate 1. 6/237 With antibiotic 2. 9/87 no antibiotic	Antibiotics reduces meningitis risk. Individual studies no significance difference but pooled data suggests otherwise.
Demetriades[61]	1992	1b	RCT	n = 157 Skull base fracture 1. No antibiotics n = 46 2. Ceftriaxone 3 days n = 50 3. Amp/sulpadiazine 3 days n = 61	Septic complications/meningitis 1. No antibiotics 4/46 (a) 1/46 Meningitis (b) 3/46 Wound infection 2. Ceftriaxone 3 days 1/50 (a) 1/50 Wound infection 3. Amp/sulpadiazine 3 days 0/61	Infectious complications in the non-antibiotic group was significantly higher than in the antibiotic group. The results of the study suggest that antibiotic prophylaxis has a role in the management of open and basilar fractures.

(*Continued*)

TABLE III.A.4. Continued

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Eljamel[59]	1993	4	Retrospective	n = 205 With traumatic CSF leak 1. 106 Antibiotics 2. 109 No antibiotics	Meningitis rate 1. 7/106 (6.6%) Antibiotics 2. 10/109 (9.1%) No antibiotic	Prophylactic antibiotics do not reduce the risk of antibiotics.
Clemenza[55]	1995	4	Retrospective	n = 88 Traumatic CSF leaks 1. 48 Antibiotic 2. 40 No antibiotics	Meningitis 1. 5/48 (10.4%) 2. 1/40 (2.5%)	No benefit in treating these patients with antibiotics.
Choi[62]	1996	4	Retrospective	n = 260 Skull base fractures 1. 197 Antibiotics 2. 73 No antibiotics	Meningitis 1. 12/197 (6%) 2. 0/73	Increased incidence of meningitis in patients with prophylactic antibiotics.
Friedman[43]	2001	4	Retrospective chart review	n = 43 1. 29 Antibiotics 2. 14 No antibiotics.	Meningitis 1. 3/29 (10.3%) 2. 3/14 (21.4%)	Prophylactic antibiotics may be effective, but insufficient numbers to attain significance.
MacGee[65]	1970	4	Retrospective	n = 58 1. 41 Antibiotic 2. 17 No antibiotic	Meningitis rate 1. 1/41 (2.4%) 2. 2/17 (11.7%)	No statistically significant conclusion can be drawn about the use of antibiotics in acute traumatic CSF fistulae.
Frazee[66]	1988	4	Retrospective	n = 347 1. Antibiotics 251 2. No antibiotics 96	Meningitis 1. Antibiotics 4/251 2. No antibiotics 2/96	Observation alone is considered appropriate management in patients with basal skull fractures.
Dagi[67]	1983	4	Retrospective	n = 168 – requested 1. Antibiotics 65 2. No antibiotics 63	Meningitis 1. Antibiotics 2/65 (3.1) 2. No Antibiotics 0/63	No clear evidence that antibiotics reduces meningitis risk.
Zrebeet[68]	1986	4	Retrospective	n = 42 1. Antibiotics n = 28 2. No antibiotics n = 14	Meningitis 1. Antibiotics n = 28 2. No antibiotics n = 14	This study does not support use of chemoprophylaxis in treatment of fractures at base of skull.

CNS = central nervous system; CSF = cerebrospinal fluid; RCT = randomized controlled trial.

attempt at localization of the skull-base defect is warranted prior to operative intervention. High-resolution CT is used as the primary imaging modality with a recommendation for magnetic resonance imaging in cases when cheaper or less invasive studies failed to diagnose or localize the CSF leak.[64] For active leaks that cannot be localized with these noninvasive imaging studies, CT cisternography with intrathecal dye injection can be definitive.

It has long been recognized that spontaneous CSF rhinorrhea is a unique clinical entity that can be managed in most cases with an EEA.[2,71] The goal of this operation is to separate the nasal and intracranial cavities to reduce the risk of ascending bacterial infections.[79] Over the past 3 decades, multiple studies have demonstrated the safety and efficacy of endoscopic repair, with consensus that endoscopic repair should be considered the standard of care.[10,24,69,70,80–83] Both intrathecal[40,84–88] and topical use[89–92] of fluorescein may augment intraoperative identification of a CSF fistula, though intrathecal usage has been associated with rare, but potentially serious complications.[87,93–96] Nuances of surgical repair and postoperative intracranial pressure management are reviewed in the following sections.

III.B.1. *Relationship between spontaneous CSF leaks and idiopathic intracranial hypertension*

Historically, spontaneous CSF leaks were described as having normal CSF pressure,[97] but a mounting body of evidence demonstrates that patients with spontaneous leaks have increased CSF pressures, specifically idiopathic intracranial hypertension (IIH).[24,82,98–107] IIH was first described in 1896 by Quincke[108] and is currently recognized as a diagnosis of exclusion in patients with increased intracranial pressures (ICP), defined by the modified Dandy criteria. These criteria include: (1) signs and symptoms of ICP; (2) absence of localizing neurologic findings; (3) absence of radiographic deformity, displacement, or

obstruction of ventricular system; and (4) no other cause of increased ICPs (eg, venous occlusion) in awake and alert individuals.[109]

Although demographic features are not part of the diagnostic criteria for either IIH or spontaneous CSF leaks, they share strikingly similar patient demographics. Multiple studies highlight the overlap in these demographics that are predominantly middle-aged, overweight women.[24,69,70,83,101,110–112] The prevalence of obesity in conjunction with spontaneous CSF leaks and IIH continues to give insight into the pathophysiology of these clinical entities. Berdahl et al.[113] demonstrated a direct linear relationship between ICPs and body mass index (BMI) in a series of more than 4200 patients who underwent a lumbar puncture at their institution. Furthermore, a matched case-control series described a dose-response effect of increasing BMI with the risk for development of IIH.[114] Moreover, Banks etal.'s[24] retrospective review demonstrated that BMI was statistically significantly higher in spontaneous CSF leaks compared to other CSF leak etiologies. Several authors note the concurrent increase of spontaneous CSF leaks (as well as IIH) in conjunction with the increasing obesity epidemic, although it is unclear if this could be increasing recognition and diagnosis of spontaneous CSF leaks.[74,102,115,116]

Radiographic signs may provide indirect evidence of elevated CSF pressures in both IIH and spontaneous CSF leaks. Patients with IIH demonstrate radiographic abnormalities indicative of increased ICP, such as empty or partially empty sella,[99,111] flattening of the posterior globes,[117] osseous erosion and widening of skull base foramina[118] and tortuosity of the optic nerves among others.[119] Friedman et al.[115] proposed that there is sufficient data such that the diagnostic guidelines for IIH should include these radiographic characteristics. A recent case-control study demonstrated that an enlarged Meckel's cave may serve as an additional indicator of elevated ICP in spontaneous CSF leak patients.[104] Multiple studies of spontaneous CSF leak patients demonstrate the presence of these same signs of elevated ICP.[120,121] In addition to radiographic signs of IIH, 2 retrospective reviews demonstrated anterior and lateral skull-base attenuation in patients with spontaneous leaks and obesity as compared to controls.[120,122]

Finally, multiple studies have demonstrated direct measurements of elevated ICP in patients with spontaneous CSF leaks.[100,101,110,123,124] Two prospective series from the same group of authors evaluating patients with primary or recurrent spontaneous CSF leaks, demonstrated a statistically significant postrepair increase in ICPs of 7.6 cm H_2O and 8.0 cm H_2O in each series.[106,107] Likewise, Aaron et al.[103] demonstrated that following spontaneous CSF leak repair, opening pressures returned to an elevated state, similar to a control group of IIH patients with papilledema. Both Aaron et al.[103] and Banks et al.[24] noted that ICPs may be normal during an active leak, because spontaneous CSF leaks may act as a release valve for increased ICPs, thereby normalizing ICPs until after the leak site is repaired. Postoperative return of elevated ICPs may put these patients at higher risk of delayed recurrent or secondary leaks.[82]

Overall, the current literature evaluating the relationship between spontaneous CSF leak and IIH supports a strong association between these two clinical entities and recognizes most spontaneous CSF leaks as a clinical variant of IIH. There are rare cases of spontaneously occurring CSF leaks in patients with arachnoid cysts or congenital/developmental skull-base deformities that are probably unrelated to IIH.[24,125] The diagnosis of IIH by strict adherence to the modified Dandy criteria can be made in most patients presenting with spontaneous CSF leaks.[101] Given similarities in patient demographics, radiographic findings, and actual CSF pressure measurements, spontaneous leaks are considered by most authors to be a variant of IIH.[24,69,83,101,110–112,124] A growing body of literature consistently supports this assertion; several evidence-based reviews, cohort and case-control studies and a large body of retrospective reviews promotes level 2B evidence with a grade B recommendation (see Table III.B.1).

- Aggregate Grade of Evidence: B (Level 3b: 5 studies; Level 4: 12 studies; Level 5: 1 study)
- Summary: There is a direct relationship between spontaneous CSF leaks and IIH; most spontaneous leaks represent a variant of IIH.

III.B.2 Control of intracranial hypertension after repair

With an etiology of increased intracranial hypertension in spontaneous CSF leaks, it is intuitive that management of idiopathic spontaneous CSF leaks would include control of increased ICP. Common management strategies for both IIH and spontaneous CSF leaks aim to control increased ICP and include lumbar drains for temporary CSF diversion in the perioperative period or CSF shunts and diuretics (eg, acetazolamide) for long-term diversion or decreased CSF production respectively.

Evidence for the management of IIH is mixed. Despite a high-quality study demonstrating improved visual outcomes, improved quality of life (QOL) measures and reduced CSF pressures following administration of oral acetazolamide in patients with IIH,[126] a recent Cochrane review concluded insufficient evidence to support or reject the use of acetazolamide.[127] In regard to surgical management of IIH, a meta-analysis examining 457 articles on surgical interventions for IIH and their role in management of visual problems and outcomes failed to be able to support or reject surgical interventions.[128]

Similar to the management of IIH, investigators have examined the role of both acetazolamide and CSF shunting procedures in the management of patients with spontaneous CSF leaks. The literature is not homogenous and is comprised mostly of level 3 and level 4 evidence.

TABLE III.B.1. Relationship between spontaneous CSF leaks and IIH

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Schlosser[98]	2002	4	Retrospective case series	Patients with multiple spontaneous encephaloceles (n = 5)	Demographics, BMI, ICP, empty sella	Spontaneous CSF leaks have similar demographics and appear to represent a variant of IIH.
Schlosser[101]	2006	4	Retrospective case series	Spontaneous CSF leaks (n = 11)	Modified Dandy criteria for IIH	72% of spontaneous leak patients meet definitive diagnosis of IIH by modified Dandy criteria, likely diagnosis of IIH in those that did not meet criteria.
Wise[70]	2007	4	Evidence-based review	Spontaneous CSF leaks	–	Most patients demonstrate symptoms of IIH or meet diagnostic criteria.
Banks[24]	2009	4	Retrospective case series	1. Spontaneous CSF leaks (n = 77) 2. Traumatic CSF leaks (n = 109) 3. Congenital CSF leaks (n = 7)	Comparison of demographics between spontaneous CSF leaks and other causes	BMI of patients with spontaneous leaks (mean, 35 kg/m^2) significantly elevated compared to BMI of traumatic (mean, 30 kg/m^2) and congenital (mean, 23 kg/m^2) leaks. Predominance of females (74%) and average age of 51 years.
Wall[116]	2010	4	Evidence-based review	IIH	–	Incidence of IIH parallels obesity epidemic.
Berdahl[113]	2012	4	Retrospective case series	Patients undergoing lumbar puncture without diagnoses, surgical procedures or medications known to affect ICPs (n = 4235)	Relationship between BMI and CSF pressures	CSF pressures have a positive, linear relationship ($r^2 = 0.2$) with BMI.
Daniels[114]	2007	3b	Matched case-control study	Patients with new diagnosis of IIH (n = 34) and matched controls (n = 41)	Logistic regression analysis between BMI and weight gain with diagnosis of IIH	Higher BMI and percentage weight gain are associated with greater risk of IIH.
Friedman[115]	2013	5	Literature review and updated diagnostic criteria proposal	Pseudotumor cerebri syndrome	–	Radiographic features of IIH: 1. Empty sella 2. Flattening of posterior globe 3. Distention of the perioptic subarachnoid space 4. Transverse venous sinus stenosis
Schlosser[99]	2003	4	Retrospective case series	1. Spontaneous CSF leaks (n = 16) 2. Non-spontaneous CSF leaks (n = 12)	Radiographic evidence of empty sella	All spontaneous leaks associated with signs of increased intracranial pressures: empty or partially empty sella; statistically significantly different from non-spontaneous group.
Seth[111]	2010	4	Retrospective case series	Spontaneous CSF leaks (n = 39)	Demographics, age, sex, BMI, empty or partially empty sella	Age, sex, and BMI consistent with prior reports. 77.4% patients with empty or partially empty sella.

(*Continued*)

TABLE III.B.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Aaron[104]	2017	3b	Case-control series	1. Spontaneous CSF leaks (n = 63) 2. Controls (n = 91)	Radiographic (MRI) evidence of Meckel's cave enlargement	Patients with spontaneous CSF leaks demonstrate statistically significantly radiographic enlargement of Meckel's cave as compared to controls.
Psaltis[120]	2014	3b	Case-control study	1. Spontaneous CSF leaks (n = 32) 2. Traumatic CSF leaks (n = 25) and non-leaking controls (n = 36)	Radiographic skull base thickness	Patients with spontaneous CSF leaks have decreased thickness of anterior cranial base (ethmoid roof, lateral lamella, and anterior face of sella).
O'Connell[122]	2016	3b	Case-control study	1. Spontaneous anterior cranial fossa CSF leaks (n = 32) 2. Non-obese controls (n = 32) 3. Obese controls (n = 32)	Composite skull base thickness	Statistically significant inverse relationship of BMI to anterior and lateral skull-base thickness.
Schlosser[100]	2004	4	Retrospective case series	1. Spontaneous CSF leaks 2. Traumatic CSF leaks	CSF pressures	Elevated ICPs may account for clinical findings of patients with spontaneous CSF leaks (mean, 32.5 cm H_2O).
Chaaban[106]	2013	4	Prospective case series	Spontaneous CSF leaks (n = 32 patients, 42 CSF leaks)	Post-repair ICPs	Increased ICPs following post-repair clamping of lumbar drain or ventriculostomy (mean, 7.6 cm H_2O).
Chaaban[107]	2014	4	Prospective case series	Spontaneous CSF leaks (n = 46 patients, 56 CSF leaks)	Post-repair ICPs	Increased ICPs following post-repair clamping of lumbar drain or ventriculostomy (mean, 8.0 cm H_2O).
Aaron[103]	2014	3b	Prospective case-control study	1. Spontaneous CSF leaks 2. Patients with IIH and papilledema	CSF pressures	1. Post-clamping ICPs of spontaneous CSF leak patients significantly increases 2. Post-clamping ICPs between spontaneous CSF leaks and patients with IIH with papilledema were similar.
Campbell[82]	2016	4	Retrospective case series	Patients meeting modified Dandy criteria for diagnosis of IIH with spontaneous CSF leaks (n = 32 patients, 44 skull base defects)	Long-term (greater than 10 year) follow-up data	Patients with IIH and CSF leaks at risk for remote recurrences or second leaks.

BMI = body mass index; CSF = cerebrospinal fluid; ICP = intracranial pressure; IIH = idiopathic intracranial hypertension.

As mentioned previously, ICP may increase as much as 8.0 cm H_2O on average following surgical repair of spontaneous CSF leaks[106,107] and thereby may provide insight into decreased primary repair success rates in the spontaneous leak population as compared to CSF leaks of other etiologies.[100,107,121,124,129,130]

Perioperative LD following endoscopic endonasal repair remains a controversial topic. A recent meta-analysis by Ahmed et al.[131] reviewed 12 studies examining the use of lumbar drains in the perioperative period following endoscopic endonasal repairs of CSF leaks of varying etiologies. The authors concluded that there was insufficient

evidence to support LD to prevent CSF leak recurrence, though there was no subgroup analysis of patients with spontaneous CSF leaks. Several small studies within this report did, however, delineate their outcomes and failed to demonstrate a difference in successful repair with or without a lumbar drain.[132–134] Similarly, a retrospective review of 46 spontaneous leaks from a single institution with mean follow-up of 16.8 months, failed to show a difference of recurrence of CSF leakage.[135] A prospective randomized study of 150 patients with CSF leaks by Albu et al.[136] also failed to demonstrate a difference in recurrence rates between patients who underwent perioperative lumbar drain placement and those that were managed without a lumbar drain. Within this study, there were 26 patients with spontaneous CSF leaks with 3 failures in both the LD and no LD cohorts. Although there were no differences in this subgroup, the small sample size may limit the subsequent conclusions.[136]

Several studies provide insight into the utility of long-term reduction in CSF pressures. The Albu et al.[136] study did not manage postoperative ICPs other than a perioperative lumbar drain and found a drastic 23% recurrence rate in patients with spontaneous leaks as compared to a 3% and 4% recurrence for traumatic and iatrogenic leaks respectively, suggesting that a long-term reduction in CSF pressures may prevent recurrence.[136] Moreover, the systematic review by Teachey et al.[112] evaluated the outcomes of 56 articles combined with their own prospective series for a total of 679 patients surgically managed for spontaneous CSF leaks. The authors demonstrated a significant difference in successful repair of patients who were managed with postoperative acetazolamide or CSF shunt systems as compared to patients with no active management of increased ICP (93% vs 82%); however, the authors could not distinguish use of a CSF diversion system from acetazolamide usage. Chaaban et al.[106] prospectively evaluated 36 patients with postoperative administration of oral acetazolamide, demonstrating a near immediate reduction in ICPs of nearly 10 cm H_2O. Finally, a case series by Campbell et al.[82] with follow-up of greater than 10 years presented an algorithm and outcomes for postoperative ICP control with medical therapy and subsequent ventriculoperitoneal shunting; however, the authors could not identify risk factors for leak recurrence.

Although there has not been direct investigation into the side effects and complications associated with acetazolamide usage or CSF shunts in the spontaneous CSF leak literature, these are well-documented in other bodies of literature. Many IIH patients do not tolerate maximal dosages of acetazolamide. These patients experience side effects such as taste disturbances and lightheadedness or dizziness; however, they also benefit from significant improvement in IIH-related quality-of-life measures.[126] Meanwhile, again, although there is limited literature regarding complications of CSF-diverting shunts in spontaneous leak patients, the risk profile of ventriculoperitoneal shunts including the operative procedure, infection, shunt failure, or obstruction is well-known.[137]

In summary, these results suggest that perioperative lumbar drains are not necessary (level 3A) for the successful repair of spontaneous CSF leaks. This data constitutes a grade B recommendation against routine lumbar drain usage given the preponderance of potential harm over benefit, though lumbar drain usage for adjunctive measures such as the administration of intrathecal fluorescein or in high risk cases, such as difficult anatomic sites or patients with extremely high BMIs should be determined on a case-by-case basis (see Table III.B.2).

In regard to long-term ICP management, postoperative ICP management should be considered in patients with spontaneous CSF leaks and documented elevated ICP (level 3B). Acetazolamide can be used as an effective ICP-lowering medication with an option of ventriculoperitoneal shunts or other CSF-shunting procedures in patients with recalcitrantly elevated ICP or recurrent CSF leak given the preponderance of benefit over harm (grade C) (see Table III.B.3).

Role of perioperative ICP management with lumbar drains.

- Aggregate Grade of Evidence: B (Level 2b: 1 study; Level 3a: 1 study; Level 4: 4 studies)
- Benefit: Administration of intrathecal fluorescein if needed. Immediate ICP reduction in high risk cases, such as patients with extremely high BMIs, prior failure or difficult anatomic sites.
- Harm: Lumbar drain–related complications (eg, headache, bleeding, infection, pneumocephalus)
- Cost: Lumbar drain–related complications (eg, headache, bleeding, infection, pneumocephalus)
- Benefit-Harm Assessment: Lumbar drains have not been shown to be efficacious in improving surgical outcomes or risk for recurrent CSF leaks.
- Policy Level: Recommendation against routine use of lumbar drains, with option in high risk cases, given preponderance of potential harm over benefit.
- Intervention: Perioperative lumbar drains are not necessary for the successful repair of most spontaneous CSF leaks. Lumbar drains remain an option for adjunctive measures such as administration of intrathecal fluorescein or high-risk cases.

Role of postoperative ICP management with acetazolamide or shunting.

- Aggregate Grade of Evidence: C (Level 2b: 1 study; Level 4: 3 studies)
- Benefit: Reduced ICP and increased CSF leak repair success rates.
- Harm: Taste disturbances and lightheadedness or dizziness with acetazolamide. Operative procedures,

TABLE III.B.2. Role of postoperative ICP control: perioperative ICP management with lumbar drains

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Ahmed[131]	2017	3a	Systemic review and meta-analysis	Lumbar drains in CSF leaks: 1. Spontaneous 2. Traumatic 3. Iatrogenic (ESS) 4. Iatrogenic (ASB)	Successful repair with perioperative lumbar drain placement	Insufficient evidence to support adjunctive lumbar drain.
Meco[134]	2007	4	Retrospective case series	Spontaneous CSF leaks with and without lumbar drains (n = 4)	Successful primary spontaneous CSF leak repair	All spontaneous CSF leaks repairs, with or without lumbar drains, were successful.
Gilat[133]	2011	4	Retrospective case series	Spontaneous CSF leaks with and without lumbar drains (n = 7)	Successful primary spontaneous CSF leak repair	All spontaneous CSF leaks repairs, with or without lumbar drains, were successful.
Caballero[132]	2012	4	Case-series	1. Spontaneous CSF leaks (n = 40) 2. Iatrogenic CSF leaks (n = 50) 3. Traumatic CSF leaks (n = 15)	Successful CSF leak repair	No difference in leak rates with or without lumbar drain.
Adams[135]	2016	4	Case series	Spontaneous CSF leaks without lumbar drain (n = 36) and with lumbar drain (n = 10)	Successful CSF leak repair	No difference in leak rates with or without lumbar drain.
Albu[136]	2013	2b	Randomized prospective trial	1. Spontaneous CSF leaks (n = 36) 2. Iatrogenic CSF leaks (n = 51) 3. Traumatic CSF leaks (n = 63)	Successful CSF leak repair	No difference in recurrent CSF leak rates with or without lumbar drain, regardless of etiology.

ASB = anterior skull base; CSF = cerebrospinal fluid; ESS = endoscopic sinus surgery; ICP = intracranial pressure.

infection, shunt failure, or obstruction with ventriculoperitoneal shunt.

- Cost: Direct costs of acetazolamide and/or operative cost of shunt procedure and shunt management-related costs.
- Benefit-Harm Assessment: Spontaneous CSF repair rates are improved with postoperative ICP management. Side effects of administration of oral acetazolamide are well-tolerated whereas CSF diversion procedures, although routine, can have serious complications.
- Policy Level: Recommendation for acetazolamide usage with an option of ventriculoperitoneal shunts given the preponderance of benefit over harm.
- Intervention: Postoperative ICP management should be considered in patients with spontaneous CSF leaks and elevated ICPs. Acetazolamide can be used as an effective ICP-lowering medication with an option of CSF-shunting procedures in patients unable to tolerate medical management or with recalcitrantly elevated ICPs or recurrent CSF leaks.

III.B.3. *Evidence for rigid, free graft, and NSF reconstruction*

The armamentarium of reconstructive methods for skull-base defects has increased tremendously in the endoscopic era. Reconstruction options include, but are not limited to, single or multilayered reconstruction, pliable or rigid methods, free mucosal grafts, synthetic grafts, fascial or fat grafts, and vascularized tissue (eg, NSF). Despite the multiple options for skull-base reconstruction in patients with spontaneous CSF leaks, there is no consensus within the literature regarding the best treatment option or offering a reconstructive ladder. This is due likely in part to the high rates of successful primary repair, which are typically greater than 90%, especially as adjuvant treatment of elevated ICPs is used postoperatively.[10,24,69,70,110,112,135,136] Perhaps more telling, however, is the University of Pennsylvania series, which over the course of greater than 2 decades, reveals a success rate of roughly 91%, suggesting that despite modern innovations, these skull-base

TABLE III.B.3. Role of postoperative ICP control in spontaneous CSF rhinorrhea repair: long-term ICP management (acetazolamide or CSF diversion)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Albu[136]	2013	2b	Randomized prospective trial	1. Spontaneous CSF leaks (n = 36) 2. Iatrogenic CSF leaks (n = 51) 3. Traumatic CSF leaks (n = 63)	Successful CSF leak repair	Increased recurrent CSF leaks in setting of increased ICP (23%) as compared to non-elevated ICP spontaneous leaks (0%), traumatic leaks (3%) or iatrogenic leaks (4%).
Teachey[112]	2017	4	Prospective case series and systematic review	Spontaneous CSF leaks with and without management of increased ICPs	Successful primary spontaneous CSF leak repair	Management of increased ICPs (acetazolamide or CSF shunt) improves primary CSF leak repair (93% success with ICP management, 82% success without ICP management).
Chaaban[106]	2013	4	Prospective case series	Spontaneous CSF leaks (n = 32 patients, 42 CSF leaks)	Effect of oral acetazolamide on CSF pressures	Near immediate reduction in ICPs by average of 9.9 cm H_2O with acetazolamide administration.
Campbell[82]	2016	4	Retrospective case series	Patients meeting modified Dandy criteria for diagnosis of IIH with spontaneous CSF leaks (n = 32 patients, 44 skull base defects)	Long-term (greater than 10 year) follow-up data	No identified risk factors for leak recurrence. Long-term follow-up is necessary given relatively high rate of delayed CSF leaks (18% revision rate).

CSF = cerebrospinal fluid; ICP = intracranial pressure; IIH = idiopathic intracranial hypertension; LOE = level of evidence.

defects can be successfully closed in a variety of ways.[24] In line with this, Psaltis et al.[120] reviewed their series of spontaneous leaks, demonstrating a 94% success rate and a relatively even distribution of vascularized flaps, free mucosal grafts, and a combination of bone with free mucosal graft for reconstruction. Nonetheless, given the chronicity of IIH and the risk for remote leaks, reconstructive methods are an important topic. As underscored by Campbell and et al.'s[82] report, with a mean follow-up time of greater than 10 years, their 18% revision rate suggests that spontaneous CSF leak patients warrant long-term follow-up given the real risk of delayed leaks. Although most recurrences occurred at the same site, temporally close to the primary repair, these authors demonstrated that recurrences may occur years later at distinct anatomical subsites despite appropriate medical management or CSF diversion for intracranial hypertension. This information suggests that in addition to medical management of elevated ICPs, a more robust reconstructive method may be required.

A meta-analysis from the University of Pittsburgh examined the relationship of reconstructive technique and materials to primary repair success for CSF leaks of all types that were repaired with an EEA. Although this analysis is smaller than some contemporary reviews, Hegazy et al.[52] failed to demonstrate a difference in outcomes in the underlay vs overlay technique and a variety of reconstructive options ranging from free mucosal grafts to multilayer reconstructions with vascularized tissue flaps. Despite a significantly larger study population, and similar methodology to the Hegazy et al.[52] review, the systematic review by Psaltis et al.[10] could not assess the outcomes of endoscopic CSF leak repair as they pertain to reconstructive technique or materials. As such, beyond the 2 aforementioned reviews and the studies they include, the literature supporting the use of different reconstructive materials is limited to expert opinion and retrospective case series, which corroborate that multiple different techniques will yield similar results.[92,124]

Taken as a whole, the literature characterizing the efficacy of different reconstructive methodologies for spontaneous CSF leaks is poor, characterizing level 4 evidence with a grade D recommendation that reconstructive technique should be left to the discretion of the surgeon with consideration of defect location, size and etiology (see Table III.B.4).

- Aggregate Grade of Evidence: D (Level 4: 7 studies)
- Benefit: High success rates of spontaneous CSF leak repair.
- Harm: Inadequate repair of spontaneous CSF leaks leads to risk of recurrence.
- Cost: Increased operative time and nasal comorbidities depending on extent of reconstruction.

TABLE III.B.4. Spontaneous CSF rhinorrhea repair: evidence for reconstruction: rigid, free graft, NSF

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Banks[24]	2009	4	Retrospective case series	1. Spontaneous CSF leaks (n = 77) 2. Traumatic CSF leaks (n = 109) 3. Congenital CSF leaks (n = 7)	Successful CSF leak repair	Greater than 90% success rate over 2 decades with a variety of reconstructive materials.
Campbell[82]	2016	4	Retrospective case series	Patients meeting modified Dandy criteria for diagnosis of IIH with spontaneous CSF leaks (n = 32 patients, 44 skull base defects)	Long-term (greater than 10 year) follow-up data	Recurrences (18%) may occur at same or distant anatomical subsites despite seemingly appropriate reconstruction and management of elevated ICPs.
Hegazy[52]	2000	4	Systematic review	Endoscopically repaired CSF leaks of all types	1. Successful CSF leak repair 2. Reconstructive technique 3. Reconstructive materials	Successful CSF leak repair achieved with variety of techniques and materials.
Psaltis[10]	2012	4	Systematic review	Endoscopically repaired CSF leaks of all types	Successful CSF leak repair	90% Success rates in primary repair, 97% success in secondary repairs. Insufficient evidence to compare reconstructive technique or materials.
Psaltis[120]	2014	4	Systematic review and retrospective case series (45 patients, 63 fistula sites)	1. Primary CSF leak repair 2. Secondary CSF leak repair	1. Success rate of primary repair 2. Success rate of secondary repair	94% Success rate with a variety of repair types (37% NSF, 30% free mucosal grafts, 30% bone and free mucosal grafts).
Woodworth[124]	2008	4	Retrospective case series (n = 56)	Spontaneous CSF leaks	Successful CSF leak repair	Operative techniques vary according to defect size and location; 95% success rate.
Banu[92]	2014	4	Retrospective case series (n = 41 patients, 50 CSF leaks)	Endoscopically repaired CSF leaks of all types	Successful CSF leak repair	Surgical approach and graft dictated by location, etiology, and volume of leak.

ICP = intracranial pressure; CSF = cerebrospinal fluid; LOE = level of evidence; NSF = nasoseptal flap.

- Benefit-Harm Assessment: Balance of benefit and harm given lack of clear superior reconstructive modality.
- Policy Level: No recommendation
- Intervention: Reconstructive technique should be left to the discretion of the surgeon with consideration of defect location, size and etiology.

IV. Intradural tumors

IV.A. Pituitary macroadenoma

Pituitary macroadenomas remain 1 of the most common indications for ESBS. Given the relative accessibility of the sella in the posterior sphenoid, transnasal approaches have long been utilized in the management of these tumors. Endoscopy provides panoramic visualization and is now a well-accepted approach for these tumors. The potential advantages of increased visualization include improved anterior and posterior gland preservation and cranial nerve (CN) decompression. The evidence for the role of ESBS in the management of pituitary macroadenoma will be evaluated in regard to visual improvement, endocrinopathies, other CN improvement, and its role in the management of apoplexy.

IV.A.1. *Visual outcomes*

Pituitary macroadenomas (>10 mm diameter) often present with visual deficits related to chiasmal compression such as visual field deficits (46-75%) and decreased visual acuity (14-44%).[138–142] In case of nonfunctioning macroadenomas visual deficits are the main presenting symptom in approximately 60%.[143,144] According to the suprasellar growth, the most common visual field defect is bitemporal hemianopia.

Depending on the anatomical position of the optic chiasm (normal position, prefixed or postfixed chiasm), pituitary adenomas with only a 10-mm to 15-mm suprasellar growth cause a chiasm defect.[145,146] Either the tumor compromises the arterial supply of the optic nerve or chiasm or directly compresses the anterior visual pathway itself. The nerve compression causes decreased axoplasmic conduction with or without axonal demyelination which can observed even after 2 days.[147] An asymmetry of the defect is attributed to a different nerve fiber strain between the nasal and temporal nerve fibers of bilateral eyes.[148] In addition to visual field (VF) defects, chiasmal compression can cause a reduction in visual acuity (VA), color perception, and atrophy of the optic disc.

The Snellen chart is the standard method to evaluate VA, which measures best-corrected VA of each individual eye. VF is tested by static or kinetic perimetry, which presents brief stimuli of varying intensities in different locations until thresholds are detected. Mean deviation is an average deviation of these threshold values from age-corrected normal values at each test location. Mean deviation represents the overall size of a VF defect, and subjects with greater VF defects have more negative mean deviation values.

The various patterns of visual field defects are related to pituitary macroadenomas. Bitemporal hemianopia is the typical type of chiasmatic compression from enlargement of the pituitary adenoma from inferiorly. Homonymous hemianopia is possible when the unilateral optic tract is compressed. The position of chiasm (normal position, prefixed or postfixed chiasm) has an influence on the pattern of visual field defect.[145] Recently, optical coherence tomography (OCT) has emerged as a quantitative objective method of measuring indirectly the axonal loss of the anterior visual pathway by evaluating the retinal nerve fiber layer thickness.[149,150] A correlation between the thickness of the retinal nerve fiber layer and VF deficits has been found in tumors that cause an optic chiasm compression.[151] Importantly, retinal nerve fiber layer thinning is associated with decreased rate of visual recovery 3 months after surgical resection.[152]

A recent meta-analysis evaluating visual outcome in endoscopic transsphenoidal surgery by Muskens et al.[153] found that pooled rate of VA improvement was 67.5% and pooled rate of VF deficit improvement was 80.8%. A meta-analysis by DeKlotz et al.[154] reported that the endoscopic approach leads to a significantly higher rate of overall visual improvement in comparison to the microscopic approach.

Longer duration of VF deficits correlate with worse visual outcomes.[155,156] Thotakura et al.[157] found that patients with long-lasting (≥1 year) preoperative visual symptoms showed significantly worse visual outcomes after resection. Good recovery rates of vision from patients with pituitary apoplexy have been reported, especially in patients where early surgical decompression has been achieved.[158,159]

Surgeon experience is positively associated with postoperative VF deficit improvement.[142,160,161] Whether the adenoma is secreting or nonsecreting does not predict visual outcome after surgery.[162,163] A lack of influence of preoperative tumor size on visual outcomes may be explained by the slow growth of most tumors, which gives the optic nerve/chiasm time to adapt. Gross total resection was also not associated with improved visual outcomes. This may be secondary to a sufficient decompression of the optic nerve/chiasm associated with partial resection.[156,164,165]

Postoperative VF deterioration after transsphenoidal surgery occurs in up to 4% of cases.[153] The mechanism can be either direct surgical damage, vascular compromise, postoperative bleeding, overpacking in sealing a CSF leak, or as a consequence of optic nerve and chiasm prolapse into an empty sella.[166] A postoperative ophthalmological and radiological control is recommended in all these cases if no clinical improvement is reported postoperatively (see Table IV.A.1).

- Aggregate Grade of Evidence: B (Level 2a: 3 studies, influence of surgeon's experience); Level C (Level 3b: 1 study, longer duration of visual field deficits leads to worse visual outcomes)
- Benefit: In experienced surgeon's hands, a high rate of improved visual outcome can be achieved.
- Harm: The possibility of postoperative deterioration.
- Cost: Low
- Benefit-Harm Assessment: High rate of visual improvement is associated with early surgical decompression in comparison to possible complications.
- Value Judgments: Preponderance of benefit
- Policy Level: Recommendation
- Intervention: Endoscopic pituitary resection can improve visual defects, both in VF as well as VA. Early intervention is associated with improved outcomes.

IV.A.2. *Anterior pituitary gland function*

The most common cause of anterior pituitary gland insufficiency (hypopituitarism) is pituitary macroadenoma. In a Spanish population study, the prevalence for hypopituitarism was 45.5 cases per 100,000. The incidence of pituitary adenoma was 4.2 cases per 100,000, with equal gender distribution. Excluding pituitary adenomas, the causes of hypopituitarism were other sellar tumors and noncancerous causes, including idiopathic cases in 11%.[168] The prevalence of partial hypopituitarism in patients with nonfunctioning pituitary adenomas ranges in studies from 37% to 85%.[169–174] Fatemi et al.[170] found that preoperative hypopituitarism was significantly lower in functioning adenoma.

The clinical presentation of hypopituitarism is varied and depends on the nature and acuity of the damage to the hypothalamic–pituitary region and the resultant order and amount of hormonal loss.[175] In contrast to microadenomas, macroadenomas (>10 mm diameter) are commonly

TABLE IV.A.1. Pituitary macroadenoma: visual outcomes

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Muskens[153]	2017	2a	Systematic review of cohort studies	35 Endoscopic studies	Complete recovery, improvement, and deterioration of visual field deficits, visual acuity and unspecified visual function	Surgeon experience was found to be a significant influence on visual outcomes. Visual deficits improved after endoscopic endonasal transsphenoidal surgery in the majority of patients while complete recovery was only achieved in less than half.
Ammirati[167]	2013	2a	Systematic review of cohort studies	13 Endoscopic studies, 14 microscopic studies	Visual loss	Pooled estimate 0.72% (0.37% to 1.19%) in endoscopic studies, 0.60% (0.23% to 1.14%) in microscopic studies.
DeKlotz[154]	2012	2a	Systematic review of cohort studies	21 Endoscopic studies (2335 patients), 17 sublabial studies (2565 patients)	Visual improvement after endoscopic or sublabial approach	Significantly higher rate of overall visual improvement after endoscopic resection.
Jacob[152]	2009	3b	Individual case-control study	42 Patients	Automated VFs and OCT (fast-RNFL program)	RNFL thinning measured by OCT puts the patient at decreased chance of recovery.

LOE = level of evidence; OCT = optical coherence tomography; RNFL = retinal nerve fiber layer; VF = visual field.

associated with deficiencies in anterior pituitary hormone axes.[171,176] As suggested by Arafah[176] and Arafah et al.,[177] the causative mechanism is compression of the portal vessels in the pituitary stalk, either secondary to tumor expansion or due to raised intrasellar pressure.

Pituitary apoplexy represents a special form of hypopituitarism. Infarction or hemorrhage leads to increased intrasellar pressure and abrupt destruction of pituitary adenoma and/or normal gland tissue. In these cases, hypopituitarism can occur rapidly, with severe complications such as adrenal insufffiency.[178,179] This is explored further in Section IV.A.5. Pituitary macroadenoma with apoplexy.

Hypopituitarism due to radiation is dose-dependent and time-dependent, with 50% to 80% in conventional irradiation series after 10 years of follow-up. However, findings suggest that hypopituitarism might be reduced by linear accelerator (Cyber Knife), Gamma Knife, or proton beam therapy. In case of Gamma Knife therapy, a rate of new onset hypopituitarism has been reported of 31.5% after 5 years.[180–182]

Preoperative hormone levels should be checked as a clinical routine examination in collaboration with endocrinology. Postoperative assessment of pituitary function should be examined periodically. The Endocrine Society suggests that serum cortisol levels should be measured at 8:00 AM to 9:00 AM as the first-line test for diagnosing central adrenal insufficiency. A cortisol level <3 μg/dL is indicative of adrenal insufficiency and a cortisol level >15 μg/dL likely excludes an adrenal insufficiency diagnosis. Corticotropin-releasing hormone stimulation test for the pituitary adrenocorticotropic hormone (ACTH) reserve is no more predictive of adrenal function than morning cortisol concentrations. A random cortisol level to diagnose adrenal insufficiency should not be used.[183] Thyroid-stimulating hormone (TSH) deficiency is suggested by low basal serum free/total thyroxine with inappropriately normal or low TSH levels. Basal plasma prolactin levels are low and fail to rise upon intravenous injection of TSH. In patients with suspected growth hormone (GH) deficiency, GH stimulation testing is recommended. Single GH measurements are not helpful.[183] In women, menstrual disturbances and amenorrhea with low serum estradiol concentration (<100 pmol/L) and normal or low concentrations of gonadotropins are typical features of hypogonadotropic hypogonadism. In postmenopausal women, failure to detect high serum gonadotropin values is highly suggestive of the diagnosis. Hypogonadotropic hypogonadism is characterized by low testosterone in men with low or normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) serum concentrations, and impaired spermatogenesis.

Following the recommendation of the 2016 Congress of Neurological Surgeons Systematic Review of nonfunctioning adenomas, routine endocrine evaluation of all anterior pituitary axes to assess for hypopituitarism is recommended. The cutoff values to initiate thyroid and adrenal replacement might be different in a patient with

panhypopituitarism vs isolated deficiencies.[184] In acute hypopituitarism, especially in pituitary apoplexy, rapid replacement with stress doses of steroids is crucial before surgery as well as postoperatively before repeating testing.[183]

The goal of transsphenoidal surgery is selective pituitary adenoma resection with preservation of normal gland tissue, which is dependent on the size and position of the normal gland on preoperative imaging.[185] In a meta-analysis by Ammirati et al.[167] a nonsignificantly higher rate of hypopituitarism was found in series using a microscopic approach in comparison to series using an endoscopic approach. It has also been advocated that urgent surgical treatment of pituitary apoplexy results in improved preservation of pituitary function.[186–188]

A wide range of recovery rates of the different hormonal axes after surgery has been reported. The recovery rate for corticotropic axis ranges from 0% to 57%,[170,171,189,190] for thyrotropic axis from 13% to 57%,[170–172,176,189–191] for gonadotropic axis from 11% to 32%,[170–172,176,189,191] and for somatotropic axis from 15% to 40%.[170,172,176] The rate of hypopituitarism after transsphenoidal surgery in elderly adults seems to be higher.[192–194] The endoscopic approach showed a reduced rate of postoperative occurrence of hypopituitarism in comparison to the microscopic approach. However, pooled estimated rates in a meta-analysis by Ammirati et al.[167] showed that there was no significant difference between the 2 methods of visualization (see Table IV.A.2).

A correlation of mortality rate to cortisol deficiency has been reported.[196] Meta-analysis of patients with hypopituitarism suggest that an increased mortality is associated with female gender and young age at diagnosis.[197]

- Aggregate Grade of Evidence: B (Level 2a: 1 study, microscopic vs endoscopic approach); Level B (Level 2a: 1 study, somatotroph axis appears to be more prone to deficit)
- Benefit: Endoscopic endonasal pituitary resection may result in decreased occurrences of postoperative hypopituitarism and is at least equal to microsurgical approaches. Recovery of pituitary dysfunction after endoscopic pituitary surgery is widely variable.
- Harm: Increased incidence of cardiovascular disorders and number of deaths among patients with longtime hormone replacement.
- Cost: Loss of hormonal function may increase both the need long-term hormonal replacement as well as increase long-term morbidity in hypopituitarism.
- Benefit-Harm Assessment: Preponderance of benefit for resection of pituitary macroadenoma with the potential for improvement of anterior pituitary gland function.
- Value Judgments: In acute hypopituitarism, rapid replacement with stress doses of steroids is crucial.
- Policy Level: Recommendation
- Intervention: Consider early operation to achieve better postoperative results, due to a higher rate of permanent insufficiency in case of a wait-and-see policy.

IV.A.3. *CN improvement/preservation*

The prevalence of eye-movement disorders associated with pituitary adenomas has varied within studies ranging from 1.4% to 4.6%.[163,198] Ocular motility dysfunction often occurs in the setting of a pituitary apoplexy, ranging from 40% to 100% in these cases.[199]

Mechanisms proposed to explain the preference of 3rd nerve involvement include pressure transmitted to the cavernous sinus by the growing/infiltrating tumor and compression of the 3rd nerve between the tumor and the interclinoid ligament.[200] Sixth nerve palsies, although much less frequent, also have been reported. A proposed mechanism for isolated 6th nerve palsy is extension of the tumor backward along the Dorello's canal, containing the 6th nerve along with the inferior petrosal sinus. Fourth nerve palsies have been described only in association with multiple CN palsies. Total ophthalmoplegia in pituitary adenomas is very rare and is suggestive of pituitary apoplexy or alternative malignant pathology such as lymphoma or metastasis.[201]

Ocular motility and alignment examination to test movement eye-by-eye and conjoint movement, as well as cover test measuring the deviation with prisms and pupil examination is the standard examination for CN injury testing.[202]

Apart from pituitary apoplexy, the abrupt-onset diplopia due to compression-related paralysis of oculomotor nerves has been rarely described as the main presenting sign of pituitary adenomas.[203–205] The oculomotor nerve is predominantly affected,[206] followed by the abducens nerve.[207] These nerves are affected in both eyes only in rare cases (aggressive pituitary adenomas and carcinomas).[205,208]

Although there are no evidence-based criteria for neurosurgical intervention in pituitary apoplexy, deterioration in the level of consciousness and significant neuro-ophthalmic signs are indications for urgent surgery intervention and stress doses of steroids.[188] Verrees et al.[209] advocate for early surgery in patients with pituitary apoplexy; they and other authors[210] found it be a successful treatment for pituitary apoplexy patients with ocular motility dysfunction. In a series of 75 pituitary apoplexy cases, Zoli et al.[211] found that ophthalmoplegia improved postoperatively in 69.2% of cases.

Radiosurgery as a second line therapy after transsphenoidal surgery using tumor-controlling doses of up to 30 to 40 Gy appears to be a relatively safe technique in treating lesions within or near the sensory and motor nerves (III-VI) of the cavernous sinus.[212–214]

Limited data is available about CN preservation or CN injury in transsphenoidal surgery. In a meta-analysis by Ammirati et al.,[167] pooled estimated rates showed that

TABLE IV.A.2. Pituitary macroadenoma: anterior pituitary gland function

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Carvalho[195]	2015	2a	Systematic review of cohort studies	63 Studies: 45 retrospective/18 prospective	Incidence rates of hypopituitarism, panhypopituitarism, specific axis deficiencies	Somatotroph function appears to be more prone to deficit than the other pituitary axes
Ammirati[167]	2013	2a	Systematic review of cohort studies	17 Endoscopic studies, 12 microscopic studies	Hypopituitarism	Pooled estimate 8.51% (5.16% to 12.59%) in endoscopic studies, 11.64% (5.14% to 20.32%) in microscopic studies

LOE = level of evidence.

TABLE IV.A.3. Pituitary macroadenoma: cranial nerve improvement/preservation

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Zoli[211]	2017	3b	Individual case-control study	75 Patients	Ophthalmoplegia was present in half of the patients at admission	Endoscopic endonasal approach represents an effective and safe technique (69% postoperative improvement)
Ammirati[167]	2013	2a	Systematic review of cohort studies	8 Endoscopic studies, 7 microscopic studies	Nerve injury	Pooled estimate 0.28% (0.05% to 0.71%) in endoscopic studies, 0.53% (0.08% to 1.34%) in microscopic studies

LOE = level of evidence.

there was no significant difference between the endoscopic and microscopic approach regarding CN injury (see Table IV.A.3).

Postoperative newly encountered ophthalmoplegia is a seldom complication (0-0.9% in large series)[166,215–218] and is dependent on the extent of tumor resection in the cavernous sinus.

- Aggregate Grade of Evidence: C (Level 2a: 1 study, microscopic vs endoscopic approach; Level 3b: 1 study, endoscopic approach represents an effective and safe technique)
- Benefit: Improvement of ophthalmoplegia in case of pituitary apoplexy has good results of postoperative improvement.
- Harm: Postoperative new encountered ophthalmoplegia is a seldom complication in transsphenoidal pituitary surgery.
- Cost: Low because the incidence is rare
- Benefit-Harm Assessment: High rate of improvement in comparison to possible postoperative CN deficit.
- Value Judgments: In acute ophthalmoplegia, early surgery is advocated for either treatment of apoplexy or definitive diagnosis.
- Policy Level: Recommendation
- Intervention: The endoscopic approach is comparable with microscopic techniques in regard to both treatment and the complication of cranial neuropathies.

IV.A.4. *Diabetes insipidus and syndrome of inappropriate antidiuretic hormone*

Water and electrolyte imbalances are commonplace after pituitary macroadenoma resection, likely secondary to direct (surgical) or indirect (decompressive or vascular) manipulation of the neurohypophysis.[219] Reported rates of water and sodium imbalance range widely in the literature, occurring in anywhere from 1% to 75% of patients following pituitary adenoma resections. Most irregularities are transient, presenting within 1 to 14 days after surgery and typically resolving during this same time period. Diagnosis of such electrolyte imbalances requires a high degree of suspicion as well as close clinical and laboratory follow-up, to prevent potentially catastrophic complications.[219,220]

IV.A.4.a. Diabetes insipidus. Diabetes insipidus (DI) occurs due to a reduction or complete absence of the nanopeptide arginine vasopressin (AVP). In patients with pituitary adenomas, it typically occurs postoperatively presumably due to disruption or surgical manipulation of

the hypothalamic-hypophyseal transit of AVP, at the level of the neurohypophysis or infundibulum. DI clinically presents as polyuria and polydipsia, with corresponding electrolyte abnormalities including serum sodium ≥145 mmol/L, serum osmolality >300 mOsm/kg, urine osmolality <300 mOsm/kg, and urine specific gravity <1.005. DI can follow 1 of 3 courses: acute (transient), chronic (permanent), or triphasic.

Transient DI typically presents within 24 to 48 hours after surgery with polyuria and generally resolves around postoperative days 3 to 5. Several large endoscopic series report the incidence of transient DI ranging from 4.6% to 8.7%.[219–223] Furthermore, recent studies comparing endoscopic and microscopic transsphenoidal adenoma resection indicate a decreased incidence of DI in patients undergoing endoscopic resection of pituitary adenomas (4.6% vs 38.5%).[220,221] With a high degree of suspicion, the clinician is typically alerted to probable DI when the urine output is greater than 300 mL for 2 consecutive hours, followed by the additional abnormal laboratory values listed in the previous paragraph.[220] Initially, in awake patients with intact thirst mechanisms, DI is treated by encouraging cold water intake. If patients are unable to consume sufficient quantities of fluids, and their laboratory abnormalities persist, desmopressin (DDAVP), an AVP analog, can be administered.[220]

Permanent DI occurs in 0.4% to 8.1% of patients undergoing endoscopic macroadenoma resection, and is defined as unresolved polyuria 6 months postoperatively.[220,221] These patients require long-term management with desmopressin either via nasal spray or tablet. The triphasic response is relatively rare and occurs due to the degeneration of hypothalamic magnocellular neurons, first with a transient lack of antidiuretic hormone (ADH) secretion, followed by a delayed oversecretion of ADH as the cells degenerate, and then long-term lack of ADH production.[220]

IV.A.4.b. Hyponatremia. Decreases in serum sodium are common in patients with pituitary macroadenomas both before and after surgery. The most common pattern is postoperative delayed hyponatremia that typically occurs between days 4 to 7 after pituitary adenoma resection. Such hyponatremia can be severe with serum sodium levels decreasing rapidly to <120 mmol/L. Delayed hyponatremia is a common cause of readmission after pituitary adenoma surgery and can present as nausea, emesis, headache, confusion, seizures, and even death.[222] The pathophysiology of delayed hyponatremia remains controversial and may in fact result from more than 1 mechanism, including either an excessive release of antidiuretic hormone from the posterior pituitary gland (syndrome of inappropriate antidiuretic hormone [SIADH]), or from an increased secretion of natriuretic factors leading to an increased excretion of urinary sodium (cerebral salt wasting [CSW]).[219,222]

Regardless of etiology, the incidence of delayed hyponatremia ranges from 4% to 20% in both endoscopic and microscopic transsphenoidal series. Risk factors include older age, greater tumor size, presumably leading to more effacement and manipulation of the neurohypophysis, as well as ACTH-producing adenomas.[222] However, a multivariate analysis of over 1000 pituitary surgeries indicated only preoperative hypopituitarism predicted postoperative hyponatremia.[223]

Initial management of hyponatremia consists of total fluid and free-water restriction. Sodium supplementation either via oral sodium chloride tablets or intravenous (IV) administration of normal or hypertonic saline has also been used effectively, especially in those with cerebral salt wasting.[219] The mean sodium correction rates are 0.4 mEq/L/hour with no treatment, 0.5 mEq/L/hour with free-water restriction, 0.7 mEq/L/hour with sodium tablets, 0.3 mEq/L/hour with IV hypertonic saline, 0.7 mEq/L/hour with the intravenous vasopressin receptor antagonist Vaprisol, and 1.2 mEq/L/hour with the oral vasopressin receptor antagonist tolvaptan.[223] Tolvaptan in particular has proven robustly efficacious in increasing the sodium in those with severely depressed levels, though caution should be exerted in those patients that might be in the SIADH phase of a triphasic response, because tolvaptan may exacerbate the impending, third-phase, DI.[220]

Ultimately, water and salt balance following pituitary adenoma resection is complex, requiring close supervision of laboratory studies and a well-developed understanding of the timing of expected irregularities, as well as their duration, to avoid overcorrection. Initial management should be as minimally disruptive as possible, including observation, and the implementation of either fluid restriction or water intake. Medications such as DDAVP, Vaprisol, and tolvaptan, should be reserved for severe and refractory cases, and used sparingly, with minimal necessary doses, and titrated to normal physiologic levels and schedules. Both DI and delayed hyponatremia occur commonly, and the pituitary surgeon, along with their multidisciplinary teams, should be familiar with the presentation, time course, and management of these disorders (see Table IV.A.4).

- Aggregate Grade of Evidence: C (Level 3a: 1 study; Level 4: 4 studies)
- Benefit: All studies emphasized the early diagnosis and treatment of both DI and delayed hyponatremia, in an effort to manage these diseases early in their course and prevent catastrophic harm including severe dehydration, seizures, and even death.
- Harm: All studies emphasized the importance of close observation of postoperative serum sodium, and in the case of DI, osmolality and urine output. Failure to do so could lead to unchecked and potentially morbid DI or hyponatremia.

TABLE IV.A.4. Pituitary macroadenoma: DI and SIADH

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Kristof[219]	2009	4	Prospective observational	Patients undergoing pituitary adenoma resection were prospectively followed from preoperatively to postoperative day 14 for water and salt balance.	Patients were monitored daily for body weight, fluid balance, electrolytes, plasma and urine osmolality, ADH levels, urine sodium, and thirst.	Water and electrolyte imbalance occurred in 75% of patients. Temporary DI was most common, peaking on POD 2, mostly resolving in 10 days, with a minority of patients experiencing long-term DI. Delayed hyponatremia reached its nadir on POD 9, mostly resolving within 5 days.
Schreckinger[220]	2013	4	Retrospective review	Consecutive patients undergoing endoscopic transsphenoidal sellar and suprasellar tumor resection were observed for postoperative DI.	Patients were monitored preoperatively and postoperatively for urine output, urine and serum osmolality, urine specific gravity, and serum sodium values.	The likelihood of DI could be predicted by a $\geq$2.5 increase in serum sodium, postoperative sodium $\geq$145, and increased preoperative urine output.
Berker[221]	2011	4	Retrospective review	Over 600 consecutive patients undergoing endoscopic transsphenoidal pituitary adenoma resection were retrospectively evaluated.	The patients were evaluated for postoperative complications including rhinologic issues, CSF leaks, infection, vascular injury, and endocrinology complications.	Transient DI was found in 4.6% of patients, permanent DI in 0.4%, and SIADH in 1.1%.
Cote[222]	2016	3a	Systematic review	Ten case series with adult patients undergoing pituitary surgery and describing delayed symptomatic hyponatremia were included.	The primary endpoint studied in the ten studies were risk factors of delayed symptomatic hyponatremia.	Risk factors of delayed symptomatic hyponatremia include older age, greater tumor size, female gender, and Cushing's disease with ACTH-producing adenomas.
Jahangiri[223]	2013	4	Retrospective review	Consecutive patients (1045) undergoing pituitary surgery were evaluated with preoperative and postoperative daily sodium checks to evaluate for postoperative hyponatremia.	Patients were monitored daily, both pre and postoperatively for daily sodium values.	Tolvaptan is the most efficient corrector of postoperative hyponatremia, while Vaprsiol is another option. Water restriction, hypertonic saline, and sodium tablets are minimally efficacious with results similar to no intervention.

ACTH = adrenocorticotropic hormone; ADH = anitdiuretic hormone; CSF = cerebrospinal fluid; DI = diabetes insipidus; LOE = level of evidence; POD = postoperative day; SIADH = syndrome of inappropriate antidiuretic hormone.

- Cost: No studies discussed the direct cost of the frequent laboratory evaluation required for the diagnosis of DI and/or hyponatremia, but one study implied the increased costs associated with readmission in the setting of delayed hyponatremia. Medications used to treat hyponatremia including Vaprisol and tolvaptan are expensive, but more efficacious and efficient in the management of hyponatremia.
- Benefit-Harm Assessment: There is a preponderance of evidence indicating relative benefit in frequent laboratory monitoring for salt and water imbalance in the first 2 weeks after pituitary adenoma resection.
- Value Judgments: Postoperative transient DI occurs in the first 1 to 2 days after surgery and typically lasts a total for 3 to 5 days. During this time, patients should be closely observed and treated appropriately. Delayed hyponatremia typically occurs 4 to 7 days postoperatively, and requires close follow-up, especially because most patients are outpatient at this time; readmission to hospital for correction of

hyponatremia is prudent in patients with serum sodium under 125 mmol/L.
- Policy Level: Optional
- Intervention: DI should first be treated with liberal oral water consumption, and if necessary, DDAVP, titrated to physiologic doses and natural urinary patterns when required for permanent DI. Delayed hyponatremia should initially be treated with fluid restriction, though these measures, along with sodium replenishment were found to be moderately to minimally effective. Vasopressin receptor antagonists, Vaprisol and tolvaptan are efficient with sodium correction.

IV.A.5. *Pituitary macroadenoma with apoplexy*

Pituitary apoplexy is a clinical syndrome characterized by hemorrhage and/or infarction of the pituitary gland, leading to headache, diplopia, diminished VA, hormonal and electrolyte dysfunction, and/or a decreased level of consciousness.[224] The clinical presentation is variable, dependent on the size and location of the adenoma, the degree of hemorrhage, edema, necrosis, and other sequelae, and can progress over hours to days, rendering optimal management controversial.[179,224]

Pituitary apoplexy occurs most frequently in the setting of previously undiagnosed or conservatively-managed pituitary macroadenomas with an annual incidence of 0.2% to 0.6%, and in 2% to 12% of all patients with pituitary adenomas.[179] Subclinical hemorrhage occurs in 25% of all patients with adenomas, though it is not considered true apoplexy without the accompanying clinical syndrome.[179]

Pituitary apoplexy presents most often as a constellation of symptoms that may include severe, acute or subacute onset of headache, diminished VF and/or VA up to and including blindness, diplopia, fatigue, and nausea. Endocrine dysfunction including life-threatening hypocortisolemia, and altered mental status from subarachnoid hemorrhage or vasospasm-mediated stroke may also occur.[179,224] Due to the nonspecific clinical symptoms, CT and preferably magnetic resonance imaging (MRI) should be performed to distinguish pituitary apoplexy from other neurosurgical conditions such as aneurysmal subarachnoid hemorrhage. Imaging studies typically demonstrate a sellar and suprasellar mass with associated hemorrhage and/or necrosis.[179] Functional impairment of CNs III, IV, and VI occurs in 52% of all patients with pituitary apoplexy. Visual disturbance occurs in one-half of all patients experiencing pituitary apoplexy, with bitemporal hemianopsia being most common, while some experience diminished VA and even blindness. Ophthalmologic evaluation, including VF testing, is recommended for all patients, even those without obvious extraocular muscle, VF, or VA deficits.[224] Endocrine function, especially hypocortisolemia, is found in up to 50% to 80% of patients, and if not recognized and treated, can be life-threatening. Additionally, thyrotrophin and gonadotrophic dysfunction is present in 50% and 70%, respectively. Another 40% of patients with pituitary apoplexy present with hyponatremia, which also requires correction.[179,224]

All patients with suspected pituitary apoplexy based on clinical and imaging findings should be given intravenous hydrocortisone for presumed acute adrenal insufficiency.

Historically, this condition was considered a neurosurgical emergency with immediate corticosteroid administration, surgical sellar decompression, hemorrhage evacuation, and tumor resection. Most agree that patients presenting with acute onset altered consciousness, and severe and/or progressive visual dysfunction and/or diplopia from cranial neuropathy, warrant rapid endonasal transsellar surgical decompression,[179,224,225] with bony sellar decompression, and microsurgical resection of the adenoma, hemorrhage, and necrosis. Endoscopic sellar decompression and adenoma resection has been shown to improve vision in nearly 75% of patients with low rates of complications and low rates of new endocrinopathy.[226] Arguments against immediate surgical decompression have focused on the potential complications of surgery, including CSF leak, DI, and hypopituitarism from damaging the normal pituitary gland, which may be obscured with hemorrhage and infarction. Fortunately, these complications are rare in experienced pituitary centers.[179]

Although surgery was previously held as the standard of care in the management of pituitary apoplexy, there has been a trend toward more conservative management, especially in less symptomatic patients.[179] Nonsurgical management has been successfully employed in carefully selected patients presenting with pituitary apoplexy, particularly those with only mild, nonprogressive ophthalmologic findings, and without alterations in mental status.[225] Mild endocrinopathy has also been shown to improve with steroid treatment, more likely in the setting of pituitary infarction alone than with overt hemorrhage.[179,225] It is important to note, however, that many patients have a more subacute and progressive presentation, and may develop delayed visual disturbance requiring surgical decompression.[179,225] As with most conditions, careful preoperative evaluation and patient selection are paramount to good outcomes.

Recovery of neurological, ophthalmologic, and endocrine function is highly variable. Altered consciousness usually improves most rapidly with corticosteroid supplementation and surgical decompression. After surgical decompression in patients with proven pituitary apoplexy, complete or partial recovery of VF deficits, VA deficits, and diplopia from cranial neuropathy occurs in 71% to 93%, 63% to 93%, and 80% to 93% of patients, respectively. Visual recovery and resolution of diplopia may require weeks to 6 months or longer for full recovery. Endocrine function also typically requires several months to fully recover, with interim hormonal supplementation often needed. Although some degree of pituitary function recovery is seen in almost 50% of patients after surgery for pituitary apoplexy, approximately 80% of patients will require permanent

replacement of at least 1 or more hormonal axes (thyroid, adrenal, gonadal, and/or vasopressin).[179]

No RCTs have been performed between surgical and medical management of pituitary apoplexy, such that most studies are subject to retrospective and patient selection bias. As a result, existing reviews have failed to demonstrate a significant difference in visual or endocrine outcomes between surgical and conservative management of pituitary apoplexy.[225] As always, careful patient selection is essential in the management of pituitary apoplexy, and urgent surgical decompression is advocated in the setting of decreased consciousness, severe visual or hormonal dysfunction, and a nonsurgical approach may be taken in those cases of mild and subacute presentations, with close monitoring and hormonal supplementation as needed (see Table IV.A.5).

- Aggregate Grade of Evidence: C (Level 2a: 1 study; Level 3a: 2 studies; Level 4: 1 study)
- Benefit: No studies demonstrate a direct benefit of observation over endoscopic sellar decompression, whereas endoscopic endonasal surgery shows good success rates for vision recovery after surgery.
- Harm: Potential harm of conservative nonoperative management in those patients with severe or progressive symptoms, especially visual dysfunction or altered consciousness.
- Cost: No studies have directly evaluated the cost of endoscopic surgery in comparison to conservative management for pituitary apoplexy, but the cost of surgical management is likely higher upfront. However, most patients with apoplexy have underlying adenomas that will likely require surgical resection at some point, such that the cost is roughly equal. It is possible the cost may be greater in the nonoperative cohort because they require closer and possibly more frequent follow-up.
- Benefit-Harm Assessment: In the short term, there is a potential harm in conservative management if the patient has progressive symptoms that do not reverse with delayed surgical decompression. Those in the surgical arm also have risks associated with their procedures, including CSF leak, vascular injury, and worsened endocrinopathy, which can be mitigated by limiting surgery to experienced centers and surgeons.
- Value Judgment: Endoscopic surgical decompression with hematoma and adenoma resection is favored for those patients with significant diplopia, diminished VA, or altered mental status in an urgent or emergent fashion. Conservative management has been safely used in those cases of pituitary apoplexy with minimal and stable symptoms, though adenoma resection in a delayed fashion is often necessary.
- Policy Level: Opinion
- Intervention: Emergent glucocorticoid (eg, hydrocortisone) administration and endoscopic endonasal sellar decompression with resection of hematoma and adenoma is recommended for all patients presenting with altered consciousness, significant CN palsies, or diminished visual function.

IV.A.6. *Reconstruction following endoscopic resection of pituitary macroadenoma*

Over the last decade, the EEA has gradually become the predominant method for pituitary adenoma removal and related parasellar tumors in many centers around the world.[227–231] After tumor removal, an effective skull-base reconstruction is essential to avoid a postoperative CSF leak and related complications such as meningitis, pneumocephalus, and reoperation.[232–235] Although many varied techniques for skull-base reconstruction and CSF leak have been proposed in both the microscopic and endoscopic eras of pituitary surgery, the majority of publications follow similar principles and methodology. The steps in skull-base repair and CSF leak prevention include: (1) intraoperative assessment of the presence and magnitude of a skull-base defect and CSF leak, (2) technical repair of the defect, and (3) possible use of CSF diversion.

IV.A.6.a. Intraoperative assessment/confirmation of a leak and CSF leak grading systems. After tumor removal is complete, inspection of the sella and parasellar space is required to determine the presence and magnitude of a CSF leak. Several grading scales ranging from 3-point to 4-point scales have been proposed in multiple publications, all of which include no leaks, small leaks, and large leaks.[235–241] Provocative testing with a Valsalva maneuver by the anesthesiologist, or use of intrathecal fluorescein, are advocated by some authors to help identify small leaks, as well as to assess the integrity of the repair.

After determining the magnitude and architecture of the skull-base defect and CSF leak, the reconstruction proceeds accordingly. For no leaks, a simpler repair is advocated. For skull-base defects associated with definitive leaks, graded repair is typically performed, with more extensive repair protocol needed for higher-grade leaks and larger, more extensive defects.[165,235,238,240,242] Given that most pituitary macroadenomas remain contained in the subdiaphragmatic space, high-grade leaks are less common than with other parasellar pathology such as craniopharyngiomas. Materials frequently used in reconstruction include autologous fat, fascia lata, septal bone, and cartilage, as well as all native sphenoid sinus mucosa, free mucosal grafts, and pedicled NSFs. Allografts frequently used include Alloderm (Allergan, Branchburg, NJ), absorbable and nonabsorbable plates, and titanium mesh, as well as collagen matrix materials, all typically in multilayered fashion.[227,232,233,235–237,239,242–258] Various types of tissue glues are also included in many of the reconstruction protocols. In the largest (high-grade) leaks, which are relatively uncommon, use of NSFs is advocated by many authors. Use of nasal packing is relatively common but variable across many studies. Additional measures

TABLE IV.A.5. Pituitary macroadenoma with apoplexy

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Tu[225]	2016	2a	Meta-analysis	Six retrospective dual-armed studies comparing outcomes between consecutive cases of surgically and conservatively managed pituitary apoplexy.	Visual and endocrine outcome at the conclusion of the individual study periods.	Conservative management of pituitary apoplexy is safe in those with mild visual symptoms and endocrinopathy, while surgery is recommended for altered mental status, decreased visual acuity or diplopia.
Briet[179]	2015	3a	Systematic review	Detailed review of 264 manuscripts regarding pituitary apoplexy including epidemiology, pathophysiology, presentation, diagnosis, and management.	Visual and endocrine outcomes were discussed in relation to the ocular palsies, defects, pituitary function and tumors.	Glucocorticoids should be administered immediately. Some advocate immediate surgery while others opt for conservative management. Non-operative apoplexy should have close and frequent follow-up.
Rajasekaran[224]	2011	3a	Systematic review	Clinical guidelines based on an international multidisciplinary panel of experts.	Standardized guidelines for the endocrine, ophthalmologic, and surgical short and long-term management of pituitary apoplexy.	A high level of suspicion and early glucocorticoid administration is advocated. Immediate surgical management is indicated for decreased consciousness, severe or progressive visual dysfunction, others can be managed conservatively.
Gondim[226]	2017	4	Retrospective review	Single-armed retrospective evaluation of patients undergoing endoscopic endonasal surgery for pituitary apoplexy.	Visual and endocrine recovery, as well as complications—CSF leak, vascular injury, infection, and mortality—were evaluated.	Endoscopic endonasal decompression in the modern era is safe with minimal complications, yet highly successful with reversing visual dysfunction and adenoma resection, though endocrinopathy is less reversible.

CSF = cerebrospinal fluid; LOE = level of evidence.

utilized frequently include care being taken in extubation to avoid bucking, use of stool softeners, and acetazolamide to decrease endogenous CSF production (see Table IV.A.6).

- Aggregate Grade of Evidence: B (Level 2b: 4 studies; Level 3a: 1 study; Level 3b: 4 studies; Level 4: 8 studies)
- Benefit: Allows low-grade CSF leaks to be reconstructed with reduced complexity and materials (including autografts and allografts), and high-grade leaks to be repaired with multiple measures including nonvascularized and vascularized mucosal flaps.
- Harm: No harm in use of grading system unless the grading of particular patients is inaccurate leading to inadequate repair.
- Cost: The use of a grading system allows for appropriate and cost-effective use of reconstruction materials.
- Benefit-Harm Assessment: A tailored/graded reconstruction protocol promotes a systematic methodology for intraoperative CSF leak repair, optimizing chances of success and resource utilization.
- Value Judgments: Each type of intraoperative CSF leak has its own risk of postoperative CSF leak. Difference in structural and anatomical characteristics are different that justify use of tailored reconstruction for each setting.
- Policy Level: Recommendation
- Intervention: Utilize a graded approach to skull-base reconstruction based on intraoperative CSF leak size.

IV.A.6.b. Prophylactic lumbar CSF diversion. The literature remains unclear on the benefit of intraoperative and perioperative CSF diversion with a lumbar drain.

TABLE IV.A.6. Reconstruction following endoscopic resection of pituitary macroadenoma

Study	Year	LOE (1a to 5)	Study design	Study groups	Clinical endpoint	Conclusion
Esposito[235]	2007	2b	Retrospective case series study	Intraoperative CSF leak grading system. 1. Grade 0: 271 2. Grade 1: 202 3. Grade 2: 93 4. Grade 3: 54	1. Postoperative CSF leak rate. By grade and before and after CSF leak graded protocol. 2. Bacterial meningitis rate.	A graded repair approach to CSF leaks avoids tissue grafts and CSF diversion in more than 60% of patients. Protocol modifications in last 340 cases reduced failure rate to 1% overall and 7% for Grade 3 leaks. Provocative tilt testing before discharge is helpful in timely diagnosis of postoperative leaks.
Han[259]	2008	2b	Retrospective cohort study	592 Patients with intraoperative or postoperative CSF leaks following transsphenoidal pituitary macroadenoma surgery.	Intraoperative and postoperative CSF leaks in relation with: 1. Surgical revision, tumor consistency, and tumor margins. 2. Tumor size, consistency, and margins.	Intraoperative and postoperative CSF leaks occurred in 14.2% and 4.4% of patients, respectively. Endoscopic and microscopic repairs were effective in managing leaks.
Tamasauskas[245]	2008	2b	Prospective cohort study	313 Patients underwent 356 transsphenoidal operations for pituitary adenoma. 29 cases where the sella fat packing was used together with Surgicel and TachoSil to cover the sella and dural defects.	1. Intraoperative and postoperative CSF leak rate. 2. Sella closure methods.	The technique of covering sella and dural defects with Surgicel and TachoSil in presence of intraoperative CSF leak appeared to be more reliable over packing sella and sphenoidal sinus with autologous fat and restoring defect of sella turcica with autologous bone.
Rabadan[260]	2009	4	Retrospective series	63 Pituitary tumors were operated by transnasal approach with intraoperative CSF leaks.	Fat graft, collagen sponge, glue, and lumbar drain for 2 to 4 days for intraoperative arachnoid opening. 1. Postoperative CSF leak rate. 2. Surgical complications.	This management of intraoperative CSF leaks had 5% rate of postoperative CSF leaks and there were no related complications.
Yano[261]	2009	4	Retrospective case series	213 Endoscopic endonasal transsphenoidal surgeries through bilateral nostrils in patients with pituitary adenoma.	1. Removal rate 2. Endocrinological remission. 3. Knosp grade. 4. Postoperative CSF leak.	The present study confirms the endoscopic approach is suitable for more extensive sellar tumors and overall postoperative CSF leak rate was 4.2%.
Cappabianca[246]	2010	4	Retrospective case series	40 Patients (28 with pituitary macroadenomas), underwent endoscopic endonasal approach for tumor/cyst removal.	Fibrin glue placed in the resection cavity "dead space". 1. CSF leak control. 2. Complications.	Fibrin glue proved effective in filling or sealing postoperative "dead space" and treating minor or initial CSF leaks.
Gondim[218]	2010	4	Retrospective case series	228 Patients with pituitary adenomas who underwent 251 procedures between December 1998 and December 2007.	1. Removal rate 2. Endocrinological remission 3. Complications 4. Postoperative CSF leak.	Endoscopic approach is safe and effective compared to microscopic approach, with low postoperative CSF leak rate of 3.5%.

(*Continued*)

TABLE IV.A.6. Continued

Study	Year	LOE (1a to 5)	Study design	Study groups	Clinical endpoint	Conclusion
Sciarretta[236]	2010	4	Retrospective case series	665 Patients underwent either transnasal transsphenoidal endoscopic or extended transsphenoidal surgery for pituitary tumors. 136 patients had either overt CSF leak or thin diaphragma sellae needing repair.	Graded CSF leak reconstruction based on 1) no leak; 2) no leak with thin diaphragma sellae; 3) small leak; or 4) larger leak through sellar or supradiaphragmatic defect. Postoperative CSF leak rate.	In a total of 136 patients undergoing multilayer technique, using fat, collagen, and in some cases mucoperiosteum from middle turbinate, postoperative CSF leak rate was 8%.
Cho[247]	2011	4	Retrospective case series	90 Cases of intraoperative CSF leaks were repaired with TachoComb® without an autologous tissue graft or lumbar CSF drainage.	1. Postoperative CSF leaks 2. Complication and infection.	Postoperative CSF leak rate was 2.2%. This method is effective alternative to autologous tissue graft technique unless there is large arachnoid defect. Lumbar CSF diversion not essential for prevention of postoperative CSF leak if effective repair performed.
Kassam[227]	2011	2b	Retrospective cohort for vascularized tissue for reconstruction.	800 Endoscopic endonasal skull-base surgeries (39% pituitary adenomas) performed between 1998 and 2007 at University of Pittsburgh Medical Center.	Using vascularize tissue. 1. Postoperative CSF leak 2. Infections 3. Neurological complications.	The incidence of postoperative CSF leaks decreased significantly with use of vascularized tissue for skull-base reconstruction (<6%).
Kono[262]	2011	3b	Retrospective case-controls series	1000 Endoscopic skull-base surgeries at the University of Pittsburgh Medical Center from 1998 to 2008.	1. Postoperative CSF leak 2. Infection risk factors: history of prior surgery, high complexity cases, external ventricular drain or VP shunt and postoperative CSF leak.	The incidence of post-op meningitis was 1.8% (18 cases) in ESBS. The most important risk factor was a postoperative CSF leak.
Strychowsky[263]	2011	2a	Systematic review of cohort studies.	10 Studies met the inclusion criteria and involved 687 patients. Endoscopic vs microscopic removal of pituitary adenomas.	GTR, recurrence, visual field change, hormone resolution or deterioration, mean blood loss, operative time, hospital length of stay, CSF leak, meningitis.	Purely endoscopic transsphenoidal resection of pituitary adenoma was overall safe and efficacious when compared to traditional microscopic approach, but had a higher postoperative CSF leak rate.
Wang[237]	2011	4	Retrospective case series	255 Endoscopic transsphenoidal surgery undertaken for pituitary pathology between 2005 and 2010. 90% were pituitary adenomas. 1. 158 grade 0 2. 74 grade 1.	1. CSF leak rate in simple purely synthetic repair of low-grade CSF leaks.	Postoperative CSF leak rate was 2.7% (2 cases). This repair is safe and comparable in efficacy while avoiding the morbidity related to more complex sellar reconstructions previously described.
Eloy[248]	2012	4	Retrospective case series	59 High-flow CSF leaks (54% pituitary adenomas) were repaired with a vascularized pedicled nasoseptal flap and other repair materials, without the use of lumbar catheter drainage.	1. Repair materials 2. Incidence of postoperative CSF leaks.	Postoperative CSF leak was 0% with nasoseptal flap. Lumbar drainage may not be necessary for routine management of high-flow CSF leaks.

(*Continued*)

TABLE IV.A.6. Continued

Study	Year	LOE (1a to 5)	Study design	Study groups	Clinical endpoint	Conclusion
Berker[232]	2013	2b	Retrospective cohorts	667 Patients treated between 2006 and May 2012 1. 50 cases with dural flap technique. 2. 135 intraoperative CSF leakage. 15 dural flap technique accompanied with fat and/or fascia lata support.	1. CSF leak rate	Of patients 135 with intraoperative leak, the dural flap technique was used in 15 patients with 0% postoperative CSF leak rate compared to 120 patients repaired without dural flap technique, 12 of whom had postoperative CSF leak (10%).
Gaynor[249]	2013	2b	Retrospective cohort	160 Cases with intraoperative CSF leak and without intraoperative LD. 1. AlloDerm 952) Autograft 46.	1. CSF leak rate	Postoperative CSF leak 8.4% with Alloderm vs 15.2% with fat autograft. AlloDerm is an effective alternative to fat autograft in cases of low-flow intraoperative CSF leak.
Horridge[250]	2013	2b	Retrospective cohort	Intraoperative CFS leaks 1. 40 Microscopic transsphenoidal surgery repair repaired with fat graft, tisseal and LD. (all pituitary adenomas) 2. 100 Endoscopic trans-sphenoidal surgery (after September 2009) repaired with nasoseptal flap. (80% pituitary adenomas).	1. CSF leak rate 2. Length of stay	Pedicled nasoseptal flap conveys significant advantage in preventing postoperative CSF leak, decreasing the morbidity associated with lumbar drain insertion and reduces the length of hospital stay.
Jalessi[264]	2013	4	Retrospective case series	240 Patients with pituitary adenoma with endoscopic endonasal transsphenoidal surgery. Intraoperative CSF leaks grading system used with repair based on grading system. 1. Grade 0: 133 2. Grade 1: 78 3. Grade 2: 29	1. Postoperative CSF leaks rate 2. Pneumocephalus 3. Meningitis	Postoperative CSF leak 0.8%. Given low leak rate, this graded strategy to repair is safe and useful for avoiding postoperative CSF leaks.
Halvorsen[265]	2014	2b	Retrospective cohort	352 Nonfunctioning and 154 hormone-secreting adenomas treated with transsphenoidal surgeries. 1. 268 microscopic; 2. 238 endoscopic	1. Complication rate: postoperative CSF leaks rate, meningitis, visual deterioration. 2. Multivariate analyses: older age, surgery for recurrent tumors, and surgery performed by a low-volume surgeon.	Overall CSF leak rate 4.7% (5% endoscopic vs 4.5% microscopic). No significant difference in the complication rate between endoscopic and microscopic techniques.
Iannelli[251]	2014	4	Retrospective case series	Retrospective review of 40 patients with macroadenoma underwent endoscopic transsphenoidal surgery; 19 with sellar floor reconstruction with fat plug positioned over oxidized and regenerated cellulose gauze.	Postoperative CSF leak rate Endocrine outcomes Late surgical complications.	No postoperative CSF leak encountered. This technique is safe and may be cost-effective in reducing surgical time.

(*Continued*)

TABLE IV.A.6. Continued

Study	Year	LOE (1a to 5)	Study design	Study groups	Clinical endpoint	Conclusion
Jakimovski[238]	2014	4	Retrospective case series	Intrathecal fluorescein was administered in 203 consecutive endoscopic endonasal pituitary surgeries for pituitary adenomas. 1. Tumors <2 cm vs ≥ 2 cm. 2. Tumors <1.5 cm^3 vs ≥ 1.5 cm^3.	1. Intraoperative CSF leak rate comparing the use of intrathecal fluorescein and tumor size. 2. Postoperative CSF leak by tumor size.	Overall CSF leak rate 3%. The rate of intraoperative CSF leak using intrathecal fluorescein is higher than previously reported. Tumor diameter and volume are predictors of the risk of intraoperative CSF leak.
Juraschka[165]	2014	2b	Retrospective cohort study for predictors of extent of resection.	73 Consecutive patients with large and giant pituitary adenomas (defined as maximum diameter ≥ 3 cm and tumor volume ≥ 10 cm^3) who underwent endoscopic endonasal transsphenoidal surgery between January 1, 2006 and June 6, 2012.	1. Resection rate 2. Experienced visual acuity improvement 3. Visual fields improvement 4. Complications: - Postoperative CSF leaks - Sinusitis	Overall CSF leak rate 10%. Endoscopic endonasal transsphenoidal surgery is an effective treatment method for patients with large and giant pituitary adenomas.
Paluzzi[252]	2014	2b	Retrospective cohort series for nasal septal flap use.	555 Patients with an EEA for removal of a pituitary adenoma. Two cohorts, one before and the other after the use of nasal septal flap.	1. Tumor resection 2. Tumor recurrence 3. Expanded approaches 4. Use of nasal septal flap 5. Endocrine outcomes 6. Postoperative CSF leak rate. For both cohorts of sellar repair.	EEA is a safe and effective surgical approach. Postoperative CSF leak decreased from 5% to 2.9% after nasal septal flap use.
Soudry[242]	2014	3a	Systematic review of case series studies.	22 Studies remaining for final analysis, all were case series. A total of 673 patients were included in the analysis.	To systematically review the literature concerning techniques of closure of endoscopically created skull-base defects based on site of skull-base defect and flow rate of CSF. Data sources: PubMed, SCOPUS, and Cochrane databases.	Level 4 evidence, in cases of low-flow intraoperative CSF leaks, skull-base reconstruction with multilayered free grafts and synthetic materials offers similar outcomes to vascularized flaps. In high-flow intraoperative CSF leaks, pedicled vascularized flaps appear to be superior. Location of the defect does not seem to be a significant factor in determining successful closure, with the exception of clival defects.
Hong[253]	2015	2b	Retrospective cohort study	Transsphenoidal approach surgery in 101 patients. - Conventional sellar closure technique with LD in 54 patients. - 47 Patients in the Tachosil® application group without LD.	1. Postop CSF leak rate. 2. Meningitis rate. 3. Length of hospital stay.	Sellar repair using Tachosil® associated with postoperative CSF leak rate of 1.9% vs 9.3% in conventional packing group. Tachosil® can be effective to prevent CSF leakage and obviate need for an autologous tissue graft or postoperative LD.

(*Continued*)

TABLE IV.A.6. Continued

Study	Year	LOE (1a to 5)	Study design	Study groups	Clinical endpoint	Conclusion
Ivan[266]	2015	2b	Retrospective cohort study	98 Consecutive expanded endoscopic endonasal surgeries performed from 2008 to 2012. Univariate and multivariate for preoperative comorbidities, intraoperative techniques, and postoperative care.	1. Postoperative CSF leak rate. 2. Meningitis rate.	Overall postoperative CSF leak rate 11%. Preoperative BMI was the most important preoperative predictor for CSF leak and infection. Other risk factors include age, intraoperative CSF leak, lumbar drain duration, and cranial combined cases.
Kim[254]	2015	2b	Retrospective cohort study	Type 1 CSF leakage developed in a total of 122 patients with pituitary adenoma. - 71 fleece-coated fibrin glue patch alone was applied onto the defect - 51 repaired with the direct suture technique	1. Postoperative CSF leak rate.	No differences between both techniques in postoperative CSF leak rate (0% with direct suture technique vs 1.4% with fleece-coated fibrin glue technique). Suture technique added 5 to 20 minutes more to the procedure. Lumbar CSF drainage not needed.
Liebelt[255]	2015	4	Case series study	200 Consecutive patients (77.5% pituitary adenomas) undergoing endonasal transsphenoidal surgery from April 2008 through December 2011 were reviewed: 1. 136 Received sellar floor cranioplasty using the Medpor® implant. 2. 64 Using autologous nasal bone.	1. Complication rate: - Postoperative CSF leak that require operative re-exploration. - Pneumocephalus, meningitis, hematoma, epistaxis.	Various autologous and synthetic options are available to reconstruct the sellar floor, and the Medpor® implant is a safe and effective option. The complication rate after surgery is equivalent to or less frequent than other methods of reconstruction.
Park[239]	2015	4	Retrospective case series	Transsphenoidal surgery with intraoperative CSF leak (73.5% pituitary adenomas): - G1: 29 - G2a: 9 - G2b: 6 - G3: 10 Tissue grafts (abdominal fat or other) and lumbar CSF drainage not used. Nasoseptal flap used in grades 2b and 3.	Nasoseptal flap used just in grades 2b and 3 1. Postoperative CSF leak rate.	Postoperative CSF leak rate 0%. Modified classification of intraoperative CSF leaks and tailored repair technique in a multilayered fashion using an en-bloc harvested septal bone and vascularize nasoseptal flaps are effective and reliable method for the prevention of postoperative CSF leaks.
Wang[267]	2015	4	Retrospective case series	577 Nonfunctioning adenomas, 180 GH secreting, 308 prolactin secreting, 26 mixed GH/PRL adenomas, 68 ACTH secreting, and 7 TSH secreting adenomas.	1. Tumor resection 2. Endocrine outcomes 3. Complications: postoperative CSF leak, DI, epistaxis	Postoperative CSF leak rate was 0.6%. The endoscopic approach is a safe and efficacious technique for the removal of pituitary adenomas.
Amano[256]	2016	2b	Case series study	500 Transsphenoidal surgeries with sphenoid sinus mucosa for patching or suturing the arachnoid defects or dural defect used for reconstruction. (62% pituitary adenomas).	1. Postoperative CSF leak rate 2. Fat graft use rate	Technique of using sphenoid sinus mucosa to repair intraoperative CSF leaks (1.9% vs 1.2%) or prevent them is effective and less invasive.

(*Continued*)

TABLE IV.A.6. Continued

Study	Year	LOE (1a to 5)	Study design	Study groups	Clinical endpoint	Conclusion
				539 Previous cases using fat graft, fascia harvested from abdomen or thigh and/or nasal septal flap. (72% pituitary adenomas).		
D'Anza[268]	2016	2a	Systematic review of cohort studies	A total of 5 articles met inclusion criteria. These comprised 376 endoscopic skull-base tumor resection and reconstruction cases.	Examine the literature for the need for LDs in contemporary skull-base reconstruction after resection of skull-base tumors.	Analysis demonstrated a lack of statistically significant improvement between patients who had a lumbar drain and patients who did not have a lumbar drain. However, available evidence is of poor quality and heterogenous. Further studies that include randomized controlled trials are needed.
Dehdashti[241]	2016	3b	Individual case-control study	180 Endoscopic endonasal skull-base reconstructions: 11 patients had postoperative leaks: Type I 0 Type II 2 Type III 7 Type IV 2	1. Rate of each type of their intraoperative grading system in the postoperative CSF leak group. 2. Rate of LD use for each type.	Overall repair failure rate was 6%. A repair protocol for endoscopic endonasal reconstructions determined by intraoperative CSF leak and preoperative planning minimizes unnecessary repair materials and additional morbidity.
El Shazly[257]	2016	4	Retrospective case series	1. 17 Patients had intraoperative CSF leakage treated immediately with intradural placement of autologous muscle graft, extradural composite septal cartilage graft (posterior cartilaginous septum with its covering mucoperichondrium on one side only). - 6 Had postoperative CSF rhinorrhea and had delayed treatment with the same technique after failure of conservative measures and LD for more than 3 days.	1. Postrepair CSF leak rate 2. Other complications 3. Evaluation of mucosal covering after 2 months	This technique is effective in the treatment of intraoperative and delayed postoperative CSF leakage following transsphenoidal pituitary surgery without the use of postoperative LD.
Jang[269]	2016	4	Retrospective case series study	Pure endoscopic endonasal transsphenoidal surgery: - 157 no functional adenomas - 174 hormone-secreting adenomas.	1. Demographic description 2. Preoperative and postoperative endocrine status 3. Radiologic features 4. Tumor resection 5. Remission in functional tumors 6. Complications 7. Hospital length of stay.	Overall postoperative CSF leak 1.8%. The pure endoscopic endonasal transsphenoidal surgery for pituitary adenomas provides acceptable and reasonable results representing a safe alternative procedure to the traditional transsphenoidal microscopic approach.
Magro[270]	2016	4	Retrospective case series	300 Endoscopic transsphenoidal surgeries for nonfunctioning pituitary macroadenomas	Intraoperative CSF leak, postoperative CSF leak; meningitis, time of surgery, mortality, detection of *S. aureus* and mupirocin	Meningitis was associated with intraoperative CSF leaks, postoperative CSF leaks, and operation times longer than 1 hour.

(*Continued*)

TABLE IV.A.6. Continued

Study	Year	LOE (1a to 5)	Study design	Study groups	Clinical endpoint	Conclusion
					treatment, epistaxis.	Preoperative treatment with mupirocin in the nostrils did not impact the occurrence of meningitis. CSF leak decreased with the use of hard reconstruction of the sella. Postoperative epistaxis decreased after stopped using monopolar coagulation.
Tien[271]	2016	3a	Systematic review of case series	8 Studies nonrandomized, prospective or retrospective series 1 literature review	Review complications associated with LDs and evidence on their usefulness in preventing postoperative CSF leak after endoscopic skull-base reconstruction.	LD is not indicated for routine low-flow CSF leaks, and are not routinely necessary in reconstructions with high-flow leaks, given the ability of pedicled flaps to minimize the risk of persistent CSF fistulae postoperatively.
Ahmed[131]	2017	1a	Systematic review; 1 RCT	12 articles comprising 508 cases met inclusion criteria. 1 randomized controlled trial and 11 case series	Conduct a meta-analysis to investigate the effect of lumbar drains on postoperative CSF leaks following endoscopic surgery.	There is insufficient evidence to support use of LD as a means to significantly reduce postoperative CSF leaks. Subgroup analysis examining only those patients whose CSF leaks were associated with anterior skull base resections demonstrated similar results.
Fraser[233]	2018	4	Retrospective case series.	615 Endoscopic endonasal approach for resection of skull base tumors. (30.7% pituitary adenomas) 103 Developed a postoperative CSF leak.	1. Postoperative CSF leak rate 2. Tumor location 3. LD use 4. Overweight and obesity 5. Pedicle mucosa flap	Overall postoperative CSF leak 16.7%. Preoperative BMI >25 kg/m^2 and tumor location in posterior fossa associated with higher rates of postoperative CSF leak. Use of a pedicled vascularized flap may be associated with reduced risk of a CSF leak, particularly in overweight patients.
Pereira[258]	2017	2b	Prospective cohort study	Endoscopic endonasal transsphenoidal surgery sellar reconstructions: - 180 Patients received DuraSeal(R) - 71 Patients not receiving DuraSeal	1. Postoperative CSF leak rate 2. LD use	Postoperative CSF leak 2.7% in patients with pituitary adenoma. No statistically significant benefit from either DuraSeal or Tisseel. Intraoperative and postoperative LD appears beneficial in patients at higher risk of postoperative CSF leak.

(*Continued*)

TABLE IV.A.6. Continued

Study	Year	LOE (1a to 5)	Study design	Study groups	Clinical endpoint	Conclusion
Peris-Celda[244]	2017	4	Retrospective case series study	50 Patients with endoscopic surgery for pituitary tumors. Reconstruction with collagen inlay and free mucosal graft overlay to cover the sellar defect. No fat grafts or lumbar drains were used.	1. Postoperative CSF leak rate. 2. SNOT-22 was performed before, 1 month, and 3 months after surgery.	There were no postoperative leaks. The nasal cavity floor free mucosal graft is safe with minimal nasal morbidity. The harvest of mucosal graft does not worsen QOL measured with the SNOT-22 test.
Zhang[243]	2017	4	Retrospective case series study	474 Consecutive cases of pituitary adenoma treated with 485 transsphenoidal surgical procedures from January 2008 to December 2011.	1. Intraoperative CSF leak rate 2. Postoperative CSF leak rate 3. Use of LD 4. Gelatin foam and fibrin glue use	Postoperative CSF leak rate was 2.7%. Procedures using gelatin foam, fibrin glue, and autologous fat graft are common and effective techniques for the management of postoperative CSF leaks.
Zhou[240]	2017	3b	Retrospective case-control study.	492 Cases with endoscopic endonasal transsphenoidal pituitary adenoma surgery 86 Intraoperative CSF leaks. Grade 1 in 30 cases Grade 2 in 25 cases Grade 3 in 31 cases.	1. Univariate and multivariate analysis for intraoperative CSF leak rate: repeat surgery; consistency of the adenoma; tumor size.	Overall postoperative CSF leak rate 1.2%. Univariate analysis factors associated with an increased intraoperative CSF leak rate: repeat surgery, adenoma consistency, tumor size. On multivariate analysis only, tumor consistency and tumor size associated with intraoperative CSF leak.

ACTH = adrenocorticotropic hormone; BMI = body mass index; CSF = cerebrospinal fluid; DI = diabetes insipidus; EEA = endoscopic endonasal approach; GH = growth hormone; GTR = gross tumor resection; LD = lumbar drainage; PRL = prolactin; QOL = quality of life; SNOT-22 = 22-item Sino-Nasal Outcome Test; TSH = thyroid-stimulating hormone ; VP = ventriculoperitoneal.

At some centers, it is used routinely with good success, predominantly for larger high-grade leaks, whereas in others it may be associated with a higher failure and meningitis rate.[131,233,238,239,241,248,250,253,257,260,262,266,268,271] Two recent meta-analyses and a review article failed to find benefit of perioperative lumbar drain placement in patients with pituitary adenomas and other skull-base tumors, and 1 emphasized potential risk of major complications including meningitis and ventriculitis.[131,268,271] However, there is also conflicting data showing that use of intraoperative LD may reduce the risk of intraoperative CSF leak.[272] However, the available data is relatively poor and the possible utility of lumbar drains in patients with poor anatomical options for reconstruction, and/or significant medical comorbidities remains poorly defined.

- Aggregate Grade of Evidence: Grade B (Level 1a: 1 study; Level 1b: 1 study; Level 2a: 1 study; Level 2b: 5 studies; Level 3a: 1 study; Level 3b: 2 studies; Level 4: 9 studies)
- Benefit: No proven benefit for reducing postoperative CSF leaks and meningitis.
- Harm: Potential increased risk of meningitis, ventriculitis and headaches.
- Cost: There is increased cost associated with lumbar drain usage, including materials, surgical time, additional days in monitored beds (intensive care unit [ICU] or Step-down unit) and prolonged length of stay and potential costs of treating lumbar drain–associated meningitis.
- Benefit-Harm Assessment: The benefits of lumbar CSF diversion in patients with pituitary macroadenomas have not been proven or established. Many studies showed no benefit of use, and some showed increased risk of meningitis and other complications.
- Value Judgments: There is no proven benefit of lumbar CSF diversion for low-grade leaks and for high-grade intraoperative CSF leaks, while there is potential increased risk of meningitis and other major complications leading to potential morbidity.
- Policy Level: Recommendation against routine use of lumbar CSF diversion in patients undergoing surgery for pituitary macroadenoma.
- Intervention: The use of lumbar drain after intraoperative CSF leak.

IV.A.6.c. CSF leak and meningitis rates in recent literature. The repair failure rate and postoperative meningitis rates in endoscopic skull-base tumor surgery have varied over the last 15 years, but the trend has been encouragingly downward. Progress has clearly been made at many centers, especially after the advent of the pedicled NSF first introduced by Hadad et al.,[273] and Kassam et al.[274] over a decade ago. Overall postoperative CSF leak and bacterial meningitis rates in 9 recent large endoscopic pituitary adenoma series (all with over 200 patients) have ranged from 0.6% to 5%, and 0% to 3.4%, respectively. NSF usage in these series ranges from 1% to 43% and planned lumbar CSF drainage from 0.6% to 21.7%.[233,240,252,258,264,265,267,269,270]

Effective skull-base repair and avoidance of postoperative CSF leaks and meningitis continue to be a challenge in ESBS. Overall, many studies have addressed this critically important issue in endoscopic skull-base surgery; however, methodology and materials use vary widely across studies. Although there have been no RCTs, the overall CSF leak repair failure rate for endoscopic pituitary adenoma surgery appears to remain relatively low at high-volume centers. Use of a grading system to assess the size of the leak appears to be useful for determining the repair materials needed. A multilayered repair protocol appears to result in a low failure rate, with increasing layers and more advanced techniques including use of vascularized flaps such as the NSF for large skull-base defects with high-grade leaks. Although prophylactic intraoperative and postoperative LD is used at some centers, the existing data does not support its routine use in endoscopic pituitary adenoma surgery.

IV.B. Functional pituitary adenoma

IV.B.1. *Endoscopic and microscopic transsphenoidal surgery for secreting pituitary adenomas*

Pituitary surgery is the first-line therapy for adrenocorticotropin-secreting adenomas and the vast majority of GH-secreting, and thyrotropin-secreting pituitary adenomas.[275–277] Additionally, surgery can have utility in select patients with medically refractory/intolerant or noninvasive prolactinomas.[278] For several decades, microscopic transsphenoidal surgery has been used to resect hormone-secreting pituitary adenomas with good outcomes.[279,280] Since the 1990s, however, pure endoscopic surgery has also been applied to functioning or secreting pituitary adenomas.[1] It has been proposed that through improved illumination, panoramic field of view, and a minimally-invasive approach, endoscopic surgery may offer advantages over traditional microscopic approaches. Several studies have sought to compare the outcomes of endoscopic and microscopic surgery for pituitary adenomas. Most studies have combined the outcomes of nonfunctional and various functional tumors. Because the management of different functional pituitary adenomas varies widely, we included only studies that specifically studied outcomes of a single hormone-secreting tumor histology.[281]

Of note, no specific cost-effectiveness analyses exist for particular subtypes of pituitary adenomas; however, data from mixed analyses of functional and nonfunctional tumors suggest that in-hospital costs are similar with endoscopic and microscopic transsphenoidal surgery.[282] Additionally, mixed analyses and analyses of nonfunctioning adenomas alone suggest that long-term sinonasal outcomes may also be similar with endoscopic and microscopic surgery.[283,284]

IV.B.1.a. Acromegaly. One systematic review on endoscopic and microscopic transsphenoidal surgery for acromegaly exists (Table IV.B.1.a).[285]

This review included 31 cohort studies, totaling 950 endoscopic and 2137 microscopic cases. The authors found greater biochemical remission with endoscopic surgery, particularly for the subgroup of noninvasive macroadenomas (84% vs 67%, $p < 0.001$). They also found greater risk of sinusitis (16% vs 3%, $p < 0.001$) and intraoperative CSF leak (22% vs 1%, $p = 0.02$) with endoscopy, but a greater risk of meningitis (1% vs 2%, $p = 0.03$) with microsurgery. The studies that reported the outcomes of microsurgery tended to have much longer average follow-up. Additionally, the review in several cases included multiple studies from the same institution and time period, likely double-counting a subset of patients.

Finally, this review included the results of 3 cohort studies that independently compared endoscopic and microscopic transsphenoidal surgery for acromegaly (Table IV.B.1.a).[287–289] These studies, along with an additional comparative cohort study, consistently revealed little difference in remission rates between approaches.[286] The single exception was the study by Lenzi et al.,[286] which suggested a significantly lower rate of remission with the microscopic approach for macroadenomas than with the endoscopic approach (19% vs 69%, $p = 0.018$). This conclusion may be limited because the rate of remission with microsurgery at experienced centers is consistently much greater.[289,290]

IV.B.1.b. Cushing's disease. One comparative approach study exists for Cushing's disease (Table IV.B.1.b).[291]

Alahmadi et al.[291] analyzed the impact of approach on endocrine outcome for a cohort of 42 patients who underwent pituitary surgery for Cushing's disease. Among 17 patients who underwent endoscopic surgery and 25 patients who underwent microscopic surgery, there were similar rates of remission (59% and 64%) and DI (24% and 28%). There were more anterior pituitary hormone deficiencies after microscopic surgery, but more CSF leaks and sinonasal complications after endoscopic surgery; however, these differences were not statistically significant.

TABLE IV.B.1.a. Endoscopic and microscopic transsphenoidal surgery for acromegaly

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Phan[285]	2017	3a	Systematic review with heterogenous cohort studies. The results of several included studies are from the same institution and are counted twice.	Patients with acromegaly who underwent 1. Endoscopic and 2. Microscopic transsphenoidal surgery	1. Endocrine remission 2. Complication risk	Greater rate of remission for noninvasive macroadenomas with endoscopy, but similar rate of remission for other types. Greater rate of sinusitis and intraoperative CSF leak with endoscopy, but greater rate of meningitis with microscopy.
Lenzi[286]	2015	2b	Retrospective cohort study	Patients with acromegaly who underwent 1. Endoscopic and 2. Microscopic transsphenoidal surgery.	Endocrine remission	Similar rate of remission with microadenomas between groups; however, there was a significantly lower rate of remission with macroadenomas and a microscopic approach. This rate (19%) is far lower than that reported from experienced centers.
Fathalla[287]	2015	2b	Retrospective cohort study	Patients with acromegaly who underwent 1. Endoscopic and 2. Microscopic transsphenoidal surgery	1. Endocrine remission 2. Extent of resection	No difference in the rate of remission between approaches; however, there was a significantly greater rate of gross total resection in the endoscopic group.
Sarkar[288]	2014	2b	Retrospective cohort study	Patients with acromegaly who underwent 1. Endoscopic and 2. Microscopic transsphenoidal surgery	1. Endocrine remission 2. Complication risk	No difference in the rate of remission between approaches; however, there was a significantly greater rate of hypopituitarism with the microscopic approach.
Starke[289]	2013	2b	Retrospective cohort study	Patients with acromegaly who underwent 1. Endoscopic and 2. Microscopic transsphenoidal surgery.	1. Endocrine remission 2. Complication risk	No difference in the rate of remission between approaches; however, there was a significantly greater rate of sinusitis with the endoscopic approach.

CSF = cerebrospinal fluid; LOE = level of evidence.

IV.B.1.c. Prolactinomas. A single study to date has compared outcomes of microscopic and endoscopic surgery for prolactinomas (Table IV.B.1.c).[292]

Cho and Liau[292] analyzed outcomes of 22 patients in each group. This analysis demonstrated similar rates of biochemical remission (66% and 75%) and visual improvement (63% and 60%) between patients treated with an endoscopic approach compared to a microscopic approach. The most pronounced difference between the 2 groups was among the rate of complications, with 1 (4.5%) in the endoscopic arm and 6 (27%) in the microscopic arm. These complications were primarily sinonasal in nature (5/6 complications).

- Aggregate Grade of Evidence: C (Level 2b: 5 studies; Level 3a: 1 study)
- Benefit: Endoscopic transsphenoidal surgery likely offers a similar rate of remission as microscopic surgery for functional pituitary adenomas. Endoscopic surgery may have some utility for selected macroadenomas.
- Harm: The complication risks of endoscopic and microscopic transsphenoidal surgery are similar.
- Cost: Data from studies also including nonfunctional pituitary adenomas suggest that in-hospital costs are similar between microscopic and endoscopic transsphenoidal surgery. With functional adenomas, long-term costs will likely be most affected by failure to achieve remission

TABLE IV.B.1.b. Endoscopic and microscopic transsphenoidal surgery for Cushing's disease

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Alahmadi[291]	2013	2b	Retrospective cohort study	Patients with Cushing's disease who underwent 1. Microscopic or 2. Endoscopic transsphenoidal surgery	1. Endocrine remission 2. Diabetes insipidus 3. CSF leak 4. Hormone deficiency 5. Sinonasal complications	The 2 groups had similar rate of remission, as well as similar rates of complications.

CSF = cerebrospinal fluid; LOE = level of evidence.

TABLE IV.B.1.c. Endoscopic and microscopic transsphenoidal surgery for prolactinoma

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Cho[292]	2002	2b	Retrospective cohort study	Patients with prolactinomas who underwent 1. Microscopic or 2. Endoscopic transsphenoidal surgery	1. Endocrine remission 2. Visual improvement 3. Length of stay 4. Complications	No difference in endocrine remission or visual improvement, but shorter length of stay and less complications with endoscopic surgery.

LOE = level of evidence.

or biochemical recurrences. Further study is required to assess this long-term cost.

- Benefit-Harm Assessment: Neither the relative benefit, nor harm, of endoscopic transsphenoidal surgery, has been established with a high LOE when compared with microscopic surgery.
- Value Judgments: Institutional and surgeon experience should dictate the use of endoscopic or microscopic transsphenoidal surgery for functional pituitary adenomas. Endoscopy may have some potential benefit in the visualization of larger tumors.
- Policy Level: Option
- Intervention: Endoscopic transsphenoidal surgery for functional pituitary adenomas is a reasonable approach for tumors that require surgical resection.

IV.B.2. *Intraoperative MRI in endoscopic surgery for secreting pituitary adenomas*

Because small remnants of pituitary adenomas can cause persistent hormone hypersecretion, complete resection, when safe, affords the greatest possibility of endocrine remission. One potential method for maximizing tumor removal is the use of intraoperative MRI (iMRI) to assess the extent of resection. This technique has been demonstrated for nonfunctioning pituitary macroadenomas by several groups.[293,294] Because remnants of macroadenomas may be difficult to visualize surgically, iMRI may reveal additional tumor that can be resected in the same setting.

Few groups have reported the results of iMRI for patients with functioning pituitary adenomas—particularly while using an endoscopic approach (Table IV.B.2).

Schwartz et al.[294] described the results of iMRI in a cohort with nonfunctioning tumors (n = 11) as well as a smaller group with functioning tumors (n = 4). They reported remission in 2 of 3 patients with acromegaly and did not report endocrine outcome in 1 patient with a prolactinoma. All patients with functioning tumors achieved a complete resection. Among the 15 patients overall, residual tumor was identified in 3 using the iMRI. Tanei et al.[296] reported the outcome of iMRI for 14 patients with pituitary microadenomas (7 acromegaly, 4 prolactinoma, 3 Cushing's disease). iMRI led to further resection that resulted in endocrine remission in 3 patients (21%). Overall remission was achieved in 79%. Finally, Netuka et al.[295] reported the largest series of patients with functional tumors in whom iMRI was used with the outcomes of 105 patients with acromegaly. They found that further resection after iMRI led to remission in 9% of patients, resulting in a total remission rate of 61%.

It remains unclear whether the use of iMRI leads to less aggressive initial resections in these cases. Further, the remission rates reported are not significantly different, and are in some cases lower, than rates reported without iMRI.[289,290] Comparative study will be necessary to better establish the utility of this modality.

- Aggregate Grade of Evidence: C (Level 4: 3 studies)
- Benefit: iMRI offers a potential benefit of more complete resection and greater likelihood of endocrine remission.
- Harm: Not evaluated to date.
- Cost: Has not been evaluated to date. iMRI use will incur greater costs over the short term; however, greater rates of remission may lead to savings over the long term.
- Benefit-Harm Assessment: Neither the benefit, nor any potential harms of this surgical adjunct have been established with a high LOE.
- Value Judgments: iMRI may have utility in maximizing extent of resection of functional pituitary tumors.

TABLE IV.B.2. Intraoperative magnetic resonance imaging in endoscopic surgery for secreting pituitary adenomas

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Netuka[295]	2016	4	Retrospective case series	105 Patients with acromegaly (16 microadenomas)	1. Endocrine remission 2. Rate of complication	Endocrine remission in 61%. Further resection after MRI was responsible for remission in 9%.
Tanei[296]	2013	4	Retrospective case series	14 Patients with functional pituitary microadenomas	Endocrine remission	Endocrine remission in 79% of patients. Further resection after MRI was responsible for remission in 21%.
Schwartz[294]	2006	4	Retrospective case series	Subset of patients with acromegaly (n = 3) and prolactinoma (n = 1) who were included in the analysis	1. Extent of tumor removal on postoperative MRI 2. Endocrine remission	Complete resection in all 4 patients. Remission in 2 of 3 patients with acromegaly. No data on patient with prolactinoma.

LOE = level of evidence; MRI = magnetic resonance imaging.

However, the endocrine results reported to date are no better than those reported from experienced centers without the use of iMRI.

- Policy Level: Option
- Intervention: iMRI may be a reasonable option in the resection of functioning pituitary tumors.

IV.B.3. *Use of the histologic pseudocapsule for endoscopic resection of secreting pituitary adenomas*

Resection of pituitary adenomas, particularly microadenomas, can be performed by removing the tumor along with a thin layer of compressed normal gland referred to as a the histologic pseudocapsule. This approach, described in detail by Oldfield and Vortmeyer,[297] has been suggested to improve complete resection of functional tumors, while preserving normal pituitary gland.[298] Applications of this technique in the endoscopic resection of functional pituitary adenomas are limited to comparative 2 cohort studies (Table IV.B.3).

Xie et al.[300] analyzed retrospective data from 2 time periods, when the authors attempted an intracapsular approach and when the authors attempted an extracapsular approach for GH-secreting pituitary adenomas. They found a significantly greater rate of biochemical remission with extracapsular resection. Ceylan et al.,[299] on the other hand, prospectively analyzed a series of patients with functional adenomas in whom pseudocapsular resection was attempted. When it was achieved, there was a 96% rate of remission, compared to 50% when it was not achieved. These particular data may be confounded by tumor extent or invasion that could affect both the ability to achieve an extracapsular resection as well as the likelihood of biochemical remission. Pseudocapsular resection also carries a theoretical benefit of a diminished CSF leak risk because a layer of normal gland protects the diaphragm from being exposed; however, neither study demonstrated this benefit.

- Aggregate Grade of Evidence: C (Level 2b: 2 studies)
- Benefit: Both studies demonstrated improved rates of biochemical remission with extracapsular resection, which is consistent with findings from microsurgical studies. There is a theoretical benefit of preservation of normal gland and a reduction in CSF leak risk; however, these have not been demonstrated by the studies to date.
- Harm: Potential harm of extracapsular resection has not been demonstrated.
- Cost: No studies to date have studied the costs related to pseudocapsular resection; however, management of persistent hormone hypersecretion may be associated with increased indirect costs.
- Benefit-Harm Assessment: Attempted pseudocapsular resection appears to afford the benefit of improved rates of biochemical remission for functional pituitary adenomas, with no demonstrated harm.
- Value Judgments: For patients in whom a histological pseudocapsule can be dissected, an extracapsular resection appears to provide a greater likelihood of biochemical remission. There is no specific rationale to not use or attempt this technique.
- Policy Level: Recommendation
- Intervention: Extracapsular resection of functional pituitary adenomas should be attempted when safe to do so.

IV.B.4. *Postoperative evaluation of patients with functional pituitary adenomas*

Consensus regarding postoperative endocrine evaluation for patients with functional pituitary adenomas has been established elsewhere. In brief, such evaluations can be divided into an evaluation of biochemical remission and evaluation of nontumor pituitary hormone function. Specifically, for acromegaly, random GH should be assessed 12 weeks after surgery.[301] Serum GH less than 1 μg/L or a nadir GH less than 0.4 μg/L after an oral glucose

TABLE IV.B.3. Use of the histologic pseudocapsule for endoscopic resection of secreting pituitary adenomas

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Ceylan[299]	2013	2b	Prospective cohort study	Patients with GH-secreting, ACTH-secreting, and prolactin-secreting tumors underwent either 1. pseudocapsular or 2. non-pseudocapsular resection	Endocrine remission	Endocrine remission was improved when a pseudocapsule was identified at surgery (96% vs 50%)
Xie[300]	2016	2b	Retrospective cohort study	Patients with acromegaly who underwent either 1. pseudocapsular or 2. non-pseudocapsular resection	1. Endocrine remission 2. Complication rate	Endocrine remission was improved in the pseudocapsular group (85.7% vs 54.4%) with no increase in complication

ACTH = adrenocorticotropic hormone; GH = growth hormone; LOE = level of evidence.

tolerance test defines remission. For Cushing's disease, morning serum cortisol 3 to 5 days after surgery should be evaluated. A result less than 1 μg/dL has a 96% positive predictive value of lasting remission.[281] Finally, postoperative evaluation of residual hormone function should include all pituitary hormone axes to assess for any new postoperative hypopituitarism.

IV.C. Rathke's cleft cysts

Rathke's cleft cysts (RCCs) are benign lesions with a location that is entirely intrasellar, intrasellar with suprasellar extension, or purely suprasellar. They originate from remnants of Rathke's pouch. RCCs are mostly small and asymptomatic; they may become large enough to cause symptoms by compression of intrasellar or suprasellar structures.

Common symptoms are headache and visual and/or endocrine disturbances. DI as a presenting symptom of RCC is reported, but rare.[302] For symptomatic RCCs, surgical decompression is commonly performed.[303]

In ESBS, intrasellar RCCs are generally approached by a standard EEA. In some intrasellar RCCs with suprasellar extension and in purely suprasellar RCCs, an extended EEA using the transtuberculum and/or transplanum route may be needed.[304]

This review identified 7 retrospective single-center case series studies evaluating EEA of RCCs with a total number of 192 patients. There has been neither an RCT nor a prospective cohort trial published yet. The low patient numbers in each study limits post hoc statistical analysis. In 82 of 192 (43%) patients, intrasellar RCC was noted. In 92 of 192 (48%) patients, an intrasellar RCC with suprasellar extension was found and 18 of 192 (9%) RCCs were purely suprasellar.

IV.C.1. *Endoscopic endonasal surgery for RCCs*

Surgical resection technique comprised gross total resection (GTR) of RCCs in 46 of 191 patients (24%), whereas in the remaining 145 of 191 patients (76%) subtotal resection (STR) of RCCs was performed. STR always included drainage of the cyst with cyst wall biopsy. In some patients, additional partial cyst wall removal was performed.

Headache was the most common presenting symptom (132/191, 69%) independent of the RCC location. This symptom overall resolved in 117 of 132 patients (89%). In 1 study with 9 suprasellar RCCs approached by extended EEA, headache improved only in 71%.[305] In another study by Ratha et al.,[306] headache was the predominant symptom in 93%. Fifty-two percent (52%) had purely intrasellar RCC and 48% had intrasellar RCC with suprasellar extension. GTR was performed in 63%, STR in 37%. The overall resolution of headache was 96%. There was no difference of GTR or STR in EEA or extended EEA affecting the outcome of preoperative headache.

Visual disturbances were present in 56 of 159 patients (35%). In the study of Madhok et al.[304] with 32 patients, no data are given concerning preoperative and postoperative visual disturbances. Visual outcome improved in 52 of 56 patients (93%) with no difference whether GTR or STR in EEA or extended EEA was performed.

Endocrinopathy was present in 103 of 191 patients (54%). Of 103 patients, 63 (61%) had a partial or total hypopituitarism, 34 of 103 (33%) showed hyperprolactinemia, and 6 of 103 patients (6%) presented with DI. Postoperatively, overall improvement rate was 51 of 103 (50%). Analyzing the subgroups, hypopituitarism improved in 20 of 63 cases (32%), hyperprolactinemia in 29 of 34 cases (85%) and DI normalized in 2 of 6 cases (33%). However, normalization of DI was only published in the study of Fan et al.[307] Also, controversial results exist regarding the subgroup of hypopituitarism. Whereas Fan et al.[307] and Xie et al.[308] reported a 50% improvement rate for hypopituitarism, the other included studies reported a 22% to 33%[305,306,309] or 0%[304,310] improvement rate.

Therefore, EEA and extended EEA in intrasellar and suprasellar RCC significantly improve clinical symptoms of headache and visual disturbances. Regarding preoperative endocrinopathies, only hyperprolactinemia was markedly improved.

Gland preservation was possible in the vast majority of the cases. The overall rate of new cases with permanent hypopituitarism of the anterior pituitary axis was 6 of 191 (3%) reported in the studies of Solari et al.[309] (4/29 cases) and Fan et al.[307] (2/49 cases). Out of the 4 patients with postoperative endocrinological worsening in the studies of Solari et al.,[309] 3 patients received STR (3/13) and 1 patient GTR (1/16). In the studies of Fan et al.,[307] both of the 2 patients received STR. It must be noted, that in the studies of Fan et al.,[307] all of their 49 patients were treated with STR, none received GTR. In all of the other studies,[304–306,308,310] the rate of permanent new hypopituitarism was 0%. Madhok et al.[304] reported 3 temporary pituitary dysfunctions.

Permanent postoperative DI occurred in 5 of 191 patients (3%) who were not affected preoperatively. Three of them received GTR and 2 of them STR. Temporary DI in previously unaffected patients was present in 10 of 191 patients (5%). Out of these patients, 6 received GTR and 4 STR.

Radiological recurrences were reported in 18 of 192 patients (9%), whereas symptomatic recurrences that required revision surgery were identified in 10 of 192 patients (5%). However, the follow-up period in the cited studies was predominantly short-term and showed a wide range from 2 to 122 months with a mean from 21 to 48 months. Solari et al.[309] did not report follow-up data but just mentioned a retrospective evaluation from 1997 to 2014. In the study with the longest mean follow-up of 48 ± 27 months (Fan et al.[307]), there was a higher radiological (7/49 cases, 14%) and symptomatic (5/49 cases, 10%) recurrence rate, suggesting that the overall recurrence rate may be higher if the follow-up period is prolonged.

Solari et al.[309] reported that none of the 16 patients that received GTR presented recurrence at follow-up. On the other hand, there were 4 of 13 (31%) recurrences in their STR group. Madhok et al.[304], Xie et al.,[308] and Fan et al.[307] performed only STR and had recurrence rates of 6%, 9%, and 14%, respectively. Frank et al.[310] reported no recurrence in their GTR group of 6 cases and 1 recurrence in their STR group of 16 cases (6%). The possible influence of the endoscopic approach (EEA or extended EEA) on recurrence rates could not be analyzed because of a lack of published data.

Finally, it must be stated that the recurrence rate in EEA and extended EEA in RCC is uncertain because of a lack of studies with appropriate follow-up periods. However, there appears to be no conclusive evidence that more aggressive resection of the cyst wall results in lower rates of recurrence. Also, there are no valuable data concerning the impact of closure of the RCC on recurrence rates. Fan et al.[307] presented a 6% incidence of packing the RCC due to a CSF leak (3/49) and had a recurrence rate of 14% (7/49). Solari et al.[309] had 52% (15/29) of their patients receiving an intraoperative closure of RCC with an altogether recurrence rate of 14% (4/29).

IV.B.2. *Management of CSF leaks after RCC surgery*

Overall, postoperative CSF leaks were reported in 10 of 191 patients (5%). Madhok et al.,[304] Jahangiri et al.,[305] and Ratha et al.[306] reported a 0% rate for CSF leaks in their patient groups. Madhok et al.[304] used a vascularized NSF in cases with an intraoperative CSF leak, typically without lumbar drain. Jahangiri et al.[305] used DuraGen for lining the defect and then an NSF. Ratha et al.[306] used floor repair with only collagen sponge in small CSF leaks, and additional fat and fascia lata sometimes with lumbar drain in large CSF leaks. Frank et al.[310] reported 2 postoperative CSF leaks in 22 patients (9%) while plugging the sella with abdominal fat when intraoperative CSF leak was observed. Solari et al.[309] used multilayer closure and an additional NSF in larger CSF leaks. Postoperative CSF leaks occurred in 2 of 29 patients (7%) with the need of further EEA and repair. Xie et al.[308] plugged the sella with abdominal fat when a CSF leak occurred intraoperatively. They reported 3 postoperative CSF leaks, 2 of which were repaired using a further EEA and 1 using a lumbar drain. Fan et al.[307] reported 3 of 49 cases (6%) with postoperative CSF leaks while using collagen sponges in small and packing with autologous fat in larger CSF leaks. All of the 3 reported postoperative CSF leaks resolved through bed rest and/or LD with no need of a further surgical repair.

In conclusion, management of CSF leaks is very heterogeneous in the reported studies. In extended EEA (EEEA) with larger skull-base defects, support of the closure by an NSF seems to be a useful technique (see Table IV.C).

- Aggregate of Evidence: C (Level 3b: 4 studies; Level 4: 3 studies)
- Benefit: EEAs appear effective in reducing symptoms such as headache
- Harm: Minimal: Pituitary gland preservation is preserved in the majority of the cohort
- Cost: Low
- Benefit-Harm Assessment: Strong benefit of symptom reduction in comparison to low rates of postoperative pituitary dysfunction and CSF leak.
- Value Judgment: Endoscopic endonasal surgery is a viable surgical option for Rathke's cleft cysts
- Policy Level: Optional: Endoscopic marsupialization of RCC is a viable option for symptomatic control with low rates of recurrence and postoperative gland dysfunction.
- Intervention: When symptomatic and surgically indicated, endoscopic endonasal surgery can be effective. However, the risk/benefit ratio between GTR vs STR resection remains unclear.

TABLE IV.C. Endoscopic endonasal surgery for RCC

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Ratha[306]	2017	3b	Retrospective case series (n = 27)	Patients undergoing EEA for RCC	Postoperative endoscopic outcomes	Radical excision does not necessarily result in endocrinological impairment and may cause a better impact on recurrence
Madhok[304]	2010	4	Retrospective case series (n = 35). No clinical data n = 3, no radiographic data n = 2	Patients undergoing EEA for RCC EEA (n = 30) EEEA (n = 3)	Postoperative endoscopic outcomes. No data for visual outcome.	No permanent pituitary dysfunction, 96% complete or significant reduction of headache
Frank[310]	2005	4	Retrospective case series (n = 22)	Patients undergoing EEA for RCC	Postoperative endoscopic outcomes	Visual disturbances and headache improved in all patients
Solari[309]	2015	3b	Retrospective case series (n = 29)	Patients undergoing EEA for RCC EEA (n = 19) EEEA (n = 10)	Postoperative endoscopic outcomes	EEEA provides a higher rate of GTR with less pituitary dysfunction in supradiaphragmatic RCC
Xie[308]	2011	4	Retrospective case series (n = 23)	Patients undergoing EEA for RCC	Postoperative endoscopic outcomes	Drainage of the cysts with partial excision of the cyst wall is usually sufficient
Jahangiri[305]	2014	3b	Retrospective case series (n = 99)	Patients undergoing EEA for RCC EEEA in suprasellar RCC (n = 30), microsurgery in intrasellar RCC (n = 68) and suprasellar RCC (n = 22)	Postoperative surgical outcomes	EEEA in suprasellar RCC gives a higher rate of complete removal and better visual outcomes than microsurgery
Fan[307]	2013	3b	Retrospective case series (n = 87)	Patients undergoing EEA for RCC EEA (n = 49), transcranial surgery (n = 38)	Postoperative surgical outcomes	GTR does not appear to reduce recurrence rate but increase the risk of postoperative complications

EEA = endoscopic endonasal approach; EEEA = extended endoscopic endonasal approach; GTR = gross total resection; LOE = level of evidence; RCC = Rathke's cleft cyst.

IV.D. Craniopharyngioma

Craniopharyngiomas are benign disembryogenetic tumors—as per the World Health Organization (WHO) classification—originating from squamous epithelial remnants of Rathke's pouch; accordingly, they can arise at any segment of its course, virtually from the nasopharynx to the hypothalamus.[311,312] They currently represent 1.4% to 4.7% of all intracranial tumors (Central Brain Tumor Registry of the United States), appearing with a bimodal distribution at childhood (mean age 5 to 14 years) and late adulthood (mean age 5 to 74 years).[311,313]

These lesions can appear cystic, solid, or as combination of both, with intralesional calcifications often observed (around 60% to 80% of cases). From a histological point of view, 2 major variants have been identified: the papillary, occurring almost exclusively in adults, and the adamantinomatous type, being much more common overall and in the pediatric population (ratio, 9/1).[314,315] Regarding macroscopic features, the adamantinomatous subtype shows an irregular interface, adhesions to surrounding structures, and cystic contents with dark "motor-oil" fluid containing cholesterol crystals. Calcification may occur in the majority of cases. On the contrary, the papillary form shows no adherence to surrounding structures and/or calcifications, while the cystic contents are often clear.

Despite the histologically benign nature, craniopharyngiomas are burdened by an aggressive clinical course related to their tendency to involve a great number of vital neurovascular structures. Adjacent to the sellar region, they grow onto surrounding areas of the skull base, adhering tightly to optic nerves and chiasm, internal carotid arteries (ICAs), the3d ventricle—above the floor—the hypothalamus, and pituitary gland, causing a variety of symptoms. This local spread is perhaps even more critical in the pediatric population. Dependent upon the lesion growth pattern, size, and location, typical presenting signs include visual dysfunction, with symptoms of chiasmatic and/or

retrochiasmatic compression, hypothalamic dysfunction, such as behavioral changes, hyperphagia, alterations of sleep patterns, apathy, or even stupor, and pituitary dysfunction, manifesting as DI and/or panhypopituitarism.[312]

Historically, different microscopic transcranial routes, namely subfrontal, frontolateral, and pterional routes, have been advocated as possible surgical options for the treatment of craniopharyngiomas.[315–323] Use of the transsphenoidal approach was introduced in the early 1960s by Gerard Guiot[324]: this technique initially was reserved only for lesions with a cystic component, with a minimal supradiaphragmatic extension in patients with an enlarged sella, preferably with panhypopituitarism. After Weiss[325] in 1987 described and termed the "extended transsphenoidal approach," it has been possible to access the suprasellar area and remove extrasellar craniopharyngiomas via the endonasal corridor.[326–329]

The endoscope is perfectly suited for this scenario: the wide and panoramic view offered by the endoscope pushed the development of a variety of modifications of the endonasal approaches expanding the targeted area to the whole median and paramedian skull base.[330–333] The endonasal technique offers a direct approach that permits access to the suprasellar, retrosellar, and retroclival space, obviating brain retraction; because craniopharyngiomas grow along a vertical axis, it provides the advantage of accessing these lesions immediately after suprasellar dural opening without optic nerve manipulation and/or retraction.

IV.D.1. *Management strategy for craniopharyngioma: GTR vs STR with radiation therapy*

Craniopharyngiomas are considered very difficult lesions to treat, due to such extremely variable growth pattern and, above all, an unpredictable behavior. Over the years, several authors advocated different classifications according to the direction of growth and the surgical route used, as related to the optic chiasm, diaphragma sellae, third ventricle, and infundibulum.[316,333–337]

As experience has grown with increasing number of cases treated via EEA, the technique has been refined and improved according to the different morphological features and location of craniopharyngiomas. Surgical anatomy and specific features of each tumor determine the pros and cons of the ability to remove each tumor and the outcomes and QOL.[228,331,338–347]

Complete removal (GTR) at first surgical attempt has been suggested as the most effective treatment.[315,316,318,348] Nevertheless, it may not always be possible because of the tumor's characteristics and/or location, its anatomical relationships, or as per the surgeon's personal preference.[349]

Indeed, debate regarding optimal treatment strategies still continues, in the literature, with several groups claiming the possibility of achieving a less risky STR, followed by either adjuvant radiotherapy or, more recently, radiosurgery.[350–355] However, craniopharyngiomas can recur even after radical resection and the surgical treatment of a recurrent lesion is often more troublesome, thus resulting in inevitably higher rates of incomplete resection and increased risk of mortality and morbidity.[315,318,344,348,356,357]

Different series analyzed clinical outcomes of different surgical approaches and compared the disease control rates achieved with GTR and the combination of an STR followed by radiotherapy (RT) (Table IV.D.1).

Both the contributions of Yang et al.[359] and Sughrue et al.[358] on wide cohorts reported that although GTR provides improved tumor control compared with STR alone, the addition of RT to STR can provide tumor control rates essentially similar to those for GTR, supporting the idea that STR + RT provides adequate tumor control while limiting hypothalamic and hypophyseal morbidity associated with aggressive resection.

In a recent meta-analysis from Zacharia et al.,[361] on a cohort of 644 patients treated for craniopharyngioma—who were registered in the Surveillance Epidemiology and End Results (SEER)—it appeared that STR and RT were independently associated with increased survival, whereas there was no survival advantage associated with GTR.

Schoenfeld et al.[360] clearly advocated the superiority of a conservative treatment (STR + RT); the outcome analysis of a cohort of 122 patients showed that such a strategy may lead to better disease control while limiting side effects: there was no significant difference in progression-free survival (PFS) and overall survival (OS) between patients treated with GTR vs STR + RT, but GTR was associated with significantly greater risk of developing long-term endocrinological disturbances.

When analyzing results of major series of craniopharyngiomas that underwent endoscopic endonasal removal, it remains clear that the adoption of conservative management is intentionally taken into account based on lesion features, surgeon's experience, and degree of involvement of neurovascular structures. Indeed, the series of Koutourousiou et al.,[362] Leng et al.,[343] and Cavallo et al.[228] all embrace the concept of safe "maximum-allowed" resection, also according to patient's age, endocrine status, and preoperative wishes, in the attempt of limiting morbidity: patients who received adjuvant RT presented similar outcomes in terms of OS and PFS. Dhandapani et al.[363] underlined the impact of extent of resection on the rates of recurrence and similarly noticed that adjuvant RT was useful to lower recurrence in cases where STR was achieved.

On the other hand, RT alone leads to lower tumor control rates and carries the risk of eventual late impairment of cognitive, hypothalamic, endocrine, and visual functions,[363] with rates of hypopituitarism being reported between 20% and 60% and optic neuropathy ranging from 2% up to 8%, at 10-year follow-up.[365–370]

In summary, there is a certain agreement in the literature that STR + RT is a valid strategy for the surgical management of craniopharyngioma, providing similar PFS and OS along with lesser morbidity rates, as compared to GTR.

TABLE IV.D.1. CP: GTR vs STR + RT

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Sughrue[358]	2011	2a	Systematic review (n = 540)	1. GTR 2. STR + RT	1. Clinical outcomes 2. Tumor control	GTR increases endocrine morbidity; RT worsens visual outcomes
Yang[359]	2010	2a	Systematic review (n = 442)	1. GTR 2. STR + RT	1. Clinical outcomes 2. Tumor control	Multimodality tailored strategy is effective
Schoenfeld[360]	2012	2b	Retrospective review (n = 122)	1. GTR 2. STR + RT	Primary: PFS/OS Secondary: DI, visual, endocrinological	STR + RT gives better clinical outcomes
Zacharia[361]	2012	2c	Retrospective review (n = 644)	1. GTR 2. STR + RT	PFS/OS; clinical outcomes	STR + RT gives better clinical outcomes
Koutourousiou[362]	2013	4	Retrospective case series	1. Adult 2. Children	Clinical outcomes	Maximum possible safe resection is better
Dhandapani[363]	2017	4	Retrospective case series	1. Primary surgery 2. Reoperations	Tumor control, EOR, BMI, visual, endocrinological	EOR is impacted by tumor volume and prior RT
Cavallo[228]	2014	4	Retrospective case series	Patients presenting with CP	Clinical outcomes	EEA is effective according to tumor features
Leng[343]	2012	4	Retrospective case series	Patients presenting with CP	Clinical outcomes; focus: EOR; BMI CSF leak	EEA is safe and effective
Gardner[364]	2008	4	Retrospective case series	Patients presenting with CP	Clinical outcomes	EEA is effective; high CSF rates
Campbell[338]	2010	4	Retrospective case series	Newly diagnosed CP	Clinical outcomes; focus: visual, endocrinological	EEA efficacy depends on tumor features
Kim[347]	2014	4	Retrospective case series	Recurrent CP	Clinical outcomes	EEA is safe and effective

BMI = body mass index; CP = craniopharyngioma; CSF = cerebrospinal fluid; DI = diabetes insipidus; EEA = endoscopic endonasal approach; EOR = extent of resection; GTR = gross total removal; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; STR = subtotal resection.

- Aggregate Grade of Evidence: C (Level 2a: 2 studies; Level 2b: 1 study; Level 2c: 1 study; Level 4: 7 studies)
- Benefit: Lower rates of hypothalamic disturbances with STR + RT.
- Harm: Potential late RT complications: vascular and endocrinological.
- Cost: Moderate.
- Benefit-Harm Assessment: Possibility of avoiding direct surgical injury.
- Value Judgments: Careful preoperative evaluation of surgical benefit-harm balance: adequate disease control and QOL are equal.
- Policy Level: STR + RT: option, when GTR is not possible; GTR: option, when vital structures are not exposed to surgical risk.
- Intervention: Consider conservative strategy with maximum allowed resection based upon lesion's features, surgical experience, and patient characteristics and requests.

IV.D.2. *Management of craniopharyngioma in pediatric vs adult population*

Aside from the incidence of the 2 different histotypes, which recognize the adamantinomatous variant more frequent in children, the tumor features are pretty similar with the same tendency of local aggressive behavior and higher risk of recurrence. Hence, it has been recognized that a third of lesions occurring in childhood present with greater rates of sellar involvement as compared to the adult population.[367,368,371–377]

When analyzing major reports, it is not possible to reach consensus in regard to the proper management of pediatric craniopharyngiomas, being even more troublesome to identify the balance between good surgical outcome that allows disease control and the need for adequate psychic and motor development and the risk of hypothalamic injury.[343]

The vast majority of cases have been treated via a transcranial approach, but standards of treatment should eventually include debulking via a variety of approaches, transsphenoidal surgery and cyst drainage procedures—with or without adjuvant treatment—in order to achieve optical pathway and hypothalamic/stalk decompression, along with good QOL.[367,369,371,372,374,378–383] The Hôpital Necker Enfants Malades group recognized that hypothalamic dysfunctions (hyperphagia/obesity, behavioral disorders, memory problems) are due to the tumor itself and its extensive removal makes things even worse: they tailored surgical strategy of management according to the preoperative degree of hypothalamic involvement.[349]

On the other hand, the report of Elliott et al.[372] definitely points out the effectiveness of GTR at both primary surgery and/or repeat surgical intervention for recurrent lesions. Their extraordinary 100% rate of total removal achieved at primary surgery with acceptably low mortality and morbidity offered the best chance of durable disease control with a good QOL; moreover, the surgical risks were not higher at reoperation. Excellent results in terms of QOL and neuropsychological outcomes following radical resection were achieved in 81% of children with primary tumors with slightly lower rates for recurrent tumors (72%).

However, few cases have disclosed data regarding the use of the endoscopic transsphenoidal approach in children; initially, this corridor has not been favored for several reasons, related to both the anatomy, with incomplete pneumatization of the paranasal sinus, and lesion features (Table IV.D.2).

Locatelli et al.[384] were the first to report the use of EEA for treatment of craniopharyngioma in a pediatric population: 4 children underwent the treatment of recurrent lesions, with 3 of them achieving cyst-sphenoid drainage.

In Jane et al.'s[376] series, 22 children underwent a transsphenoidal approach, 6 of whom were operated on via a purely endoscopic endonasal technique: their data are consistent with those reported in the adult population. Interestingly, they achieved a 100% rate of GTR, when this was the stated goal of the primary surgery with postoperative overall rate of panhypopituitarism of 67% and obesity of 37% related to hypothalamic malfunction. It is worth noting that most of the cases were intrasuprasellar, ultimately infradiaphragmatic lesions, which are more amenable to the transsphenoidal corridor. According to Cavallo et al.,[228] who reported 20 pediatric cases in their series, the results were similar to the adults in terms of GTR and endocrinological outcomes, as well as higher rates of GTR in primary compared with recurrent surgery. On the other hand, they had much higher visual improvement in children and reported no cognitive or psychic sequelae as they accepted a lesser extent of resection (EOR) with hypothalamic tumor invasion. Finally, Koutourousiou et al.[362] did find several differences in the outcomes between adult and pediatric populations in their series: the rate of near total removal (>95%) was significantly higher in childhood corresponding to higher rates of postoperative new-onset DI and pituitary dysfunction.

EEA seems to offer similar results in both adulthood and childhood for craniopharyngioma. When defining the surgical options, it should be born in mind that increased risk of endocrinological and hypothalamic dysfunction may occur postoperatively in the pediatric population, considering the growth pattern in this subset of cases.

- Aggregate Grade of Evidence: C (Level 2a: 1 study; Level 2c: 1 study; Level 4: 5 studies)
- Benefit: Good functional outcomes and disease control; possibility of limiting complications with STR + RT in both groups.
- Harm: Higher rate of hypothalamic and endocrinological disorders in children.
- Cost: Moderate.
- Benefit-Harm Assessment: Possibility of tailored strategy of treatment.
- Value Judgments: In pediatric patients, it is preferable to realize a subtotal surgical resection when hypothalamus is involved.
- Policy Level: GTR: option, when vital risks are acceptable; STR + RT: option, when GTR is not possible.
- Intervention: Consider maximum safe removal and adjuvant therapy, with regard to the risk of postoperative complications and the needs of psychic and motor development.

IV.D.3. *Adjuvant therapies for craniopharyngioma*

The possibility of considering combination of surgery with other therapeutic approaches in order to achieve long-term control of craniopharyngiomas has been reported extensively in the literature, both for children and adult populations[352,370,385–394] (Table IV.D.3).

Sometimes, a 2-stage surgical strategy could be adopted with the transcranial approach complimenting the endonasal, with each route being adopted to overcome the limitations of the other.[228,333,400]

Several authors suggested adjuvant RT in all incomplete tumor removal cases, advocating the fractionated technique as the most suitable RT treatment of craniopharyngiomas.[353,354,365,366,398,401–404]. On the other hand, stereotactic radiosurgery seems to provide favorable control rates at 5 years posttreatment.[366,405–409]

Effectiveness of postoperative irradiation though depends on tumor progression history: in cases of small residual tumors with calcified fragments that are adherent to neurovascular vital structures, which demonstrate no growth, a watchful waiting strategy with close neuroradiological follow-up can be adopted; in case of rapidly growing residual tumors, an early second surgical procedure can be preferred to achieve relief from symptoms.[228,329,343,357]

In the pediatric subset of patients, several groups adopted a more conservative strategy reporting the use of intralesional therapies, administered via an indwelling catheter with the objective of postponing or sparing the adverse effects of disruptive surgical treatment—above all for the hypophyseal and hypothalamic functions—and/or late sequelae due to RT. The management of craniopharyngiomas via stereotactic aspiration of the cystic component with the instillation of antibiotics, radionucleotides, and/or cell-cycle inhibitors resulted in successful and effective minimally invasive strategies of treatment.[381,397,399,410–412]

Recently, interferon-alpha[396] is becoming increasingly favored as antiproliferative agent when delivered intracavitarily: a recent international, multicenter retrospective analysis on a wide cohort of pediatric patients, showed that

TABLE IV.D.2. Management of CP with EEA in pediatric and adult population

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Clark[383]	2013	2a	Systematic review (n = 531)	1. GTR 2. STR + RT	1. Clinical outcomes 2. Tumor control	Similar tumor control rates regardless EOR
Elliott[372]	2011	2c	Outcome analysis	Pediatric CP treated: 1. TCA 2. TS	Clinical outcomes	Better outcomes are achieved when approach is chosen upon tumor features
Dhandapani[363]	2017	4	Retrospective case series	1. Primary surgery 2. Reoperations	Tumor control, EOR, BMI, visual, endocrinological	EOR is impacted by tumor volume and prior RT
Cavallo[228]	2014	4	Retrospective case series	Patients presenting with CP	Clinical outcomes	EEA is effective according to tumor features
Leng[343]	2012	4	Retrospective case series	Patients presenting with CP	Clinical outcomes; focus: EOR; BMI CSF leak	EEA is safe and effective
Jane[376]	2010	4	Retrospective case series	Children presenting with CP	Clinical outcomes	Effective especially for infradiaphragmatic lesions
Koutourousiou[362]	2013	4	Retrospective case series	Patients presenting with CP	Clinical outcomes	Maximum possible safe resection is better

BMI = body mass index; CP = craniopharyngioma; EEA = endoscopic endonasal approach; EOR = extent of resection; GTR = gross total removal; LOE = level of evidence; RT = radiotherapy; STR = subtotal removal; TCA = transcranial approach; TS = transsphenoidal surgery.

TABLE IV.D.3. Adjuvant therapies for CP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Jeswani[395]	2016	2b	Retrospective review (n = 46)	1. TCA 2. EEA	Clinical outcomes	Similar outcome for EEA and TCA; higher CSF leakage in EEA
Kilday[396]	2017	2b	Retrospective review	Children with progression of CP treated with IFN-alfa	Clinical outcomes	Intracystic IFN can delay tumor progression
Minniti[365]	2009	2c	Outcome analysis	CP cases treated with adjuvant RT	1. Tumor control 2. Radiation toxicity	Excellent tumor control
Turel[357]	2016	4	Retrospective review	Recurrent CP	Clinical outcomes	Adapt treatment to the tumor
Derrey[397]	2008	4	Retrospective case series	CP treated with intracavitary 186(Re)	1. Clinical outcomes 2. Tumor cyst control	Effective tumor control with lower morbidity
Dhandapani[363]	2017	4	Retrospective case series	1. Primary surgery 2. Reoperations	Tumor control, EOR, BMI, visual, endocrinological	EOR is impacted by tumor volume and prior RT
Cavallo[344]	2009	4	Retrospective case series	Recurrent CP	Clinical outcomes	EEA is safe and effective
Moon[398]	2005	4	Retrospective case series	1. Early RT 2. Late RT	1. Clinical outcomes 2. PFS	Poor QOL with late RT
Hasegawa[399]	2004	4	Retrospective case series	CP treated with intracavitary 32(P)	1. Clinical outcomes 2. Tumor cyst control	Effective tumor control with lower morbidity
Koutourousiou[362]	2013	4	Retrospective case series	Patients presenting with CP	Clinical outcomes	Maximum possible safe resection is better
Minniti[353]	2007	4	Retrospective case series	CP cases treated with adjuvant FSCRT	1. Clinical outcomes 2. PFS	Good tumor control with low toxicity

BMI = body mass index; CP = craniopharyngioma; CSF = cerebrospinal fluid; EEA = endoscopic endonasal approach; EOR = extent of resection; FSCRT = fractionated sterotactic conformal radiotherapy; IFN = interferon; PFS = progression-free survival; QOL = quality of life; RT = radiotherapy; TCA = transcranial approach.

the use of interferon-alpha hindered the progression of tumor whether patients had received or not received previous treatment, with less morbidity.

In our current era of genomics and molecular targeted therapies, it has been established that the vast majority of adamantinomatous craniopharyngioma and papillary craniopharyngioma present exclusive clonal driver mutations in the CTNNB1[413–415] and BRAF genes.[416] The latter is responsible for activation/regulation of mitogen-activated protein kinase (MAPK) signaling pathways, thus conferring growth advantage through modulation of cell proliferation, differentiation, and cell survival. CTNNB1 is involved in Wnt signaling pathway and its mutations lead to b-catenin accumulation into the cytoplasm and nucleus,[386,417] with the possibility to assess the mutations of the gene with standard immunohistochemical stains for this latter protein.[418] Concrete targeted therapy has not yet been validated but it is worth highlighting the report of Brastianos et al.,[419] who saw an extraordinary response to combined BRAF and MEK-targeted therapy in a single case of multiply recurrent papillary craniopharyngioma with genetically confirmed BRAFV600E mutation.

It remains clear in the literature that treatment of craniopharyngioma requires a multidisciplinary management; many adjuvant therapies have been found viable and effective. None of them is definitive as a single treatment, while each should be intended as a proper asset in the multimodality tailored therapy scheme.

- Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 2c: 1 study; Level 4: 8 studies)
- Benefit: Adequate OS and PFS along with less morbidity.
- Harm: Failure: need for salvage treatment.
- Cost: Moderate to high.
- Benefit-Harm Assessment: Possibility of tailored therapies.
- Value Judgments: Adjuvant therapies are not complication-free and are not valuable as single therapy.
- Policy level: RT: option for tumor progression; GammaKnife: option for tumor progression; Intracystic therapy: option for tumor progression. Genetic therapy: not recommended yet.
- Intervention: Consider multimodality management.

IV.D.4. *Pituitary gland and stalk preservation during craniopharyngioma resection*

Different degrees of hypopituitarism and DI represent significant but commonly accepted morbidities, especially following radical excision of craniopharyngioma, although pituitary gland/stalk loss of function could also be reasonably attributed to tumor invasion. The surgical decision making towards stalk sacrifice remains a dilemma[368,420–422]: on one hand, its preservation could reduce the risk of altered endocrine functions after surgery; on the other, it might also lead to hypothalamus functional disorders and, increase the risk of recurrence.

In a recent meta-analysis by Li et al.,[421] the strength of the relationship between stalk preservation and clinical outcomes was evaluated: surprisingly they identified reduced risks of anterior pituitary functions impairment and DI occurrence, but no statistical relevance was observed in terms of recurrences.

Pratheesh et al.[422] disclosed that radical excision, recurrent tumor surgery, pituitary stalk injury, and transcranial approach are associated with higher incidence of postoperative DI, being in their series as high as 80%. They pointed out that fluid/electrolytes disorders, especially the so-called "triphasic response" more commonly seen in children frequently leads to a differential diagnosis of DI vs SIADH.[368,420,421,423] So, the immediate postoperative response of stalk/hypothalamus manipulation is temporary dysfunction with polyuria, followed by the antidiuretic phase due to the uncontrolled release of vasopressin from the posterior pituitary or the damaged hypothalamus; finally, another polyuric phase, when the ADH reserves are depleted.

It is worth observing that rates of postoperative endocrinopathy using EEA are slightly lower compared to those reported per transcranial approaches.[372,395,424–426] DI rates after endoscopic endonasal removal of craniopharyngiomas range between 31.6% found in the series of Jeswani et al.[395] up to the 55.5% reported by Wannemuehler et al.[425]; this latter group, on the other hand, reported very low rates of panhypopituitarism (33.3%) statistically different from the average values reported in the literature of 47.2%.

On the other hand, there was no significant difference in between the rates of recurrence with regard to the strategy of pituitary gland/stalk management: it can be assumed, though, that recurrence rates were similar after both GTR and STR + RT (Table IV.D.4).

There is low evidence that stalk preservation can lead to better endocrinological outcomes and reduce rates of postoperative DI, but the association with tumor recurrence cannot be ruled out.

- Aggregate Grade of Evidence: C (Level 2a: 1 study; Level 2b: 2 studies; Level 2c: 2 studies; Level 3b: 1 study)
- Benefit: Better endocrinological outcomes.
- Harm: Potential increase of recurrence rates.
- Cost: N/A.
- Benefit-Harm Assessment: Possibility of improving QOL.
- Value Judgments: Fluid/electrolytes disorders and hypopituitarism are common endocrinological complications as related to surgical maneuvers at stalk area.
- Policy Level: Preserve gland/stalk: option
- Intervention: Consider stalk preservation unless it is widely invaded by tumor and preoperative endocrinological defects are already present.

TABLE IV.D.4. Pituitary gland and stalk preservation during CP resection

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Li[421]	2015	2a	Systematic review (n = 420)	1. Stalk removed 2. Stalk maintained	1. DI rates 2. Recurrences 3. Endocrine results	Better endocrine results if stalk preservation
Wannemuehler[425]	2016	2b	Retrospective review (n = 21)	1. TCA 2. EEA	Clinical outcomes	EEA is the approach of choice in selected cases
Jeswani[395]	2016	2b	Retrospective review (n = 46)	1. TCA 2. EEA	Clinical outcomes	Similar outcome for EEA and TCA; higher CSF leakage in EEA
Elliott[372]	2011	2c	Outcome analysis	Pediatric CP treated: 1. TCA 2. TS	Clinical outcomes	Better outcomes are achieved when approach is chosen upon tumor features
Pratheesh[422]	2013	2c	Retrospective review (n = 102)	1. Adult 2. Children	1. DI rates 2. Recurrences 3. Endocrine results	Radical excision is a predictor of DI
Patel[346]	2015	3b	Retrospective review (n = 33)	1. EEA for macroadenoma 2. EEA for CP	1. Clinical outcomes 2. QOL	QOL is kept as preoperative

LOE = level of evidence; CP = craniopharyngioma; DI = diabetes insipidus; EEA = endoscopic endonasal approach; QOL = quality of life; TCA = transcranial approach; TS = transsphenoidal surgery.

IV.D.5. *Reconstruction after EEA for craniopharyngioma*

It has to be said that postoperative CSF leakage represents a significant complication and 1 of the main issues of the endoscopic endonasal technique.[235,274,427–429] An effective watertight reconstruction of the skull base is thought mandatory to restore the natural intra and extradural compartment integrity: a failure could result in serious complications, such as meningitis, brain herniation, and tension pneumocephalus. Particularly, during an EEA to craniopharyngiomas, a large osteodural opening is created and cisternal space widely dissected and, eventually, the third ventricle chamber entered. It is mandatory to perform the reconstruction, because the result is a Grade 3 leakage according to Kelly's paradigm,[235] being sure to address the following: (1) obliteration of dead spaces; (2) isolation of the intradural compartment; (3) water/airtight closure; (4) preserving desiccation and infection of neurovascular structures; (5) promotion of the healing process; (6) preservation and rehabilitation of function; and (7) management of risk factors. In some situations, prior radiation therapy, the need for postoperative treatment, and/or previous surgeries via the nasal corridor, the presence of scar tissue and absence of autologous material available may hinder the closure.

Along with the refinement of the endonasal technique, different methods of skull-base reconstruction, along with the use of new materials, and vascularized flaps[228,273,274,427,430–432] have been reported. In most of the reported series, the osteodural defect has been closed according to the "gasket seal" or "grandma's cap" technique.[427,428] Although univocal consensus with regard to the use of LD is not yet achieved,[268] the introduction of the nasoseptal Hadad pedicled flap[273,274] has considerably reduced the risk of postoperative CSF leakage.

Koutourousiou et al.[362] reported an overall rate of 23.4% of postoperative CSF leaks, much lower than the 58% reported in the initial 16 cases of the same group[364]: accordingly, they noticed CSF leakage rates were significantly lower after routine use of a NSF was adopted. According to Cavallo et al.,[228] the postoperative CSF leak rate was 14.6%, being higher (27.8%) in those cases where the lesion involved the third ventricle: in this series, the use of new material and techniques, along with an increase in the authors' experience made the CSF leak rate drop to 4% in their last 25 procedures. Finally, Leng et al.[343] reported an extreme low rate of 3.8% CSF leakage: in this series lumbar drain was adopted and the authors attributed failure of reconstruction to technical errors of the osteodural sealing and/or to the lesions' features (Table IV.D.5).

There is no doubt that watertight closure of the osteodural defect is mandatory after endoscopic endonasal removal of craniopharyngiomas; however, postoperative CSF leakage risk is a major concern because of related morbidity. Reported postoperative CSF leak rates are still high and different risk factors can be identified, though the adoption of a multilayer reconstruction technique, supported by mucosal flap—either free or pedicled—represents a valid solution.

- Aggregate Grade of Evidence: C (Level 2c: 2 studies; Level 4: 6 studies)
- Benefit: Separation of the intracranial compartment from external environment.

TABLE IV.D.5. Reconstruction after EEA for CP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Elliott[372]	2011	2c	Outcome analysis	Pediatric CP treated: 1. TCA 2. TS	Clinical outcomes	Better outcomes are achieved when approach is chosen upon tumor features
Moussazadeh[424]	2016	2c	Retrospective review	1. TCA 2. EEA	Clinical and radiological outcomes	EEA is safe and effective
Cavallo[228]	2014	4	Retrospective case series	Patients presenting with CP	Clinical outcomes	EEA is effective according to tumor features
Leng[343]	2012	4	Retrospective case series	Patients presenting with CP	Clinical outcomes; focus: EOR; BMI CSF leak	EEA is safe and effective
Gardner[364]	2008	4	Retrospective case series	Patients presenting with CP	Clinical outcomes	EEA is effective; high CSF rates
Campbell[338]	2010	4	Retrospective case series	Newly diagnosed CP	Clinical outcomes; focus: visual, endocrinological	EEA efficacy depends on tumor features
Jane[341]	2010	4	Retrospective case series	Adults presenting with CP	Clinical outcomes; EOR	EEA is effective; high risk of postoperative endocrinopathy
Koutourousiou[362]	2013	4	Retrospective case series	Patients presenting with CP	Clinical outcomes	Maximum possible safe resection is better

BMI = body mass index; CP = craniopharyngioma; CSF = cerebrospinal fluid; EEA = endoscopic endonasal approach; EOR = extent of resection; TCA = transcranial approach; TS = transsphenoidal surgery.

- Harm: Potential complications: tension pneumocephalus and meningitis.
- Cost: Moderate to high secondary to the risk of serious complications.
- Benefit-Harm Assessment: Although EEA is an increasingly utilized technique in the management of craniopharyngioma, the rates of postoperative CSF leaks are higher than other routes. Effective skull-base reconstruction is critical.
- Value Judgments: Osteodural defect closure is mandatory.
- Policy Level: Multilayer reconstruction: recommended; Vascularized flap: option; Lumbar drain: option.
- Intervention: Perform watertight reconstruction of the skull base after lesion removal.

IV.E. Tuberculum sella and planum meningiomas

First classified by Cushing and Eisenhardt[433] in 1929, suprasellar meningiomas account for 5% to 10% of all intracranial meningiomas and were initially defined as tumors arising from the tuberculum sella. Al-Mefty et al.[434] later reclassified suprasellar meningiomas as those arising via arachnoid cap cells from the planum sphenoidale, tuberculum sella, diaphgrama sella, and anterior clinoid process; de Divitiis et al.[435,436] later distinguished clinoidal meningiomas from other suprasellar meningiomas. In this review, we refer to suprasellar meningiomas as being inclusive of tumors originating from either the planum sphenoidale or tuberculum sella.

With growth, these tumors can expand into the parasellar region with subsequent tumor encroachment upon eloquent neurovascular structures including the optic nerves and chiasm, internal carotid and anterior cerebral arteries inclusive of their branches, cavernous sinuses, infundibulum, and hypothalamus. Because of encroachment upon the optic chiasm, these tumors often present with progressive, asymmetric visual loss with incongruous visual fields, a finding described as "chiasmal syndrome" by Cushing in 1930.[437] Various prognostic scoring systems have been proposed to classify these tumors.[438–441] These systems have all included tumor size while variably including optic canal invasion, vascular invasion, brain invasion, peritumoral edema, previous surgery, previous radiation, and duration of visual symptoms in their schemes. These proposed classification schemes have yet to be externally validated, widely adopted, or prospectively used to guide surgical approaches.

Cushing was the first to successfully resect a suprasellar meningioma via a transcranial approach (TCA) in 1916,[442] and Jho[443] was the first to report resection of such a tumor via the EEA in 2001. Since this time, use of the EEA has been increasingly adopted as an equally effective or possibly preferred route over TCAs in well selected cases. Relative to TCAs, the EEA allows for (1) direct extradural access to the tumor's meningeal origin and osseous attachment; (2) upfront devascularization of the tumor's meningeal blood supply; (3) early, extradural, bilateral, and wide optic nerve decompression; (4) direct identification and access to the paraclinoidal internal carotid artery (ICA); the medial

aspect of the optic canal, the diaphragm, and the pituitary stalk; (5) minimization of brain and optic nerve manipulation; (6) tumor debulking prior to approaching the optic apparatus; and (7) arguably a better cosmetic result. Possible weaknesses of EEA include lack of ability to remove a subtle dural tail that extends beyond the endonasal corridor and higher rates of CSF leak, anosmia, and sinusitis.

The differentiation between planum sphenoidale meningiomas and tuberculum sella meningiomas in clinical presentation and the extent of surgical approach, specifically in relation to the optic nerve, is important. Planum sphenoidale meningioma can grow to considerable size prior to becoming symptomatic. These tumors often become symptomatic when the tumor displaces the frontal lobe and/or results in frontal lobe edema. In contrast, tuberculum sella meningioma and diaphragmatic meningioma tend to present at smaller sizes secondary to the propensity to involve the optic canals. The surgical treatment often includes optic nerve decompression. However, the state of the current literature is limited. In this section, these 2 suprasellar meningioma types are grouped for further systematic review.

Prospective studies directly comparing the efficacy and adverse effect profile of the TCA vs EEA are currently lacking in the literature. Case series describing 3 or fewer patients, sublabial endoscopic cases, pediatric series, and series solely evaluating endoscopic augmentation of TCAs were excluded. To avoid duplication of patients among several published series from single institutions, only the report with the largest relevant cohort from each institution was included in this review.

A total of 3540 reports were captured through our database search. After applying the exclusion criteria, 16 manuscripts, published between 2007 and 2017, met inclusion criteria for this review and have formed the foundation of this evidence-based review.

IV.E.1. *Extent of resection in suprasellar meningioma*

In 11 non-overlapping, retrospective, single-institution series totaling 212 patients, GTR rates for suprasellar meningiomas approached via EEA ranged from 53.8% to 83.3% with a weighted average rate of GTR equaling 75.9% (Table IV.E.1).[444–455]

The largest EEA-specific series, with a total of 70 patients, averaged a gross total resection rate of 77.5%.[451] Four series attempted to study factors associated with greater extent of resection using EEA; tumor size less than 2.3 cm, greater operative experience, and lack of vascular encasement by the tumor were all associated with greater rates of GTR.[447,451,452,455]

Five additional papers featured analyses of patients treated via TCA (n = 109) vs EEA (n = 71).[444,456–459] Within these papers, the rate of EEA GTR ranged from 50.0% to 85.7% with a weighted average rate of GTR equaling 76.3% (Table IV.E.2, Table IV.E.3).

In contrast, the rate of GTR following TCA ranged from 22.2% to 87.5%, with a weighted average rate of GTR equaling 74.3% (Table IV.E.2, Table IV.E.3).[458,459]

IV.E.2. *Suprasellar meningioma: visual improvement after EEA*

Among 170 patients included in 11 non-overlapping, retrospective series, rates of vision improvement ranged from 33.3% to 91.7% following EEA for suprasellar meningioma resection with a weighted average rate of vision improvement of 77.6% (Table IV.E.1, IV.E.3).[444–453,455,456] The largest EEA-specific series averaged a rate of vision improvement of 85.7%.[451] One study demonstrated a trend toward improved vision outcomes with greater operative experience.[452]

Five additional papers, featuring analyses of TCA (n = 121) vs EEA (n = 87), demonstrated a rate of vision improvement ranging from 33.3% to 97.7% for those undergoing EEA, with a weighted average rate of vision improvement equaling 82.8%. In contrast, the rate of vision improvement in the TCA group ranged from 18.8% to 61.4%, with a weighted average rate of vision improvement equaling 44.6% (Table IV.E.2, Table IV.E.3).[444,456–459] In 1 study, multivariate analysis, patient age less than 55 years old, and use of EEA were found to be associated with significantly higher odds of vision improvement.[459]

IV.E.3. *Risk of postsurgical CSF leak after EEA for suprasellar meningioma*

In 6 single-institution series encompassing 153 suprasellar meningioma patients in which all patients received a vascularized NSF, rates of postoperative CSF fluid leak ranged from 20.0% in early series to 0.0% in the most recent series, with an overall average leak rate of 9.8%.[448,450–452,455,459] Two series reported leak rates prior to and following adoption of a vascularized NSF for closure. Ottenhausen et al.[452] and Koutourousiou et al.[451] reported leak rates of 25.0% and 69.2%, respectively, prior to the use of vascularized NSFs, though these rates dramatically decreased to 0.0% and 16.1%, respectively, following the use of a vascularized flap for closure. Improved leak rates over time likely reflect greater experience with use of vascularized flaps over the surgical learning curve.[345,444–459] In contrast, 7 series not including use of a vascularized NSF demonstrated an overall leak rate of 22.2% among 97 patients.[445,447,449,451–453,456] Five papers reported CSF leak rates following TCA (n = 121) for tuberculum sellae meningiomas.[444,456–459] The associated CSF leak rate ranged from 0.0% to 8.3% with an overall leak rate of 4.1%.

IV.E.4. *Risk of postsurgical pituitary dysfunction after EEA for suprasellar meningioma*

New pituitary dysfunction following EEA for suprasellar meningiomas was reported in 14 retrospective series including 286 patients. New anterior pituitary dysfunction

TABLE IV.E.1. Evidence for endoscopic endonasal surgery outcomes in patients with suprasellar meningiomas

Study	Year	LOE	Study design	Study group	Clinical findings	Conclusion
Wang[445]	2010	4	Retrospective case series	12 Patients followed for an average of 28 months Multilayered closure with no NSF	GTR: 91.7% (11/12) Vision improvement: 91.7% (11/12) CSF leak: 8.3% (1/12) Anterior pituitary dysfunction: 0.0% (0/12) Posterior pituitary dysfunction: 8.3% (1/12, transient DI)	EEA is safe and effective in improving visual symptoms for tuberculum sella meningioma.
Van Gompel[446]	2011	4	Retrospective case series	13 Patients followed for an average of 13 months Unspecified closure	GTR: 53.8% (7/13) Vision improvement: 61.5% (8/13) CSF leak: 0.0% (0/13) Vascular injury: 7.7% (1/13; ACA injury)	Long-term outcomes are lacking, but EEA is feasible for anterior cranial base meningioma in appropriately selected cases.
Ogawa[447]	2012	4	Retrospective case series	19 Patients followed for an average of 35.8 months Multilayered closure with no NSF	GTR 78.9% (15/19) Vision improvement: 73.7% (14/19) CSF leak: 5.3% (1/19) Pituitary dysfunction: 0.0% (0/19)	EEA is equivalent to alternative approaches in meningiomas less than 30 mm.
Bohman[448]	2012	4	Retrospective case series	5 Patients followed for an average of 7.8 months Closure with NSF	GTR: 80.0% (4/5) Vision improvement: 80.0% (4/5) CSF leak: 20.0% (1/5) Posterior pituitary dysfunction: 40% (2/5, transient DI)	EEA may have higher rates of CSF leak, but less injury to the optic apparatus.
Chowdhury[449]	2012	4	Retrospective case series	6 Patients followed for an average of 7 months Multilayered closure with no NSF	GTR 83.3% (5/6) Vision improvement: 33.3% (2/6) CSF leak: 16.7% (1/6) Pituitary dysfunction: 0.0% (0/6)	EEA is more effective in small or medium size tumor.
Gadgil[450]	2013	4	Retrospective case series	5 Patients followed for an average of 15 months Closure with NSF	GTR: 80.0% (4/5) Vision improvement: 40.0% (2/5) CSF leak: 20.0% (1/5) Anterior pituitary dysfunction: 0.0% (0/5) Posterior pituitary dysfunction: 60.0% (3/5, transient DI)	EEA has equivalent or improved visual outcomes.
Ottenhausen[452]	2014	4	Retrospective case series	20 Patients followed for an average of 51.5 months Multilayered closure with no NSF through January 2008; multilayered closure with NSF after January 2008	GTR (overall): 80% (16/20) Pre-NSF GTR: 68.5% (5/8) Post-NSF GTR: 91.7% (11/12) Vision improvement (overall): 14/17 (82.4%) Pre-NSF vision improvement: 75.0% (6/8) Post-NSF vision improvement: 88.9% (8/9) CSF leak (overall): 10.0% (2/20) Pre-NSF CSF leak: 25.0% (2/8) Post-NSF CSF leak: 0.0% (0/12) Anterior pituitary dysfunction: 0.0% (0/20)	High GTR rates with low complications in well-selected cases.

(*Continued*)

TABLE IV.E.1. Continued

Study	Year	LOE	Study design	Study group	Clinical findings	Conclusion
					Posterior pituitary dysfunction (overall): 10.0% (2/20, transient SIADH) Pre-NSF posterior pituitary dysfunction: 25.0% (2/8) Post-NSF posterior pituitary dysfunction: 0.0% (0/12)	
Koutourousiou[451]	2014	4	Retrospective case series	75 Patients followed for an average of 29 months Multilayered closure with no NSF in first 13 patients; multilayered closure with NSF in final 62 patients	GTR: 76.0% (57/75) Vision improvement: 85.7% (48/56) CSF leak (overall): 25.3% (19/75) Pre-NSF CSF leak: 69.2% (9/13) Post-NSF CSF leak: 16.1% (10/62) Posterior pituitary dysfunction: 6.7% (5/75; 1/75 permanent DI; 4/75 transient SIADH) Vascular injury: 1.3% (n = 1, Heubner artery injury)	EEA is effective for both GTR and visual improvement for suprasellar meningiomas.
Ceylan[453]	2015	4	Retrospective case series	23 Patients followed for a range of 2-70 months Multilayered closure transitioned from no NSF to use of NSF during this series, though unclear when this transition occurred	GTR: 73.9% (17/23) Vision improvement: 70.0% (14/20) CSF leak: 8.7% (2/23) Posterior pituitary dysfunction: 8.7% (1/23 permanent DI; 1/23 transient DI)	EEA is a safe approach with a high rate of visual improvement.
Hayhurst[454]	2016	4	Retrospective case series	9 Patients followed for an unspecified period of time Unspecified closure	GTR: 66.7% (6/9) Vascular injury: 11.1% (1/9; ACA injury)	EEA is effective with appropriate case selection.
Elshazly[455]	2018	4	Retrospective case series	25 Patients followed for an unspecified period of time Closure with NSF	GTR: 76.0% (19/25) Vision improvement: 88.2% (15/17) CSF leak: 8% (2/25) Anterior pituitary dysfunction: 0.0% (0/25) Posterior pituitary dysfunction: 12.0% (3/25 transient DI) Vascular injury: 4.0% (1/25; unspecified arterial injury with resultant subarachnoid hemorrhage)	EEA is effective in regard to visual improvement.

CSF = cerebrospinal fluid; DI = diabetes insipidus; EEA = endoscopic endonasal approach; GTR = gross total resection; NSF = nasoseptal flap; SIADH = syndrome of inappropriate antidiuretic hormone.

following EEA was reported in 6 series totaling 82 patients. Five of these series[445,450,452,455,458] (n = 68) reported a 0.0% rate of anterior pituitary dysfunction; 1 series[457] (n = 14) reported a 21.4% rate of anterior pituitary dysfunction, including a 14.2% rate of delayed hyponatremia (n = 2) and a 7.1% rate of new postoperative hypoadrenalism (n = 1). The average rate of new anterior pituitary dysfunction totaled 3.7%.

New posterior pituitary dysfunction following EEA was reported in 14 series totaling 277 patients. Rates of new posterior pituitary dysfunction from various series ranged from 0.0% to 40% with the average rate of new posterior pituitary dysfunction totaling 7.2% (Table IV.E.1, Table IV.E.2). The overall average rates of transient SIADH, transient DI, and permanent DI were 2.2%, 2.2%, and 5.3%, respectively.

TABLE IV.E.2. Evidence comparing endoscopic endonasal surgery outcomes vs transcranial outcomes in patients with suprasellar meningiomas

Study	Year	LOE	EEA cohort	EEA clinical findings	TCA cohort	TCA clinical findings
Kitano[456]	2007	3b	16 Patients followed for at least 3 months Multilayered closure with no NSF	Average EOR: 98.5% Vision improvement: 81.3% (13/16) CSF leak: 12.5% (2/16) Pituitary dysfunction: 0.0% (0/16) Vascular injury: 12.5% (2/16; asymptomatic perforating artery infarct)	12 Patients followed for at least 3 months	Average EOR: 99.0% Vision improvement: 33.3% (4/12) CSF leak: 8.3% (1/12) Pituitary dysfunction: 0.0% (0/12) Vascular injury: 25% (3/12; 2/12 asymptomatic perforating artery infarcts; 1/12 symptomatic perforating artery infarct)
de Divitiis[460]	2008	3b	7 Patients followed for a range of 3 weeks to 20 months Unspecified closure	GTR: 85.7% (6/7) Vision improvement: 71.4% (5/7) CSF leak: 28.6% (2/7) Posterior pituitary dysfunction: 14.3% (1/7 permanent DI) Vascular injury: 14.2% (1/7 intraventricular hemorrhage)	44 Patients followed for a range of 9 months to 21 years	GTR: 86.4 (39/44) Vision improvement: 61.4% (27/44) CSF leak: 6.81% (3/44) Posterior pituitary dysfunction: 4.5% (2/44 transient DI) Vascular injury: 0.0% (0/44)
Fatemi[457]	2009	3b	14 Patients followed for an average of 27 months Multilayered closure with no NSF	GTR: 50.0% (7/14) Vision improvement: 64.3% (9/14) CSF leak: 28.6% (4/14) Anterior pituitary dysfunction: 21.4% (3/14; 2/14 delayed hyponatremia; 1/14 new hypoadrenalism) Posterior pituitary dysfunction: 14.3% (2/14 transient DI) Vascular injury: 0.0% (0/14)	9 Patients followed for an average of 15 months	GTR: 22.2% (2/9) Vision improvement: 55.6% (5/9) CSF leak: 0.0% (0/9) Anterior pituitary dysfunction: 0.0% (0/9) Posterior pituitary dysfunction: 0.0% (0/9) Vascular injury: 11.1% (1/9 cavernous carotid injury)
Linsler[458]	2017	3b	6 Patients followed for an unspecified period of time Multilayered closure with no NSF	GTR: 83.3% (5/6) Vision improvement: 33.3% (2/6) CSF leak: 0.0% (0/6) Anterior pituitary dysfunction: 0.0% (0/6) Posterior pituitary dysfunction: 0.0% (0/6)	16 Patients followed for an unspecified period of time	GTR: 87.5% (14/16) Vision improvement: 18.8% (3/16) CSF leak: 6.3% (1/16) Anterior pituitary dysfunction: 6.3% (1/16) Posterior pituitary dysfunction: 0.0% (0/16)
Song[459]	2018	3b	44 Patients followed for a median of 27 months Closure with NSF	GTR: 84.1% (37/44) Vision improvement: 97.7% (43/44) CSF leak: 2.3% (1/44) Pituitary dysfunction: 6.8% (3/44 transient DI) Vascular injury: 0.0% (0/44)	40 Patients followed for a median of 43.5 months	GTR: 60.0% (26/40) Vision improvement: 37.5% (15/40) CSF leak: 0.0% (0/40) Pituitary dysfunction: 15.0% (6/40 unspecified pituitary dysfunction) Vascular injury: 2.5% (1/40 ICA injury)

CSF = cerebrospinal fluid; DI = diabetes insipidus; EEA = endoscopic endonasal approach; EOR = extent of resection; GTR = gross total resection; ICA = internal carotid artery; LOE = level of evidence; NSF = nasoseptal flap; TCA = transcranial approach.

Five papers reported new pituitary dysfunction following TCA (n = 121) for tuberculum sellae meningiomas.[444,456–459] Two of these series failed to specify anterior vs posterior dysfunction; rather, these series reported overall new postoperative pituitary dysfunction rates of 0.0% (n = 12) and 15.0% (n = 40).[456,459] The additional 3 series reported cumulative (n = 69) rates of new anterior and posterior pituitary dysfunction manifest as transient DI (n = 2) totaling 1.4% and 2.9%, respectively.

TABLE IV.E.3. Summary rates of GTR, postoperative CSF leak, and postoperative vision improvement in 16 studies reporting outcomes following EEA and TCA to suprasellar meningiomas

	GTR % (n)	CSF leak % (n)	Vision improvement % (n)
EEA	76.3% (216/283)	Overall 14.4% (35/243) With NSF 9.8% (15/153) Without NSF 22.2% (20/90)	79.3% (204/257)
TCA	74.3% (81/109)	4.1% (5/121)	44.6% (54/121)

CSF = cerebrospinal fluid; EEA = endoscopic endonasal approach; GTR = gross total resection; NSF = nasoseptal flap; TCA = transcranial approach.

IV.E.5. *Suprasellar meningioma: risk of vascular injury*

Among the 11 EEA-specific series included in this review, 4 series reported an intraoperative vascular injury.[446,451,454,455] A total of 4 episodes of vascular injury were documented in these 4 series (n = 122), inclusive of 2 anterior cerebral artery (ACA) injuries,[446,454] 1 recurrent artery of Heubner injury,[451] and 1 unspecified arterial injury with resultant subarachnoid hemorrhage,[455] averaging an overall 3.3% rate of intraoperative vascular injury among these 4 series. The 2 patients with ACA injuries both developed completed strokes, with 1 patient developing new postoperative right leg weakness and the other patient developing new postoperative abulia.[446,454] The patient with the recurrent artery of Heubner injury developed a completed stroke with associated contralateral weakness.[451] The patient with subarachnoid hemorrhage developed hydrocephalus requiring external ventricular drain (EVD) placement and vasospasm requiring intraarterial nicardipine injection; the patient developed no permanent focal deficits.[451,455]

Among the 5 series reporting outcomes in TCA vs EEA patients, 3 vascular injuries were reported in the EEA subset of patients (n = 87), inclusive of 2 asymptomatic perforating artery infarcts and 1 delayed intraventricular hemorrhage (IVH), for an average EEA vascular injury rate of 3.4%.[444,456] The patient with delayed IVH had a history of severe hepatic dysfunction and presented with IVH 3 weeks after surgery, ultimately dying. In contrast, the TCA subset of patients (n = 121) reported in these series accumulated 5 vascular injuries, inclusive of 2 asymptomatic perforating artery infarcts, 1 symptomatic perforating artery infarct, 1 cavernous carotid injury, and 1 ICA injury, for an average TCA vascular injury rate of 4.1%.[345,456,459] No additional clinical details were available regarding the patient who developed a symptomatic perforating artery infarct or the patient with ICA injury.[456] The patient who developed a cavernous carotid injury had previously been treated with a craniotomy as well as an EEA for debulking; the injury was repaired with a muslin gauze and the patient developed no pseudoaneurysm and no neurological deficits.[455]

Summary for the role of EEA in suprasellar meningiomas. Currently available data via retrospective series from 2007 through 2017 suggest that EEA for resection of suprasellar meningiomas is a safe and effective treatment option. When compared to select TCAs, patients undergoing EEAs appear to have similar rates of tumor resection and posterior pituitary dysfunction with improved rates of postoperative vision. Postoperative CSF leak rates have dramatically decreased from an average of 22.2% to 9.8% following use of the NSF.[274] Vascular injury remains an uncommon but concerning complication for both TCAs and EEAs.

Three prior systematic reviews that focused on outcomes following EEA for suprasellar meningiomas reported outcomes similar to our findings.[461–463] Specifically, rates of GTR in these reviews ranged from 77.2% to 79.9% and rates of postsurgical vision improvement ranged from 79.5% to 87.0%, similar to the findings in our study. These older reviews report rates of CSF leak ranging from 21.5% to 24.3%, primarily reflecting older series, predating widespread use of a vascularized NSF. Our analysis of CSF leak rates with use of a vascularized NSF demonstrates an average leak rate of 9.8%. Prior reviews reported rates of pituitary dysfunction ranging from 9.4% to 11.7%, with most dysfunction manifest as only transient dysfunction, similar to our findings. Vascular injury was reported in only 1 prior systematic review at a rate of 2.6%, demonstrating the relatively rarity of these injuries.[463]

Two prior systematic reviews focused on comparing outcomes between EEA and TCA for suprasellar meningiomas also demonstrated similar findings to our study.[464,465] These prior reviews have reported rates of GTR ranging from 71.8% to 88% in the EEA group relative to rates of 73.1% to 87% in the TCA group, with no statistically significant difference noted between groups. Similarly, rates of vision improvement were consistently greater in the EEA group, with rates ranging from 73.5% to 87%, relative to the TCA group, with rates ranging from 54.8% to 60%. Finally, rates of CSF leak were significantly higher in the EEA group, with rates ranging from 19% to 24.8%, relative to the TCA group, with rates ranging from 4.3% to 5%.

Prospective studies directly comparing the efficacy and adverse effect profile of the TCA vs EEA are currently lacking in the literature. Future studies may take the form of prospective, multi-institutional registries using proposed tumor classification schemes to categorize

patients.[334,438–440] Variables of interest would include tumor size, goals of surgery, duration of visual symptoms, objective measures of vision (such as the German Ophthalmologic Society Scale),[466] detailed history of past treatments and operative approaches, and presence as well as degree of optic canal invasion, peritumoral edema, and arterial involvement.

- Aggregate Grade of Evidence: C (Level 3b: 5 studies; Level 4: 11 studies)
- Benefit: Use of the EEA for tuberculum sella meningiomas has been associated with similar rates of extensive resection and excellent rates of visual improvement relative to the TCA.
- Harm: Potential harm associated with the EEA for resection of suprasellar meningiomas includes pituitary dysfunction, vascular injury, and CSF leak.
- Cost: No widely reported studies have yet described costs associated with use of EEA for resection of suprasellar meningiomas. One study comparing EEAs and TCAs noted longer operative times for the TCA group, although it is unclear if this increased operative time lead to significantly greater intraoperative and postoperative costs.[458]
- Benefit-Harm Assessment: Greater operative experience with EEA seems to be associated with decreased harm and improved rates of extensive resection.[451] Use of a vascularized NSF has been associated with decreased rates of cerebrospinal fluid leak.[461]
- Value Judgments: Use of EEA for suprasellar meningiomas allows for (1) direct extradural access to the tumor's meningeal origin and osseous attachment; (2) upfront devascularization of the tumor's meningeal blood supply; (3) early, extradural, bilateral, and wide optic nerve decompression; (4) direct identification and access to the paraclinoidal ICA, the medial aspect of optic canal, the diaphragm, and the pituitary stalk; (5) minimization of brain and optic nerve manipulation; (6) tumor debulking prior to approaching the optic apparatus; and (7) a potentially better cosmetic result.
- Policy Level: Opinion
- Intervention: Use of EEA for suprasellar meningiomas is likely the preferred surgical approach for small-size to medium-size tuberculum sellae meningioma with inferomedial optic canal invasion.

IV.F. Olfactory groove meningioma

There have been significant advances in the EEA to the skull base over the past 15 years and they have become a valuable addition to the skull-base surgeon's armamentarium. Indeed, EEAs have in many cases replaced open procedures especially in benign extradural pathologies of the paranasal sinuses. Although increasingly accepted and currently widely used for other pathologies and locations including pituitary adenomas, clival chordomas, and suprasellar tumors such as craniopharyngiomas, their role in other skull-base lesions is still a matter of debate and controversy. This is especially true for anterior skull-base meningiomas including olfactory groove meningiomas (OGMs).

OGMs account for 8% to 13% of all intracranial meningiomas. They are slow growing tumors, often remaining clinically silent in their early phases of growth and reaching large sizes by the time of diagnosis thus making them surgically challenging. They have traditionally been approached using a number of open transcranial approaches. The EEA for OGM offers a number of theoretical advantages over traditional transcranial approaches including: (1) a direct midline access to the skull base providing a wide panoramic view of the relevant anatomy; (2) avoiding brain retraction, possibly leading to less neurosurgical morbidity; (3) early tumor devascularization prior to dural opening, by ligation of anterior and posterior ethmoidal arteries and coagulation of the dural base; (4) removal of any hyperostotic bone of the skull base during the approach allowing for a more complete removal and thus minimizing the risk of recurrence[467]; and (5) improved cosmetic result.

Although the EEA has been increasingly used for OGMs, its role has not been properly defined and there is no consensus in terms of GTR, complication rates, and importantly the criteria for proper patient selection to achieve best possible patient outcomes. This can be partially explained by the paucity of published literature and heterogeneity of studies reporting EEA series. Studies comparing EEA and transcranial approaches have many important limitations including selection bias, varied lesion characteristics, and lack of uniformity in reporting, thus making interpretation of any conclusions debatable.

Eleven studies met our inclusion criteria, 4 of which were systematic reviews.[444,454,461,462,468–474] Reviewed studies with clinical endpoints and conclusions are summarized in Table IV.F.

There is also paucity, heterogeneity, and selection bias in the literature regarding EEA for OGM. However, over the past few years with increasing experience and awareness of the learning curve for EEA, there has been a better understanding of the indications and limitations of the approach. An EBR of the literature is important in understanding what if any advantages the EEA has to offer for OGM and may help to define the criteria for proper patient selection in order to optimize outcomes.

IV.F.1. *Rate of GTR in OGM*

There is considerable heterogeneity in the literature regarding GTR rates for EEA in OGM. In the most recent systematic review by Shin et al.[462] in 2015, which included 80 patients, GTR was reported in 87.5%. In 2 previous systematic reviews, each including 30 patients, the GTR rate was reported to be 73% and 89.7%.[461,470] In the first systematic review in 2012 by Komotar et al.,[471] which included 19 patients, GTR was reported to be 63.2%. In the largest series of 50 patients, Koutourousiou et al.[472]

TABLE IV.F. Evidence for EEA for olfactory groove meningiomas

Study	Year	LOE	Study design	Study group	Clinical findings	Conclusion
Hayhurst[454]	2016	4	Case series	9 Patients	GTR: 88.8% CSF leak: 0%, intraoperative lumbar puncture, fat graft, nasoseptal flap Olfaction preservation: "Some patients" with unilateral approach Complications: Meningitis (1/9)	Careful patient selection to EEA leads to low rates of morbidity.
Shin[462]	2015	4	Systematic review of case series	80 Patients	GTR: 87.5% CSF Leak: 26% Visual outcome: improved 92.3% Complications: 8.8% serious neurological deficits, 12.5% possibly fatal systemic complications as DVT/PE	EEA outcomes in literature are suboptimal. Small round tumors extra-arachnoidal are the best candidates for EEA. Unacceptable high rates of CSF warrant consideration of reconstruction techniques.
Banu[468]	2016	4	Case-control	Endoscopic endonasal (6 patients) Endoscopic assisted supraorbital eyebrow (7 patients) Combined approach (6 patients)	GTR: 50% (EEA group). CSF leak: 16%, routine LD, intrathecal fluorescein, gasket seal (EEA group) Visual outcome: Improved 100% (1/1 EEA group) Olfaction preservation: 100% Anosmia (EEA group and combined group) Complications: 83.3% (EEA group)	EEA is associated with lower rates of resection and more complications than endoscopic assisted supraorbital eyebrow approach. EEA can be useful in tumors extending to ethmoid sinus either alone or combined with TCAs.
De Almeida[469]	2015	4	Case-control (matched pair)	EEA (10 patients) Bifrontal craniotomy (BFC) (10 patients)	GTR: 70% (EEA group) CSF Leak: 40% (EEA group) Complications: 40% (EEA group)	EEA can provide good outcomes in selected patients. Less post-operative radiographic frontal lobe injury than TCAs. Clinical correlation of these findings needs to be further investigated.
Koutourousiou[472]	2014	4	Case series	50 Patients	GTR: 66.7% (45 patients with intended GTR) CSF leak: 30%, multilayer reconstruction, nasoseptal flap, no routine LD. 2 Patients with leaks were managed by extracranial pericranial flaps. Brain herniation in 1 patient managed by VP shunt. Visual outcome: improved or restored in 86.7%. Complications: 58%	Tumors $<$4 cm, with cortical vascular cuff and no calcifications are the best candidates for EEA. Extension beyond mid orbit in coronal plane and to posterior table of the frontal sinus in the sagittal plane is an indication for a TCA. CSF leak rates are high, more with lobular tumors, and require innovative measures.
Graffeo[461]	2014	4	Systematic review of case series	30 Patients	GTR: 89.7% CSF leak: 21.9% Visual outcome: improved 78.9%, unchanged 21.9% Complications: 5.9%	EEA can be safe alternative to TCAs in selected cases. CSF leaks are higher in EEA compared to TCAs.

(*Continued*)

TABLE IV.F. Continued

Study	Year	LOE	Study design	Study group	Clinical findings	Conclusion
Khan[470]	2014	4	Case series and systematic review of case series	6 Patients (case series) 30 Patients (systematic review)	GTR: 66.7% to 73% CSF leak: 33% to 30%, multilayer reconstruction, fat graft, nasoseptal flap Visual outcome: improved 100% (2/2)	EEA can be safe alternative to TCAs in selected patients. Lateral extension, significant mass effect and calcifications are relative contraindications.
Komotar[471]	2012	4	Systematic review of case series	EEA group (19 patients) TCA group (474 patients)	GTR: 63.2% (EEA group) CSF leak: 31.6% (EEA group) Visual outcome: improved (20%), stable (80%) (EEA group)	EEA show less GTR rates and more CSF leak rates than TCAs. EEA can be safe and effective with proper patient selection and multilayer closure techniques.
Padhye[473]	2012	4	Case series	10 Patients	GTR: 90% CSF leak: 40%, multilayer reconstruction, fat graft, nasoseptal flap. Brain herniation managed by 2 endoscopic revision surgeries Complications: 10%	EEA can provide safe alternative, with significant advantages, to TCAs in carefully selected patients.
Zhang[474]	2012	4	Case series	6 Patients	GTR: 100% CSF leak: 16%, multilayer reconstruction, fat graft Visual outcome: improved 100% (2/2) Complications: 16%	EEA is safe and feasible for anterior skull-base meningiomas with intracranial and extracranial extension in one stage procedure.
de Divitiis[444]	2008	4	Case series	4 Patients	GTR: 100% CSF leak: 25%, multilayer reconstruction, nasoseptal flap	EEA is a minimally invasive approach. CSF leak needs further refinement of technique. More studies with longer follow-up are needed to ascertain benefits.

CSF = cerebrospinal fluid; DVT = deep vein thrombosis; EEA = endoscopic endonasal approach; GTR = gross total resection; LD = lumbar drainage; PE = pulmonary embolism; TCA = transcranial approach; VP = ventriculoperitoneal.

reported a GTR rate of 66.7% in 45 patients where GTR was the intended goal of surgery. Thus, although GTR rates have improved over the years, they remain less than GTR rates for transcranial approaches, which are reported to be in the range of 92.8% to 93.6%.[461,471]

Tumors with dural attachment extending beyond the mid-orbital line in the coronal plane and with anterior extension to the posterior table of frontal sinus have been cited as important anatomical limitations for GTR via EEA.[468,472] In the coronal plane anteriorly, the orbit represents the lateral limit of the approach while, posteriorly, the optic nerve and the clinoid segment of the internal carotid artery are stated to represent the lateral limits. The EEA for OGM also poses challenges in skull-base reconstruction, because the NSF, so commonly used in extended endoscopic procedures, may not able to cover the entire defect, with some authors reporting augmenting the reconstruction with extracranial pericranial flaps.[472] Other factors reported to pose a limitation for GTR in EEA include: (1) absence of a cortical cuff with neurovascular encasement; (2) significant brain edema; and (3) tumor size >4 cm.[454,470,472,475] These factors have been flagged as relative contraindications, the importance of which having often been left to the discretion of the surgeon. Thus, although some authors consider the absence of cortical cuff and vascular encasement as an absolute contraindication,[454] others have deemed them not as important in predicting outcomes when compared to proper patient selection and surgeon experience.[476] In the largest series of 50 presented by Koutourousiou et al.,[472] absence of cortical cuff, tumor calcifications, and tumor size >4 cm were shown to be statistically significant limitations for GTR.

IV.F.2. *Risk of postsurgical CSF leak after EEA for OGM*

CSF leak rates have often been described as the major limitation for EEA to the skull base. CSF leak rates in the

literature have been consistently high in EEA for OGM. In studies with the largest number of patients it has been reported to be between 26% and 30%.[462,472] The CSF leak rates reported following transcranial surgery are reported to be around 9.2%.[461] Although the introduction of the NSF has significantly decreased CSF leak rates following EEA,[477] this does not seem to be the case for OGM when compared to other pathologies. Reconstruction techniques adopted and reported by different centers are variable, all with the same principle of a multilayer reconstruction and the use of a vascularized flap.[234,478,479] Routine LD and rigid skull-base reconstruction (using fat, muscle, septal cartilage and/or titanium mesh, and Gasket seal closure) are highly debatable topics with no consensus as to the best technique. Likewise, the role of the different materials used has not been well investigated because the majority of reports in the literature report reconstruction outcomes following EEA for different skull-base pathologies collectively. The current literature continues to show that reconstruction following EEA for OGM (large cribriform defects) is much more challenging, with higher rates of failure compared to other skull-base pathologies. Another factor for which there is no consensus is the use of some form of nasal packing (Foley, Vaseline gauze, etc.) to support the relatively heavy reconstructive materials and their impact on CSF leak rates. A recent study reported by Fathalla et al.[480] reported that although both NSF and nasal packing individually did reduce CSF leak rates following EEA for skull-base pathologies, it is recommended that both are needed.

Another important and overlooked issue with reconstruction includes brain herniation into a large cribriform defect following EEA for OGM.[481] Although brain herniation following EEA to OGM is indeed rare, it has been reported in a number of series[473,475,481–483] and may have serious sequelae. Risk factors and management of this issue requires further investigation.

IV.F.3. *Visual outcomes after EEA*

Patients with OGM with posterior extension to the planum and tuberculum sella that involve the optic nerve and chiasm may present with visual symptoms including decreased VA, VF defects, or both. EEA has shown consistently better outcomes in the literature regarding visual symptoms when compared to transcranial approaches.[470,471] In the systematic review by Graffeo et al.,[461] visual symptoms were improved or stable in 78.9% and 21.1%, respectively, with no visual deterioration reported in the EEA group. In the transcranial group, visual symptoms were improved, stable, or deteriorated in 63.8%, 29.3%, and 2.7%, respectively.[470] Unlike transcranial approaches, EEA allows early decompression of the optic nerves, avoiding any manipulation of the already compromised optic apparatus either by compression or ischemic insult. Further decompression of the optic nerve can be achieved by drilling the medial opticocarotid recess and opening the inferomedial part of the optic canal. EEA also allows for superior visualization of the blood supply to the undersurface of the optic apparatus, namely branches from the superior hypophyseal artery, an important factor in determining the visual outcome.[445] A major limitation of the EEA is optic canal invasion superolateral or lateral to the optic nerve.

IV.F.4. *Olfaction preservation after resection of OGM*

The issue of olfaction preservation is often overlooked in the literature, and anosmia often regarded as minor morbidity, despite its significant impact on the QOL of patients.[484] None of the reviewed studies formally reported olfaction outcomes, with the exception of Banu et al.[468] reporting 100% anosmia and noting that anosmia is "inevitable" following EEA. Hayhurst et al.[454] reported olfaction preservation in "some patients" with a unilateral approach, but recommend advising the patients that anosmia is "almost certain" following EEA. This may be an important factor in deciding the best approach for OGM in patients with preserved olfaction. Jang et al.[484] investigated factors associated with olfaction preservation following transcranial approaches to OGM in a series of 40 patients. They reported olfaction preservation in 55% of patients. They concluded that in tumors <4 cm olfaction preservation is "high" via transcranial approaches. This raises the bar for EEA because smaller tumors (<4 cm) are the ones deemed as best candidates for EEA, and the ones most likely to achieve better outcomes.[472] This highlights the importance of investigation and formal reporting of preoperative and postoperative olfactory outcomes following EEA as well as transcranial approaches with validated olfactory measuring tools.

Recently there have been reports in the literature of more tailored minimally invasive EEA to OGM.[485–487] Youssef et al.[487] presented a case report following a cadaveric study where a unilateral transcribriform approach with septal transposition was able to preserve preoperative olfaction. The author suggested that for this approach to be successful, strictly unilateral cribriform involvement with functional contralateral olfactory epithelium is a prerequisite. Though these are preliminary reports, which need to be studied in larger series, these approaches have the potential of decreasing sinonasal morbidity following EEA and possibly preserving olfaction in small unilateral OGMs.

IV.F.5. *Role of multistage surgical resection in OGM*

Koutourousiou et al.[472] reported staged EEA in 18 patients in their 50-patient series. Staged procedures were reserved for large tumors with a mean maximum diameter of 52 mm. De Divitiis et al.[444] also reported a staged procedure in 1 out of 4 cases they presented in their study. Staged EEA procedures can be useful for large tumors with significant vertical extension in the sagittal plane. The aim of the first procedure is to debulk the tumor and ideally see

brain pulsations transmitted through the walls of the resection cavity. This allows the debulked residual tumor to descend, making it more accessible in a second-stage procedure. Staging of EEA procedures also allows for shortening the individual procedure time, which helps ease the burden on the surgical team and patient as EEA for OGM can have long operative times. The disadvantages of staged procedures are increased collective operative time, increase in hospital stay, and repeat general anesthetic, which makes patients more prone to complications.[462,472] The decision to proceed with a staged EEA procedure should be carefully discussed with the patient. Transcranial approaches are often sufficient to achieve complete resection of the tumor in a single stage, representing a significant advantage of this approach with the potential for lower cost.

IV.F.6. *Complications excluding CSF leak associated with OGM resection*

In the most recent systematic review presented by Shin et al.,[462] 8.8% of 80 patients in the EEA cohort had serious neurological deficits; cerebral hemorrhage (3 patients), brain abscess (3 patients), and 10 patients (12.5%) had potentially fatal systemic complications including deep venous thrombosis (DVT) and pulmonary embolism (PE). In the largest series of 50 patients reported by Koutourousiou et al.,[472] the overall complication rate was 58%: hydrocephalus 3 patients (6%), new onset seizures 2 patients (4%), meningitis 1 patient (2%), frontopolar artery injury 1 patient (2%), brain abscess (6%) DVT/PE 10 patients (20%), sinus infection 5 patients (10%), and respiratory failure 4 patients (8%). This high rate of complications, in this study, can be attributed to long operating times (average 9 hours) and the fact that 40% of patients had a staged EEA procedure.[462,472] There was positive correlation between DVT/PE with elderly patients and tumors >4 cm.

Although some studies suggest that the complication rates of EEA are higher than that of transcranial approaches, others suggest no significant difference between the 2 groups.[468,469] In the 2 systematic reviews where comparison of postoperative complications between the EEA cohort and transcranial cranial cohort was made, no significant difference was found between the 2 groups[461,471] excluding CSF leak.

Summary

GTR rates following EEA for OGM show heterogeneity in the literature. More recent reports show increased rates of GTR but still less than those reported for transcranial approaches. Limitations of GTR include: (1) extension beyond mid-orbit in the coronal plane; (2) extension to the posterior table of the frontal sinus in the sagittal plane; (3) absence of a cortical cuff with neurovascular encasement; (4) extensive calcification; and (5) tumor size >4 cm.[454,472,475,484]

Although CSF leak rates reported in the literature have improved with time, they remain high following EEA for OGM, ranging from 26% to 30%.[462,472] This warrants reconsideration of reconstructive techniques used. The routine use of lumbar drains, rigid skull-base reconstruction, and nasal packing are possible measures that may improve CSF leak rates and should be a focus for future research. The potential for brain herniation into large cribriform defects (though rare) also requires further investigation looking at possible risk factors and their management.

Visual outcomes are generally reported as being better following EEA for OGM than transcranial approaches. Although this may favor EEA, this usually applies to larger lesions with posterior extension to the optic apparatus and so this has to be weighed against size and significant lateral extension of the tumor.

Current evidence suggests that staged EEA procedures for OGM are associated with an increased incidence of complications. Therefore, larger tumors for which staged EEA are usually reserved are potentially better managed through a transcranial approach.

Case selection bias limits attempts to adequately compare transcranial and endoscopic approaches for skull-base lesions. Outcomes of EEA for OGM are largely dependent on proper patient selection. Relatively small tumors (<4 cm) showing no significant lateral extension, no extension to the posterior wall of the frontal sinus in the sagittal plane with a cortical vascular cuff and compromised olfaction are the best candidates for EEA for OGM. Additionally, patients with extension of the tumor into the nasal cavity and/or paranasal sinuses may also benefit from an EEA approach alone or in conjunction with a transcranial approach. Patients with intact olfaction preoperatively have a higher chance of olfaction preservation through a transcranial approach. Unilateral transcribriform approaches with septal transposition may have the potential for olfactory preservation in very select patients with strictly unilateral OGM with functioning contralateral epithelium. Skull-base reconstruction and CSF leak are still major concerns with EEA and need to be addressed with new innovative changes in the current techniques. Until many of these issues are resolved, transcranial approaches remain the procedure of choice for the majority of OGMs. The EEA may provide certain potential advantages in selected cases including those with significant paranasal sinus extension.

- Aggregate Grade of Evidence: D (Level 4: 11 studies)

IV.G. Petroclival meningioma

Petroclival meningiomas (PCMs) are rare tumors accounting for 3% to 10% of posterior fossa meningiomas and less than 2% of intracranial meningiomas.[488] However, given their deep and complicated location, PCMs have long represented a formidable challenge and the optimal strategy for approaching this type of lesion remains controversial.[488–492]

PCMs exhibit an indolent yet progressive growth rate, with small-to-medium sized lesions prone to growing at a faster speed. These tumors originate around the petroclival synchondrosis, and it is not uncommon for highly eloquent neighboring structures to become compromised,[493,494] warranting frequent follow-up and timely management as a strategy to limit morbidity.

The advantages of surgical management of meningiomas are well-documented in cases involving rapidly progressive lesions, the need for immediate decompression of critical structures, and the occasional need for pathological diagnosis.[495,496]

IV.G.1. *Surgery for PCM*

The theoretical goal of PCM surgery is to achieve Simpson Grade 1 resection (GTR) without the development of a new neurologic deficit or the exacerbation of a previous one. Historically, resection of petroclival meningiomas was associated with 50% mortality.[497] With improvements in skull-base surgery techniques, better technology and less aggressive resections, the mortality has decreased to 10%.[496] However, accomplishing Simpson Grade 1 GTR for PCM is extremely challenging and infrequent. Thus, the routine use of traditional grading systems is inaccurate and impractical to assess PCM resection.[498] Fortunately, various classification systems highlighting the importance of the degree of brainstem re-expansion have been proposed.[492] In light of these changes, the goal of surgery is now to achieve brainstem decompression regardless of the extent of resection.[492]

The focus of current practice is to achieve as extensive a resection as possible while limiting the development of neurological deficits.[488,491,492,496] This new paradigm applies in particular to lesions demonstrating preoperative radiologic invasion, with compromise of the brainstem and surrounding neurovascular structures or of sizes >4 cm in either plane. Additionally, tumor capsule devascularization was recently proposed as a technique to improve tumor control and thereby limit their growth.[499] With less aggressive surgery, most deficits are self-limited, with most patients showing signs of improvement 3 months after surgery, followed by a return to the preoperative baseline or continuous long-term improvements.[500,501]

For subtotal resections, regardless of the selected approach, studies have noticed that significantly favorable postoperative outcomes are associated with younger patients, primary tumors, and tumors <4 cm without evidence of posterior circulation encasement.[496,499] However, it should be noted that patients who were eligible for resection with "less invasive" techniques such as EEA tend to have slightly greater postoperative functional improvement and lower complication rates as opposed to patients whose tumors were resected through lateral or combined surgical routes.[496,501]

The benefits of adjuvant RT in the management of skull-base meningiomas have been reported. Consequently, many surgeons have shifted to combined-treatment paradigms with STR followed by adjuvant therapy of the remnant. Nonetheless, recent studies have demonstrated a strong inverse correlation between the extent of tumor resection, a risk of radiologic progression, and rate of volumetric growth.[502] The latter is especially true for cases where <70% of the preoperative tumor volume was resected, with disease progression rates ranging from 2.9% to 66.7%.[488,499,503] By contrast, GTR has been equated with lower recurrence rates. Despite this, a lack of correlation between GTR and higher survival rates has been observed.[502]

In general, residual tumors can be followed on periodic imaging until progression is evident.[504] However, the optimal schedule for such imaging has not yet been defined. Alternatively, adjuvant stereotactic radiosurgery (SRS) can be employed for small remnant control, with minimal morbidity. The latter is preferred particularly in patients with evidence of tumor progression detected on serial imaging or indicated by the new onset or worsening of symptoms.[491,492,495,499,505,506]

Prior to surgery, 2 imperative elements should be considered. First, the MRI appearance, with particular attention to T2-weighted imaging, is helpful for estimating the degree of brainstem invasion, which can appears on imaging as edema of the brainstem. The vast majority of petroclival meningiomas are not high grade and do not develop brainstem invasion. However, this finding has shown an increased risk of developing long-term morbidity after surgical intervention, particularly when the surgeon attempts complete resection.[504] Second, attention should be paid to the presence or absence of the arachnoid plane between the brainstem and the lesion. Absence of the arachnoid plane indicates pial invasion and is considered a strong predictor of a more difficult resection.[493] Similarly, this can result in brainstem edema on T2-weighted MRI. Pirayesh et al.[501] showed that the presence of arachnoid plane was associated with 80% of gross total resection cases, whereas in 88% of the cases with near total resection, the latter was absent.

Preoperative angiography helps assess the intracranial vascular involvement of the tumor. This is essential for determining if preoperative tumor embolization is necessary.[507] Although embolization is not an absolute requirement and is often not feasible, this technique may be useful to increase resectability, at times making the tumor consistency less fibrotic and decreasing intraoperative blood loss. Importantly, tumor size >4 cm was recently found to be a significant independent determinant of the degree of intraoperative bleeding.[508]

The risks and benefits of preoperative embolization have to be carefully considered. Although rare, direct vessel injury or ischemic injury from vascular occlusion can occur. Also, there may be significant risk of tumor swelling in the immediate postembolization period. In general, embolization is considered a safe procedure, with an average complication rate of 1% to 6%.[508–511]

Numerous surgical approaches are available to resect PCMs. However, during approach selection, in addition to patient and surgeon factors, tumor factors such as lesion extension and degree, and direction of neurovascular displacement are essential to consider. Given that PCMs originate around the petroclival fissure, lesion growth often causes CNs V, VII, VIII, IX, X, and XI to be displaced posterolaterally with the brainstem often displaced posteriorly and medially. By contrast, the direction to which CN VI is displaced is variable.

Although PCM can be approached via EEA, the approach is limited laterally precluding adequate resection of laterally extending tumor components, and for such cases, a combination with transcranial approaches is preferred. In appropriately selected cases, however, EEA alone is especially useful to resect lesions with a predominant midline extension because it allows for early devascularization of the clival and petroclival dura, significantly minimizing intraoperative blood loss. In addition, EEA provides a direct route to the petroclival region and completely avoids the need for cerebral, cerebellar, and CN retraction.

However, for lesions that originate further laterally in the paramedian skull base, lateral transcranial techniques (ie, retrosigmoid, presigmoid, far lateral, and anterior petrosectomy approaches) are favored. For lesions confined to the lateral skull base, exclusive use of lateral transcranial techniques is warranted. However, as mentioned earlier, for tumors with medial components, lateral techniques can be adequately combined with EEA. The latter applies particularly to cases where both approaches can complement each other such as when CN VI is displaced medially, or encasement of the posterior circulation is present.

To summarize, the primary aim of surgery should be to achieve total resection balancing any other risk with the main goal of avoiding neurological complications. For that reason, subtotal lesion resection is absolutely reasonable in patients showing signs of impending neurologic compromise or presenting with neurologic symptoms. This strategy should also be implemented in the management of asymptomatic patients with larger lesions. By contrast, in older patients with asymptomatic small-size to medium-size lesions or patients presenting a low baseline functional status, a more conservative strategy with periodic imaging surveillance or radiosurgery should be sought. In such cases, surgery should be reserved for patients presenting with the sudden onset of symptoms or with proved significant tumor growth.

The degree of tumor resection and the morbidity associated with the procedure are dependent on various factors, including but not limited to surgical experience. In addition, patient-specific factors such as comorbidities and preoperative functional status (in particular CN VII/VIII status), as well as tumor-specific factors, such as location, size, consistency, and critical neurovascular relationships, should all be considered.[488–492,496,499]

IV.G.2. *Cranial neuropathies*

The most common clinical presentation observed in up to 60% of the patients with PCM arises secondary to brainstem compression.[496] Although, in most cases, the pattern of CN involvement is variable, lower CN compression is seen in up to 50%, followed by CN VIII (48.6%), CN V (23.5-31.2%), and CN III, IV, and VI, with signs of extraocular movement deficits (28.1%).[496,499]

The most common complication of surgery involves CN deficits, occurring in up to 44% of the cases regardless of the selected approach, with extraocular muscle deficits being the most frequently encountered complication.[488,491,496,499,504] Depending on the series, an overall rate of new postoperative cranial neuropathies was observed in up to 53.1% of the cases, whereas 33.3% presented with worsening of preoperative diplopia,[496] with 72% of patients presenting during the immediate postoperative period, becoming permanent in 17%.[501]

With increased adoption of less aggressive approaches such as EEA and retrosigmoid, the most frequently affected nerves are now CN VI (18.7%), followed by the lower CNs (3.1.%).[496] By contrast, with lateral approaches, the most frequently affected nerve is CN VII,[488,490,491,501] being temporary in 33%, whereas a permanent dysfunction was observed in 11% of the cases.[501] On the other hand, lower CN deficits were observed in 22% of the cases during the immediate postoperative period, with 6% of the deficits remaining unresolved.[501] Overall, the severity of cranial neuropathies tends to be higher immediately after surgery, with most patients experiencing long-term improvements.[496]

Understanding the direction of CN displacement by the tumor is paramount to the surgeon for minimizing complications. PCMs have their primary base at the petroclival fissure, anterior to the internal auditory canal (IAC), displacing CNs V, IX, X, and XI and, in particular, CNs VII and VIII,[489,492] posteriorly, while displacing CN VI medially.[512] Neurophysiologic monitoring is the mainstay for safe and efficient resection of the lesion, and its use should be routine.[491,492,496,499]

Tumor size >4 cm in any plane,[496] as well as GTR, have been found to be significant risk factors for the development of cranial neuropathies, reaffirming the decision to shift toward less aggressive approaches with more conservative local resections.[491,492,496,499,503]

IV.G.3. *Hydrocephalus management*

The development of postoperative hydrocephalus in patients treated for PCM occurs in about 6% to 18% of the cases, the majority requiring ventriculoperitoneal shunt placement.[488,496,501] The diagnosis of hydrocephalus is usually made during the immediate postoperative period. Although not statistically significant, a greater incidence of postoperative hydrocephalus has been observed in patients who underwent resection via a lateral surgical approach as opposed to those in which a less aggressive approach (ie, EEA, retrosigmoid) was employed.[496,499]

Ventriculoperitoneal shunt placement should only be performed in patients with clinical hydrocephalus. In asymptomatic patients with ventriculomegaly detected on imaging, ventricular size monitoring is recommended, with shunt placement only after the new onset of symptoms or deterioration of clinical status occurs.

Summary of literature

The summary of the literature and conclusions is presented in Table IV.G with the respective LOE.

Conclusions

PCM is 1 of the most challenging tumors in neurosurgery. Its treatment is still controversial. There is no evidence in the literature supporting 1 approach vs the other when all "flavors" of petroclival meningiomas are grouped together. It can be managed via conservative observation, radiation, or surgery. Most would agree that the decision to treat should be based on location, growth rate, and if the patient is symptomatic. Every tumor is different, and the epicenter of the tumor seems to be a very important consideration in order to understand the pathway of tumor progression and dislocation/encasement of CNs and vessels. The position of the CNs will dictate the approach to these tumors allowing the least manipulation of neurovascular structures as possible. The surgery has been and can be approached via multiple standard transcranial approaches including anterior transpetrosal, posterior transpetrosal, combined approach, complete petrosectomy, and retrosigmoid approach with known outcomes. ESBS may also serve as an option when the goal of surgery is central debulking to relieve brainstem decompression. This may also be used in preparation for other adjuvant treatment options such as radiosurgery. However, the role of the EEA for PCM is controversial and needs to be further clarified.

- Aggregate Grade of Evidence: D (Level 4: 1 study)

V. Benign lesions

V.A. Juvenile nasopharyngeal angiofibroma

Juvenile angiofibroma (JNA) was first described in the 4th century BC by Hippocrates.[513] With a general incidence of 1:150,000, accounting for 0.5% of all head and neck tumors, JNAs are rare, benign, and highly vascular.[514] JNAs most commonly affect males, 9 to 19 years old, who present with nasal obstruction (76-90%) and epistaxis (45-72%).[515] Arising from the lateral basisphenoid, extension occurs through existing foramina and fissures including: (1) the sphenopalatine foramen into the nasopharynx and paranasal sinus, (2) the pterygomaxillary fissure into the infratemporal fossa, and (3) the infraorbital fissure into the orbit and middle fossa. JNAs have the potential for skull base erosion and intracranial extension, as seen in 10% to 20% of cases.[516]

Although JNA are classified as benign tumors, some consider them to be vascular malformations.[517] This theory is supported by the identification of laminin α-2 in the vessel walls, a marker of early developmental angiogenesis.[518] Clinically, they usually originate from the posterior nasal cavity, near the basisphenoid and the superior margin of the sphenopalatine foramen. Extensive vascularity derives from vascular contributions from both the internal maxillary and the internal carotid arteries.[519] Hormonal factors, although controversial, have been considered to explain the occurrence of JNAs in young men.[520] Tumors express various levels of estrogen, progesterone, and androgen receptors. Exogenous testosterone was found to induce tumor growth, yet correlation with tumor growth, proliferative index, and hormonal receptors has not been confirmed.[520]

Both CT and MRI are used to assess JNAs. On CT, JNAs appear as a lobulated, heterogeneous soft tissue mass. There is intense enhancement after iodine contrast administration. The sphenopalatine foramen will mostly commonly be widened or eroded, but all skull-base fissures and foramina can be involved. Anterior bowing of the posterior wall of the maxillary sinus, also known as the Holman-Miller sign, was originally described for plain films but can be seen on 80% of CT scans.

On MRI, JNAs appear isointense to hyperintense on T1-weighted and T2-weighted sequences. Flow voids related to small, high-flow vessels supplying the tumor can be seen. There is intense enhancement following administration of gadolinium contrast.[521]

V.A.1. *Staging systems for JNA*

Many staging systems have been proposed for JNA. A good staging system should be universal, have prognostic value, and therapeutic correlation. Khoueir et al.[522] performed a systematic review of JNA staging, identifying 92 studies. Thirty-two percent of the cases did not specify a staging system. The most common staging systems used were Radkowski (31%), Fisch (14%), Andrews (12%), Chandler (4%), Sessions (3%) and Bremer (1%). The authors concluded that, as the existing staging systems were established prior to the advent of endoscopic approaches, a new staging system was needed. In 2010, Snyderman et al.[523] developed an updated staging system (UPMC staging system) that included prognostic factors for endoscopic techniques. Residual vascularization following embolization is 1 of the key components in addition to skull-base erosion and intracranial extension. Compared to previous staging systems, the UPMC staging system demonstrated stronger correlation with intraoperative blood loss and the need for multiple surgeries (staged, residual, or recurrent tumor). For the purpose of this review, the UPMC staging system will be used. This staging system considers orbital and cranial base involvement (stage III to V) as part of advanced-stage JNA. Table V.A.1 outlines the major characteristics of the available staging systems.

TABLE IV.G. PCM

Study	Year	LOE	Study design	Study group	Clinical endpoint	Conclusions
Pirayesh[501]	2016	4	Retrospective review	Patients with PCM treated surgically with various skull-base techniques.	1. Preoperative radiological features (MRI) 2. EOR 3. Postoperative clinical outcome	1. Preoperative radiological feature analysis is the mainstay for predicting EOR and postoperative clinical outcome. 2. Brainstem edema statistically correlates with long-term postoperative deterioration. 3. Irregular tumor margins and absence of an arachnoidal plane (especially if edema is present) are predictors of surgical radicality but have no influence on postoperative clinical outcome.
Nanda[488]	2011	4	Retrospective review	Patients with PCM treated surgically with various skull base techniques.	1. Presenting symptoms 2. EOR 3. Postoperative neurological outcome (GOS) 4. Postoperative complications 5. Tumor recurrence rate	1. Maximal tumor removal represents the best chance for cure and should be the primary goal of surgery while preserving neurological function. 2. GTR was achieved in 28%. 3. SRS is the modality of choice for residual or recurrent disease.
Xu[491]	2013	4	Retrospective review	Patients with large (ie, >3 cm) PCM treated surgically with various skull-base techniques.	Postoperative clinical outcomes	1. GTR or NTR of large petroclival meningiomas should be the primary goal of surgical treatment. 2. Tumor location in relation to the IAC, involvement of one or both cranial fossae, and preoperative hearing functional status are critical considerations in determining the optimal strategy. 3. Retrosigmoid craniotomy is a workhorse approach for the management of most PCM cases regardless of tumor size. 4. Treatment of tumors medial to IAC and spanning MCF and PCF is best achieved with combined transpetrosal approaches.
Hunter[499]	2018	4	Retrospective review	Patients with PCM treated surgically with: (1) STR (EOR >70%) or (2) PR (EOR <70%) achieved with various skull-base techniques	1. Radiological tumor progression. 2. Rate of tumor volumetric growth.	EOR is strongly associated with tumor progression and rate of volumetric growth.
Koutourousiou[496]	2017	4	Retrospective review	Patients with PCM treated surgically with: 1) lateral (retrosigmoid or far-lateral); 2) anterior midline (EEA); or 3) combined approaches.	1. Postoperative clinical outcome 2. Postoperative functional status (KPS).	1. EEA and RSA are effective alternatives to transpetrosal approaches for debulking petroclival meningiomas associated with a significantly greater potential for improved KPS, significantly earlier clinical improvement, and limited major surgical complications. 2. Opposite to EEA and RSA, combination surgery did not offer significant benefits.

EEA = endoscopic endonasal approach; EOR = extent of resection; GOS = Glasgow Outcome Scale; GTR = gross total resection; IAC = internal auditory canal; KPS = Karnofsky performance scale; LOE = level of evidence; MCF = middle cranial fossa; MRI = magnetic resonance imaging; NTR = near total resection; PCF = posterior cranial fossa; PCM = petroclival meningioma; PR = partial resection; RSA = retrosigmoid suboccipital approach; SRS = stereotactic radiosurgery; STR = subtotal resection.

TABLE V.A.1. Current staging systems for juvenile angiofibroma

Source	Year	Stage I	Stage II	Stage III	Stage IV	Stage V
Snyderman[523]	2010	Nasal cavity, medial PPF	≥1 Sinus, lateral PPF; no residual vascularity	Skull base erosion, orbit, ITF; no residual vascularity	Skull base erosion, orbit, ITF; residual vascularity	Intracranial extension, residual vascularity; M, medial extension; L, lateral extension
Carrillo[524]	2008	(A) Medial, limited to NP, nasal fossae, maxillary antrum and anterior ethmoid	(B) invasion to PMF or anterior ITF with tumor <6 cm	(C) extension to PMF or anterior ITF with tumor >6 cm	(D) extension to posterior ITF or root of skull base	(E) extensive skull base and intracranial invasion
Onerci[525]	2006	Nose, NP, ethmoid and sphenoid sinuses or minimal extension into PMF	Maxillary sinus, full occupation of PMF, extension to anterior cranial fossa, limited extension into ITF	Deep extension into cancellous bone at pterygoid base or body and GW sphenoid, significant lateral extension into ITF or pterygoid plates, orbit, cavernous sinus obliteration	Intracranial extension between pituitary gland and ICA, tumor localization lateral to ICA, middle fossa extension, and extensive intracranial extension	NA
Radkowski[526]	1996	IA: limited to nose or NP IB: as in stage Ia with extension into 1 sinus	IIa: Minimal extension into medial PMF IIb: Full occupation of PMF, displacing posterior wall of maxilla forward, orbit erosion IIc: ITF, cheek, posterior to pterygoid plates	IIIa: Minimal intracranial extension IIIb: Extensive intracranial extension ± cavernous sinus	NA	NA
Andrews[527]	1989	Limited to NP; minimal bone destruction or limited to SPF	Invading PPF or maxillary, ethmoid or sphenoid sinus with bone destruction	Invading ITF or orbit: IIIa: No intracranial IIIb: Extradural, parasellar	Intracranial, intradural: IVa: With IVb: Without cavernous sinus, pituitary or optic chiasm infiltration	NA
Antonelli[528]	1987	Limited to NP or nasal fossa	Extending into sphenoid sinus or PMF	Extension to ≥1 of: maxillary sinus, ethmoid, orbit, ITF, cheek, palate	Intracranial extension	NA
Bremer[529]	1986	Ia: Limited to posterior nares or NP Ib: Extension to ≥ 1 sinus	IIa: Minimal lateral extension through the sphenopalatine foramen in medial PPF IIb: Full occupation of PPF displacing posterior wall of antrum forward, superior extension eroding orbital bone IIc: Extension through PMF into cheek and ITF.	III: Intracranial extension	NA	NA
Chandler[530]	1984	Limited to NP	Extension into nasal cavity or sphenoid sinus	Tumor into antrum, ethmoid sinus, PMF, ITF, orbit ± cheek	Intracranial extension	NA
Fisch[531]	1983	Limited to NP and nasal cavity without bone destruction	Invading the PMF and ≥1 sinus with bone destruction	Invading ITF, orbit, parasellar region remaining lateral to the cavernous sinus	Massive invasion of the cavernous sinus, the optic chiasmal region, or pituitary fossa	NA
Sessions[532]	1981	Stage Ia: limited to nose and NP Stage Ib: extension into ≥1 sinus	IIa: Minimal extension into PMF IIb: Full occupation of PMF ± orbit erosion IIIc: ITF ± cheek extension	Intracranial extension	NA	NA

GW = greater wing; ICA = internal carotid artery; ITF = infratemporal fossa; NA = not applicable; NP = nasopharynx; PMF = pterygomaxillary fossa; PPF = pterygopalatine fossa; SPF = sphenopalatine foramen.

V.A.2. *Preoperative embolization*

Embolization is typically performed 24 to 48 hours before surgery. The vascular supply of JNA is most commonly from the distal internal maxillary and vidian arteries. Involvement of the basisphenoid and pterygoid canal, which contains the vidian artery, has been associated with recurrence.[533] Larger tumors, depending on their extension, can receive additional blood supply from the ascending pharyngeal, accessory meningeal, deep temporal, facial, and middle meningeal arteries.[534,535] With orbital and intracranial extension, vascularization from the ophthalmic artery, inferolateral trunk, and meningohypophyseal trunk of the ICA can be seen.

Although the routine use of preoperative embolization has been contested in early-stage tumors,[536–539] most authors consider it an important component of management. The main benefit of preoperative embolization when using an endoscopic approach is to improve visualization and reduce blood loss, especially in large tumors that may require tumor transection. Furthermore, postembolization angiography may reveal residual vascularity and optimize planning of tumor resection. In their meta-analysis of 345 cases (individual patient data), Boghani et al.[515] found that preoperative embolization reduced the average blood loss in endoscopic cases in a statistically significant fashion from 828.3 to 406.7 mL. Bilateral external carotid artery supply, which can be seen in 54% of tumors, can be safely embolized. Although ICA branches can be embolized, the risk of a complication (stroke, visual loss, facial paralysis, carotid dissection) is high and its use is therefore not recommended.[538,540–542] The presence of vascularity from the ICA has been associated with increased operative blood loss, multiple procedures, residual disease, and recurrence.[523,535,543] Therefore, preoperative angiography of both external and internal carotid vessels will help tumor staging and treatment planning. Preoperative balloon occlusion testing of the ICA can be considered when the tumor extensively invades the cavernous sinus or encases the ICA, especially in postradiation cases where the risk of vessel injury is higher. In patients with adequate collateral circulation and favorable balloon occlusion test results, the artery can be occluded preoperatively or intraoperatively if an injury occurs.

V.A.3. *Endoscopic surgery for early-stage JNA*

Case reports and case series using endoscopic only approaches for early stage tumors were first published in the 1990s. Endoscopic techniques became more popular with the advent of technical refinements such as preoperative embolization, development of hemostatic materials, and 2-surgeon–4-hand technique dissection.[544] This led to reduced blood loss and improved visualization of deep anatomical landmarks such as the clivus, foramen lacerum, pterygoid plates, and infratemporal fossa.[545] The objective of surgery for these tumors is complete tumor resection, preservation of major neurovascular structures, and minimizing morbidity such as blood loss. Early-stage disease includes tumors involving the nasal and sinus cavities without orbital or skull-base involvement (UPMC stage I and II).

In their systematic review, Boghani et al.[515] analyzed individual patient data from 345 cases (either endoscopic only, endoscopic-assisted, or open procedures). Of these, operative blood loss was available for 138 cases. Although highly susceptible to selection bias, they found that the average blood loss in the endoscopic surgery group was statistically decreased compared to open surgery (544 vs 1579.5 mL, respectively). Because of the small intravascular blood volume in younger pediatric patients, management of blood loss is imperative. The reduced blood loss identified by Boghani et al.[515] potentially reflects the avoidance of osteotomies and improved plane of dissection afforded by endoscopic techniques.

The average recurrence rate for endoscopic only procedures compared to open procedures was 10.8% (range, 0.0% to 23.1%) and 14.5% (range, 0.0% to 50.0%), respectively. Of these patients, staging was available for 105 patients using the Radkowski or Sessions systems. When controlled for tumor stage, there was no difference in recurrence rates between endoscopic (60 cases) and open procedure (44 cases). Therefore, exclusively endoscopic procedures are at least as effective as open procedures in terms of recurrence rates for early stage tumors (UPMC stages I and II).

Khoueir et al.[522] did a systematic review of exclusively endoscopic treatment, identifying 62 studies with reported complications (699 patients). The estimated complication rate was 9.3% (95% confidence interval [CI], 7.2% to 11.5%). Complications included synechiae (n = 19), neurologic disorders (most commonly infraorbital nerve hypoesthesia) (n = 12), bleeding (n = 9), ocular disorders (n = 5), facial edema/atrophic rhinitis (n = 5), Eustachian tube dysfunction (n = 2), and 1 case of CSF leak. The authors concluded that the nature and rate of complications from endoscopic approaches is favorable compared to open approaches.

No RCTs were identified comparing endoscopic to open procedures. All data included in published meta-analyses and systematic reviews[515,522] are from heterogeneous case series and case reports. Nonetheless, the available data suggests that purely endoscopic surgery for early stage JNA offers similar or improved recurrence rates with reduced blood loss and morbidity, compared to open approaches. A systematic review of the available published outcomes is listed in Table V.A.2.

V.A.4. *Endoscopic surgery for advanced-stage JNA*

Advanced-stage JNAs are challenging because of involvement of neural and vascular structures. Open approaches have traditionally been the mainstay of treatment. Midfacial degloving gives access to both nasal cavities;

TABLE V.A.2. Evidence for EEA in early stage juvenile angiofibroma (Radkowski staging unless specified)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Khoueir[522]	2014	3a	Systematic review	821 Cases, all endoscopic	Blood loss, complication rate, residual and recurrence rates	Blood loss 564 mL, complication rate 9.3%, residual 7.7%, recurrence 10%
Boghani[515]	2013	3a	Systematic review	Individual patient data: 158 endoscopic, 15 combined, 172 open	Average blood loss, recurrence rate.	Blood loss: Endoscopic 544.0 mL (20–2000 mL) vs open 1579.5 (350–10,000 mL). When controlled for tumor stage, no difference in recurrence between endoscopic, combined or open.
Overdevest[535]	2018	4	Case series	Endoscopic: 2 UPMC stage III, 6 stage IV, 2 stage V Combined: 1 stage II, 1 stage IV Open: 3 stage II, 2 stage III, 5 stage IV, 2 stage Vm	Blood loss	Endoscopic 1690 mL Combined 412 mL Open 1380 mL Bilateral arterial supply is predictive of increased blood loss ($p < 0.1$).
McLaughlin[546]	2016	4	Case series	16 Traditional endoscopic, 13 Radiofrequency-assisted endoscopic 12 UPMC stage II, 6 stage III, 3 Stage IV, 8 stage V.	Blood loss, duration of surgery, recurrence rate	Blood loss: traditional endoscopic 375 mL vs FRA 500 mL ($p = 0.27$) Duration: traditional endoscopic 6.3 hours vs RFA 7.8 hours ($p = 0.29$) Recurrence: traditional endoscopic 25% vs FRA 23% ($p = 0.99$) Combined recurrence 7/29.
Janakiram[541]	2016	4	Case series	15 Endoscopic cases. No individual stage	Blood loss, length of hospitalization, complication, residual and recurrence rate	Blood loss 67.2 mL, length of hospitalization 3.66 days, 2/15 residual, 1/15 recurrence.
Garofalo[547]	2015	4	Case series	Endoscopic: 1 Onerci stage I, 3 stage II, 1 stage III Combined: 2 stage III Open: 2 stage II, 4 stage III	Transfusion rate Length of hospitalization Recurrence rate	Transfusion: endoscopic 0, combined 0, open 2 Hospitalization: endoscopic 8 days vs open + combined 14 ($p = 0.02$) Recurrence: endoscopic 1, combined 0, open 0
Chan[548]	2014	4	Case series	Endoscopic only (9), combined (17), open procedures (11) 3 stage IA, 3 stage IB, 14 stage IIA, 3 stage IIB, 5 stage IIC, 5 stage IIIA, 4 stage IIIB.	Blood loss, complication rates, recurrence rates	2660 mL additional blood loss with open vs endoscopic only. With every 100-mL increase in the EBL, the odds of complication increased by 5% (95% CI, 0%–10%).
Huang[549]	2014	4	Case series	Endoscopic: 4 stage IA, 5 stage IB, 6 stage IIA, 11 stage IIB, 24 stage IIC, 6 stage IIIA, 10 stage IIIB Open: 10 stage IA, 10 stage IB, 22 stage IIA, 6 stage IIB, 30 stage IIC, 10 stage IIIA, 8 stage IIIB	Blood loss, complication, recurrence rate	Blood loss: endoscopic 800 mL vs 1100 open ($p = 0.017$) Complication: endoscopic 1 vs open 10 Recurrence: endoscopic 17/60 (28%) vs open 32/96 (33%)
Ballah[550]	2013	4	Case series	Endoscopic: 1 UPMC stage I, 1 stage II, 3 stage IV, 2 stage V Combined: 2 stage I, 4 stage II, 1 stage IV, 2 stage V Open: 1 stage V	Blood loss Complication Recurrence rate	Blood loss: 450 mL (50-2000 mL), endoscopic 644 mL, combined 637 mL, open 1500 Complication: endoscopic 0/7, combined 1/8, open 1/1 Recurrence 2/17

(*Continued*)

TABLE V.A.2. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
El Sharkawy[536]	2013	4	Case series	All endoscopic 6 stage Ia, 7 stage Ib, 5 stage IIA No angioembolization	Blood loss, complication, residual, and recurrence rates	342.3 mL blood loss. 2 Orbital hematomas, 1 epistaxis. 2/18 residual, 0% recurrence. The endonasal endoscopic approach is a safe and effective technique for stage IA&B and IIA without preoperative angiographic embolization.
Cloutier[545]	2012	4	Case series	Group 1 2000–2005 (45.1% endoscopic); group 2 2005–2010 (82.9% endoscopic) 2 Stage IB, 3 stage IIA, 8 stage IIB, 8 stage IIC, 34 stage IIIA, 17 stage IIIB; 48 endoscopic, 24 open approach	Average blood loss, duration of hospitalization, complication rate, recurrence rate	No difference in complication Hospitalization: endoscopic 6.76 days vs open 9.74 days Residual: group 1 (n = 10), group 2 (n = 3) ($p = 0.015$) Recurrence: group 1 (n = 3), group 2 (n = 3) ($p = 0.94$) Endoscopic approach associated with reduced blood loss and duration of hospitalization. Similar complication and recurrence rate
Lopez[551]	2012	4	Case series	11 Endoscopic (all Andrews-Fisch stage I and II) 37 Open (stage II to IVb)	Blood loss, residual, and recurrence rate	Blood loss: endoscopic 895 mL vs open 2833 mL Residual: endoscopic 3/11 vs open 10/37 Recurrence: endoscopic 0/11 vs open 2/37. Recommend endoscopic resection for early stage tumors (stages I to IIIA).
Fyrmpas[552]	2011	4	Case series	10 Endoscopic. 1 Stage Ia, 2 stage 1B, 1 stage IIA, 2 stage IIb, 2 stage IIc, 2 stage IIIA	Blood loss, length of hospitalization, and recurrence rates	Blood loss 444 mL. Hospitalization 5 days. 1 Recurrence in stage IIb underwent repeat excision.
El Morsy[553]	2011	4	Case series	15 Endoscopic cases, all stage IIc	Blood loss, residual, and recurrence rate	Blood loss 350 mL, Residual 0%, Recurrence 3/15. Endoscopic 2-surgeon technique is an excellent approach for managing JNA extending to the pterygopalatine and infratemporal fossae
Baser[554]	2011	4	Case series	12 Endoscopic. 7 Fisch stage II, 4 stage IIIA, 1 stage IIIb	Complication and recurrence rate	0 complication, 0 recurrence. Endoscopic excision is a very effective method to resect JNA even for extensive tumors.
Ye[555]	2011	4	Case series	23 Endoscopic (all Fisch stage I) 11 Coblation 12 Traditional	Blood loss, duration of surgery, recurrence rate	Blood loss: coblation 121 mL vs traditional 420 mL ($p < 0.001$); Duration: coblation 87 vs traditional 136 min ($p < 0.001$). 0 recurrence.
Hyun[556]	2011	4	Case series	4 Endoscopic: 3 stage IIA, 1 stage IIc 16 Open	Complication and recurrence rate	Recurrence: endoscopic 1/4, open 6/16 Complication: endoscopic 0, open 4/16 Endoscopic surgery is the treatment of choice for stage IIA and IIb tumors

(*Continued*)

TABLE V.A.2. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Wang[557]	2011	4	Case series	All stage I or II 11 Endoscopic, 13 Open (all transpalatine)	Blood loss, duration of surgery, complication, recurrence rate.	Blood loss: endoscopic 375 vs open 635 mL Duration of surgery: endoscopic 115 vs open 141 minutes Complication: Endoscopic 1/11 vs open 6/13 No significant difference in recurrence rate
Nicolai[543]	2010	4	Case series	47 Endoscopic: 5 Andrews stage I, 24 stage II, 14 stage IIIA, 3 stage IIIb	Blood loss, complication, duration of hospitalization, residual and recurrence rate	Blood loss 580 mL, 0 complication, duration of hospitalization 5 days. 8.6% overall residual disease (3 observed and stable, 1 re-operated). 1/29 recurrence in early stage
Mohammadi[539]	2010	4	Case series	23 Endoscopic: 2 stage IA, 4 stage IB, 2 stage IIA, 3 stage IIB, 4 stage IIC, 4 stage IIIA, 4 stage IIIB	Blood loss Treatment cost Recurrence rate	Blood loss: embolized group 1260 $\pm$ 1060 mL; non-embolized group 1625 $\pm$ 1140 mL ($p = 0.472$) Treatment cost: embolized \$1700 $\pm$ 380 vs non-embolized \$970 $\pm$ 340 Recurrence: 2/23
Bleier[558]	2009	4	Case series	10 Endoscopic, 8 open. 1 Andrews stage I, 8 stage 2, 5 stage 3a, 1 stage Iva, 3 stage 4b	Blood loss, length of hospitalization	Blood loss: endoscopic 506 mL vs open 934 mL Hospitalization: endoscopic 3 vs open 4 days No recurrence in endoscopic group
Midilli[559]	2009	4	Case series	12 Endoscopic: 2 stage IB, 6 stage IIA, 1 stage IIB, 2 stage IIC, 1 stage IIIA 30 Open approach; 6 stage IB, 6 stage IIA, 5 stage IIB, 8 stage IIC, 4 stage IIIA, 1 stage IIIB	Blood loss, duration of hospitalization, recurrence rate	Reduced bleeding in endoscopic group (no values) Hospitalization: endoscopic 4–5 days vs open 5–9 Recurrence: endoscopic 0 vs open 7/30
Ardehali[560]	2010	4	Case series	45 Endoscopic: 5 stage IA, 9 stage IB, 4 stage IIA, 2 stage IIB, 21 stage IIC, 3 stage IIIA, 1 stage IIIb	Blood loss, duration of hospitalization, recurrence rate	Blood loss: 1336.2 mL Hospitalization: 3.1 days Recurrence rate: 19.1%
Hackman[561]	2009	4	Case series	31 cases: 15 Endoscopic, 12 Combined 4 Open (no individual stage)	Blood loss, operative time Recurrence rate	Blood loss: endoscopic 280 mL, combined 1850 mL, open 2500 mL Operative time: endoscopic 128 minutes, combined 268 minutes, open 410 minutes Recurrence: endoscopic 1, combined 3, open 1
Yiotakis[562]	2008	4	Case series	9 Endoscopic, 11 Open. 3 stage Ia, 3 stage 1B, 3 stage IIA, 8 stage IIb, 3 stage IIc	Blood loss, duration of hospitalization, complication rate, recurrence	Blood loss: endoscopic 248.8 mL, midface degloving 880 mL, transpalatal 925 mL. Hospitalization: endoscopic 2 days, midfacial degloving 4.4 days, transpalatal 6.8 days. Complications transpalatal group 2, others 0 Recurrences: transpalatal group 2, other 0

(*Continued*)

TABLE V.A.2. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Gupta[563]	2008	4	Case series	28 Endoscopic. 6 stage I, 14 stage IIA, 6 stage IIb, 2 stage IIc	Blood loss, residual and recurrence rate	Blood loss: 154 mL for primary surgery, 390 mL for revision surgery. 1 residual (IIc), no recurrence.
Fonseca[537]	2008	4	Case series	Endoscopic only (7): 5 Fisch stage I, 2 stage II Combined (3): 1 stage II, 2 stage III Open (5): 4 stage II, 1 stage III	Units of red blood cells, complication, and recurrence rate	Units RBC: endoscopic 2 u/pp combined 1 u/pp, open 0.6 u/pp Complication: endoscopic 1, combined 0, open 2 Recurrence: endoscopic 1 combined 1, open 1
Eloy[564]	2007	4	Case series	6 Endoscopic: 1 stage Ia, 1 stage 1B and 4 stage IIb	Blood loss, recurrence rate	Blood loss: 575 mL. 2 recurrences: 1 re-operated, 1 observed.
Andrade[565]	2007	4	Case series	All endoscopic: 8 Andrews stage I, 4 stage II	Blood loss, duration of hospitalization, residual and recurrence rate	Blood loss: 200 mL. Duration of hospitalization: 33 hours stage I, 54 hours stage II. No residual no recurrence.
Tosun[566]	2006	4	Case series	Endoscopic (9):2 stage IA, 2 stage IB, 3 stage IIA, 2 stage IIIA open approach (15): 9 stage IA, 2 stage IIA, 1stage IIB, 3 stage IIIA	Complication and recurrence rate	No complication, no recurrence in endoscopic group. 1 Recurrence in open group (stage IIA), 1 complication in open group (stage IIA)
Sciarretta[567]	2006	4	Case series	All endoscopic: 1 stage Ia, 4 stage IIA, 1 stage IIb, 2 stage IIc, 1 stage IIIA.	Blood loss, recurrence rate	Blood loss: 300 mL Recurrence 1/9
Borghei[538]	2006	4	Case series	23 Endoscopic: 5 stage IA, 9 stage IB, 4 stage IIA, 5 stage IIB	Blood loss, complication, recurrence rate	3 Postoperative synechiae. 1 recurrence at 19 months
Chen[568]	2006	4	Case series	8 Endoscopic. 1 stage Ia, 2 stage IIA, 1 stage IIb, 1 stage IIc, 3 stage IIIA	Blood loss, residual and recurrence rates	1 Major bleed (IIIA) due to cavernous dissection. 1 Recurrence (IIA) 28 months postoperation.
Hofmann[569]	2005	4	Case series	21 Endoscopic. (Andrews/Fisch) 1 stage 1, 15 stage II, 5 stage IIIA	Blood loss, residual and recurrence rates	Blood loss 541 mL. 3 Recurrences: 2 resected, 1 gamma knife.
Pryor[570]	2005	4	Case series	6 Endoscopic (stages not available) 59 Open	Blood loss, length of hospitalization, complication and recurrence rates	Blood loss: endoscopic 225 mL vs open 1250 mL Hospitalization: endoscopic 2 days vs open 5 days Recurrence: endoscopic 0% vs open 24%
Mann[571]	2004	4	Case series	15 Endoscopic 15 Open (no individual stage)	Recurrence rates	1/15 Recurrence in the endoscopic group. 5/15 in open group.
Naraghi[572]	2003	4	Case series	All endoscopic: 2 Bremer stage Ia, 2 stage Ib, 3 stage IIA, 5 stage IIB	Length of hospitalization, Complication rate, recurrence rate	Hospitalization 3.5 days No complication. 2 Recurrences (18%)
Wormald[573]	2003	4	Case series	All endoscopic: 1 stage I and 2 stage IIA, 3 stage IIB, 1 stage IIC	Recurrence rate	Recurrence: 0%

(*Continued*)

TABLE V.A.2. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Onerci[574]	2003	4	Case series	All endoscopic: 1 stage IB, 2 stage IIA, 4 stage IIB, 1 stage IIC, 4 stage IIIA	Blood loss, residual and recurrence rate	Early stage blood loss: 1000 mL. Advanced stage: 1500 mL. 2 Residual diseases observed and stable (stage IIIA) Endoscopic resection of JNA in this group of patients must be the treatment of choice
Roger[575]	2002	4	Case series	All endoscopic 4 Stage I 7 Stage II 9 Stage IIIA	Blood loss, duration of surgery, complication, residual and recurrence rate	Blood loss: 350 mL, duration 135 minutes, 2 infraorbital nerve anesthesia. 2 residual disease (IIC and IIIA) observed and stable. No recurrence.
Hazarika[576]	2002	4	Case series	7 Endoscopic only, 2 combined. All stage II or less	Recurrence rate	Recurrence: endoscopic 0, combined 1/2
Scholtz[577]	2001	4	Case series	7 Endoscopic (Stage IIB or less), 7 open	Complication and recurrence	0 Complication, 2/14 recurrence
Jorissen[578]	2000	4	Case series	All endoscopic (13): 2 stage Ia, 2 stage Ib, 2 stage IIA, 2 stage IIB, 4 stage IIC, 1 stage IIIA	Recurrence rate	Recurrences: endoscopic 1/7 (stage IIA), open 1/7 (stage IIC)
Schick[579]	1999	4	Case series	5 Fisch type II	Recurrence and residual rates	0 Residual, 0 recurrence

EBL = estimated blood loss; JNA = juvenile angiofibroma; LOE = level of evidence; pp = per patient; RBC = red blood cells; RFA = radiofrequency ablation-assisted; u = unit.

maxillary, ethmoid, and sphenoid sinuses; pterygopalatine fossa; nasopharynx; and infratemporal fossa. Intracranial extension that remains medial or inferomedial to the cavernous sinus can be accessed with anterior craniofacial approaches.[580,581] Lateral approaches allow access to tumor extension in the middle cranial floor, carotid canal, and the lateral aspect of the cavernous sinus. However, morbidity and complication rates of 6% to 80% have been reported with these classical approaches.[548,581]

The EEA is now increasingly being used for selected advanced tumors. Endoscopic approaches allow access to deep neurovascular structures and avoid facial incisions and osteotomies. Hemostatic control becomes critical to maintain visualization and optimize outcome.[548] Improvements in instrumentation and surgical techniques have allowed better visualization and thus, better tumor dissection. Preoperative angioembolization and 4-hand–2-surgeon dissection technique are now being increasingly used. Radiofrequency coblation, potassium titanyl phosphate (KTP), Nd:YAG laser, and ultrasonic cautery are other instrumental adjuncts that have been described.[577,582] When approaching large JNAs endoscopically, multiple surgical corridors can be employed: the traditional endonasal endoscopic approach with posterior septectomy, complete posterior ethmoidectomies, and sphenoidotomies can be augmented with unilateral or bilateral anterior maxillotomies (Caldwell-Luc). Medial maxillectomies can be included to improve access to the masticator space and infratemporal fossa, provide additional room for instrumentation, and allow early identification of the internal maxillary artery and the second division of trigeminal nerve (V2). The tumor can be dissected in vascular segments, corresponding to major feeding arteries. Each vascular segment is approached sequentially, leaving devascularized intracranial extensions for last. This organized approach reduces blood loss and allows optimal staging of the surgery, if needed.[534]

There is an increasing body of literature supporting endoscopic only techniques in advanced JNA. Langdon et al. performed a multi-institutional review, identifying 74 patients with Radkowski stage IIIA or IIIB JNAs.[583] Seventy-one patients underwent preoperative angiography and embolization with 19% having an ICA contribution. The mean operative blood loss was 1279.7 mL (median, 600 mL). The authors found that the blood loss was positively correlated with increased number of involved subsites. Complete surgical resection was performed in 77.7% of cases. Of the 18 patients with residual disease, 1 underwent adjuvant RT, 1 underwent re-resection plus adjuvant RT. The remaining 16 patients were observed and showed no growth with a mean follow-up of 35.6 months. Regarding postoperative complications, 3 patients had V2 paresthesia or neuralgia, 1 patient had a transient 6th nerve palsy, and 1 patient had palatal insufficiency. Other large

TABLE V.A.3. Evidence for EEA in advanced stage juvenile angiofibroma (Radkowski staging unless specified)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Langdon[583]	2016	3a	Multicenter retrospective review	Endoscopic (74) resection of stage IIIA or IIIB	Blood loss, residual rate	Blood loss 1279.7 mL (positive correlation between number of involved subsites and blood loss). Residual: 33.3% (18/54) (16 observed and stable, 1 adjuvant radiation therapy, 1 revision surgery and radiation therapy)
Leong[584]	2013	3a	Systematic review	Endoscopic (5), combined (2) and open approach (65) for stage IIIA or IIIB	Blood loss, complication rates, rate of persistence and recurrence	Blood loss: endoscopic 2998 mL (2 cavernous sinus injuries) vs open 1500 mL ($p < 0.05$) Complication rate 46% (all groups combined) Recurrence rate 18% (all groups combined)
Boghani[515]	2013	3a	Systematic review	7 Stage IIIA and B: 3 endoscopic, 4 open	Recurrence rate	Recurrence: endoscopic 0% vs open 25% ($p = 1.00$)
Huang[549]	2014	4	Case series	Endoscopic: 6 stage IIIA, 10 stage IIIB Open: 10 stage IIIA, 8 stage IIIB	Blood loss, complication, recurrence rate	No individual patient data. Recurrence rate in stage IIIB was 61.1%
Liu[585]	2016	4	Case series	2 Endonasal (IIA, IIC), 2 combined (IIIA, IIIB)	Residual rate	Residual rate: 0%
McLaughlin[546]	2016	4	Case series	10 Traditional endoscopic, 7 radiofrequency assisted endoscopic 6 UPMC stage III, 3 Stage IV, 8 stage V	Blood loss, duration of surgery, length of hospitalization, recurrence rate	No individual patient data
Chan[548]	2014	4	Case series	5 Stage IIIA, 4 stage IIIB	Blood loss, complication rates, recurrence rates	No individual patient data
Godoy[586]	2014	4	Case series	All stage IIIA Endoscopic: 3 Combined: 3 Open 7	Complication rate, residual, recurrence rate	Complication: endoscopic 1, combined 2, open 1 Residual: endoscopic 0, combined 1, open, 1 Recurrence: endoscopic 0, combined 3, open 3
Ballah[550]	2013	4	Case series	Endoscopic: 3 UPMC stage IV, 2 stage V Combined: 1 stage IV, 2 stage V Open: 1 stage V	Blood loss Complication Recurrence rate	Blood loss: endoscopic 880 mL, combined 1066 mL, open 1500 mL Complication: endoscopic 0, combined 0, open 1 Recurrence: endoscopic 1, combined 1, open 0
Cloutier[545]	2012	4	Case series	Radkowski stage IIIA (34) and IIIB (17).	Average blood loss, duration of hospitalization, complication rate, recurrence rate	No individual patient data. Open approach for ICA encasement, foramen lacerum invasion and cavernous invasion
Baser[554]	2011	4	Case series	Endoscopic: 4 stage IIIA, 1 stage IIIB	Complication and recurrence rate	0 Complication, 0 recurrence. Blood loss average 720 mL
Nicolai[543]	2010	4	Case series	Endoscopic: 17 Andrews stage IIIA, 1 stage IIIB	Blood loss, complication rate, recurrence rate	3/17 Residual. Contraindications for an endoscopic approach are encasement of ICA, intracranial extension lateral to the paraclival segment of ICA, or intradural dura growth

(*Continued*)

TABLE V.A.3. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Ardehali[560]	2010	4	Case series	Endoscopic: 3 stage IIIA, 1 stage IIIB	Blood loss, complication rate, recurrence rate	Stage III blood loss 3450 mL, 2 recurrence (IIIA). 2 cavernous sinus injuries. 1 multiple cranial nerve injuries. Best to refer stage IIIB with cavernous invasion or ICA encasement to radiotherapy.
Khalifa[587]	2008	4	Case series	All Andrews Stage III A) Endoscopic assisted with antral window + preoperative embolization (16) vs B) Endoscopic assisted midfacial degloving (16)	Blood loss, operative time, complication rate, residual and recurrence rate	Blood loss group A 575 mL vs group B 1.075 mL ($p < 0.001$). Operative time reduced by 16% in group A. No major complication. Recurrence: Group A 2/16 recurrence, group B 2/16 recurrence. Endoscopic assisted with antral window offers similar results as more invasive combined approaches
Eloy[564]	2007	4	Case series	6 Endoscopic: 1 stage Ia, 1 stage 1b and 4 stage IIB	Blood loss, recurrence rate	Blood loss: 575 mL. Recurrence: 2 (1 re-operated, 1 observed)
Tosun[566]	2006	4	Case series	Endoscopic: 2 Stage IIIA Open approach: 3 stage IIIA	Complication and recurrence rate	No complication no recurrence in both groups
Hofmann[569]	2005	4	Case series	Endoscopic: (Andrews/Fisch) 5 stage IIIA	Blood loss, residual and recurrence rates	Blood loss 590 mL. 1 Recurrence (had gamma knife therapy)
Onerci[574]	2003	4	Case series	4 Stage IIIA	Blood loss, residual and recurrence rate	Blood loss 1500 mL. Residual in 2 but no growth at 2 years.
Roger[575]	2002	4	Case series	9 Stage IIIA	Blood loss, residual and recurrence rate	No individual patient data. 1 Residual observed and stable. No recurrence.

ICA = internal carotid artery; LOE = level of evidence.

case series have shown similar results using endoscopic only approach in advanced stage tumors.[515,523,543,545,575] Table V.A.3 presents the available published data using endoscopic approach in advanced disease. Series with more than 2 advanced-stage cases were included. The reported average blood loss from endoscopic approaches varied between 575 mL and 3450 mL. Reported rates of GTR ranged from 77.7% to 100% and recurrence rates varied between 0% and 61.1% (see Table V.A.3).

The limits of the endoscopic approach are still evolving. Advanced JNA with intracranial extension, residual vascularity after embolization, cavernous sinus invasion, or ICA encasement remains a challenge. In these cases, the goals of surgery should be clear, and surgeons should consider staging the surgery if needed. A systematic surgical approach by an experienced skull-base team of surgeons will provide the best outcomes.

V.A.5. *Radiation therapy for JNA*

The use of radiation therapy is controversial as JNAs are benign tumors affecting a young population. The potential for growth impairment, encephalopathy, radiation-induced tumors, and malignant transformation is still unknown. Furthermore, the location of these tumors is associated with strict radiation dose constraints to organs at risk such as the brainstem, ocular lens, cochlea, optic nerve, and retina. In addition, as demonstrated by the study by Langdon et al.,[583] the vast majority of residual tumors can be observed with little or no growth.

Fractionated radiation therapy has been described in retrospective series for definitive treatment of primary tumors, recurrent tumors, and in the adjuvant setting. Cummings et al.[588] published a series of 55 patients, 42 of which were treated with RT as the primary modality. The remaining patients were treated for recurrence after surgical therapy. A total of 30 to 35 Gy was delivered in 14 to 16 fractions, with local control achieved in 80% of patients. Two patients developed secondary tumors: 1 basal cell carcinoma (13 years posttreatment) and 1 thyroid carcinoma (14 years posttreatment). Other large series have reported similar outcomes.[589–591] Amdur et al.[592] reported a potential dose response for tumor control with patients who

received 36 Gy having higher control rates than patients treated with 30 Gy or less (91% vs 77%).

Lopez et al.[520] described the use of adjuvant Gamma Knife radiosurgery in the setting of postoperative residual disease. Out of their series of 48 cases, 10 patients had residual disease in challenging surgical locations: cavernous sinus, ICA, and orbital apex. Six were treated with adjuvant fractionated RT and 4 with Gamma Knife radiosurgery. In the latter group, 3 had stable disease and 1 had significant tumor reduction at 3-year follow-up.

In patients with advanced stage JNA considered unresectable because of involvement of critical structures, surgical debulking with adjuvant radiation therapy has been described. The extracranial portion of the tumor is resected, leaving a smaller tumor volume for radiation therapy. This potentially reduces the radiation field and thus potential for complications.[520,589,593] Other authors advocate for a wait-and-see policy in case of residual or recurrent disease.[525,549]

V.A.6. *Follow-up and management of recurrence in JNA*

Tumor recurrence is most likely due to incomplete resection of the primary tumor and usually occurs within 6 to 36 months.[520,594] It is associated with increased number of involved subsites and is reduced by drilling the basisphenoid and base of pterygoids.[514,516,543,583] Most investigators recommend follow-up with nasal endoscopy and MRI for at least 3 to 5 years postoperatively.[516,594] The management of recurrence depends on the size, growth rate, location, and patient symptoms. A second endoscopic surgery is the recommended option when the likelihood of complete tumor resection is high, and the risk of morbidity is low.[561,584] Medical therapies are in the investigative stages and there is no current consensus for their use.[595–600] Ardehali et al.[560] found no difference in recurrence rate when comparing the endoscopic approach in primary (6/31) to revision surgery (3/16). When complete resection of recurrent disease is impossible or high risk (cavernous sinus, ICA, intracranial), a wait-and-see policy can be adopted.[516,574,594] Adjuvant stereotactic radiosurgery or fractionated RT have both been described in small series but have never been compared to observation.

- Aggregate Grade of Evidence: C (Early stage JNA: Level 3b: 2 studies; Level 4: 42 studies; Advanced-stage JNA: Level 3b: 3 studies; Level 4: 16 studies)
- Benefit: Endoscopic only approach offers comparable recurrence rates to classical open approaches in selected advanced-stage tumors.
- Harm: Endoscopic approach is associated with low complication rates and morbidity. Advanced-stage disease has a higher incidence of residual disease.
- Cost: No studies have examined the issue of cost.
- Benefit-Harm Assessment: The majority of studies support the efficacious use of endoscopic endonasal surgery for the resection of JNA with minimal morbidity.
- Value Judgment: In experienced hands and with modern technological advances, endoscopic resection of selected advanced-stage JNA offers better tumor visualization and safe resection. Conversion or combination with an open approach should be available if necessary.
- Policy: Recommendation
- Intervention: Advanced-stage JNA should be managed in an institution that offers preoperative embolization and experienced endoscopic and open team(s) of surgeons.

V.B. Fibro-osseous lesions

Fibro-osseous lesions (FOLs) are common benign bony abnormalities that affect the paranasal sinuses with common subtypes being osteoma, ossifying fibroma (OF), and fibrous dysplasia (FD).[601] These lesions share similar symptoms and presentation but can have unique features that require different management. Treatment varies from conservative observation to partial or complete excision using open, endoscopic or a combination of approaches.[602–604] Surgery may be indicated to relieve symptoms, manage complications, or address cosmesis.[602] Observation with periodic imaging is a preferred option for asymptomatic or minimally symptomatic FOL as most are slow growing or do not grow at all.[605]

Although many FOL are identified incidentally on imaging studies, presenting symptoms can include headaches (36%), pain/pressure (19%), and nasal obstruction (17%).[601] In severe circumstances these lesions have the potential for expansion into the orbit, resulting in proptosis, diplopia, and/or visual disturbances (4.5%).[601] Intracranial extension has the potential for dural erosion, cerebral compression, increased intracranial pressure, and neurological symptoms including headaches, facial pain, CN palsies, convulsions, seizures, and meningitis.[605]

CTs are the mainstay of imaging for paranasal sinus FOL.[606] Classic radiologic characteristics of osteoma and FD do not necessarily warrant biopsy but the preoperative diagnosis of OF or indeterminate lesions may warrant biopsy to establish the diagnosis.[607] Serial imaging can be used to monitor growth of the lesion during watchful waiting.[608]

V.B.1. *Common FOLs*

V.B.1.a. Osteoma. Osteomas are composed of dense, compact lamellar bone, similar to cortical bone, and tend to be unifocal and slow growing, found mostly in the frontal sinus, followed by the ethmoid, maxillary, and sphenoid sinuses.[604,609,610] Osteomas have been found in 1% of frontal sinus radiographs in asymptomatic individuals.[611] Osteomas typically have a slow pattern of growth and may not change in size over the course of a patient's life, whereas others may grow rapidly such that ongoing surveillance is recommended.[601] The presence of multiple osteomas may be an indication of Gardner's syndrome (a variant of familial adenomatous polyposis), an autosomal dominant condition associated with increased risk of colon and

thyroid cancers, epidermal cysts, fibromas, and dermoid cysts.[612] If Gardner's syndrome is suspected, genetics and cancer screening workup by a primary care physician is warranted. On CT, osteomas appear as homogenous, well-circumscribed lesions that are very dense.[613]

V.B.1.b. OF. OFs are rare FOLs further subdivided into cemento-ossifying fibroma and juvenile-ossifying fibroma (JOF).[614] In general, OF is a rare, benign FOL with similar symptoms as the other subtypes. Cemento-ossifying fibroma occur mostly in the mandibulo-odontal region whereas juvenile-ossifying fibroma are more common in the paranasal sinuses.[610,614] Cemento-ossifying fibromas are usually painless, slow-growing tumors that can be excised surgically with limited recurrence. Extramandibular lesions in the paranasal sinuses tend to be more aggressive and grow more rapidly.[615] On CT imaging, OFs are well-circumscribed, expansile masses covered with a bony shell of varying densities.[615] This sharply demarcated bony shell is considered the most important radiological sign for distinguishing it from FD, where there is merging of diseased bone with healthy bone.

V.B.1.c. FD. FD exists in monostotic (70-75%) and polyostotic (25-30%) forms, with the monostotic form being more common in the craniofacial bones.[616] The underlying genetic cause is due to a subunit of G-protein receptors, found on chromosome 20 (20q13). Patients with the monostotic form are frequently asymptomatic and are often diagnosed incidentally during radiographic evaluation for another purpose. Conversely, patients with the polyostotic form have early manifestations including bone pain and/or bone deformity.[617] FD may be associated with other syndromes such as McCune–Albright (precocious puberty, FD, and cutaneous pigmentation–cafe au lait spots).[616] The polyostotic form has a more aggressive phenotype and higher risk of malignant transformation usually to osteosarcoma (4%, compared to the monostotic risk of transformation of 0.5%).[618]

FD on CT scanning shows bone replaced with a more radiolucent, "ground-glass" pattern with no visible trabecular pattern.[618] There may be endosteal scalloping of the inner cortex, but the periosteal surface is smooth and nonreactive. On MRI, FD has intermediate signal on T1 and hypointense signal on T2. In the absence of CT imaging, FD is often misinterpreted as an aggressive bone neoplasm with MRI alone. FD is usually much more irregular or ill-defined on imaging than both osteoma and OF.

V.B.2. *Management*

Because most FOLs are benign, slow growing, and asymptomatic, watchful waiting is a reasonable option with regular imaging to monitor the growth of the lesion.[611,619,620] The location and extent of the FOL as well as the experience of the surgical team are critical factors in choosing an open, endoscopic, or combined approach if surgery is required. In most cases, osteomas and OFs can be completely removed.[621,622] For FD, complete removal is often technically challenging or impossible and most often, a partial resection or debulking surgery to improve symptoms or cosmesis is performed.[623]

In cases where the lesion is causing intracranial/orbital complications, facial deformities, or when conservative treatments fail, the lesion should be removed. Historically, open procedures were preferred, but with improvements in technology and techniques, endoscopic endonasal resections are being utilized more commonly.[621,622] EEAs are useful for midline lesions, whereas open approaches are more suitable for lesions located beyond the medial orbital wall.

Chiu et al.'s[624] frontal sinus osteoma grading system considers the location of tumor attachment, anterior-posterior dimension of the lesion, and tumor location relative to the virtual sagittal plane through the lamina papyracea when deciding the approach (see Table V.B).

For grade II or lower, an endoscopic approach is recommended. Open surgical or combination approach is recommended for grade III/IV due to risk of CSF leak and difficulty in accessing the tumor for total resection.[621,624] Open procedures used to treat FOL in the frontal sinus include trephination, frontoethmoidectomy (Lynch procedure), and osteoplastic flaps.[606] Although Ledderose et al.[604] showed that 3 of 16 grade III/IV patients could be treated endoscopically, the majority still required an open or combination approach. An open approach is preferred in the presence of large lesions (occupying >75% of the frontal sinus), posterior table erosion, attachment to the floor of the frontal sinus, narrow frontal anteroposterior dimension, previous meningitis or CSF leak, extensive intracranial extension, supraorbital involvement, and orbital mucocele formation.[611,625]

OFs have 2 distinct subtypes, each with contrasting prognosis. Mandibular lesions are usually asymptomatic and thus conservative management is preferred. However, OFs outside of the mandible tend to be more aggressive and locally destructive, requiring a complete resection.[613] Radical resection of paranasal OF is widely considered the treatment of choice due to their locally aggressive behavior.[514] Endoscopic approaches are viable in some settings.[626,627] However, surgeons must be prepared for open or endoscopic approaches depending on the individual characteristics of the patient and pathology concerned. RT is ineffective for dealing with OF and may result in malignant transformation.[628] Because of the relatively common rate of recurrence, close follow-up and long-term surveillance is recommended after surgical resection.[629]

FDs are rare and may stabilize over time.[514] Because of the low risk of malignant transformation, asymptomatic FD may be monitored radiologically.[629] When the disease is not associated with symptoms, partial or radical resection is not indicated.[623] Bone pain and risk of fractures can be treated medically with bisphosphonates.[630]

TABLE V.B. Frontal sinus osteoma grading system (as proposed by Chiu[624])

Grade	Criteria
I	• Base of attachment is posterior–inferior along the frontal recess • Tumor is medial to a virtual sagittal plane through the lamina papyracea • Anterior–posterior diameter of the lesion is 75% of the anterior–posterior dimension of the frontal recess
II	• Base of attachment is posterior–inferior along the frontal recess • Tumor is medial to a virtual sagittal plane through the lamina papyracea • Anterior–posterior diameter of the lesion is 75% of the anterior–posterior dimension of the frontal recess
III	• Base of attachment is anterior or superiorly located within the frontal sinus and/or • Tumor extends lateral to a virtual sagittal plane through the lamina papyracea
IV	• Tumor fills the entire frontal sinus

Endonasal endoscopic optic nerve decompression for symptomatic compressive optic neuropathy in FD has been shown to be effective in experienced hands.[631] Meta-analysis shows most patients with FD remain asymptomatic during long-term follow-up, and expectant management is recommended even in the presence of radiologic optic nerve compression because surgery is associated with visual deterioration in otherwise asymptomatic patients.[632]

FD has an irregular growth pattern and is thought to be active during adolescence and pregnancy, intimating a hormonal association.[633] FD may also stabilize over time, and given this tendency and the overall low risk of malignant transformation, lesions that are asymptomatic may be observed with both clinical and radiological monitoring.[605] Symptomatic, disfiguring, or suspicious lesions may be treated; however, the exact approach (open vs endoscopic), and extent of resection depends on individual characteristics of the patient and the disease. Efforts should be made to decompress any affected structures and/or to restore cosmesis as best as possible. Often, complete resection of these lesions is difficult due to the lack of defined borders of the lesion itself, with added desire to avoid damage to major structures. For these reasons, FD has a relatively high recurrence rate.[610]

V.B.3. *Complications*

Certain anatomical features must be identified prior to and during surgical procedures to prevent serious complications. The surrounding structures of the paranasal sinuses such as the orbit, anterior ethmoidal artery, and the skull base require close attention. Injury to the eye, the optic nerve, or the extraocular muscles may lead to vision changes.[621] Damage of the arteries can lead to intranasal or intraorbital hemorrhage.[634] CSF leak and/or serious central nervous system infection are rare.[603,604,611]

Conclusion

FOLs are a heterogeneous group of benign bony lesions of the paranasal sinuses. The most common type is an osteoma, followed by OF and FD. They are most often discovered incidentally. Observation is often recommended in asymptomatic osteoma and FD patients. Large, symptomatic, or complicated bony FOL should be excised completely (or partially removed if not feasible) using techniques appropriate to the lesion (endoscopic, open, or combination depending on the training and skill-set of the surgical team). Patients should be followed with serial imaging to monitor for growth or recurrence.

V.C. *Cholesterol granuloma*

Cholesterol granulomas (CGs), also called xanthogranulomas, are expansile, cystic lesions within an air-filled space (ie, air cells of the paranasal sinuses or temporal bone) caused by a chronic, giant cell–mediated, granulomatous reaction to cholesterol crystals. Within the confines of ESBS, CGs can occur in the petrous apex of the temporal bone (most common site[635]), sella and parasellar region, frontal sinus (most common sinonasal site[636]), ethmoid sinus, and sphenoid sinus (as well as the maxillary sinus, middle ear, and mastoid cavity, though generally without skull-base involvement, and thus is not discussed). Although the exact mechanism for pathogenesis is unclear, it is thought that blood products containing cholesterol content, either from trauma or iatrogenic causes, may incite a foreign body response and lead to CG formation over time.[637] In a systematic review, Durgam and Batra[636] found that only 14% and 11% of patients with CGs of the paranasal sinuses had a history of craniofacial trauma and prior surgery, respectively. Sellar and parasellar CGs are thought to have a distinct pathogenesis, wherein inflammation develops around RCCs or craniopharyngiomas (46% and 20% have xanthomatous change on pathologic examination, respectively[638]) and leads to formation of CG.[639] As a result of being associated with these conditions, sellar and parasellar CGs are often misdiagnosed as neoplasms as opposed to inflammatory lesions.[640]

Clinical manifestations of skull-base CGs are related to local pressure upon surrounding structures exerted by the lesion and include headache, oculo-orbital symptoms (retro-orbital pain, visual changes, proptosis, displacement of orbital contents), sinonasal symptoms (nasal obstruction, rhinorrhea), or, in some cases, may be

asymptomatic.[636] As in many benign skull-base pathologies, asymptomatic lesions are generally those that are small and have not expanded outside normal anatomic boundaries yet. Leonetti et al.[641] reported that, in a series of 88 patients with incidentally discovered petrous apex lesions on MRI obtained for unrelated reasons, 14 (16%) were CGs.

CGs appear as hypodense, expansile, and rounded masses on CT; this appearance is often nonspecific and difficult to distinguish from other benign lesions (eg, cholesteatoma, mucocele, epidermoids, congenital, or acquired cysts)[642,643] or even indolent chondroid tumors such as chondrosarcoma. There is often cortical thinning with eventual dehiscence of the surrounding bone due to slow, gradual expansion of the lesion. However, on MRI, CGs are generally hyperintense on both T1-weighted and T2-weighted sequences (78% and 67%, respectively, in 1 review[2]), and do not enhance with gadolinium contrast.[642]

V.C.1. *Traditional management*

The mainstay of treatment for CGs involves marsupialization of the lesion cavity and decompression of its contents, which often appears thick, "greasy," and dark with cholesterol crystals. To confirm the diagnosis, the surgeon may consider sending some expressed contents for histopathologic examination, which usually shows giant cells, cholesterol crystals, and hemosiderin deposits. Traditionally, petrous apex CGs have been primarily managed by neurotologists and approached via a transtemporal approach (eg, transcanal infracochlear, transmastoid infralabyrinthine, translabyrinthine, transotic), often with placement of stents or irrigating catheters or middle fossa approaches.[644] Sellar and parasellar CGs and sinonasal skull-base CGs may frequently be managed via EEA, though lesions located in difficult-to-access areas (eg, lateral frontal sinus, orbital roof) may require an open approach.

V.C.2. *Endoscopic endonasal treatment and outcomes*

More recently, with endonasal endoscopic techniques gaining in prominence, a subset of petrous apex CGs may be successfully approached through an EEA approach (Table V.C.1).

Those lesions that have eroded into the medial sphenoid sinus, especially medial to the ICA, in the setting of a well-pneumatized sphenoid are generally good candidates.[648] Needless to say, the surgeon should be mindful about the location of the paraclival and petrous ICA segments, which underscores the importance of anatomical understanding and the use of intraoperative image guidance during dissection.[647] When compared to transtemporal approaches, the aggregate evidence to date suggests excellent outcomes with regard to symptomatic improvement with the endoscopic approach. In a systematic review of 53 patients, Eytan et al.[645] reported that only 7.5% experienced recurrent symptoms. In contrast, transtemporal approaches are effective in management of symptoms as well, but outcomes are generally more guarded. Of note, 3 of the largest series involving otoneurological management of CGs yielded a symptomatic recurrence rate of 15.4% (Sanna et al.,[666] 3/15, 20%; Brackmann and Toh,[644] 6/34, 18%; and Kusumi et al.,[667] 1/16, 6%).

In a series of 17 patients, Paluzzi et al.[653] proposed an objective radiographic metric to determine the optimal EEA to petrous apex CGs based on its location relative to the ICA. On review of preoperative MRI, one can define the "V angle" as a measure of the surgical corridor, where the vertex is the lateral edge of the piriform aperture contralateral to the CG, the lateral limit is the lacerum segment of the internal carotid artery, and the medial limit is medial edge of the CG cavity.[653] If the V angle is ≥ 5 degrees, the authors advocated for a transsphenoidal, transclival approach; if <5 degrees, then the paraclival carotid may need to be exposed and retracted laterally for access; and if the angle were negative (carotid is more medial than CG cavity), then an infrapetrous approach involving Eustachian tube dissection may be required.[653,668]

Paranasal sinus CG tends to have excellent outcomes following surgical treatment. According to Durgam and Batra's[636] systematic review, 91.8% of patients experience complete symptomatic resolution following treatment. Maintaining patency of the marsupialized cavity mirrors those principles employed for functional endoscopic sinus surgery and mucoceles, wherein wide access will prevent scarring over time. For those lesions within the frontal sinus, consideration should be given to performing a modified endoscopic Lothrop procedure for access, decreased risk of restenosis, and postoperative cavity surveillance.[669]

To maintain functional patency of the marsupialized CG cavity within the petrous apex, many reports advocate for placement of a stent, which is removed months later after healing is complete.[653,655] Additionally, some authors have emphasized the importance of using an NSF (full-length or mini) to promote remucosalization of the cavity.[653–655,663] Based on the only systematic review on this topic, stents were used in 45.1% of cases, with an overall cavity restenosis rate of 20%.[645] Symptomatic recurrence occurred in 4.3% with stent use as compared to 10.7% without stent use, though this difference did not reach statistical significance ($p = 0.6$).[645]

The major risk associated with endonasal management of petrous apex CG is ICA injury. Eytan et al.,[645] in their systematic review, found no such cases of this. Surgery for sellar and parasellar CGs have a similar risk profile to that of any pathology surrounding the pituitary gland—namely, hypopituitarism, DI, visual loss, CSF leak, and stroke. For sellar and parasellar CGs, numerous case reports and case series have described relatively poor outcomes for endocrine function postoperatively, whereas visual outcomes are much better (Table V.C.2).

Potential risks encountered in management of paranasal sinus CGs parallel those in any endoscopic sinonasal

TABLE V.C.1. Evidence for endoscopic endonasal surgical management of petrous apex CGs*

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Eytan[645]	2014	2a	Systematic review of case series and case reports	53 Cases with petrous apex CG	1. Symptomatic improvement 2. Tract patency 3. Complications	45.1% used stenting; 97.7% symptomatic resolution or improvement; 20% restenosis rate; 13.2% complication rate; 7.5% symptomatic recurrence
Griffith[646]	1996	4	Case series	2 Patients with petrous apex CG	1. Symptomatic improvement 2. Tract patency	Resolution of symptoms with limited tract patency at 12–18 months follow-up
Kingdom[647]	2003	4	Case series	1 Patient with petrous apex CG	Lesion marsupialization	Complete endonasal approach with IGS is safe and cost-effective
Georgalas[648]	2008	4	Case series	4 Patients with petrous apex CG	Symptomatic improvement	All patients had symptomatic improvement at 6 months to 10 years follow-up. Those lesions that have extended medial to the carotids are good candidates.
Jaberoo[649]	2010	4	Case series	2 Patients with petrous apex CG	1. Symptomatic improvement 2. Tract patency	Resolution of symptoms with tract patency at 18–24 months follow-up
Prabhu[650]	2010	4	Case series	2 Patients with petrous apex CG (both 30 mm)	Symptomatic improvement	Resolution of symptoms at 6 months follow-up
Emanuelli[651]	2012	4	Case series	5 Patients with petrous apex (4) or clival (1) CG	1. Recurrence 2. Complications	No complications intraoperatively or postoperatively with no recurrence at 12–50 months follow-up
Sade[652]	2012	4	Case series	3 Patients with petrous apex CG (22-37 mm)	1. Functional patency 2. Recurrence	All patients had functional patency of marsupialized cavity at 10–36 months follow-up. 2 recurrences (67%) which required revision surgery.
Paluzzi[653]	2012	4	Case series	17 patients with petrous apex CG, 11 stented, 4 had miniflap	1. Symptomatic improvement 2. Recurrence 3. Tract patency	All patients had symptomatic improvement at 3–67 months follow-up. 2 recurrences (12%) that required revision surgery. No major complications (1 epistaxis, 1 transient sixth nerve palsy). V angle determines approach of choice.
Karligkiotis[654]	2015	4	Case series	10 Patients with petrous apex CG	Recurrence	90% (9/10) Symptomatic resolution; 1 failure was due to technical error
Shibao[655]	2015	4	Case series	2 Patients with petrous apex CG	1. Recurrence 2. Tract patency	Nasoseptal flap with silicone T-tube placed for stenting of cavity; no recurrence at 12–24 months follow-up
Bruchhage[656]	2017	4	Case series	3 Patients with petrous apex CG	Symptomatic improvement	Endoscopic transsphenoidal approach is superior when anatomic is conducive; infralabyrinthine approach can be used otherwise
DiNardo[657]	2003	5	Case report	1 Patient with petrous apex CG	1. Symptomatic improvement 2. Tract patency	Resolution of symptoms with tract patency at 12 months follow-up
Oyama[658]	2007	5	Case report	1 Patient with petrous apex CG	1. Symptomatic improvement 2. Recurrence	Initial presentation of trigeminal neuralgia; resolution of symptoms with no recurrence at 24 months follow-up
Presutti[659]	2006	5	Case report	1 Patient with petrous apex CG	Symptomatic improvement	Resolution of symptoms at 3 months follow-up; T-shaped stent placed
Dhanasekar[660]	2011	5	Case report	1 Patient with petrous apex CG (58 mm)	Symptomatic improvement	Uneventful recovery; very large lesions are likely easier to drain

(*Continued*)

TABLE V.C.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
McLaughlin[661]	2012	5	Case report	1 Patient with petrous apex CG (25 mm)	1. Symptomatic improvement 2. Recurrence 3. Tract patency	After initial drainage, symptoms resolved but cavity scarred at 4 months; intrapetrous approach was performed with placement of Doyle splint
Park[662]	2013	5	Case report	1 Patient with petrous apex CG (21 mm)	Symptomatic improvement	CG was located directly posterior to carotid which made surgical approach challenging; clival plexus bleeding and CSF leak encountered, but symptoms resolved after drainage
Terranova[663]	2013	5	Case report	1 Patient with petrous apex CG	1. Symptomatic improvement 2. Recurrence 3. Tract patency	Nasoseptal flap used to maintain tract patency; resolution of symptoms with no recurrence at 3 years follow up
Miyamura[664]	2014	5	Case report	1 Patient with petrous apex CG	Symptomatic improvement	Improvement of ocular symptoms postoperatively
Turan[665]	2016	5	Case report	1 Patient with petroclival CG (22 mm)	1. Symptomatic improvement 2. Recurrence	CG was lower than usual with conchal sphenoid pneumatization, and thus a high nasopharyngeal corridor was used. Stable improvement at 9 months follow-up.

*Size range reported whenever available.
CG = cholesterol granuloma; CSF = cerebrospinal fluid; IGS = image guided surgery.

surgery and include CSF leak, orbital injury, epistaxis, hyposmia, or intracranial injury.

CGs of the skull base can present in the petrous apex of the temporal bone, the sellar and parasellar regions, frontal sinus, and sphenoid sinus. They typically present with headache and retro-orbital pressure, though they may be asymptomatic in some cases. On CT, they present as expansile, hypodense lesions, while they are characteristically hyperintense on both T1-weighted and T2-weighted images on MRI (and do not enhance). Contemporary management of skull-base CGs involves EEA with wide marsupialization; stenting or coverage with an NSF may promote remucosalization and patency of the tract. Overall recurrence rates are under 10%, and complication rates appear to be extremely rare.

- Aggregate Grade of Evidence: D (Level 2a: 2 studies; Level 4: 20 studies; Level 5: innumerable; Table V.C.1, Table V.C.2, and Table V.C.3)

V.D. Trigeminal schwannoma

Trigeminal schwannomas (TSs) are the most common skull-base schwannomas after vestibular schwannomas and account for up to 0.36% of all intracranial neoplasms and 8% of skull-base schwannomas.[699–727] Most of them develop in the Gasserian ganglion, but they can occur anywhere along the course of the trigeminal root, ganglion, and peripheral branches. Therefore, they can be intradural, interdural, and extradural, can exist in the posterior fossa and middle fossa/Meckel's cave, and extend along V1 into the orbit, V2 into the pterygopalatine fossa (PPF), and V3 into the infratemporal fossa.[699–727]

Main symptoms are due to involvement of trigeminal roots and compression of surrounding structures and include hypoesthesia, paresthesia, pain in the area of innervation of the respective trigeminal branches, and reduction of the corneal reflex. If there is large amount of tumor in the posterior fossa, there may be symptoms of cerebellopontine angle nerves, especially VI to VIII. In advanced lesions, there may be a cerebellar syndrome.[710]

Most TSs are benign, have a soft consistency and are almost avascular in nature, with few exceptions. They are usually separable from neighboring neurovascular structures, because CNs and ICA are typically displaced rather than engulfed. They do not intrude into the cavernous sinus and subdural space.[699–724]

Jefferson introduced a classification of TSs in 1953. Yoshida and Kawase modified Jefferson's classification scheme by adding Type D (Table V.D).

Indications for surgical intervention are demonstrated growth of a previously diagnosed tumor and newly diagnosed lesion with associated symptoms. The goal of surgery is complete resection.[700,705,727] However, radiosurgery can also be effective in the treatment of some TSs. In some cases, leaving tumor behind for observation or radiosurgery may be acceptable.[705]

Several open surgical approaches have been reported in the surgical management of TSs.[705,725] EEAs have also added new options in the management of TSs. Thirty-three manuscripts were identified.

TABLE V.C.2. Evidence surrounding surgical management of sellar and parasellar CGs*

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Jung[670]	2006	4	Case series	2 Patients with sellar CG treated via transsphenoidal approach (both 25 mm)	None	Both lesions initially suspected to be craniopharyngioma
Kamoshima[671]	2011	4	Case series	5 Pediatric patients with sellar CG treated via endoscopic transsphenoidal approach (4) or transcranial approach (1)	1. Recurrence 2. Postoperative visual function 3. Postoperative pituitary function	Improved postoperative visual function and no recurrence, but no improvement of pituitary function at 6 months follow-up
Rahmani[639]	2015	4	Case series	4 Patients with parasellar CGs treated via extended endoscopic transsphenoidal approach (10–21 mm)	1. Postoperative CSF leak 2. Postoperative visual function 3. Postoperative pituitary function 4. Recurrence	All patients had improvement of visual function with no recurrence at 61 months mean follow-up. No CSF leak. Two (50%) patients developed hypopituitarism.
Kleinschmidt-DeMasters[672]	2017	4	Case series	14 Patients with xanthogranulomas of the sella	1. Recurrence 2. Postoperative pituitary function 3. Postoperative DI	Variable postoperative pituitary function and DI through 4 months to 7 years of follow-up
Kurisaka[673]	1998	5	Case report	1 Patient with suprasellar RCC treated via microscopic transsphenoidal approach	1. Symptomatic improvement 2. Recurrence	Resolution of symptoms with no recurrence at 8 months follow-up
Hama[674]	1999	5	Case report	1 patient with RCC treated via transsphenoidal approach	1. Recurrence 2. Postoperative pituitary function 3. Postoperative DI	No recurrence at 7 years with complete recovery of pituitary function. Persistence of DI.
Nakasu[675]	1999	5	Case report	1 Patient with suprasellar RCC treated via transsphenoidal approach	1. Recurrence 2. Postoperative pituitary function	Recurrence 4 years after initial surgery requiring revision. No improvement in pituitary function postoperatively.
Yonezawa[676]	2003	5	Case report	1 Patient with sellar CG treated via transsphenoidal approach	1. Weight 2. Postoperative pituitary function	Improved weight but no improvement in pituitary function at 3 months follow-up
Liu[677]	2008	5	Case report	1 Patient sellar CG treated through transcranial approach	None	Only reported case to cause obstructive hydrocephalus
Sugata[678]	2009	5	Case report	1 Patient with suprasellar CG treated via interhemispheric approach	1. Postoperative visual function 2. Postoperative pituitary function 3. Recurrence	Improved postoperative visual function and no recurrence, but no improvement of pituitary function at 12 months follow-up
Arai[679]	2010	5	Case report	1 Patient with suprasellar CG treated via endoscopic transsphenoidal approach	1. Recurrence 2. Symptomatic improvement 3. Postoperative pituitary function	Resolution of symptoms and no recurrence, but no improvement of pituitary function at 18 months follow-up
Miyajima[680]	2011	5	Case report	1 Patient with suprasellar CG associated with RCC treated via pterional approach	Postoperative DI	No improvement in DI. CG definitively associated with RCC.

(*Continued*)

TABLE V.C.2. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Agarwal[681]	2012	5	Case report	1 Patient with suprasellar CG treated via endoscopic transsphenoidal approach	1. Recurrence 2. Postoperative pituitary function	No recurrence and partial recovery of pituitary function at 6 months follow-up
Nishiuchi[682]	2012	5	Case report	1 Patient with suprasellar CG treated via transsphenoidal approach (18 mm)	1. Symptomatic improvement 2. Postoperative visual function 3. Postoperative pituitary function	Resolution of symptoms and improvement in visual function, but no improvement of pituitary function postoperatively
Gurcay[683]	2016	5	Case report	1 Patient with suprasellar CG treated via endoscopic transsphenoidal approach	1. Recurrence 2. Symptomatic improvement 3. Postoperative visual function	Resolution of symptoms, no recurrence, and improvement of visual function at 15 months follow-up
Dai[684]	2017	5	Case report	1 Patient with sellar CG treated via transsphenoidal approach (18 mm)	1. Recurrence 2. Symptomatic improvement 3. Postoperative pituitary function	Resolution of symptoms, no recurrence, and improvement of pituitary function at 36 months follow-up

*Size range reported whenever available.
CG = cholesterol granuloma; CSF = cerebrospinal fluid; DI = diabetes insipidus; RCC = Rathke's cleft cyst.

Most of the literature on endonasal endoscopic resection of TSs consists of case series. High-quality trials comparing endoscopic to open approaches are lacking. Raza et al.[700,705] described 4 patients who had undergone a purely endoscopic transpterygoid approach. There were no major complications or CSF leaks. In follow-up, there was 1 case of regrowth that was treated with radiosurgery. They concluded that tumors in the posterior fossa were associated with a more difficult approach, risk of incomplete resection, and CN injuries.[700,705] Several other studies describe resection techniques including combined approaches in different tumor stages. Those studies demonstrate the feasibility of endoscopic resections of TSs.[708,711,714]

Konovalov et al.[710] reported ESBS in 5 cases. In 4, tumor resection was performed in 2 stages combining the retrosigmoid suboccipital approach (RSA) and lateral extended transsphenoidal endoscopic approach; in 1 case, the TS was resected in a single session via EEA.

Other uses of the endoscope for the resection of TS have also been described. Haidar et al.[703] described 2 cases of infratemporal fossa schwannomas that were completely resected using minimally-invasive approaches: the first case using an open preauricular subtemporal approach and the second case using a purely endoscopic transnasal approach. Wallace et al.[716] described a case of a 59-year-old patient with TS involving the ventral margin of Meckel's cave and the cavernous sinus, abutting the ICA. They described a unique technique of endoscopic-assisted resection via lateral orbitotomy. Samii et al.[709] described an endoscope-assisted retrosigmoid intradural suprameatal approach for dumbbell TSs. Twenty patients were enrolled: 8 had dumbbell-shaped tumors, 8 had middle fossa tumors, 3 had extracranial extension, and 1 had a posterior fossa tumor. GTR was achieved in 15 and near-total resection (NTR) in 5 patients. They conclude that endoscopy enlarges the surgical view and may be safely applied to increase tumor resection rate.

Several microsurgical and endoscopic approaches, ranging from ventral to anterolateral, lateral, and posterolateral, have been reported in the surgical management of TSs. Functional outcomes have varied depending on the existence of preoperative symptoms, tumor size, location, and surgical team experience.[699–727]

In larger reported series, either permanent or transient postoperative deterioration in neurological function, including trigeminal neuropathy, abducens nerve palsy, and trigeminal neuralgia, was experienced. When microsurgery alone is applied, up to 85% of cases can be safely resected, with minor complications reported.[699–724] The most challenging type is the dumbbell-shaped tumor that crosses the petrous apex to occupy the posterior and middle cranial fossa or has both intracranial and extracranial extension.[700,705,707,709]

Providing a ventral trajectory, EEAs to Meckel's cave and surrounding structures have been described alone or in combination with microsurgery to increase resection and decrease overall complications. Type A tumors could

TABLE V.C.3. Evidence surrounding surgical management of sinonasal skull-base CGs*

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Durgam[636]	2012	2a	Systematic review of case series	135 Patients with paranasal sinus CG	1. Symptomatic improvement 2. Recurrence	Frontal sinus CG was approached by open (18, 22%) or endoscopic approaches. Overall symptomatic improvement was 91.8% at 34.5 months mean follow-up, with 8.2% recurring within that time frame.
Butler[685]	1989	4	Case series	2 Patients with frontal sinus CG approached through osteoplastic flap	None	Open approach ultimately indicated for superior orbital location
Hill[686]	1992	4	Case series	31 Patients with frontal sinus CG	Recurrence	1 (3%) Recurrence at 2 years
Arat[687]	2003	4	Case series	8 Patients with orbitofrontal CG approached through subbrow incision (7) and frontal sinus exploration (1)	1. Symptomatic improvement 2. Recurrence	Resolution or improvement of symptoms with no recurrence at 1–9 years follow-up. 1 patient required a second surgery to further improve symptoms.
Hughes[688]	2016	4	Case series	4 Patients with orbitofrontal CG approached through fronto-orbital craniotomy (15-25 mm)	Recurrence	No recurrence at 1–20 years follow-up. 7% recurrence rate overall when combined with literature review. Bony curettage of cavity is critical.
Shrirao[689]	2016	4	Case series	4 Patients with orbitofrontal CG approached through superior lid crease approach	Recurrence	No recurrence at 22 months mean follow-up; endoscopic-assisted approach through superior lid crease incision can expand access
Armengot[690]	1993	5	Case report	1 Patient with ethmoid sinus CG approached through external frontoethmoidectomy	Symptomatic improvement	Improvement in vision and exophthalmos at 1 month follow-up
Ochiai[691]	2001	5	Case report	1 Patient with frontal sinus CG approached through bicoronal incision with cranioplasty (60 mm)	Symptomatic improvement	Resolution of ocular symptoms at 1 month follow-up
Aferzon[692]	2002	5	Case report	1 Patient with frontal sinus CG approached through medial brow incision with frontal sinus obliteration	Symptomatic improvement	Resolution of headache at 5 months follow-up
Weiland[693]	2007	5	Case report	1 Patient with pterygoid plate CG approached through fluoroscopic needle aspiration	Symptomatic improvement	Needle aspiration is a potential option for accessible lesions, though the lesion may eventually require marsupialization
Hwang[694]	2009	5	Case report	1 Patient with sphenoid sinus CG approached through endoscopic transsphenoidal surgery	Visual function	Partial improvement of visual function as confirmed on formal testing
Hammami[695]	2010	5	Case report	1 Patient with frontal sinus CG approached through eyebrow incision	1. Symptomatic improvement 2. Recurrence	Resolution of seizures, headache, and eye swelling without recurrence at 2 months follow-up
Korbmacher[696]	2011	5	Case report	1 Patient with sphenoid sinus CG approached through endoscopic transsphenoidal surgery (55 mm)	Lesion size	Partial reduction in size, currently under observation
Marco[697]	2012	5	Case report	1 Patient with frontal sinus CG approached through combined Lynch incision and endoscopic sinus surgery	1. Recurrence 2. Frontal sinus patency	Frontal recess patent with no recurrence at 18 months follow-up

(*Continued*)

TABLE V.C.3. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Deep[669]	2014	5	Case report	1 Patient with frontal sinus CG approached through modified endoscopic Lothrop	1. Recurrence 2. Frontal sinus patency	Wide marsupialization of frontal sinuses via modified endoscopic Lothrop allows for excellent surveillance and frontal recess patency
Imre[698]	2015	5	Case report	1 Patient with orbitofrontal CG approached through osteoplastic flap (37 mm)	1. Symptomatic improvement 2. Recurrence	Resolution of symptoms with no recurrence at 1 year follow-up

*Size range reported whenever available.
CG = cholesterol granuloma.

TABLE V.D. Modified Jefferson staging for trigeminal schwannomas

Type A	Middle cranial fossa lesions derived from the gasserian ganglion
Type B	Derived from the root of the trigeminal nerve
Type C	Middle and posterior fossa (dumbbell-shaped tumors) and are derived from the Gasserian ganglion
Type D	Extracranial tumor with intracranial and infratemporal fossa extension

be managed by extradural supraorbital, subtemporal, or endonasal transpterygoid approaches. Type D could be reached by a transpterygoid approach, effectively exposing the pterygopalatine fossa, foramen rotundum, and Meckel's cave along the course of V2.[700,705,707] A Type D tumor with a small amount of infratemporal fossa extension could be resected via the extradural subtemporal approach. However, the transmaxillary transpterygoid approach would be more suitable for Type D tumors that are primarily located in the infratemporal fossa.[700,705,707,710]

Some proposed contraindications for an EEA resection are significant disease extension into the posterior fossa; tumor size larger than 2.5 cm within Meckel's cave and the middle cranial fossa. Preexisting V1 neuropathy, due to the elevated risk of vidian nerve injury with a transpterygoid approach, can place patients at risk for postoperative corneal keratopathy if they have diminished corneal sensation.[700,705]

With respect to Type B tumors, endoscopic remains controversial. Purely posterior fossa tumors may be resected with open retrosigmoid surgery or retrosigmoid approach assisted with endoscopy. In dumbbell-shaped Type C tumors, the extradural subtemporal approach can optimally expose the structures around Meckel's cave, and an endoscopic-assisted anterior petrosectomy would create a corridor to the posterior cranial fossa. Alternatively, stereotactic radiosurgery can be used to control residual disease in the posterior fossa if decompression of the brainstem is not required.[699–724]

Because of the location of TSs adjacent to or within the cavernous sinus, the trigeminal nerve, its branches, and the 4th and 6th nerves are more vulnerable to injury and care is needed in lateral EEA approaches. Risk of injury is probably related to tumor size and preoperative dysfunction.[699–727] Surgical injury to the abducens nerve (8%), trochlear nerve (3.7%), and oculomotor nerve (1.9%) have been reported. The abducens nerve is the most threatened CN because of its close relationship with trigeminal roots, its long path in the posterior fossa, and its superficial disposition along the cavernous sinus. The limitation of the endoscopic approach in accessing posterior fossa disease is supported by the higher rate of abducens palsy. The rates of dry eye and corneal neurotrophic keratopathy require consideration given that either can be a devastating complication.[699–727]

Direct access to many TSs via EEA offers advantages such as avoiding any need for temporal lobe exposure or retraction, avoiding temporalis muscle split, and minimizing surgical opening. One of the most common complications of EEA, CSF fistula, has been mitigated with multilayer reconstruction with autograft or allograft.[699–727]

Conclusions

Although guidelines for the application of EEA for resecting TSs are still lacking, growing evidence in the form of case series is revealing a pertinent role for endoscopic surgery in maximizing resection and minimizing complications with less invasive procedures. Additionally, due to the rarity of TSs, even most referral centers are still on the learning curve.

As a general rule, extracranial (Type D) and Meckel's cave tumors are ideal candidates for an EEA. The optimal choice between EEA or conventional approaches must depend on the anatomic details of each case, patient preference, and the surgeon's level of comfort and expertise.

- Aggregate Grade of Evidence: D

VI. Optic nerve and orbit

VI.A. Endoscopic optic nerve decompression for traumatic and nontraumatic optic neuropathy

Optic neuropathy (ON) is defined as damage to the optic nerve and resultant visual loss. The etiology of ON is multifactorial and can be broadly classified as traumatic or nontraumatic. Nontraumatic causes include ischemia, inflammation (optic neuritis), and compression or infiltration by tumors. Traumatic ON may be due to various mechanisms, including direct injury to the nerve by fractured bony fragments, intraneural edema, shearing injury, or compression from hematoma.[728]

The EEA for decompression of the intracanalicular segment of the optic nerve, eg, endoscopic optic nerve decompression (EOND), has been extensively described in the literature,[729–735] and provides a minimal access route to obtain excellent exposure of the orbital apex and optic nerve. Although high-dose corticosteroid therapy is considered the initial and/or mainstay of treatment for traumatic ON,[736,737] some evidence suggests no benefit or even detrimental effects of steroids in these patients.[738,739] Thus, there have been multiple studies that attempt to assess the utility of endoscopic decompression in management of traumatic ON.[728,740–753] To date, evidence is limited to 1 systematic review and several retrospective case series. Evidence for nontraumatic ON is even more limited, with only small case series available,[728,754–758] highlighting the need for evidence-based recommendations regarding surgical management of this rare and challenging patient population.

The available evidence for EOND in traumatic ON that is not responsive to corticosteroid therapy and nontraumatic ON was reviewed in regard to the postintervention visual outcomes, timing of surgical intervention, and the safety and complications of EOND were evaluated. Inclusion criteria included evaluation of EOND for either traumatic or nontraumatic ON, case series of at least 10 EOND, and clearly defined endpoints.

There were 21 studies that met criteria and were included in this review. There were 15 studies representing 718 patients that assessed EOND in the setting of traumatic ON, 5 studies representing 58 patients in nontraumatic ON, and 1 study that assessed EOND in both etiologies (15 patients with traumatic ON and 4 with nontraumatic ON).

Of the 58 patients with nontraumatic ON, 40 (69%) were caused by tumors. The most common tumor was meningioma (23/40, 58%). There were 10 patients who underwent EOND for IIH and papilledema, 4 for fibrous dysplasia, and 4 for endocrine orbitopathy (Table VI.A).

VI.A.1. *Visual outcomes after EOND*

There was significant heterogeneity of studies in reporting visual outcome measurements, with most studies considering any improvement in vision a surgical success. In patients undergoing EOND for nontraumatic ON, visual acuity improved in 28% to 89% of patients.[728,754–758] In those with traumatic ON, improvement was seen 35% to 82% of the time.[728,740–753] Although there was no data assessing differences in outcomes in patients who present with clinical blindness (no light perception [NLP]) compared to those with partial visual loss in the setting of nontraumatic ON, in cases of traumatic ON evidence suggests that patients with partial vision (light perception or better) have better visual outcomes postoperatively. Rates of improvement in patients presenting with NLP range from 0% to 62%,[741,743,747,750,753] whereas rates of improvement in those with partial vision loss range from 50% to 100%.[741,743,747,750,752,753] In a large systematic review of traumatic ON, rates of improvement were decreased in those with NLP preoperatively (41% vs 84-93% in patients with partial vision loss).[740] Although improvement in vision is seen in the majority of cases, there is insufficient granularity and follow-up data to establish whether the improvements seen in these patients are clinically meaningful. Only 1 study on traumatic ON in this review actually reported on rates of "useful vision" (equivalent of 20/60 or better) after EOND, and demonstrated a rate of 24% (10/42).[752]

VI.A.2. *Timing of surgery in EOND*

The timing of EOND for optimization of visual outcomes remains controversial. Although optic nerve axon damage has shown to occur after 72 hours,[759] evidence in the literature is equivocal in terms of the benefit of early intervention. For patients with nontraumatic ON, no evidence exists on the benefit of early intervention. This is likely due to delayed presentation of these patients in the setting of a more insidious onset of ON. In cases of traumatic ON, 3 studies suggested better visual prognosis if surgery is performed ≤3 days from diagnosis.[745,747,750] A large systematic review of 576 patients did not show any significant difference in outcomes with early vs late surgical intervention.[740]

VI.A.3. *Complications after EOND*

Complications were inconsistently reported in the included studies, with 4 articles assessing EOND in patients with traumatic ON not documenting any complications.[744,746,749,750] In patients with traumatic ON, the rate of major complications was 2.3% (14/622). These included 10 CSF leaks, 6 bleeding complications (including 1 carotid artery injury and 1 cavernous sinus hemorrhage), 4 infections, and 2 cases of worsened vision. The largest systematic review to date on traumatic ON reported 52 total complications, of which 42 (80.7%) were considered minor.[740]

In patients with nontraumatic ON, the overall rate of complications reported in 5 studies was 8 of 58 (13.8%). Major complications included 4 cases of visual changes (2 decreased visual acuity, 2 worsened diplopia) and 1 CSF leak. Another small case series reported 1 case of

TABLE VI.A. Evidence for endoscopic optic nerve decompression

Study	Year	LOE	Study design	Study group	Clinical endpoints	Conclusion
Dhaliwal[740]	2016	3	Systematic review of case reports/case series	567 Patients with traumatic optic neuropathy	Visual acuity, time to surgery	Visual acuity improved in 309/567 (54%) of patients. There was no significant increase in improvement with early surgery ($\leq$3 days). Patients with NLP at presentation less likely to recover (41%) compared to those with intact vision (LP 89%, HM 93%, FC or better 84%)
Berhouma[754]	2014	4	Retrospective case series	11 Patients nontraumatic optic neuropathy (8 meningiomas, 1 trigeminal neuroma, 1 ossifying fibroma, 1 orbital pseudotumor)	Visual acuity, visual fields, and fundoscopy at 6-month follow-up	Visual acuity improved in 6/11 (54%); visual acuity stable in 4 (36%); visual acuity worsened in 1 (9%). Visual fields improved in 3/11 (27%). Fundoscopy improved in 2/11 (18%)
Emanuelli[746]	2015	4	Retrospective case series	26 Patients with traumatic optic neuropathy	Visual acuity	Visual acuity improved in 17/26 (65%)
Hameed[747]	2014	4	Prospective case series	10 Patients with traumatic optic neuropathy	Visual acuity, complete vs partial visual loss preoperatively, time to surgery	Visual acuity improved in 7/10 (70%) patients. 1/3 (33%) with NLP improved, 6/6 (100%) with partial vision loss improved. 2/2 (100%) with surgery $\leq$3 days improved vs 5/6 (83%) with surgery $>$3 days.
Sencer[755]	2014	4	Retrospective case series	10 Patients with nontraumatic optic neuropathy (idiopathic intracranial hypertension)	Visual fields, visual acuity, fundoscopy	Visual fields improved in 8/10 (80%). Visual acuity improved in 8/9 (89%). Papilledema resolved in 7/9 (78%).
Xu[748]	2014	4	Retrospective case series	74 Patients with traumatic optic neuropathy	Visual acuity, optic nerve sheath incision	Visual acuity improved in 47/74 (64%) patients overall; 19/31 (61%) improved with nerve sheath incision vs 28/43 (65%) without.
Song[749]	2013	4	Retrospective case series	85 Patients with traumatic optic neuropathy	Visual acuity, time to surgery	Visual acuity improved in 38/85 (44%). Visual acuity improved in 19/45 (42%) of patients with surgery $\leq$3 days, 19/40 (48%) of patients with surgery $>$3 days.
Yang[750]	2012	4	Retrospective case series	96 Patients with traumatic optic neuropathy	Visual acuity, complete vs partial visual loss preoperatively, time to surgery	Visual acuity improved in 39/96 (41%) overall, 19/72 (26%) in NLP patients, 20/24 (83%) in LP or better patients. Surgery $>$3 days significantly associated with unrecovered visual acuity. No significant association with optic nerve sheath incision.
Murchison[756]	2011	4	Retrospective case series	18 Patients with nontraumatic optic neuropathy (14 skull base tumors, 1 meningioma, 3 inflammatory cases)	Visual acuity, diplopia	Visual acuity improved in 5/18 (28%), stable in 10/18 (56%); diplopia improved in 5/6 (83%)
Peng[751]	2011	4	Retrospective case series	41 Patients with traumatic optic neuropathy	Visual acuity, time to surgical intervention	Visual acuity improved in 33/41 (81%) overall; 27/28 (96%) improved when surgery $<$7 days, 6/13 (46%) improved when surgery $>$7 days.
Thaker[752]	2009	4	Retrospective case series	55 Patients with traumatic optic neuropathy	Visual acuity, optic nerve sheath incision, complete vs partial visual loss preoperatively	Visual acuity improved in 1/13 (8%) of patients with NLP preoperatively and 34/42 (81%) of patients with LP or better preoperatively. Visual acuity $\geq$6/18 in 8/24(33%) of patients undergoing sheath incision, 2/18 (11%) with sheath intact ($p = 0.14$).

(*Continued*)

hyponatremia and 1 corneal abrasion in patients with nontraumatic ON.[757]

Most studies did not discuss minor complications, with only 1 study describing a rate of intranasal synechia formation of 26% in patients with traumatic ON.[741] The rate of minor complications noted in both the traumatic and nontraumatic ON groups is likely also underestimated as most studies focused solely on rates of major complications including CSF leak, bleeding, worsening vision or blindness, and diplopia. Although the

TABLE VI.A. Continued

Study	Year	LOE	Study design	Study group	Clinical endpoints	Conclusion
Li[753]	2008	4	Retrospective case series	176 Patients with traumatic optic neuropathy	Visual acuity	Visual acuity improved in 96/176 (55%) patients. In patients with NLP, 41/108 (38%) improved vs 86/129 (67%) in those with partial visual loss.
Wang[741]	2008	4	Retrospective case series	46 Patients with traumatic optic neuropathy	Visual acuity, complete vs partial visual loss preoperatively	Visual acuity improved in 29/46 (63%) overall, 21/34 (62%) in NLP patients, 7/8 (88%) in LP or better patients
Li[753]	2008	4	Retrospective case series	42 Patients with traumatic optic neuropathy	Visual acuity, time to surgery	Visual acuity improved in 4/42 (9.5%). 14/42 (33%) had surgery within 3 days, 19/42 (45%) between 3 and 7 days, 9/42 (21%) ≥7 days.
Pletcher[757]	2007	4	Retrospective case series	7 Patients with nontraumatic optic neuropathy (4 fibrous dysplasia, 2 meningioma, 1 mucopyocele, 1 osteoma, 1 endocrine orbitopathy)	Visual acuity	Visual acuity improved in 7/10 (70%) eyes
Lund[758]	2006	4	Retrospective case series	12 Patients with nontraumatic optic neuropathy secondary to meningiomas	Visual acuity, visual fields, ocular balance, ductions, exophthalmometry	Visual acuity improved in 7/12 (58%); ocular balance/ductions improved in 4/12 (33%); 2.3 mm mean reduction in proptosis
Rajiniganth[742]	2003	4	Prospective case series	44 Patients with traumatic optic neuropathy	Visual acuity, time to surgery	Visual acuity improved in 16/23 (70%) patients undergoing surgery at <7 days vs 5/21 (24%) >7 days.
Jiang[743]	2001	4	Retrospective case series	17 Patients with traumatic optic neuropathy	Visual acuity, time to surgery	Visual acuity improved in 6/17 (35%) patients. 0/2 (0%) improved with surgery <7 days, both NLP. 6/12 (50%) improved with surgery ≥7 days (all patients with partial vision loss).
Kountakis[744]	2000	4	Retrospective case series	17 Patients with traumatic optic neuropathy	Visual acuity	Visual acuity improved in 14/17 (82%) patients.
Luxenberger[728]	1998	4	Retrospective case series	15 Patients with traumatic optic neuropathy, 4 with endocrine orbitopathy	Visual acuity	Visual acuity improved in 7/15 (47%) of traumatic patients, 3/4 (75%) of endocrine patients
Nayak[745]	1991	4	Retrospective case series	63 Patients with traumatic optic neuropathy	Visual acuity, time to surgery	Visual acuity improved in 19/63 (30%) overall, 18/26 (69%) <3 days, 1/14 (7%) ≤7 days, 0/23 (0%) >7 days.

FC = finger counting; HM = hand motion; LOE = level of evidence; LP = light perception; NLP = no light perception.

major complication rate of 2.3% in patients with traumatic ON is likely underestimated given the heterogeneity of reporting practices in the literature, current evidence suggests that EOND is a safe procedure in experienced hands.

In comparison to EOND, the lateral orbitotomy approach first described by Kronlein in 1889 has more recently been modified to gain access to lesions of the lateral orbit, orbital apex, parasellar region, and middle fossa while avoiding the need for craniotomy.[760–763] In the 2 largest series to date, complication rates were comparable to EOND for nontraumatic ON. One study of 13 patients reported postoperative CSF leaks in 3 of 13 (23%) patients, supraorbital numbness in 2 of 13 (15%) patients, and partial ptosis in 2 of 13 (15%) patients.[763] Another study of 18 patients reported no postoperative CSF leaks, transient lateral rectus paresis in 3 of 18 (17%) patients, decreased visual acuity in 1 of 18 (6%) patients, and worsened diplopia in 1 of 18 (6%) patients.[762]

The currently available evidence on EOND for traumatic and nontraumatic ON suggests the possibility for improvement in visual acuity, although the ability to provide clinically meaningful visual improvement has yet to be clearly established. The heterogenous pathology involved, the varying severity of presentation as well as the relative rarity of patients with ON undergoing EOND precludes the ability to determine a statistically significant improvement in visual outcomes in these patients. Moreover, the majority of available evidence assesses traumatic ON, with data on nontraumatic causes notably lacking. Based on this evidence, management of patients with traumatic ON unresponsive to corticosteroids would include the option of EOND. There is insufficient data to assess whether timing of surgery improves outcome, although there is no evidence

of harm with earlier intervention. Patients presenting with NLP are less likely to achieve benefit from EOND than those presenting with partial vision loss (Table VI.A).

Although the available evidence is quite limited for nontraumatic causes of ON, it appears that based upon the pathology involved and overall prognosis for the patient, having an experienced surgeon perform an EOND could improve visual outcomes and potentially enhance success in underlying disease management (eg, in the case of tumors). There is insufficient data for specific recommendations or further stratification at the present time on the role of EOND in nontraumatic ON.

- Aggregate Quality of Evidence: C (Level 3: 1 study; Level 4: 20 studies).
- Benefit: Improved visual acuity
- Harm: Potential for major complications such as CSF leak, worsening vision loss, major bleeding. Risks of general anesthesia, sinonasal complications
- Cost: Moderate, requires operative intervention under general anesthesia.
- Benefit-Harm Assessment: Preponderance of benefit over harm (when performed by experienced surgeons).
- Value Judgments: Additional studies with larger sample sizes and prospective studies are needed to improve the LOE and determine efficacy and timing of intervention; however, a preponderance of benefit over harm favors option in appropriately selected patients.
- Recommendation Level: Option
- Intervention: EOND may be considered in traumatic ON as an adjunctive treatment in patients with minimal response to corticosteroid therapy. EOND may also be considered an option in appropriately selected cases of nontraumatic ON.

VI.B. Intraconal tumors

Intraconal tumors have historically been addressed via open approaches by ophthalmic plastic and neurosurgeons. With the proliferation of endoscopic skull-base surgery, endoscopic approaches to intraconal orbital tumors have gained popularity. For appropriate lesions, endoscopic approaches offer the advantage of enhanced visualization and illumination of the posterior inferomedial orbit with reduced morbidity as compared to external techniques.[764–769] A multidisciplinary team approach is an essential component for surgical planning and management.

Orbital tumors are rare with an incidence of only 3 to 5 tumors per 1 million people per year.[770,771] Most orbital tumors present in patients between the 4th and 7th decade. Vasculogenic lesions are most common and account for 17% of orbital masses. Among these, orbital cavernous hemangiomas (OCH) are the most common. Other common benign lesions include optic nerve glioma (4%), meningioma (4%), and pseudotumor (8%). The most common malignant lesion is non-Hodgkin's lymphoma (8%) followed by orbital metastases.

Due to the relatively recent application of the endoscopic approach and the low incidence of intraconal tumors, to date, no RCTs or cohort studies have been performed. The majority of data has been acquired by retrospective case reports and case series. The highest LOE has been provided by 2 systematic reviews as well as 2 multicenter retrospective review studies.[769,772–774]

Adaptation of the endoscopic approach to address intraconal lesions represents a natural evolution from the more established techniques of medial orbital decompression and transsphenoidal optic nerve decompression. Modifications for increasing bony exposure, such as resection of the orbital process of the palatine bone have been described in order to facilitate bimanual dissection of intraconal lesions. This technique has been shown to enhance surgical exposure by a volume of 0.36 ± 0.42 cm^3, facilitating extraocular muscle retraction as well as circumferential tumor dissection.[775]

The medial rectus muscle represents the doorway to the intraconal space and must be safely retracted to provide adequate access. Described retraction techniques include external medial rectus muscle retraction at the globe insertion point by using a vessel loop, static transseptal and retrochoanal retraction using a vessel loop, and dynamic 4-handed transseptal retraction using an instrument such as a ball-tipped probe.[773,774,776,777] Both transseptal techniques provide the greatest intraconal exposure by surface area; however, the 4-handed approach allows for continuous adjustments in tension, leading to increased protection of the neuromuscular inputs to the medial rectus muscle.[776] This view is supported by other studies[773] in which avoidance of prolonged tonic medialization is recommended over concerns of potential neurovascular traction injury.[777]

Within the intraconal space, considerable variability of the neurovascular supply to the medial and inferior rectus muscles is evident. However general branching patterns of the inferior division of the oculomotor nerve and inferomedial muscular trunk of the ophthalmic artery enable a conceptualization of the medial intraconal space into 3 zones. As lesions move from the anterior inferior to posterior superior zones, the complexity of the dissection and risk of neurovascular injury increase.[778] These zones may therefore also be used to provide a graduated approach as orbital teams gain experience in tackling these lesions.

The largest multicenter study of endoscopic management of orbital lesions focused specifically on methods of OCH resection. As compared to extraconal lesions, methods for approach and resection of intraconal OCHs were associated with a larger disparity in techniques. The majority (69.6%) of all cases were performed as a team approach. Postoperative outcomes were favorable, with an improved visual acuity in 52.2% of the cases, while no patients showed worsening of vision. Postoperative diplopia rates were also favorable, with 78.3% of cases resulting in a symmetric eye position. Immediate preservation of binocular vision was achieved in 60.9% of patients, while

the majority of patients with iatrogenic diplopia resolved within 2 to 3 months. These rates are comparable to open approaches including transconjunctival, transorbital, and craniotomy techniques.[779–782]

As compared to extraconal lesions, intraconal lesions were more likely to be associated with incomplete resection (31.25% and 14.29%, respectively). Additionally, intraconal lesions showed a higher risk of immediate postoperative diplopia and enophthalmos, prompting a higher rate of immediate orbital reconstruction. Among all patients with postoperative diplopia, none were associated with the use of the transseptal dynamic retraction technique. Binarial approaches after performance of a septectomy or septal window were exclusively used for intraconal lesions. Among those, 37.5% used a 4-handed approach.

The second, earlier, multicenter study mainly addressed the extent of medial rectus retraction techniques. The authors concluded that detachment of the medial rectus muscle (MRM) was useful in the setting of intraconal tumors.[767] However, in light of subsequent demonstration of the utility dynamic MRM retraction, the need for MRM disinsertion has been called into question.

In the majority of extraconal lesions, formal orbital reconstruction is not required. However, in the setting of extensive intraconal dissection, recapitulation of the medial and inferior orbital walls helps to prevent enophthalmos and resultant diplopia. An NSF has been shown to be capable of providing complete coverage of the entire medial and inferior orbit.[783,784] This technique is favored because it contracts around the orbitotomy in a delayed fashion, allowing for immediate blood egress and resolution of edema thereby obviating the risks of orbital compartment syndrome associated with immediate rigid reconstruction. However, evidence is weak and based on limited small case series and expert opinions.

Although the field of endoscopic intraconal surgery remains in its infancy, the limited available studies suggest that the functional outcomes are comparable to external approaches with the advantage of improved visualization, decreased morbidity, and the avoidance of scars[767,769,774,775] (see Table VI.B). As the field continues to expand through the growth of multidisciplinary orbital teams, additional higher-quality outcomes data is anticipated.

- Aggregate Grade of Evidence: D (Level 3a: 4 studies; Level 4: 23 studies)
- Benefit: Endoscopic approaches for intraconal tumors show a reduced morbidity as compared to open approaches, including avoidance of globe retraction and external incisions in appropriately selected cases. The major indication for the endoscopic orbital surgery is for tumors medial to the optic nerve.
- Harm: Potential optic nerve and ophthalmic artery injury, diplopia, vision loss, and enophthalmos.
- Cost: No studies have examined the issue of cost related to endoscopic orbital surgery.
- Benefits-Harm Assessment: Although the evidence mainly consists of small case series and expert opinions, endoscopic orbital approaches are described as safe, associated with reduced external morbidity, and do not appear to have an increased recurrence or complication rate as compared to open approaches. Because of changes in the extraocular muscle vectors after endonasal orbitotomy, the risk of diplopia might be increased as compared to open approaches, although no study specifically addressed this issue.
- Value Judgment: Endoscopic orbital surgery appears to provide comparable functional outcomes and short-time recurrence rates as compared to traditional open approaches. No study to date has compared endoscopic and open approaches directly. However, for patients with tumors medial to the optic nerve, the endoscopic orbital approach, if needed as a multidisciplinary orbital team approach, is an option with similar resection outcomes and reduced external morbidity.
- Policy Level: Option
- Intervention: Endoscopic orbital surgery is likely a reasonable option for patients with tumors medial of the optic nerve. A multidisciplinary approach should be strongly considered.

VII. Vidian neurectomy

The evolution of endoscopic skull-base surgery combined with improved understanding of the anatomy and function of the vidian nerve has led to a resurgence of interest in the procedure of vidian neurectomy.[799–801] The procedure was very popular in the 1970s and 1980s before it lost favor because of reports of complications and questions regarding long-term efficacy.[802–806] Golding-Wood is credited with the development of vidian neurectomy in 1961. However, studies soon after started noting short-term and long-term recurrence of symptoms. Adverse effects such as dry eyes resulting from decreased lacrimation as well as severe arterial bleeding from the sphenopalatine artery and maxillary artery were being reported. Other complications such as numbness of the cheek and palate, ophthalmoplegia, and even blindness were reported. These complications, along with the development of pharmacologic therapy for rhinitis, resulted in disfavor for vidian neurectomy by the 1990s.[804] Robinson and Wormald[801] were critical to the reintroduction of the technique after publishing their case series in 2006. More selective procedures that may spare secretomotor innervation to the lacrimal gland such as posterior nasal neurectomy and in-office posterior nasal tissue cryoablation have now been described.[805,806]

Vidian neurectomy has been described for treating symptoms of allergic, nonallergic, and mixed rhinitis refractory to medical therapy.[800] In particular, several authors describe its utilization in intractable vasomotor rhinitis, a

TABLE VI.B. Intraconal tumors

Study	Year	LOE	Study design	Study group	Study endpoint	Conclusion
Bleier[772]	2016	3a	Retrospective, multicenter study	23 Patients from 6 centers with cavernous hemangioma	Endoscopic endonasal outcomes with cavernous hemangioma	Management for intraconal and extraconal is similar; there is more variability for intraconal lesions due to increased technical complexity, continued research is needed
Lenzi[773]	2016	3a	Systematic review	12 Papers, 17 cases with cavernous hemangioma	Endoscopic endonasal outcomes with cavernous hemangioma	MRM management is key. Larger multi-institutional studies needed.
Yao[774]	2016	3a	Review	N/A	Endoscopic endonasal outcomes with cavernous hemangioma	A multidisciplinary team approach, including an oculoplastic surgeon, is essential; as the cumulative surgical experience increases, the indications for this approach will likely continue to expand
Wu[785]	2013	3a	Multicenter, retrospective case series	12 Patients with cavernous hemangioma	Endoscopic endonasal approaches with medial rectus detachment as an adjunct via transcaruncular approach	Detachment of the medial rectus muscle can be useful for intraconal tumors
Mueller[775]	2018	4	Morphometrical analysis, cadaveric study, surgical validation	59 Human dry skulls, 15 cadaveric and live orbits	Necessity of resection of the OPPB, retraction of inferior rectus muscle	Complete surgical resection of the OPPB improves surgical exposure facilitating retraction of the inferior rectus muscle and circumferential dissection of lesions within this space.
Lin[776]	2016	4	Cadaver dissection	8 Orbits	Medial rectus retraction techniques	Transseptal MRM retraction was most favorable and provided the largest endoscopic corridor to the medial intraconal space.
Alimohamadi[786]	2015	4	Retrospective case review	5 Patients (chronic, granulomatous inflammation, malignant peripheral nerve sheath tumor of trigeminal nerve, chordoma, angiofibroma, meningioma)	Endoscopic sublabial and transmaxillary approach	The combined endoscopic sublabial and endonasal transmaxillary approach is a safe and effective method for resection of lesions in the PPF and inferomedial orbital apex.
Chhabra[769]	2014	4	Anatomic cadaveric study	5 Orbits	Feasibility of vascularized flap for reconstruction of medial and inferior orbit	Immediate vascularized flap reconstruction of the orbit may help to limit the attendant morbidity including diplopia and enophthalmos. Feasibility was demonstrated
Bleier[778]	2014	4	Cadaveric study	10 Orbits	Neurovascular supply to medical rectus muscle; compartmentalization of Intraconal space into 3 spaces	The neurovascular supply to the medial rectus muscle describes a varied but predictable pattern.
Bleier[787]	2014	4	Surgical dissection	12 Orbits	Orbital floor decompression with inferomedial strut preservation	Orbital floor decompression with inferomedial strut preservation may be reliably performed using purely endoscopic techniques.
Berhouma[754]	2014	4	Retrospective chart review	11 Patients (spheno-orbital meningioma (4), optic nerve meningioma (3), trigeminal neuroma (1), orbital apex meningioma (1), ossifying fibroma (1), inflammatory pseudotumor (1))	Orbital and optic nerve decompression	Endoscopic endonasal optic nerve decompression is a safe, effective, and minimally invasive technique affording the restoration of visual function in patients with nontraumatic compressive processes of the orbital apex and optic nerve.

(*Continued*)

TABLE VI.B. Continued

Study	Year	LOE	Study design	Study group	Study endpoint	Conclusion
Jacquesson[788]	2014	4	Retrospective surgical review	N/A	Visual outcomes with transorbital approaches.	This strategy proved to be beneficial for patients and showed improvements in visual outcome. Further studies are needed.
Felippu[789]	2013	4	Retrospective case review	100 Patients with lesions of the orbital apex, cavernous sinus, optic nerve, clivus, parapharyngeal space, infratemporal fossa, or pterygopalatine fossa	Surgical instrument positioning	The surgeon can precisely identify the position of the surgical instrument without losing his or her way, thereby significantly reducing the rate of complications
Sia[790]	2012	4	Retrospective case series	2 Patients with fibrous dysplasia, meningioma	Orbital/optic nerve decompression, additional lateral wall decompression	Transnasal endoscopic approach may be a viable option for decompression of benign orbital apex lesions.
Murchison[756]	2011	4	Retrospective chart review	18 Patients with cavernous hemangioma (2), juvenile angiofibroma (2), sino-orbital aspergillosis (2), SCCa (3), Wegener granulomatosis (1), idiopathic orbital inflammatory disease (2), cavernous sinus/superior orbital foramen (1) schwannoma (1), atypical meningioma(1), metastatic renal cell carcinoma (1), osteoblastoma (1), chondrosarcoma (1), chordoma (1)	Efficacy of endonasal approaches with transconjunctival supplementation	In carefully selected cases, this technique provides excellent visualization and access to the orbital apex and avoids larger craniofacial surgeries.
Vohra[791]	2011	4	Review	N/A	Differential diagnosis for orbital apex lesions	An awareness of common imaging patterns can help to generate a focused differential diagnosis of orbital apex tumors.
Lee[792]	2012	4	Retrospective case review	5 Patients with fibrous dysplasia (2), ethmoid adenoid cystic carcinoma (1), schwannoma (1), cavernous hemangioma (1)	The safety of orbital apex decompression for sino-orbital apical lesions.	The endonasal endoscopic technique can be a safe, effective and minimally invasive surgical modality for the removal of sino-orbital and orbital apical lesions.
Chen[793]	2010	4	Retrospective case series	10 Patients with cavernous hemangioma	Outcomes with transnasal transssphenoidal microsurgical approaches	Transnasal transsphenoid microsurgical approaches are minimally invasive surgeries for cavernous hemangiomas located at inferomedial part of orbital apex.
Almond[794]	2009	4	Retrospective chart review	5 Cases with fibrous dysplasia (1), hemangioma or schwannoma (3), cavernous hemangioma (1)	Orbital decompression for visual improvement	Orbital apex lesions can often be effectively and relatively safely treated by endoscopic decompression alone.
Murchison[795]	200	4	Retrospective case review	3 Patients	Access to the orbital apex with a posterior septectomy	The use of posterior nasal septectomy in endoscopic surgery improves visualization and surgical access to the orbital apex.
Miller[796]	2008	4	Case report	1 Patient with solitary fibrous tumor	Endoscopic transethmoidal approach for biopsy of a posterior orbital lesion.	The transnasal endoscopic technique is useful in both biopsy and removal of posterior medial orbital lesions.
Kloek[797]	2006	4	Retrospective interventional case series	5 Patients with cavernous hemangioma.	Orbital decompression (5) (endoscopic endonasal) plus external lateral orbitotomy (2) for compressive optic neuropathy	Orbital decompression is a therapeutic option for patients with compressive optic neuropathies from benign orbital apex tumors.

(*Continued*)

TABLE VI.B. Continued

Study	Year	LOE	Study design	Study group	Study endpoint	Conclusion
Karaki[768]	2006	4	Case study	1 Patient with cavernous hemangioma	Endoscopic transethmoidal approach for cavernous hemangioma.	An endoscopic transethmoidal approach provides excellent cosmetic results with less bleeding.
Tsirbas[798]	2005	4	Retrospective case series	3 Patients with cavernous hemangioma (1), anaplastic high-grade sarcoma (1), myxoid liposarcoma (1)	Transantral endoscopic approach using a modified Caldwell-Luc incision, medial and inferior, orbital decompression, lateral decompression, frontal craniotomy for orbital apex lesions	Benefit from a multidisciplinary and individualized plan for apical lesions. Endoscopic approaches can be used to improve visualization and access to a difficult surgical area. They also allow extra instrumentation to be used through the relatively capacious paranasal sinuses.
Sethi[767]	1997	4	Case series	6 Patients with orbital apex lesions	Orbital decompression, transnasal endoscopic technique to biopsy the orbital apex	The transnasal endoscopic approach to the orbital apex provides excellent illumination, magnification, and a panoramic view.

LOE = level of evidence; MRM = medial rectus muscle; N/A = not applicable; OPPB = orbital process of the palatine bone; PPF = pterygopalatine fossa; SCCa = squamous cell carcinoma antigen.

form of chronic rhinitis that is characterized by watery rhinorrhea presumed to be resulting from an imbalance of parasympathetic and sympathetic input to the nose.[801] In the realm of skull-base surgery, vidian neurectomy as well as resection of pterygopalatine fossa contents is often intentionally performed to treat or access a skull-base lesion. Complications or sequelae from vidian neurectomy should therefore also be known to nonrhinologic skull-base surgeons.

Eighteen original studies published after 1997 are discussed in Table VII.[801,806–822]

The year 1997 was chosen to evaluate the efficacy and safety of vidian neurectomy in the past 2 decades, after evolution and adoption of contemporary endoscopic endonasal techniques. Of these 18 studies, two-thirds were case series (12/18). Other original studies also included: 3 case-control studies,[807,811,814] 1 cohort trial,[813] and 2 RCTs.[810,815]

VII.A. Indication for the use of vidian neurectomy

Five of the 18 studies were selectively performed in patients of vasomotor rhinitis.[801,808,809,812,819] Most studies employed surgery when symptoms were refractory to medical therapy, although descriptions of inclusion criteria varied (Table VII). Preoperative therapy, when reported, included intranasal corticosteroids, oral antihistamines (6 studies), immunotherapy and septoplasty, or inferior turbinate surgery (1 study). In these situations, vidian neurectomy was performed based on poor response to therapeutic interventions. Robinson and Wormald[801] used a good response to anticholinergic nasal spray as an indication for a prediction of good response to vidian neurectomy. Eleven studies were performed in patients with allergic rhinitis, or a mixed population.[806,807,810,811,813–818,820–822]

VII.B. Efficacy of vidian neurectomy

Studies reported efficacy of vidian neurectomy in the management of vasomotor rhinitis and allergic rhinitis (Table VII) in the short term. Where outcomes were reported, all the studies reported a significant improvement in rhinorrhea and most of them also observed an improvement in nasal obstruction for vasomotor rhinitis[801,808,809,812,819] (Table VII). Studies on allergic rhinitis subjects also reported improvement in rhinorrhea and nasal obstruction but had mixed results in terms of benefits for sneezing and itching.[806,807,810,811,813–818,820–822] Results are detailed in Table VII.

In a recent study, in-office cryosurgical posterior nasal tissue ablation was performed under local anesthesia in 27 patients with allergic or nonallergic rhinitis.[806] Total nasal symptom scores were significantly reduced at 7 days, and sustained at 365 days, and no complications were reported.[806] Of the remaining 17 studies, endoscopic vidian neurectomy was studied in 11 (61%) and posterior nasal neurectomy in 6 (33.3%) studies.

The studies however had variable follow-up, with a minimal average of 18.5 months in the studies reporting follow-up.[800] At this duration, patient-reported symptoms and physician-recorded objective measurements were noted to be improved (Table VII provides details). The average maximal follow-up time reported in 18 studies with 1622 patients was 65 months, and patients were noted to have improved symptoms and objective measures in these studies as well. Ten studies (470 patients) reported a mean follow-up time of 33.6 months.[800] The relatively short mean duration of follow-up makes predication of long-term efficacy problematic. However, in general, vidian neurectomy appears to be relatively safe and effective in the modern surgical era.

TABLE VII. Evidence for the efficacy and complications associated with vidian neurectomy

Study	Year	LOE	Study design	Study group	Surgical technique (sides where reported)	Clinical endpoint(s) studied	Complications reported
Lai[807]	2017	3b	Case control	118 Patients with "refractory rhinitis" with a poor treatment response to 6-month trial of corticosteroid nasal sprays	Diode laser-assisted endoscopic intrasphenoidal vidian neurectomy (43) vs cold instrument (75); (217 sides; breakout not reported)	Significant reduction in VAS score for global rhinitis symptoms in both groups at 6 months	Temporary dry eyes, mild nasal crusting, cheek numbness and severe postoperative bleeding. Authors reported: "All complications subsided within 6 months." No statistically significant difference in epistaxis was noted (rates not reported) between the groups. Epistaxis requiring return to surgery reported in 3 patients in the cold instrument group.
Hwang[806]	2017	4	Case series	27 Patients with AR or nonallergic rhinitis	Cryosurgical posterior nasal tissue ablation; office-based under local anesthesia	TNSS was reduced significantly at 7 days postintervention. Improvement sustained at 30 days, 90 days, and 365 days	No complications were noted to occur during the study
Zhang[808]	2015	4	Prospective case series	11 Patients of VMR refractory to medical therapy and with significant impact on QOL, negative allergy history and skin testing. CT to rule out skull-base defect or CSF fistula	Transnasal EVN via PPF approach; with navigation system; bilateral in all	Average follow-up: 19.4 months. Statistically and clinically significant improvement in SSQ and SNOT-22 compared with baseline scores ($p < 0.0001$). Rhinorrhea and nasal congestion significantly improved ($p < 0.05$).	No incidence of permanent or measurable dry eye by testing (existence of dry eyes, visual disturbance, reflex tearing) upon comparison of preoperative and 3-month postoperative testing. Other complications: None reported.
Ma[809]	2014	4	Case series	45 Patients with VMR and at least a 3-year history of chronic rhinitis symptoms	Transnasal EVN; bilateral PPF approach	On Chinese traditional symptom scoring system, 88.2% had complete response, 8.9% had partial response and 8.9% had no response in 8.9%. RQLQ: improved in 82.2%; $p < 0.05$; sneezing and rhinorrhea had best response ($p < 0.01$)	Temporary (3–6 month) dry eyes in 33.3% by Schirmer test 3 days postoperation. Palatal numbness in 22.2% (resolved) "No serious complications" reported
Su[810]	2014	2b	Randomized, double-blind (patients and ophthal-mologic examiner), controlled study (1:1)	Group 1: cauterization was used in both distal and proximal vidian nerve stumps in 40 patients Group 2: only the proximal vidian nerve stump was cauterized in 23 patients (40 sides). Subjects were classified as Group 1 if 2 nerve stumps distal (caudal or SPG side) could be precisely cauterized and Group 2 where 1 vidian nerve stump was cauterized proximal to SPG (cranial side): 21 patients (40 sides)	Primary outcome studied was incidence of dry eye, measured by Schirmer's test and OSDI before surgery, and at 7–10 days postoperation and 30 days postoperation. The mean follow-up period was 24 months	In Group 1, the Schirmer's test showed a mean decline of 20 mm (20/30, 66%) at 7–10 days and 15 mm (15/30, 50%) at 30 days. In Group 2, the Schirmer's test revealed significantly lesser dry eye problems, with a mean decline of 16 mm (16/30; 52%) at 7–10 days and 2 mm (2/30; 6%) at 30 days. OSDI at 7–10 days, but not 30 days was better for Group 2. "Complete cessation" of nasal obstruction, sneezing, rhinorrhea without recurrence of symptoms reported for follow-up period.	Postoperative nasal bleeding occurred in 3 patients (6.8%) with 1 patient from group 1 (4.3%) and 3 patients (14.3%) from group 2. Temporary dry eye occurred in both groups, less in Group 2.

(*Continued*)

TABLE VII. Continued

Study	Year	LOE	Study design	Study group	Surgical technique (sides where reported)	Clinical endpoint(s) studied	Complications reported
Albu[811]	2014	3b	Case control	76 Patients with AR with severe ITH	EMAIT: 13; EMAIT plus transnasal PNN: 63	Outcomes similar in both groups. Nasal obstruction, rhinorrhea, sneezing, snoring decreased ($p < 0.001$); RQLQ, nasal resistance significantly improved in both groups by rhinomanometry.	Higher rate of postoperative bleeding in EMAIT-PNN (28%) vs EMAIT (6%) ($p < 0.043$). Mucociliary clearance decreased significantly in both groups in "postoperative period". No serious or other complications reported.
Hsu[812]	2013	4	Case series	8 Patients with VMR	EVN bilateral by powered instrumentation and coblation	No objective or patient reported outcomes reported	No complications occurred in any patient
Tan[813]	2012	2b	Prospective cohort	199 Patients AR (3 groups of intervention)	Group 1: transnasal bilateral EVN; PPF) in 85 patients; Group 2: partial inferior turbinectomy -septoplasty in 46 patients; Group 3: medical treatment in 68	RQLQ and VAS scores at 6 months, 1 year, and 3 years after treatments in groups 1 and 2 significantly lower than group 3. Effect sustained after 3 years in group 1. No improvement with EVN in 10%. Schirmer's test – only used to determine whether vidian nerve was cut off; results not reported	Dry eyes in 30.6% for <1 month; mild nasal dryness: 15.3%; palate numbness: 9.4% (all temporary) Loss of emotional tearing in females only: 7 (8.2%) No epistaxis other severe complications reported
Kobayashi[814]	2012	3b	Case control	24 Patients with drug therapy-resistant, intractable AR	Group 1: endoscopic transnasal selective resection of peripheral branches of posterior nasal nerve identified submucosally in the inferior turbinate (13 patients) vs Group 2: endoscopic PNN (11 patients) All patients had inferior turbino-plasty/septoplasty	Sneezing, rhinorrhoea, obstruction significantly improved in both groups without significant difference between groups. Postoperative drug therapy not required in 54% patients	Postoperative epistaxis requiring packing in 3.33%; transient upper dental numbness in 6.7%. Both complication in Group 2 with PNN. No "major complications" in either group reported
Cassano[815]	2012	2b	Randomized control study	60 Patients with VMR with bilateral nasal polyps	Group 1: FESS and PNN with inferior turbinoplasty in 30 patients vs FESS with IT in 30 patients	Nasal breathing improved at 1-year and 3-year follow-up ($p < 0.001$) in both groups. Rhinorrhea ($p < 0.001$), sneezing and itching improved only in Group 1 ($p < 0.01$). Statistically significant improvement in rhinorrhea and nasal itching ($p = 0.002$) and in sneezing ($p < 0.001$) in Group 1 at 3 years. Rhinomanometry improved in both treatment groups ($p < 0.01$).	Group 1 (FESS + IT PNN): intraoperative nasal packing for bleeding in 2 patients (6.7%); no postoperative epistaxis; nasal dryness in 2 patients (6.7%). Group 2 (FESS + IT): intraoperative nasal packing for bleeding in 4 patients (13.3%), postoperative epistaxis requiring nasal packing in 2 (6.7%) synechia in 1 (3.3%). No orbital or cerebral complications reported in either group

(*Continued*)

TABLE VII. Continued

Study	Year	LOE	Study design	Study group	Surgical technique (sides where reported)	Clinical endpoint(s) studied	Complications reported
Su[816]	2011	4	Case series	174 Patients with AR with poor response to 3 months therapy with intranasal corticosteroid spray	Transsphenoidal EVN; bilateral in 62 patients, unilateral in 112 (236 sides) Mean follow-up 23 months	VAS scores for rhinorrhea, sneezing, obstruction, nasal and eye itching, postnasal drainage significantly improved and sustained at 23 months. However, *p* values were not reported. Failure rate: 1.27% at 1 year	Temporary dry eyes reported 172 of 174 patients (98.85%) with mean duration of 23 days. Long-term dryness over 6 months reported in 6 patients (3.44%) Transient maxillary (V2) nerve numbness was reported in 7 patients (4%) with duration less than 21 days. Epistaxis was reported in 6 patients (3.44%)
Lee[817]	2011	4	Case series	VMR (75) and AR (14)	Transsphenoidal EVN; bilateral Septoplasty was co-intervention in 3 patients	84 of 89 Patients completed postoperative QOL questionnaires; 91.7% subjectively satisfied with results. Failure rate was 8.3%	Temporary dry eyes in 23.8% (20/84) patients; postoperative epistaxis requiring SPA cauterization: 1.2%
Jang[818]	2010	4	Case series	6 Patients with "intractable rhinitis" Non-allergic rhinitis: 1 AR: 5	Transsphenoidal EVN, PPF	Changes in VAS significant for nasal obstruction ($p < 0.05$) and rhinorrhea ($p < 0.05$) sustained for up to 7 years postoperatively. During the follow-up period, no patient needed additional treatment, such as antihistamines or corticosteroids. 1 patient reported mild deterioration of symptoms compared to the immediate postoperative period	Dry eyes postoperatively in 100%; 1 patient (16.67%) continued to have dry eyes at 2 months. Schirmer's test significantly decreased at 1 day, 1 month and 2 months Temporary cheek numbness in 1 (16.7%) that resolved in 1 week Postoperative bleeding controlled with cauterization resolved in 1 (16.7%) No cases of numbness of the palate or teeth, visual disturbance, or facial pain reported.
Liu[819]	2010	4	Case series	67 Patients with VMR	Studied transnasal vs transsphenoidal EVN (106 sides, laterality not reported) Transsphenoidal approach was performed successfully on 42 of 106 sides (39.6%), while the transnasal approach was performed successfully on 91 of 106 sides (85.8%).	Transsphenoidal approach was successful only in patients without an embedded canal. A deviated septum made the transsphenoidal approach more difficult, resulting in failure of this approach in 6 patients. Authors reported "rhinorrhea, obstruction, sneezing significantly improved but not postnasal drip"	Dry eyes in 6 procedures and one patient had long-term dry eyes (1.49%) requiring treatment. No changes in visual acuity were noted. Authors reported: "No intraoperative complications were encountered"
Ikeda[820]	2008	4	Case series	VMR: 3 AR: 5 patients Surgery after a minimum of 8 weeks after discontinuation of oxitropium bromide	Transnasal with "partial" septoplasty and cartilage graft coverage of resected PNN	Primarily studied effect of PNN on functional and morphological changes in the inferior turbinate mucosa Authors reported significant improvement in rhinorrhea and nasal obstruction, noting that " the effect of surgery on rhinorrhea resembled that of oxitropium bromide, suggesting that the pharmacological effect of section of the PNN can be explained by inhibition of the parasympathetic nerve"	No discussion

(*Continued*)

TABLE VII. Continued

Study	Year	LOE	Study design	Study group	Surgical technique (sides where reported)	Clinical endpoint(s) studied	Complications reported
Ogawa[821]	2007	4	Prospective case series	23 Patients with AR resistant to medications and ITH	Submucosal reduction of inferior turbinate plus transturbinate PNN, septoplasty	Sneezing, rhinorrhea, and nasal obstruction were decreased until 3 years after surgery. Levels of IL-5 and eotaxin significantly decreased after surgery in the nasal lavages, but RANTES remained unchanged. Histopathology showed that the inflammatory cells and nasal glands numbers were markedly reduced in lamina propria, with epithelial layer metaplasia to stratified columnar cells	Transient numbness of gingiva and teeth in 4.3%
Ikeda[822]	2006	4	Case series	AR: 55 patients with failure with topical inhalant steroids, oral antihistamine and antileukotriene treatment 1 patient with nonallergic rhinitis with eosinophilia syndrome	Submucosal reduction of the inferior turbinate and resection of the posterior nasal nerve (intraturbinate or extraturbinate) IT outfracture, septoplasty was also performed in 53 patients	Postoperative data available for 50 patients. Rhinorrhea, nasal obstruction, and nasal resistance by significantly improved ($p <$ 0.01). Failure rate: 4%	1 patient (1.78%) reported both transient palatal numbness and dry eyes. 1 hospitalized for "severe and excessive nasal blowing." No postoperative epistaxis requiring surgical management
Robinson and Wormald[801]	2006	4	Case series	9 Patients with VMR	Transnasal EVN; bilateral (5), unilateral (4) with total of 14 sides. Mean follow-up 25 months (range 21–36 months)	Obstruction, sneezing, rhinorrhoea, PND. Significant improvement in rhinorrhea ($p < 0.018$) and nasal obstruction ($p <$ 0.011) by symptom scores. There was no significant postoperative improvement for PND and sneezing. Seven patients (50%) reported success for rhinorrhea, and 57% in nasal obstruction. Worsened sneezing noted in 3 patients (33.3%); patient satisfaction: poor = 1; good = 13. 1 patient (7.14%) reported poor result within 6 months	Complications reported in 7 of 14 procedures (50%). Mild crusting was noted in 28%. Mild dry eye was reported with 35%, with 1 permanent dry eye requiring treatment (11.1% of patients). Temporary cheek and palate numbness were reported in 1 patient (11.1%)

AR = allergic rhinitis; CSF = cerebrospinal fluid; CT = computed tomography; EMAIT = endoscopic microdebrider-assisted inferior turbinoplasty; EVN = endoscopic vidian neurectomy; FESS = functional endoscopic sinus surgery; IL-5 = interleukin 5; IT = inferior turbinoplasty; ITH = inferior turbinate hypertrophy; LOE = level of evidence; OSDI = ocular surface disease index; PND = postnasal drip; PNN = posterior nasal neurectomy; PPF = pterygopalatine fossa; QOL = quality of life; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SNOT-22 = 22-item Sino-Nasal Outcome Test; SPA = sphenopalatine artery; SPG = sphenopalatine ganglion; SSQ = Sinusitis Symptom Questionnaire; TNSS = Total Nasal Symptom Score; VAS = visual analogue scale; VMR = vasomotor rhinitis.

VII.C. Complications associated with vidian neurectomy

The most frequent complication in all was temporary dry eye, which occurred in up to 30% of patients (range, 23.8-100%[805] of the patients, depending on the study; Table VII). In 1 report, temporary dry eye occurred in 98.85% of patients undergoing endoscopic transsphenoidal vidian neurectomy, with long-term eye dryness lasting more than 6 months reported in 6 of 174 (3.45%) patients with

allergic rhinitis.[816] The other most frequently reported complications were postoperative epistaxis requiring packing or surgical management, and temporary numbness of the palate, cheek, or gingiva in 2.97% to 22.2% of patients.[805] Mild nasal crusting and dryness were also recorded in 15.3% to 28% of patients.[805] Major complications such as CN deficit (CN III, IV, or VI) or disturbances of eye movement were not reported in any study since 1997. Since 2006, after the report by Robinson and Wormald,[801] all procedures were performed using an endoscopic approach. CN injury or eye-movement disturbance were not reported in any of these studies. Temporary dry eyes and palatal numbness were the most common adverse events reported in almost all patients. Lin et al.[823] presented a single case report of bilateral neurotrophic keratopathy after vidian neurectomy in 2001. Su et al.[816] were the only authors that compared complication rates between the intrasphenoidal and transsphenoidal approaches; they reported dry eyes in 67% of patients undergoing intrasphenoidal procedure vs 73% of those in the transsphenoidal group.[816] No patient in the intrasphenoidal group experienced cheek or palatal numbness, but 3% of subjects in the transsphenoidal group did.[816] Thirteen percent of the patients who underwent the pterygopalatine fossa approach to approach the anterior end of the vidian canal experienced palatal/gingival numbness compared with 2% of the patients who had a transsphenoidal approach ($p < 0.00001$).[816]

VII.D. Posterior nasal neurectomy

Posterior nasal neurectomy was studied in 6 public ations.[811,814,815,820–822] Four studies were performed on patients with allergic rhinitis,[811,812,821,822] whereas 1 was performed for vasomotor rhinitis patients with nasal polyposis[815] and 1 had a mixed population of allergic and nonallergic rhinitis patients.[820] However, almost all studies reported on the results of posterior nasal neurectomy in the setting of simultaneous submucous reduction or resection of the inferior turbinate; septoplasty was also deployed in some patients. Endoscopic sinus surgery was performed simultaneously in 1 study.[815] These variables confound studying the outcomes of posterior nasal neurectomy. Postoperative bleeding was most common complication from posterior nasal neurectomy, with a risk in up to 17.5% when combined with inferior turbinate reduction.[811,814,815] Other complications from posterior nasal neurectomy are rare; transient numbness of the gingiva and teeth occurred in about 1.7% of patients.[814,821] Transient dry eye and hypesthesia of the soft palate[821,822] have also been reported.

Summary of published systematic reviews for vidian neurectomy

In 2016, Marshak et al.[800] published a systematic review of the evidence base for vidian neurectomy in managing rhinitis. They evaluated 32 studies for qualitative synthesis. Of the 2185 patients, 59% (1291) were diagnosed with vasomotor rhinitis, 36.15% (790) with allergic rhinitis, and 4.75% (104) with "rhinitis." Patient-reported outcome measures were reported in 8 studies with a total of 529 patients. Significant improvement in rhinorrhea was reported in all 8 studies. Thirty studies (93.75%) reported on postoperative complications (n = 2134). Temporary dry eye may occur in 96.46% of cases, but usually resolves within 6 months in most patients. Paresthesia in the maxillary CN (CN V2) distribution is the next most common adverse event, reported in 8.2% of patients and usually transient. Postoperative infection was reported in 5.34%; palatal fistula in 4.85% and epistaxis in 1.75%. Major complications such as CN deficit (CN III, IV, or VI) or disturbances of eye movement were reported in 11 studies in 2.42% (25/1029) cases. All of these patients underwent vidian neurectomy via the traditional non-endoscopic approach.

Halderman and Sindwani[805] published a systematic review in 2015 on the surgical management of vasomotor rhinitis. Their study focused on the safety and efficacy of vidian neurectomy and posterior nasal nerve section for treatment of vasomotor rhinitis. The authors studied 6 studies on vidian neurectomy with a total of 403 patients. The average follow-up time reported in the studies was 37 months (range, 19.6 to 82.8 months). Four studies focused on allergic or mixed rhinitis, and 2 on vasomotor rhinitis.[801,809] Success rates for endoscopic vidian neurectomy for vasomotor rhinitis varied between 50% and 91%. Rhinorrhea improved significantly in both studies,[801,809] but only 1 (Robinson and Wormald[801]) showed significant improvement in nasal obstruction. Ma et al.[809] reported that sneezing significantly improved, but Robinson and Wormald[801] did not. No significant improvement in symptoms was noted by 8.9% to 50% of patients immediately following surgery,[801,809] but in those that showed benefit, relapse of symptoms occurred only in 1 patient (1.9%). Halderman and Sindwani[805] proposed that these results suggest that in patients with immediate benefit from endoscopic vidian neurectomy, long-term control of vasomotor rhinitis symptoms are likely to be sustained. The most common complication after vidian neurectomy for all 6 of the studies was temporary postoperative xerophthalmia in 23.8% to 100% of patients[801,809,813,816–818] that resolved in 1 to 6 months. No long-term complications from dry eyes were reported. Nasal crusting or dryness occurred in 15.3% to 28% of patients.[801,816] Temporary numbness of the cheek, palate, and/or gingival numbness that resolved in 1 week to a year occurred in 2.97% to 22.2% of patients[801,809,813,816,817]; no case of permanent numbness was reported. Postoperative bleeding occurred in 8 of 403 of patients (2%), with sphenopalatine artery cauterization performed in 0.49%. Dry eyes occurred in 52 of 150 sides/patients (35%) in those undergoing the pterygopalatine fossa approach vs 192 of 320 sides/patients (60%) in those who underwent a transsphenoidal approach ($p < 0.00001$).[805] Halderman and Sindwani[805] also concluded that the endoscopic approach was associated with less morbidity compared to the transantral approach for vidian neurectomy, with no reported long-term sequelae.

The authors[805] then focused on 5 studies of posterior nasal neurectomy with a total of 174 patients (average follow-up time of 22.5 months; range, 9.7 to 36). All studies for posterior nasal neurectomy in their study period focused on allergic rhinitis and patients showed improvement in nasal obstruction, rhinorrhea, and sneezing symptoms.[814,820,822]

A limitation of this reiterative review is the heterogeneous nature of surgical interventions, subject populations, and nonstandardized outcome measures. Most of the studies are case series. Patient-reported outcomes were also not available in many studies. These factors limit the ability to conduct a meta-analysis. Conclusions are also difficult to draw regarding the best indications and techniques for vidian neurectomy. In general, authors propose that it be used for cases that are refractory to medical therapy (which is also either not described or heterogeneous).

The data supporting vidian neurectomy are supportive of the technique, with the majority of studies being case series. The procedure appears to be a relatively safe procedure in the modern era, when performed by experienced surgeons in relieving symptoms of rhinorrhea and nasal congestion in subjects with vasomotor rhinitis. Allergic rhinitis subjects also reported improvement in rhinorrhea and nasal obstruction but had mixed results for sneezing and itching. Endoscopic vidian neurectomy is effective and safer than traditional transantral vidian neurectomy. Endoscopic vidian neurectomy does have a role in the surgical management of refractory rhinitis (allergic, nonallergic, and mixed), particularly in patients with nonallergic rhinitis or mixed rhinitis where pharmacotherapy may not be as effective as it is for allergic rhinitis. Temporary dry eyes, temporary palatal numbness, and epistaxis are the most common adverse events reported for endoscopic vidian neurectomy. Permanent CN deficits (CN III, IV, VI) and visual disturbances have been reported with traditional transantral vidian neurectomy but are rare with modern endoscopic vidian neurectomy.

- Aggregate Grade of Evidence: C (Level 2b: 3 studies; Level 3a: 2 studies; Level 3b: 5 studies; Level 4: 34 studies)
- Benefit: Robust data on long-term benefits are lacking, but in the short term, the procedure appears to be efficacious for relieving rhinorrhea and nasal obstructive symptoms.
- Harm: Endoscopic vidian neurectomy may result in temporary dry eyes and palatal numbness. Severe complications are rare.
- Cost: Moderate direct costs for testing, treatment, and postoperative care. May reduce need for postoperative medical therapy.
- Benefit-Harm Assessment: Preponderance of benefit over harm only in well-selected patients (allergic, nonallergic, and mixed rhinitis patients that have failed optimal medical therapy)
- Value Judgments: None.
- Policy Level: Option
- Intervention: Endoscopic vidian neurectomy is an option for allergic, nonallergic, and mixed rhinitis patients that have symptoms refractory to optimal medical therapy.

VIII. Sinonasal malignancies

VIII.A. Olfactory neuroblastoma and esthesioneuroblastoma

Though historically treated surgically through an open bifrontal craniotomy, olfactory neuroblastoma (ONB) has been in the forefront of ESBS for malignant sinonasal tumors. ONB is particularly well-suited for endoscopic resection because of its origin in the midline ventral skull-base, typically presenting with a large exophytic component compared to a relatively focal area of local invasion. In contrast to a soft-tissue sarcoma with multiple sites of circumferential peripheral invasion, the invasive component of ONB is typically isolated at the base of the tumor stalk at the central skull-base. In the early stages the lesion rarely extends laterally beyond the orbits, making it ideal for endoscopic resection. Additionally, after removal of the bulk of the tumor, close endoscopic inspection can potentially facilitate a complete margin-negative resection. Indications for an open approach remain, however, and include the degree of intracranial involvement, orbital invasion, lateral extent of tumor growth past the midplane of the orbital roof, extensive frontal sinus invasion, and posterior extension to the optic canal and cavernous sinus.[824]

As techniques improve, high-volume skull-base centers have the ability to tackle increasingly large tumors with even greater intracranial extension. Through the use of vascularized flaps, reconstruction of even large skull-base defects rivals the closure rates in open surgery.[477] Additionally, there is evidence that endoscopic approaches to skull-base tumors may provide benefits in neurological,[469] visual,[825] and functional[826] outcomes when compared to traditional open surgery.[827] Finally, patients undergoing an endoscopic resection have been found to recover faster with shorter hospital stays postoperatively.[828]

Because ONB is a rare malignancy making up only 3% to 5% of all sinonasal tumors, most cases in the medical literature have been described as case reports or small case series.[829] In recent years, multicentered investigations and meta-analyses have enabled the aggregation of data in order to draw conclusions regarding the safety and long-term outcomes of endoscopic skull-base tumors in the management of ONB. Previous studies have been limited by an intrinsic selection bias given that those tumors selected for resection via an endoscopic skull-base approach are on average lower-stage than those treated with an open approach. Additionally, because skull-base surgery is a more recent development in the surgical treatment of ONB, the average time to follow-up is shorter than in patients treated with an open approach, which could affect comparisons of long-term outcomes between the 2 groups.

Only studies that reported 10 or more patients were included. Studies that had been included in a subsequent published systematic review, non-English, nonsurgical, or were not peer-reviewed were excluded. In the past 5 years alone, the search resulted in n = 916 titles (Medline n = 225, Embase n = 691).

VIII.A.1. *Endoscopic endonasal resection of ONB*

Most of the research completed to date has been limited by the rarity of the disease. Most studies are retrospective case-series and can involve very low patient numbers, but there have been a few recent cohort studies describing differences in patient outcomes by their surgical approach.[824,830] By combining patient numbers in multicentered studies, the recent data has been more convincing. There have been some excellent systematic reviews of case-series previously published, but most of these have now been superseded by more recent reviews that incorporate historical studies and more recent publications.[831–833] This summary presents the updated findings but acknowledges the prior research efforts (Table VIII.A.1).

The most recent meta-analysis was performed in 2016 by Fu et al.,[831] who compiled a systematic review of 36 studies including 609 patients. The goal of this study was to evaluate outcomes in patients with ONB treated with craniofacial resection (CFR) vs endoscopic resection while controlling for known prognostic factors such as Kadish stage and Hyams grade. Endoscopic resection was found to have statistically better OS and DFS ($p = 0.001$ and $p = 0.004$, respectively) but was not found to have any difference in locoregional control or metastasis-free survival (MFS). Advanced stage was associated with worse DFS, locoregional control, and MFS ($p = 0.02$, $p = 0.001$, $p = 0.03$, respectively). Advanced Hyams grade was not found to correlate with any outcome, though data was limited.

There was a significant difference between the surgical modality used in terms of Kadish stage distribution ($p < 0.001$), Hyams grade distribution ($p = 0.02$), and percentage of people receiving chemotherapy ($p = 0.01$). The endoscopic group had a lower proportion of advanced Kadish stage (C/D) tumors ($p = 0.04$) but a higher proportion of advanced Hyams grade (III/IV) tumors ($p = 0.004$). In those with advanced Kadish stage, patients managed with endoscopic resection had a higher OS ($p = 0.04$); however, no differences were detected in DFS, locoregional control, or MFS ($p = 0.051$, $p = 0.56$, $p = 0.82$, respectively). In patients with advanced Hyams grade, tumors treated endoscopically were seen to have higher OS and DFS ($p = 0.001$ and $p = 0.002$, respectively). No difference was seen between the groups for locoregional control or MFS ($p = 0.15$ and $p = 0.78$, respectively).

When compared to the CFR group, the rate of CSF leak was higher in the endoscopic resection group, though this was not statistically significant (12.7% vs 10.3%, $p = 0.62$). Endoscopically-treated patients were found to have lower rates of intracranial complications (7.5% vs 20.1%, $p < 0.001$) and total complications (28.1% vs 52.9%, $p = 0.001$). The endoscopic resection group was also found to have lower crude rates of locoregional recurrence (17.4% vs 45%, $p < 0.001$), distant metastasis (1.1% vs 7.5%, $p = 0.02$), cause-specific mortality (0% vs 15.2%, $p < 0.001$), and overall mortality (0% vs 19.9%, $p < 0.001$).

Within this larger meta-analysis, a major contributing article was included with long-term retrospective data by Rimmer et al.[830] This study analyzed a large cohort of 95 patients with CFR (65 patients) or endoscopic resection (30 patients) of ONB over a 35-year period. OS was found to be 83.4% at 5 years and 76.1% at 10 years. DFS was found to be 80% at 5 years and 62.8% at 10 years. Mean follow-up was 88.66 months (range, 1 to 309 months). Endoscopic resection was found to have significantly improved OS and DFS compared to the CFR group ($p = 0.004$ and $p = 0.022$, respectively). As expected, patients with advanced staging ($p = 0.008$), orbital involvement and/or brain involvement ($p = 0.05$) were significantly more likely to undergo CFR.

DFS was significantly worse for more advanced-stage tumors using both the Kadish and Dulguerov staging systems. Using a Cox regression analysis, significant independent factors affecting outcome were found to be orbital extension and intracranial involvement. Degree of orbital and intracranial involvement significantly impacted DFS. Patients without orbital involvement had better 5-year DFS compared to those with periosteal involvement, who again did better than those with frank involvement of the globe. Similarly, DFS was found to be significantly higher without intracranial involvement than if the dura was involved. Understandably, intracerebral disease demonstrated the worst DFS.

Local recurrence was found in 25.3% of patients at an average of 59 months (range, 3 to 233 months). Twenty-five percent of cases recurred within a year; however, 33% developed after 5 years and 8% after 10 years, indicating the importance of long-term surveillance. Identifying and treating local recurrence prolonged survival by an average of 29 months (range, 3 to 58 months) in those who eventually died, and by an average of 93 months to date (range, 3 to 128 months) in those still alive.

A comparative cohort study between open and endoscopic surgical treatment in stage-matched patients from 6 tertiary hospitals in the United States and Australia has been recently reported.[824] At presentation, 10.1% were found to have Kadish A stage, 24.8% had Kadish B stage, and 65.1% had Kadish C stage disease. Tumor histology was grade I in 9.1%, grade II in 46.8%, III in 36.4%, and IV in 7.8%. Dural involvement was found in 54.7% of patients on histology and regional disease within 7.4% of patients at presentation, all found in level 2. Median follow up was 42.1 months (range, 6 to 421 months). Of those treated surgically, endoscopic resection was performed in 61.5%, endoscopic-assisted in 17.4%, and CFR in 21.1% of patients. RT was used as adjuvant therapy in 75.2%, neoadjuvant in 9.2%, and surgery alone in 15.6%. The use of RT

TABLE VIII.A.1. Evidence for ONB

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Harvey[824]	2017	2b	Retrospective and prospective cohort study	Patients with ONB undergoing treatment at 6 tertiary hospitals via radiotherapy, surgery, and combinations. Surgery was defined as endoscopic, endoscopic assisted, or open CFR (n = 109)	1. Local recurrence 2. Regional recurrence 3. Distant metastasis	1. Stage-matched survival was better in the endoscopically treated group compared to CFR. 2. Margin-negative resection regardless of approach is a major predictor of DFS. 3. Those with Kadish C tumors treated endoscopically had better DFS than those treated with CFR.
Rimmer[830]	2014	2b	Retrospective cohort study	Patients with ONB undergoing CRF vs endoscopic resection (n = 95)	1. DFS 2. OS 3. Locoregional metastases 4. Distant metastases	1. Endoscopic resection found to have better OS and DFS compared to CRF, though also lower stage on average. 2. Intracranial and orbital involvement were independent factors affecting OS and DFS. 3. Long-term surveillance necessary with recommendation for exam and MRI of neck and intracranial compartment every 4 months for 2 years, then every 6 months for the until 5 years, then every 9 months for life.
Konuthula[834]	2017	2c	Outcomes research	Patients with ONB in the National Cancer Database (n = 1167)	1. OS 2. 5-year survival	1. Kadish B had greater survival than Kadish A regardless of treatment. 2. Age <60 years, female sex, having private insurance, and margin-negative resection was found to be associated with improved survival on univariate analysis.
Stokes[835]	2015	2c	Outcomes research	Males and females with ONB in the SEER program from 1988 to 2010 (n = 611)	1. DFS	1. Male patients presented with higher grade and a trend toward higher stage. 2. Male patients had worse DFS than female patients (significance was lost after case-matching).
Tajudeen[836]	2014	2c	Outcomes research	Patients in the SEER database with diagnosis of ONB between 1973 and 2010 (n = 281)	1. OS 2. DFS	1. Advanced tumor grade and modified Kadish stage were associated with worse DFS. 2. RT improved DFS. 3. Surgery was found to be the only prognostic factor for DFS in low-grade tumors. 4. In high-grade tumors, modified Kadish stage predicted worse DFS and RT independently predicted improved DFS.
Fu[831]	2016	3a	SR of retrospective case series	Patients with ONB undergoing CRF vs endoscopic resection; subgroup analysis in patients with high Kadish stage and Hyams grade (n = 609)	1. DFS 2. OS 3. Locoregional control 4. MFS	1. Endoscopic approaches have improved OS for all patients, those with Kadish C/D disease, and those with Hyams III/IV disease. 2. Endoscopic resection shows improved DFS for all patients and Hyams III/IV disease but not higher Kadish stage.
Komotar[832]	2013	3a	SR of retrospective case series	Patients with ONB undergoing CRF, cranionasal, vs endoscopic resection (n = 453)	1. OS 2. DFS	1. Endoscopic cohort had a greater proportion of Kadish stage A tumors 2. Gross total resection was achieved in 98.1% in the endoscopic group compared to 81.3% in the CFR group and 100% in cranionasal cohorts. 3. Cranionasal and endonasal approaches can be safe and effective.
Higgins[833]	2011	3a	SR of retrospective case series	Patients with sinonasal malignancies (including ONB) undergoing CRF vs endoscopic resection (n = 226)	1. OS 2. DFS 3. Locoregional control	1. Statistically improved outcomes were seen in endoscopic resection over CFR in 5-year OS in all ONB. 2. There was no statistical significance between surgical approaches in low-stage ONB.

(*Continued*)

TABLE VIII.A.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Xiong[837]	2017	4	Retrospective case series	Patients with ONB treated in China between 1981 and 2015 (n = 187)	1. OS 2. DFS	1. Surgery combined with radiotherapy with or without chemotherapy led to improved OS and DFS ($p < 0.0001$). 2. Patients who underwent surgery with or without another treatment modality had better OS and DFS compared to those treated with other treatment modalities without surgery. 3. Independent prognostic factors of poor survival included distant metastasis and unimodality treatment. All results were not separated by staging.
Schmidt[838]	2016	4	Retrospective case series	Patients with ONB treated with curative intent between 2000 and 2014 (n = 11)	1. OS 2. DFS	1. Late locoregional recurrence suggests that long-term follow-up is necessary.
Nakagawa[839]	2018	4	Retrospective case series	Patients with ONB treated between 2008 and 2016 with unilateral or bilateral endoscopic resection (n = 22)	1. OS 2. DFS 3. Postoperative olfaction 4. Locoregional control	1. Unilateral resection is a valid surgical approach to ONB with 95.5% of patients achieving margin-negative resections (100% of patients treated unilaterally and 90% of those treated with bilateral endoscopic resection) and DFS comparable to previous literature. 2. 91.6% of patients with unilateral resection maintained olfactory function.
Konig[840]	2017	4	Retrospective case series	Patients with ONB treated or palliated between 1998 and 2016 (n = 20)	1. OS 2. DFS	1. Negative margins, tumor size <40mm, Kadish stage A/B, and TNM stages I–III were associated with improved outcomes regardless of open surgical approach (endoscopic resection not studied).
Zhang[841]	2016	4	Retrospective case series	Patients with ONB treated between 2000 and 2010 with endoscopic resection with or without RT vs combined RT and chemotherapy (n = 13)	1. OS 2. DFS 3. Locoregional 4. Distant metastasis	1. Related prognostic factors included TNM stage, N stage, M stage, Kadish stage, and treatment modality. 2. Combined treatment including surgery achieved improved outcomes compared to nonsurgical treatments.
Yin[842]	2016	4	Retrospective case series	Patients with ONB evaluated between 1979 and 2014 (n = 113)	1. OS 2. Locoregional control 3. MFS	1. Overall survival was found to be best in the preoperative RT group, followed by postoperative RT group, and worst in those treated only with RT. 2. No survival difference for patients treated by primary RT vs combined treatment was seen between those in Kadish A/B stages. 3. In patients with node-negative Kadish C disease, combination treatment was superior, with preoperative RT demonstrating the best survival.
Tajudeen[843]	2016	4	Retrospective case series	Patients with ONB who underwent endoscopic unilateral resection with preservation of 1 olfactory bulb between 2003 and 2015 (n = 14)	1. Olfactory function 2. Locoregional control	1. No patient had disease recurrence at mean follow-up of 51.7 months, all with margin-negative resection. 2. Olfactory testing showed 43% had residual smell function and 14% with normal or mildly reduced smell function.
Manthuruthil[844]	2016	4	Retrospective case series	Patients with ONB undergoing endoscopic resection between 2010 and 2013 (n = 10)	1. Locoregional control 2. SNOT-20 score 3. Complication rates	1. Postoperative SNOT-20 scores were not statistically different from preoperative scores. 2. Endoscopic resection in select patients may demonstrate equivalent or improved outcomes.

(*Continued*)

TABLE VIII.A.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Banuchi[845]	2016	4	Retrospective case series	Patients with ONB presenting between 1979 and 2009 (n = 57)	1. OS 2. Locoregional control 3. MFS	1. Intracranial tumor extension, positive margins, neck metastases were associated with worse OS. 2. Regional metastasis developed in 17% at a median time of 60 months; distant metastasis in 39% at a median time of 40 months. 3. Advanced stage (Kadish C/D) had increased risk of distant failure. 4. Survival was decreased in patients with regional and distant metastasis.
Tsang[846]	2015	4	Retrospective case series	Patients with ONB treated by endoscopic assisted CFR (n = 14)	1. OS 2. DFS	1. Endoscopic-assisted CFR technique has comparable outcomes to CFR alone technique.
Tajudeen[847]	2015	4	Retrospective case series	Patients undergoing treatment for ONB (n = 36)	1. OS 2. DFS	1. Modified Kadish Stage was the only factor to affect OS. 2. Tumor grade had an independent impact on DFS. 3. No difference in OS between surgical approach (CFR with craniotomy, transfacial CFR without craniotomy, expanded endoscopic endonasal craniofacial resection).
Petruzzelli[848]	2015	4	Retrospective case series	Patients with ONB evaluated from 1994 to 2012 (n = 37)	1. OS 2. DFS	1. Kadish stage C and stage T3/4 tumors were associated with worse outcome. 2. Total radiation dose, margin status, patient age were not found to have significant prognostic value. Only n = 3 had a curative resection.
Feng[849]	2015	4	Retrospective case series	Patients with ONB treated with only endoscopic resection between 2011 and 2012 (n = 24)	1. OS 2. DFS	1. Dulguerov staging predicted OS 2. Kadish staging predicted DFS between early and advanced stages. 3. Endoscopic resection showed successful survival rates (3 year OS and DFS of 82% and 70.8%) with decreased complications.
Bell[850]	2015	4	Retrospective case series	Patients with ONB evaluated and treated (n = 124)	1. OS 2. DFS 3. Locoregional recurrence 4. 4) Distant metastasis	1. High grade of ONB was associated with poor outcome, but not with advanced stage. 2. DFS was worse for high-grade than low-grade ONB. 3. No statistically significant differences between recurrence, distant metastases, or 5-year OS were identified via the Kadish or the TNM staging system.
Ow[851]	2014	4	Retrospective case series	Patients with ONB treated between 1992 and 2007 (n = 70)	1. OS 2. DFS 3. Locoregional control	1. Patients treated with surgery with postoperative radiation had a statistically significantly improved DFS.
Montava[852]	2014	4	Retrospective case series	Patients with ONB treated endoscopically from 2000 to 2013 (n = 18)	1. OS 2. DFS 3. Locoregional control 4. Distant metastasis	1. Dural extension and frontal invasion were associated with recurrence and should be treated with aggressive treatment. 2. Endoscopic resection shows low rate of perioperative morbidity and efficient local control.
Gallagher[853]	2014	4	Retrospective case series	Histology of patients with ONB 1995–2007 (n = 27)	1. OS 2. DFS 3. Locoregional control	1. Necrosis and mitoses were associated with OS (but not in multivariate analysis). 2. Gland hyperplasia was found to be a positive prognostic variable and associated with OS and DFS but only in combination with no spindle features and without necrosis.
Modesto[854]	2013	4	Retrospective case series	Patients with ONB treated between 1998 and 2010 (n = 43)	1. OS 2. DFS 3. Locoregional control	1. Major prognostic factor was modified Kadish stage. 2. Cervical lymph node relapses occurred in 9% of patients with Kadish stage B and C disease without elective nodal irradiation and 0% with elective irradiation.

(*Continued*)

TABLE VIII.A.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Malouf[855]	2013	4	Retrospective case series	Patients with ONB treated between 1979 and 2009 (n = 44)	1. OS 2. DFS 3. Locoregional recurrence	1. T staging of TNM staging and Hyams grade >III were independent prognostic factors for OS. 2. Patients with high-grade ONB were found to have higher T4 staging, frequent lymph node involvement, and more often unresectable. 3. High-grade ONB more frequently displayed leptomeningeal metastasis vs low-grade ONB more typically experience late locoregional recurrence.
Kumar[856]	2013	4	Retrospective case series	Patients with ONB treated between 2006 and 2010 (n = 15)	1. OS 2. DFS 3. Locoregional control 4. Distant metastasis	1. Multimodality approach is necessary to achieve good control.
Back[857]	2012	4	Retrospective case series	Patients with ONB from 1990 to 2009 (n = 17)	1. OS 2. DFS 3. Locoregional recurrence	1. Inconsistency in management was noted in the management of ONB and the treatment should be managed by an experienced head and neck surgeon. 2. Multimodality treatment and long-term follow-up is preferred.

CFR = craniofacial resection; DFS = disease-free survival; LOE = level of evidence; MFS = metastasis-free survival; MRI = magnetic resonance imaging; ONB = olfactory neuroblastoma; OS = overall survival; RT = radiotherapy; SEER = Surveillance, Epidemiology, and End Results; SR = systematic review; SNOT = Sino-Nasal Outcome Test; TNM = tumor-node-metastatis.

increased with Kadish stage ($p = 0.011$). Positive regional disease was treated with surgery with or without adjuvant RT.

Local recurrence occurred in 12.8% of patients, regional metastasis in 9.2%, and distant metastasis in 15.6% of patients. The 5-year and 10-year DFS were 85% and 63%, respectively. There was no clear relationship between Kadish stage and regional disease ($p = 0.43$), but a trend toward Kadish stage and development of metastatic disease was found ($p = 0.06$).

Importantly, it was found that the ability to achieve clear surgical margins was greater in the endoscopic resection group compared to the open surgery group for both Kadish B (90% vs 71.4%, $p = 0.001$) and Kadish C (84.2% vs 53.1%, $p = 0.001$). The ability to clear surgical margins was a major predictor of survival for the group as a whole ($p = 0.004$). Dural involvement and delayed regional disease were also found to impact DFS ($p = 0.032$ and $p < 0.001$, respectively). Interestingly, positive neck disease at presentation did not affect survival ($p = 0.82$). Hyams grade did not significantly affect DFS ($p = 0.61$) and also did not correlate with Kadish stage ($p = 0.61$).

As endoscopic techniques and equipment have evolved, most intracranial extension has been successfully managed in highly-skilled skull-base centers. Overwhelmingly, recent retrospective data has shown that endoscopic resection is superior to CFR if margin-negative resection is achievable after considering clinical and radiographic assessment regardless of staging.[824,830–833,844,846,847,849,852] Residual microscopic margin status remains an important prognostic factor. Though traditional oncologic principles favor en-bloc resection of malignancies, the bulk of disease in tumors such as ONB has the potential to obscure the site of invasion. Thus, systematic piecemeal resection with aid of magnifying endoscopes is ideal in the resection of malignancies such as ONB. It is also important to note that use of intranasal vascularized flaps must not be prioritized over margin status. If intranasal flap options are not available, then dural reconstruction can be accomplished via graft techniques or optimally via tunneled pericranial flap or secondary flap options.[477,858,859] The current staging system does not stratify patients well in terms of prognostic groups. High-risk features should guide the use of adjuvant treatment of the local site and N0 neck (N0 indicates no cancer in nearby lymph nodes).

Historical teaching in the surgical resection for ONB includes resection of the bone, dura, falx, olfactory bulbs, and tracts bilaterally. However, given the improvement in outcomes with current endoscopic techniques, modification of the traditional surgical concepts for improvement in QOL factors may be considered as long as the modification does not impact patient survival or margin-negative status. A recent study by Tajudeen et al.[843] has examined outcomes in unilateral resection of the bone, dura, olfactory bulbs and tract, showing improved smell outcomes without sacrificing patient survival. This same principal could also be applied in CFR for appropriate patients, but as always, the surgeon should strive for a complete margin-negative resection.

Outcomes studies performed on large, population-based databases have also been performed in recent years to identify key prognostic factors. Identifying patients at risk of poor outcome can potentially help to guide the need for

adjuvant treatment. These studies have found improved survival with age less than 60 years, female sex, having private health insurance, lower tumor grade, lower Kadish stage, N0 neck status, and margin-negative resection.[834–836] Furthermore, male patients were found to present with higher-grade disease and a trend toward higher stage.[835] RT was found to improve survival in high-grade tumors.[836]

- Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 2c: 3 studies; Level 3a: 3 studies; Level 4: 21 studies).
- Benefit: There is good evidence that patients undergoing endoscopic surgery spend less time in hospital, avoiding approach-related morbidity, lower complications rates, quicker return to daily activities, and better QOL outcomes. In centers with strong tumor care programs data has shown increased margin-negative resection rates in tumors treated via an endoscopic approach.
- Harm: Potential harm of more endoscopic surgery is the possible compromise of oncologic outcomes with an incomplete excision or higher rates of positive margins, though this has not been seen in data from high-volume skull-base centers.
- Cost: Cost comparison has not yet been examined in clinical study.
- Benefit-Harm Assessment: Endoscopic surgery for olfactory neuroblastoma at experienced centers appears to provide as good or better oncologic results for appropriately selected cases.
- Value Judgments: Kadish B tumors have equivalent or better outcomes when performed by open or endoscopic resection, but the avoidance of frontal lobe injury favors the endoscopic approach. Approach for surgical treatment of Kadish C tumors are a heterogenous and dependent on tumor location.
- Policy Level: Recommendation for endoscopic surgery for Kadish A and B. Option for Kadish C.
- Intervention: Kadish A and B tumors should be resected endoscopically. Kadish C tumors should be performed endoscopically where negative margins can be obtained endonasally. Kadish C involving the orbit, spread lateral to the orbital axis, hard/soft palate, or midface should be resected with an open approach.

VIII.A.2. *Treatment of the neck in ONB*

Staging systems have often neglected to stratify regional metastases. Morita et al.[860] revised the traditional Kadish staging system to establish a group D for patients with cervical or distant metastases. Dulguerov et al.[861] also proposed a tumor-node-metastasis (TNM) staging system to allow for staging of the neck. However, these staging systems have still not superseded the most commonly used Kadish staging system, which does not take regional disease into account.

In a recent multicenter retrospective review with long-term follow-up by Nalavenkata et al.,[862] it was found that 7.1% of patients presented with primary neck disease and an additional 8.8% of patients went on to develop neck disease. The ipsilateral level 2 was commonly involved, followed by level 3 and 4. Retropharyngeal lymph nodes were uninvolved in all 113 patients studied although have been reported.[862] Patients with primary neck disease were found to have a higher Hyams grade; however, higher grade did not portend a higher risk of developing delayed regional metastasis. No patients with Kadish A tumors were found to have delayed neck disease, whereas 6.7% and 11.1% of Kadish B and C lesions developed neck disease ($p = 0.42$). This corroborated prior findings by Demiroz et al.[863] that there was no increased risk of developing neck disease with increased staging between Kadish B and C tumors.

Delayed neck disease was previously attributed to slow tumor grown from occult metastasis. However, given that the only major risk factor for the development of delayed neck disease was found to be a positive surgical margin (17.9% in positive surgical margins vs 5% in clear margins, $p = 0.034$), it is possible that in this subpopulation, delayed metastases are due to local recurrence and regional spread. Examination and follow-up of regional disease was found to be important, with 5-year survival determined to be significantly lower in patients with delayed neck disease (73.8% vs 91.8%, $p = 0.043$).

Current recommendation is for the treatment of positive neck disease with selective neck dissection with adjuvant RT if histology finds >1 positive lymph node, extracapsular spread, or high-grade features.[862] Trimodality treatment with surgery, RT, and chemotherapy has yielded promising results; however, no consensus exists.[864] Elective treatment of the N0 neck is less clear. In studies with smaller populations, the rate of regional metastasis has been found to be >20% and thus a case could be made for elective treatment of the neck. Incidence of delayed regional metastasis has been highly variable in the literature; however, low patient numbers have been a major limitation of many of these studies (Table VIII.A.2[824,830,832,837,845,862,863,865–869]

Nalavenkata et al.[862] has published the largest retrospective review to date investigating this clinical question, showing only an 8.8% delayed regional metastasis rate, suggesting that elective treatment of the neck in all patients with ONB may be overtreatment. Instead, the authors recommend for long-term active surveillance in the N0 neck, with salvage surgery and RT reserved for those with delayed cervical metastases. Consensus was determined for clinical review every 3 months for 2 years, then every 6 months until 5 years, then yearly thereafter with serial imaging of the neck at 6 months and 1 year and yearly thereafter.

Alternatively, other recent studies have shown significantly worse OS and DFS in patients with delayed regional metastasis.[824,837,845,867] Harvey et al.[824] recently showed in a multicentered review that delayed regional disease was a major predictor of mortality even despite subsequent therapy (log rank $p < 0.001$). Prophylactic treatment of the N0 neck with radiation has been reviewed in small groups with improvements in regional control.[868,869] In a previous

TABLE VIII.A.2. Evidence regarding elective treatment of the N0 neck in ONB

Study	Year	LOE	Study design	Study groups	Incidence of primary neck disease (%)	Incidence of regional failure (%)	Conclusions
Harvey[824]	2017	2b	Retrospective and prospective cohort study	Patients with ONB undergoing treatment at 6 tertiary hospitals via radiotherapy, surgery, and combinations. Surgery was defined as endoscopic, endoscopic assisted, or open CFR (n = 109).	7.4	9.2	1. Delayed regional disease was a significant predictor of mortality despite subsequent therapy. 2. No clear relationship between Kadish stage and regional recurrence.
Rimmer[830]	2014	2b	Retrospective cohort study series	Patients with ONB undergoing CRF vs endoscopic resection (n = 95)	5.3	18.9	1. Of those patients with delayed neck recurrence, 61.1% had no evidence of local disease at the time (11.1% of the total population). 2. In the CFR group 21.5% developed cervical metastasis compared to 13.3% in the endoscopic group.
Komotar[832]	2013	3a	SR of retrospective case series	Patients with ONB undergoing CRF, cranionasal, vs endoscopic resection (n = 453)	N/A	6.0 in endoscopic group; 17.3 in CFR; 8.3 in cranionasal	1. Outcomes are improved with the addition of the endoscope to surgical approach with equivalent complication rates.
Naples[867]	2016	3a	SR of retrospective case series	Patients with ONB where study data included mortality from disease in patients with neck recurrence (n = 269)	N/A	14.1	1. OS and DFS were worse for patients with neck recurrence (32% vs 26%). 2. There was an increased incidence of neck recurrence seen in Kadish stage D compared to stage A.
Xiong[837]	2017	4	Retrospective case series	Patients with ONB treated in China between 1981 and 2015 (n = 187). Incidence of elective treatment of the neck not discussed.	11.2	14.5	1. Regional metastasis was associated with DFS but not OS. Specific treatment of the neck was not discussed.
Peacock[865]	2017	4	Retrospective case series (n = 52)	Patients with ONB and N0 neck disease who did not undergo elective neck treatment (n = 52)	0	41	1. Delayed regional metastases are common, indolent, and effectively salvaged. 2. 4-year cervical node RFS is 70%, 5-year OS is 39%. 3. Patients with ONB and N0 neck status may forgo elective treatment of the neck.
Marinelli[866]	2018	4	Retrospective case series, retrospective cohort study	Patients with ONB who presented with or developed neck disease (n = 61)	15	21	1. Within the entire population, ipsilateral neck involvement was most often observed (level 2 in 83%, then level 1 in 54%). 2. Contralateral neck disease was found to be unrelated to the degree of laterality of the primary tumor.

(*Continued*)

TABLE VIII.A.2. Continued

Study	Year	LOE	Study design	Study groups	Incidence of primary neck disease (%)	Incidence of regional failure (%)	Conclusions
Nalavenkata[862]	2016	4	Retrospective case series	Patients with biopsy-proven ONB (n = 113)	7.1	8.8	1. Tumor grade was higher in patients with primary neck disease. 2. Positive surgical margins were associated with a higher risk of developing delayed neck disease
Banuchi[845]	2016	4	Retrospective case series	Patients with ONB presenting between 1979 and 2009 that did not undergo elective neck irradiation (n = 57)	9	17	1. Patients developing regional and distant metastasis had significantly decreased survival.
Jiang[868]	2016	4	Retrospective case series	Patients with N0 ONB who underwent irradiation as part of their treatment between 1970 and 2013 (n = 71)	0	18.3	1. 31% of patients studied underwent elective neck irradiation (n = 22) and none of these went on to develop neck disease. 2. Elective neck irradiation was associated with improved regional control but not OS or DFS.
Yin[869]	2015	4	Retrospective case series	Patients with newly diagnosed ONB from 1979 to 2014 (n = 116)	28	23% without; 2% with elective radiation	1. Regional failure rate decreased significantly from 23% to 2% after elective neck irradiation. 2. Elective neck irradiation was an independent favorable predictor for regional control.
Demiroz[863]	2011	4	Retrospective case series	Patients with clinically N0 ONB without elective neck therapy (n = 26)	0	27	1. DFS was significantly better in those who received postoperative RT. 2. Regional failure was seen in those with Kadish stage B and C disease. 3. Elective treatment of the neck with RT was recommended in addition to the tumor bed.

CFR = craniofacial resection; DFS = disease-free survival; LOE = level of evidence; MFS = metastasis free survival; N0 = no cancer in regional lymph nodes; ONB = olfactory neuroblastoma; OS = overall survival; RFS = recurrence-free survival; RT = radiotherapy; SR = systematic review.

of a large population of 95 patients, regional metastases developed in 18.9% after an average of 74 months (range, 3 to 233 months).[830] Out of these, 61.1% had no evidence of recurrent local disease at the time of regional metastasis (11.1% of the total subject population). Two patients went on to have further regional recurrence after treatment at intervals of 1 and 7 years. In those treated with CFR, 21.5% developed regional metastasis compared to 13.3% in the endoscopic group. Intracranial metastases were seen in 20% overall, all within the CFR group at an average time of 58 months (range, 1 to 139 months). Metastatic disease to the spine, liver, and skin was also observed in 1 patient each. It has been shown that regional and distant metastasis can present up to 10 years after treatment in as great as 10% and 20% of patients, respectively, highlighting the need for long-term surveillance.[830]

Management of the N0 neck in ONB.

- Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 3a: 2 studies; Level 4: 8 studies).

- Benefit: Delayed regional involvement in the neck is common. Those patients with delayed regional involvement have a worse OS and DFS and the benefit from elective treatment of the N0 neck is unknown. Regional recurrence has been described as occurring over 10 years following treatment. Elective treatment of the neck with irradiation shows improved regional control in small studies.
- Harm: Surgical resection of the regional disease is associated with complications including hematoma, wound infection, and CN palsies among others. RT of the regional neck nodes is also associated with increased xerostomia, skin changes, and long-term toxicity.
- Cost: There are no studies investigating the costs of upfront or delayed treatment of the N0 neck.
- Benefit-Harm Assessment: Upfront treatment of the N0 neck in high-grade and high-stage local disease may equate to better long-term DFS.
- Value Judgments: For high-grade tumors and those with advance local stage, elective treatment of the N0 neck is likely to prevent long-term regional recurrence.
- Policy Level: Option.
- Intervention: In a node-positive neck, the role of surgical treatment with or without adjuvant treatment is well established. However, in patients with an N0 neck and high Hyams grade (3/4) and Kadish C stage involving more than dura, elective treatment of the neck should be considered. Long-term surveillance (over 10 to 20 years) of the neck is recommended.

VIII.B. Squamous cell carcinoma

Sinonasal squamous cell carcinoma (SNSCC) represents a rare malignancy of the upper aerodigestive tract with a recent SEER database analysis by Sanghvi et al.[870] revealing an average incidence of 0.36 cases per 100,000 patients, with males accounting for 64.44% (3218/4994) of the study cohort, resulting in a male incidence of 0.52 cases per 100,000 patients. A comparable SEER database analysis of paranasal sinus squamous cell carcinoma (SCC) by Ansa et al.[871] identified 2553 patients during the study period of 1973 to 2009, with males representing 63.6% (1623/2553) of the study cohort.

Subgroup analyses in each study revealed that the majority of patients were white (75.7-82.50%) and the vast majority were greater than 55 years of age at the time of diagnosis.[870,871]

Sanghvi et al.[870] found that the nasal cavity was defined as the primary site in 46.08% (2301/4994) of the cohort, whereas the paranasal sinuses were defined as the primary site in the remaining 53.92% (2693/4994) of the cohort. Ansa et al.[871] found that the maxillary sinus represented 76.3% (1947/2553) of the cohort followed by the ethmoid sinuses (10.5%), sphenoid sinus (4.1%), and frontal sinus (1.9%). It should be noted that in 7.3% of the cohort there was overlapping or nonspecific data. Interestingly, the proportion of patients with advanced disease at presentation was highest in the ethmoid sinuses (12%) and sphenoid sinus (11%).

Ansa et al.[871] found that the 5-year relative survival (RS) remained relatively stable over the study period. Additionally, the 5-year and 10-year OS estimates were 30.2% and 21%, respectively, with corresponding 5-year and 10-year RS estimates of 34.8% and 28.3%, respectively. Sex-specific and race-specific OS and RS estimates were higher in males than females and higher in white patients. Of note, patients who underwent surgical therapy as part of the treatment plan had better survival outcomes compared to those patients who did not receive tumor-directed therapy.

Sanghvi et al.[870] performed survival analyses on a patient cohort from 1973 to 1989 to allow at least 20-year survival data. This revealed a mean 20-year OS of 29.37%. Subgroup analyses revealed 5-year, 10-year, and 20-year RS of 54.26%, 46.80%, and 30.68% for males, respectively, and 50.52%, 40.60%, and 26.35% for females, respectively. White patients were found to have the highest 20-year RS of 30.93% compared to black patients who had a 20-year RS of 19.23%. It should be specifically noted that although trend analyses revealed a statistically significant decline in the incidence of SNSCC during the study period, a statistically significant difference in survival was not noted.[870,871]

The last several decades have seen vast improvements in endoscopic endonasal instrumentation/technology with concurrent advances in the surgical manipulation of the sinonasal tract and skull base with resultant application in patients with SNSCC. Appraisal of the literature reveals a relative lack of data specifically evaluating SNSCC. Table VIII.B summarizes the data acquired from manuscripts including evaluation of endoscopic resection of SNSCC.

These manuscripts include 1 retrospective cohort study, 1 systematic review, and 7 retrospective case series. EBR of these studies revealed comparable oncologic outcomes between endoscopic and open resection of SNSCC in properly selected patients with experienced surgeons/centers.

The European Position Paper on Endoscopic Management of Tumours of the Nose, Paranasal Sinuses, and Skull Base[514] published in 2010 represents the most current and comprehensive evidence-based review; this concluded that the data on endoscopic resection of SNSCC was limited, but promising, with overall DFS comparable with conventional open approaches, recognizing outcome is related to the completeness of resection. A pooled data analysis of 150 patients with SNSCC found only 23 patients undergoing purely endoscopic resection with available data. This cohort had a mean age of 59.8 years with a 2:1 male:female ratio and a preponderance (65.2%) of low-stage (T1 to T2) disease at presentation. Local recurrence was noted in 6 patients (26.8%) and distant metastases were noted in 2 patients. At last reported follow-up, 19 patients (82.6%) were alive with no evidence of disease. It should be noted that follow-up ranged from 3 to 92

TABLE VIII.B. Evidence for endoscopic surgery for SNSCC

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
de Almeida[872]	2015	4	Retrospective case series	Patients undergoing endoscopic surgery for SCC: 1. Definitive resection (a) de novo (b) associated with IP 2. Debulking surgery	1. Staging 2. Overall survival 3. Disease-free survival 4. Complications	1. Definitive resection of sinonasal SCC with EEA provides sound oncologic outcomes. SCC arising from IP does not have prognostic significance.
Lund[514]	2010	3a	Systematic review	Studies reporting outcomes following endoscopic resection of SCC with clear description of pathology	1. Survival outcomes 2. Endoscopic vs open approaches	1. Data on endoscopic surgery for sinonasal SCC is limited but the accrued data from the pooled patients appears promising. 2. For both open or endoscopic approaches there is good evidence that the outcome is related to completeness of resection. 3. The use of an endoscopic approach depends on factors related to the patients' general health and medical co-morbidities together with their availability for long-term follow-up should be an important consideration. 4. Survival outcomes of SCC arising from IP were comparable to primary sinonasal SCC, although some patients presented with highly aggressive disease with hematogenous distant metastasis.
But-Hadzic[873]	2011	4	Retrospective case series	Patients with concurrent IP and SCC of nasal cavity and paranasal sinuses	1. Clinical characteristics 2. Treatments 3. Outcomes	1. For operable sinonasal IP/SCC, initial surgery and postoperative radiotherapy to the tumor bed with dose levels comparable to those used for invasive SCC are recommended. 2. For nonresectable disease, radical radiotherapy to a dose of 66–70 Gy could be of benefit.
Karligkiotis[874]	2016	4	Retrospective case series	Patients treated with endoscopic approach for IP-SCC between 1997 and 2014	1. Disease characteristics 2. Overall and disease-free survival 3. Recurrence-free survival	1. The endoscopic approach provides encouraging oncologic outcomes for sinonasal IP-SCC, comparable to those observed with traditional open approaches while minimizing morbidity for patients. 2. Advanced pathologic T classification, high grade of differentiation of the tumor, expanded surgical approach, and recurrences of disease were factors negatively affecting the prognosis. 3. Recurrent disease can develop after a prolonged period of time requiring long-term follow-up.
Kilic[875]	2018	2b	Retrospective cohort	Patients from National Cancer database with sinonasal SCC treated between 2010 and 2014. 1. Endoscopic approach 2. Open approach	1. Clinical/disease characteristics 2. Overall Survival	1. Patients with sinonasal SCC treated with endoscopic surgery had statistically similar 5-year overall survival compared to patients treat with open approaches. 2. Poorer survival associated with large tumor size, advanced stage, and positive margins. 3. Endoscopic approach associated with shorter hospital stays.
Luong[876]	2010	4	Retrospective case series	Patients with sinonasal malignancy treated with endoscopic approach	1. Clinical/disease characteristics 2. Overall survival 3. Disease-free survival	1. Patient outcomes support efficacy of endoscopic approach. 2. The endoscopic approach also useful in select case for palliative resection.

(*Continued*)

TABLE VIII.B. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Nicolai[877]	2008	4	Retrospective case series	Patients with malignant sinonasal tumors treated between 1996 and 2006. 1. Endoscopic only 2. Open and endoscopic	1. Tumor characteristics 2. Clinical characteristics 3. 5-year disease-specific survival	1. Endoscopic surgery alone or with adjuvant treatment may be an effective alternative to standard approaches.
Shipchandler[878]	2005	4	Retrospective case series	Patients undergoing endoscopic resection of sinonasal SCC.	1. Patient and tumor characteristics 2. Oncologic treatments 3. Recurrence rates 4. Overall and disease-free survival	1. Endoscopic approach in conjunction with adjuvant therapy is a viable alternative to open approaches.
Yan[879]	2017	4	Retrospective case series	Patients with sinonasal SCC from 2000 to 2015 1. de novo SCC 2. IP-SCC	1. Clinical outcomes 2. Surgical approach 3. Overall and disease specific survival	1. Patients with IP-SCC had improved disease-specific survival compared to de novo SCC. 2. Difference between tumors noted in early stages. 3. Endoscopic approaches have similar outcomes to open approaches. 4. Distant metastases are a poor prognostic indicator for all SCC.

EEA = endoscopic endonasal approach; IP = inverted papilloma; LOE = level of evidence; SNSCC = sinonasal squamous cell carcinoma.

months with an average follow-up of 41.6 months in this cohort.

A recent National Cancer Database review of SNSCC by Kilic et al.[875] compared outcomes of endoscopic and open resection of SNSCC. This retrospective cohort review identified 353 patients undergoing endoscopic resection and 1130 undergoing open resection. Propensity score matching generated a cohort of 652 patients with equal endoscopic and open contributions with no statistically significant difference in OS between the 2 groups (50.8% in the endoscopic group and 63.5% in the open group). Interestingly, analysis of the entire cohort revealed a relatively greater proportion of stage IVB tumors treated endoscopically, but subgroup analysis revealed a greater rate of margin positivity in this group, suggesting that a less invasive approach without a goal of complete resection was employed.

Retrospective case series represent the remaining included studies each showing comparable rates of oncologic outcomes between endoscopic and open resection techniques.[872–874,876–879] Of the noted studies, only 2 studies included outcome data specific to the endoscopic resection of SNSCC. Nicolai et al.[877] noted an overall recurrence rate of 16.2% (7/43) with a 12% (3/25) recurrence rate in those treated with endoscopic resection and 22.2% (4/18) recurrence rate in those treated with open resection. Histologic stratification based on biologic aggressiveness (adenocarcinoma, squamous cell carcinoma, and salivary tumors) revealed a 5-year disease-specific survival (DSS) of 78.6%.

Luong et al.[876] reported 21 patients undergoing endoscopic resection of SNSCC with an OS of 93.3% and calculated 2-year and 5-year DFS of 43.8% and 25%, respectively. The remaining studies included patients with de novo SNSCC and SNSCC originating from inverted papilloma (IP).[872–874,878,879] These studies showed comparable oncologic results when comparing endoscopic and open techniques. Interestingly, de Almeida et al.[872] found no prognostic significance in those SNSCC arising from IP, whereas Yan et al.[879] found that SNSCC arising from IP appeared to have DSS benefit as compared to de novo SNSCC primarily among early-stage tumors. It should be noted that in these analyses de Almeida et al.[872] only included endoscopic tumor resection, whereas Yan et al.[879] included both endoscopic and open tumor resection.

EBR of the available literature reveals favorable oncologic outcomes in SNSCC managed via endoscopic resection as compared to those treated with open techniques. It is clear that appropriate patient selection and thorough margin-negative surgery confers optimal outcome. It is important to emphasize that evidence-based guidelines for appropriate patient selection are limited and insufficient, but expert opinion has suggested the following criteria would indicate a patient is not an appropriate candidate for endoscopic resection of SNSCC: hard palate, anterior maxillary,

inferior maxillary, extensive posterior maxillary, orbital floor, ascending process of the maxilla, nasal bone, anterior table of the frontal sinus, or posterior table of the frontal sinus osseous extension, soft palate extension, extensive ptergyopalatine fossa/infratemporal fossa extension, CN extension to or beyond their respective skull-base foramen, cavernous sinus extension, orbital extension, brain parenchymal extension, or involvement of the soft tissues of the face. Given the low incidence of SNSCC, sufficient provider/center experience is a requisite to management of this pathology and ongoing data acquisition for continued critical appraisal of the endoscopic management of SNSCC (see Table VIII.B).

- Aggregate Grade of Evidence: C (Level 2b: 1 study; Level 3a: 1 study; Level 4: 7 studies[872–874,876–879])
- Benefit: Oncologic outcomes are similar between endoscopic and open approaches in select patients. Survival outcomes of SCC arising from IP appear comparable to primary SNSCC.
- Harm: Inappropriate patient selection may lead to less optimal outcomes.
- Cost: Insufficient data to make recommendation.
- Benefit-Harm Assessment: Evidence of benefit for endoscopic approaches for resection of SNSCC.
- Value Judgments: Proper patient selection is imperative in the decision-making process for whether to utilize endoscopic, open, or combined approaches.
- Policy Level: Endoscopic resection of SCC or IP-SCC is an option in properly selected patients and experienced surgeons.
- Intervention: Patients with SNSCC may have favorable oncologic outcomes when treated with endoscopic surgery and appropriate adjuvant therapies.

VIII.C. Neuroendocrine and sinonasal undifferentiated carcinoma

Neuroendocrine malignancies of the sinonasal tract encompass several distinct entities that included ONB or esthesioneuroblastoma (ENB), neuroendocrine carcinoma (NEC), sinonasal undifferentiated carcinoma (SNUC), and small cell carcinoma (SmCC). These tumors can be divided into ENB and non-ENB neuroendocrine carcinomas based on the observation that local treatment of ENB often leads to lasting locoregional and distant control of the disease, whereas this is not the case with NEC, SNUC, or SmCC.[880] NEC was first described by Silva et al.[881] in 1982 as uniform cells growing from benign glandular epithelium, whereas SNUC was first described by Frierson et al.[882] in 1986 as neoplasms forming nests, trabeculae, and sheets containing medium-sized cells with small to moderate amounts of eosinophilic cytoplasm. They were thought to originate from Schneiderian epithelium or from the nasal ectoderm of the paranasal sinuses.[882] Since this classification, there has been ongoing debate about how to pathologically classify SNUC.[883] More recently the cytokeratin (CK) pattern on immunohistochemistry has been employed to differentiate SNUC from other sinonasal tumors because they have been reported to express CK8, CK7, and CK19[884] while lacking CK5 and CK6.[885] SNUCs have also been investigated using a mass spectroscopy–based approach, but the authors were unable to identify any activating mutations in the 95 single-nucleotide variations examined.[886]

Viral factors have been posited in the etiology of both NEC and SNUCs, but the evidence in the literature is mixed. Alos et al.[887] reported that although NEC samples tested were positive for p16, this was due to dysregulation of the retinoblastoma pathway rather than human papillomavirus (HPV) infection because all the samples tested negative for this. Conversely, Thompson et al.[888] reported that 3 of 10 NEC samples tested were positive for HPV infection; admittedly though, 2 of these samples came from tumors arising in the oropharynx. With regard to SNUC, Jeng et al.[889] reported that Epstein-Barr virus (EBV) infection does not play a role in its pathogenesis. However, the situation is less clear in relation to HPV infection because Wadsworth et al.[890] found no HPV infection in their study, but Gray et al.[891] found that 9 of 11 SNUC samples had evidence of infection.

Although it is clear that the diagnosis of these 2 rare entities is an evolving situation, the advent of modern molecular biology may soon lead to improved diagnostic testing, with the real possibility that both NEC and SNUC may be recognised as a variety of closely related but new pathological entities.[892,893] Separate from the histological and molecular biological advances, improvements in imaging, specifically CT–positron emission tomography (PET), may also soon be able to reliably differentiate SNUC from other sinonasal tumors.[894]

Both NEC and SNUC often present late with a poor outcome. However, 5-year survival of NEC is considerably better than that of SNUC (70.2% vs 35.9%).[895] Frequently, the presenting complaint will include unilateral nasal obstruction, headache, and facial pain. In a study of SNUCs by Musy et al.,[896] serosanguinous rhinorrhea was the most common complaint (57%), whereas visual change and diplopia were also common (47%). Dural invasion was observed in 50% of patients, 30% had orbital involvement, whereas another 30% had disease extending to the cavernous sinus at presentation. If left untreated, the natural history of these lesions is for rapid growth, locoregional recurrence, and distant metastasis, accounting for the poor prognosis.

The Kadish staging system[897] for ENB has been used for SNUC. Kuan et al.[898] demonstrated that advanced-stage and increasing tumor size is associated with worse survival and that surgery with adjuvant RT was associated with improved survival. Others argue that the Hyams system can be used for staging SNUC[899]; however, this is not universally employed. Whichever staging system is used, advanced clinical stage or pathological grade of SNUC have poorer prognosis.[898,899] Additionally, O'Reilly et al.[900]

performed a retrospective review in 12 patients with SNUC, showing that dural invasion and/or orbital involvement at time of diagnosis were negative prognostic indicators, whereas surprisingly cribriform plate involvement or intracranial involvement did not predict prognosis. Similarly in NEC, Patel et al.,[901] in a retrospective review of 201 patients, demonstrated that advanced disease was associated with poorer survival as was tumor site (maxillary and ethmoid origin were worse than nasal cavity). They also showed that survival was better in those treated with surgery with or without RT rather than primary RT. In contrast, Rawal et al.[902] showed that in patients who underwent EEA surgical resection, the pathological grade of tumor was associated with survival while overall stage was not.

VIII.C.1. *Treatment of SNUC and NEC*

Following the ICAR:ESBS protocol, 738 articles were initially identified, the titles and abstracts were examined, and studies were excluded if they did not pertain to SNUC or NEC. More than 30 single-patient case reports were identified, but they were excluded and only studies with greater than 3 patients were included. Finally, only studies with multiple treatment groups and survival data were included in the final analysis. This left 28 studies that are described in Table VIII.C.

The evidence presented in Table VIII.C is comprosed, at best, from pooled analysis of small-sized to medium-sized case series. The data is heterogeneous and the quality of the data, in terms of treatment and outcomes, is often poor. There are no RCTs, nor any prospective trials of any nature reported in the literature. Thus, it is extremely difficult to arrive at any firm conclusions. However, the vast majority of studies do recommend some form of multimodal treatment for both NEC and SNUC, the exact form of this therapy is contentious.

The 4 largest studies were Kuo et al.,[904] van der Laan et al.,[895] Reiersen et al.,[917] and Xu et al.[913] Kuo et al.[904] was a retrospective cohort study (level 2b evidence); as such, it was the study with the highest LOE. They performed a multivariate analysis on 435 patients with SNUC; they determined that surgery with adjuvant chemoradiation or primary chemoradiation was associated with significantly improved OS compared to surgery with adjuvant RT or RT alone. Van der Laan et al.[895] and Reiersen et al.[917] performed meta-analyses of the published case series (level 3a evidence). Van der Laan et al.[895] identified 701 cases (127 NEC, 459 SNUC, 115 SmCC); tumor type was the biggest predictor of survival (5-year survival: SNUC [35.9%], NEC [70.2%]). They reported that SNUCs were best treated with surgery and adjuvant RT (5-year survival 57.7%), whereas surgery alone and primary RT did less well, with 5-year survival of 15.7% and 17.9%, respectively. In their study chemotherapy did not appear to benefit survival. With respect to NEC, they reported that surgery was the best form of treatment, with a 5-year survival of 83.3%, whereas if the patient was not treated with surgery they had an increased risk of dying (odds ratio [OR] 11.464; CI, 1.125 to 116.796; $p = 0.039$). Reiersen et al.[917] had fewer patients in their meta-analysis (167 patients), but broadly agreed with the other studies. They had similar OS to other studies, with 26.3% alive with no evidence of disease and 21% alive with disease. They reported that surgery with adjuvant chemoradiation had a 260% increase in survival compared to surgery alone. They were unable to perform any other comparisons with different treatment groups because of the lack of data in the underlying studies. Finally, Xu et al.[913] presented 20 patients from their own institution with a review of the literature (level 4 evidence). They identified 140 patients in literature with SNUC in addition to their own 20 patients. The majority of the patients received multimodal treatment with a median OS of 12.7 months. On Cox regression analysis they did not show any difference in DFS based on initial treatment, whether single or multimodal in nature.

VIII.C.2. *Chemotherapy regimens for SNUC and NEC*

When considering which chemotherapy regime might be best for NEC and SNUC, one is again hampered by the paucity of high-level evidence within the literature. Patil et al.[928] reported on 25 patients, 13 with SNUC and 12 with ENB, treated with neoadjuvant cisplatin and etoposide then, if amenable, surgery with concurrent chemoradiation. They concluded that this strategy improved outcomes with reported 2-year OS of 78.5%. Rischin et al.[924] reported favorable results treating SNUCs when employing induction chemotherapy followed by concurrent chemoradiation, with 2-year OS of 64%, whereas Mourad et al.[909] used platinum-based chemotherapy concurrently with RT with or without induction chemotherapy, reporting 4-year survival of 56%. Ansari et al.[929] reported a novel chemotherapy regime to treat SNUC in 2 patients using cisplatin, etoposide, doxorubicin, and metformin with adjuvant melatonin therapies based on morphoproteomic guidance. However, the majority of treatment studies in Table VIII.C used platinum-based chemotherapy regimens. Rosenthal et al.[880] treated both NEC and SNUC with induction chemotherapy before surgery or RT with or without concurrent chemotherapy, reporting 5-year OS of 63% for SNUCs and 64% for NEC, respectively. Likhacheva et al.[918] recommended a multimodal approach in treating NEC, combining surgical resection and adjuvant chemoradiation. The chemotherapy was given as neoadjuvant, concurrently or in an adjuvant setting, either cisplatin plus etoposide or 5FU or carboplatin plus etoposide or docetaxel. They reported an OS of 59 months. Finally, Fitzek et al.[930] performed a prospective study of ENB, NEC, and other tumors with some neuroendocrine features. They employed a strategy of induction chemotherapy with cisplatin and etoposide followed by either proton or photon RT with reported OS of 74% at 5 years.

TABLE VIII.C. Treatment of neuroendocrine carcinoma and SNUC

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Bhasker[903]	2017	4	Retrospective case series	Sx + RT (3), Sx + CRT (4), RT (6), CRT (4), PRT (4),	Survival	Surgery is best treatment for SNUC with postoperative RT for advanced disease and close margins
Kuo[904]	2017	2b	Retrospective cohort study	Sx (37), Sx + RT (32), Sx + CRT (157), Sx + C (14), RT (16), CRT (120), C (25), No Rx (34)	Survival	CRT or Sx + CRT has improved survival compared to other groups in SNUC
Hosokawa[905]	2016	4	Retrospective case series	Sx (2), Sx + RT (1), CRT (8)	Survival	CRT is a reasonable treatment for head and neck SNECa
van der Laan[895]	2016	3a-	Meta-analysis of case series	SNUC: Sx (15), RT (43), C (7), Sx + RT (54), Sx + C (2), Sx + CRT (110), CRT (85), Palliative (31); SNEC: Sx (22), RT (4), Sx + RT (22), Sx + C (3), Sx + CRT (16), CRT (21), Palliative (2)	Survival	Surgery should be the cornerstone of treatment, supplemented by RT in poorly differentiated subtypes (SNUC, SmCC). Chemotherapy does not appear to contribute to survival.
Lund[906]	2015	4	Prospective case series	Sx + CRT (5)	Survival	Supports use of CRT followed by wide-field ES to staging/confirm response and excise residual tumor
Lopez[907]	2015	4	Retrospective case series	Sx + CRT (10), Sx + RT (1), C + Sx + CRT (3), CRT (3)	Survival	Sx + RT gave best outcomes in SNUC
Christopherson[908]	2014	4	Retrospective case series	Sx + CRT (10), Sx + RT (5), CRT (6), RT (2)	Survival	Sx + CRT where possible offered the best treatment
Mourad[909]	2013	4	Retrospective case series	Sx (3), Sx + CRT (5), CRT + Sx (7), CRT (3)	Survival	Trimodality approach (Sx and CRT) offered best LC and lower DM
Yoshida[910]	2013	4	Retrospective case series	Sx (6), Sx + CRT (4), CRT (6)	Survival	Sx + CRT gave best outcomes in SNUC
van der Laan[911]	2013	4	Retrospective case series	Sx (2), RT (4), CRT + Sx (6), PRT (3)	Survival	CRT + Sx gave best outcomes in SNUC/SNEC
Gorner[912]	2013	4	Retrospective case series	CRT + Sx (2), C + Sx (4), C (2), RT + Sx (1)	Survival	Multimodal treatment including the combination of platinum-based chemotherapy drugs should be first-line treatment
Xu[913]	2013	4	Retrospective case series and review of literature	No Rx (2, 5), single modality (7, 42), CRT (4, 37), Sx + RT (3, 22), Sx + CRT (4, 34)	Survival	No evidence that Sx + RT offer any survival advantage compared to other modalities
Al-Mamgani[914]	2013	4	Retrospective case series	CRT (7), C + Sx + RT (7), Sx + RT (5), Sx + CRT (2)	Survival	2 or 3 modality treatment offers best LC
Fried[915]	2012	4	Retrospective case series	CRT (8), CRT + Sx (11)	Survival	CRT + Sx seems to be an efficacious sequence of multimodality therapy
Mitchell[916]	2012	4	Retrospective case series	Sx + RT (5), Sx (6), CRT (10), Sx + C (1), C (4), Sx + CRT (1)	Survival	Definitive treatment with Sx or RT offers durable LC. Chemotherapy response could help to stratify patients in to treatment groups
Reiersen[917]	2012	3a-	Meta-analysis of case series	C (6), RT (21), CRT (36), Sx (15), Sx + C (1), Sx + RT (46), Sx + CRT (34), No Rx (8)	Survival	Surgery and adjuvant treatment (RT and/or C) is the best option for SNUC
Likhacheva[918]	2011	4	Retrospective case series	MDNEC: Sx + RT (3), Sx + CRT (4); PDNEC: Sx (1), Sx + C (2), CRT (4), Sx + RT (3), Sx + CRT (3)	Survival	Recommends multimodal treatment

(*Continued*)

TABLE VIII.C. Continued

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Lin[919]	2010	4	Retrospective case series	CRT + Sx (10), CRT (7), C (1), RT (1)	Survival	Suggest neoadjuvant RT or CRT gives best chance of LC but Sx is mainstay of treatment
Tanzler[920]	2008	4	Retrospective case series	Sx (1), Sx + RT (9), RT (5)	Survival	Sx + RT offers best treatment option for SNUC
Chen[921]	2008	4	Retrospective case series	Sx + CRT (17), CRT + Sx (2), CRT (2)	Survival	Gross surgical resection is a key component of treatment before or after another modality therapy
Babin et al.[922]	2006	4	Retrospective case series	CRT (5), RT (3), C (2), Sx + RT (5), Sx + CRT (5), Sx (1)	Survival	No evidence of one treatment better than any other
Kim[923]	2004	4	Retrospective case series	Sx + RT (2), Sx +CRT (2), Sx (1), CRT (3)	Survival	Recommends multimodality treatment including surgical resection
Rischin[924]	2004	4	Retrospective case series	CRT (7), RT (1), Sx + RT (2)	Survival	Induction chemotherapy followed by concurrent chemoradiation is promising treatment strategy for SNUC
Musy[896]	2002	4	Retrospective case series	CRT + Sx (10), CRT or PRT (10)	Survival	If patients are fit recommend CRT + Sx, if not then CRT
Smith[925]	2000	4	Retrospective case series	4 SNEC, 6 SNUC, Sx + CRT (1), Sx + RT (7), Sx + C (1), CRT (1)	Survival	Supports use of adjuvant chemotherapy and RT
Gorelick[926]	2000	4	Retrospective case series	Sx + CRT (4)	Survival	Supports use of radical surgery in combination with CRT
Righi[927]	1996	4	Retrospective case series	Sx + CRT (1), Sx + RT (3), RT (1), CRT (2)	Survival	Recommends multimodal treatment
Frierson[882]	1986	4	Retrospective case series	CRT (2), RT (4), Sx + RT (2)	Survival	No conclusion on treatment but first detailed account of histology of SNUC

(a, b) = number of people treated by that modality in case series, number treated in literature review; C + Sx + CRT = neoadjuvant chemotherapy then surgery and postoperative chemoradiation; C = chemotherapy; CRT + Sx = chemoradiation therapy then surgery; CRT = chemoradiation therapy; Sx + C = surgery + chemotherapy; DM = distant metastases; ES = endoscopic surgery; LC = local control; MDNEC = moderately differentiated neuroendocrine carcinoma; No Rx = no treatment; PDNEC = poorly differentiated neuroendocrine carcinoma; PRT = palliative radiation therapy; RT = radiation therapy; SmCC = small-cell carcinoma; SNEC = small-cell neuroendocrine carcinoma; SNUC = sinonasal undifferentiated carcinoma; Sx + CRT = surgery then chemoradiation therapy; Sx + RT = surgery followed by RT; Sx = surgery.

VIII.C.3. *Endoscopic vs open surgery in the management of SNUC and NEC*

Various early studies have demonstrated that endoscopic endonasal surgery could be comparable to CFR in selected cases in terms of survival in sinonasal malignancies in general.[876,931] Revenaugh et al.[932] have published the only study specifically looking at EEA in the treatment of SNUC. Their preliminary results, although based on only 13 patients, show that EEA can play a role in selected patients as part of a multimodal treatment with overall DFS of 57% with a mean follow-up of 32.3 months, which is comparable with other published data on SNUC. Although not specifically looking at treatment of SNUCs alone, Rawal et al.[902] reported that, assuming the cases are suitable for EEA and the principles of oncologic resection can be adhered to, in their meta-analysis of pooled case series (952 patients with various tumors including ENB, sinonasal carcinoma, SCC, and SNUC), 2-year and 5-year survival was comparable between the CFR and EEA groups.

Conclusions

Although there is a consensus within the literature about the need for multimodal treatment for SNUC and possibly for NEC, the temporal relationship of the various therapies has not been clearly resolved. There is certainly no answer in terms of whether surgery with adjuvant chemoradiation is necessary or whether chemoradiation alone is sufficient. Also, the role of induction chemotherapy has not been established; some studies strongly advocate this approach, whereas others found no role for it. Despite the heterogeneity of the studies' data, it is probably reasonable to conclude that SNUC and NEC are best treated with a multimodal strategy that should at least involve chemoradiation with possibly EEA or if necessary CFR surgery. The advantage of EEA is that it can provide a low-morbidity confirmation of response to chemoradiation by undertaking a wide-field excision once the effects of the chemoradiation have settled.[906]

This situation could be clarified with better study data. Fortunately, there are currently 2 phase II trials recruiting

patients, SINTART 1 and 2; these are 2 open-label, phase II, multicenter clinical trials, designed to assess the efficacy in term of progression-free survival of a multimodality treatment in patients with sinonasal carcinomas (intestinal-type adenocarcinoma, SNUC, NEC, squamocellular cancer, Hyams grade 3-4 ENB; Clinicaltrials.gov identifier: NCT02099175 and NCT02099188).

- Aggregate Grade of Evidence: D (Level 2b: 1 study; Level 3a: 2 studies; Level 4: 25 studies).
- Benefit: Majority of studies have shown benefit in multimodal treatment of both SNUC and NEC.
- Harm: Multimodal treatments appear to offer survival advantages over single-therapy treatments for both SNUC and NEC.
- Cost: No studies examined the costs of the various different multimodal strategies.
- Benefit-Harm Assessment: The heterogeneity of the studies included here, combined with the poor outcomes and rarity of the tumors, make it very difficult to assess the harm that the various proposed strategies might cause long term in surviving patients. However, it is clear that some form of multimodal treatment improves survival.
- Value Judgments: These are rare tumors with no high-level evidence to support clinical decision making; however, multimodal treatment appears to offer a survival advantage and surgery can be considered for tumors that are resectable with negative margins.
- Policy Level: Option.
- Intervention: Chemoradiation with or without surgery in the form of ESBS if amenable or CFR if not.

VII.D. Sinonasal adenoid cystic carcinoma

Sinonasal tract adenoid cystic carcinoma (ACC) is a rare malignant tumor arising most frequently from minor salivary glands. These tumors account for approximately 3% to 15% of all paranasal sinus malignant tumors and are the third most common sinonasal malignancy overall, following SCC and adenocarcinoma. An American Cancer Society SEER study based on a population of 3026 patients with head and neck ACC from 1973 to 2007[933] found that oropharynx and nasopharynx ACC accounted only for 4.56% of cases. Within the sinonasal tract, 47% to 60% arise from the maxillary sinus and 25% to 30% from the nasal cavity.[934,935] The rate of adenoid cystic cancers tends to be higher in females.[933,936,937]

Sinonasal tract ACC originates from the respiratory epithelium or the underlying mucoserous glands. Usually, 2 cell populations can be identified: epithelial and myoepithelial cells. Histological types and subtypes are tubular, cribriform, solid, or mixed. Sinonasal tract ACC is characterized by a variety of histologic growth patterns, all of which may be exhibited in a single tumor mass. The cribriform (most common) and tubular patterns exhibit low-grade behavior, and the solid, high-grade pattern confers a worse prognosis. Histologically, sinonasal tract ACC should be differentiated from ONB, epitheial-myoepthelial carcinoma, basaloid SCC, and small-cell neuroendocrine carcinoma.

An association between high-risk HPV and sinonasal tract ACC has been described,[938,939] which is different from ACCs outside of the sinonasal tract where no such association exists. Enigmatically, p16 overexpression does not necessarily suggest HPV association as a potential etiology, as it does for oropharyngeal carcinoma. Thompson et al.[938] found p16 overexpression in 86 sinonasal tract ACC cases; however, none of his cases exhibited high-risk HPV. In sinonasal tract ACC, strong and diffuse p16 staining can be observed in the absence of HPV E6/E7 messenger RNA (mRNA) expression.[939] Interestingly, HPV-related carcinoma with adenoid cystic–like features does not exhibit perineural invasion (PNI), unlike true ACC. In the cases reported thus far, the clinical behavior seems to be less aggressive than other high-grade sinonasal malignancies. At the immunohistochemical level they are the same; however, unlike true ACC, HPV-related carcinoma with adenoid cystic–like features does not harbor MYB gene fusions. Thus, it is important to differentiate this ACC-like from true sinonasal tract ACC for prognostic reasons.

ACCs have a high propensity for PNI. Neuronal cell adhesion molecules are expressed by ACC, which accounts for their tendency for PNI in up to 55% to 66% of cases.[940] There is no difference in the incidence of PNI between ACC from major salivary glands and the minor salivary glands from the oral cavity or paranasal sinuses[941]; in addition, there is no statistical correlation between PNI and stage with the ability of the tumor to invade adjacent structures such as the orbit and dura[942] (probably due to close proximity to these structures). For these reasons the role of PNI on sinonasal ACC is still a matter of debate.

Sinonasal tract ACCs are tumors with slow and insidious growth, discovered at a locally advanced stage (III/IV) in more than 55% to 70% of cases.[943,944] ACC can present with subtle symptoms of nasal obstruction, clear/purulent rhinorrhea, and anosmia, in many instances mimicking chronic sinusitis. As they progress, symptoms can start to become more aggressive, such as epistaxis, facial deformity, proptosis, diplopia, cutaneous involvement, or neurological deficits. Lymph node and distant metastasis are rare because of the sparse lymphatic system in the sinonasal tract; more than 90% are N0 and no metastasis (M0) at initial presentation (N0 96.4% and M0 92.9%).[944] Imaging studies for assessment of skull-base tumors mainly include CT and MRI with and without gadolinium. CT scan is useful to assess craniofacial bony abnormalities (erosion, hyperostosis). Contrast MRI is the best study to evaluate soft-tissue masses, as well for the evaluation of the presence of perineural spread.

VIII.D.1. *Management of sinonasal ACC*

Table VIII.D summarizes the available literature.

Surgical resection is the backbone of curative therapy. In 5 retrospective reviews,[946–948,954,955] patients treated with surgery followed by RT were noted to have a survival

TABLE VIII.D. Evidence in the treatment of sinonasal ACC

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Thompson[945]	2014	4	Retrospective review (n = 86)	Sinonasal tract ACC (single institution)	Histology, immunohistochemistry demographics, stage, prognostic factors, treatment outcomes, survival rates	Poor prognostic factors include high tumor stage, skull-base involvement, lymphovascular invasion, solid histology, bone invasion, perineural invasion, mixed anatomical site, and recurrence status. Postoperative RT does not affect outcome 5-year OS + 67.4%
Amit[943]	2014	2a	Meta-analysis (n = 520)	99 International cohort 421 patients from 15 PubMed	Overall survival, disease-specific survival	Margin status and tumor site significant predictors of outcome Sphenoid and ethmoid poor prognosis PORT/CRT did not improve outcome 5-year OS = 62%, DSS = 67%.
Lupinetti[946]	2007	4	Retrospective review (n = 105)	Sinonasal tract ACC	Prognostic factors Treatment outcomes Recurrence patterns survival rates	Surgery/PORT offers durable local control Best 5-year OS 62.9% and DSS of 70.9%
Askoxylakis[947]	2016	4	Retrospective review (n = 122)	Primary (82) and recurrent (40) sinonasal tumors - multiple histologies. Sinonasal tract ACC (n = 47)	Survival outcomes	RT in the primary or postoperative setting improves tumor control 5-year OS = 60%
Wiseman[948]	2002	4	Retrospective review (n = 35)	Sinonasal tract ACC (single institution)	Treatment outcomes Survival rates	Surgery/PORT best disease control 5-Year OS = 65%
Liu[949]	2011	4	Retrospective review (n = 80)	Maxillary sinus ACC	Prognostic factors Treatment outcomes Survival rates	Surgery/PORT improves the LC/survival. 5-year OS = 65.2%
Husain[950]	2013	2a	Systematic review (n = 86)	Case reports/series (n = 86), Large case series/institutional reviews/prospective studies (n = 366)	Incidence Presentation Treatment outcomes	Poor prognosis Surgery and surgery/PORT equivalent. Slight benefit from PORT
Michel[951]	2013	4	Retrospective review (n = 25)	Sinonasal tract ACC	Clinical features Prognostic factors	5-year OS 63% and DSS 43%Factors that improve 5-year OS: 1. TNM stage ($p = 0.03$) 2. Histological subtype($p = 0.023$) 3. Surgery/PORT ($p = 0.03$) 4. Local control ($p = 0.05$) Positive margins poor 5-year DFS
Seong[952]	2014	4	Retrospective review (n = 30)	Sinonasal tract ACC	Clinical features Prognostic factors	Local recurrence rate = 26.7% Distant metastasis rate = 23.3% Stage IV and T4 worse survival Distant metastasis affects disease-free survival but not disease-specific survival
Rhee[953]	2006	4	Retrospective review (n = 25)	Chart review of patients with sinonasal tract ACC	Clinical features Treatment outcomes	5-year OS 86%, 5-year local recurrence rate 30%, distant metastasis rate 25%. Presence of distant metastasis correlated with decreased 5-year survival ($p = 0.001$)

ACC = adenoid cystic carcinoma; CRT = chemoradiation therapy; DFS = disease-free survival; DSS = disease-specific survival; LC = local control; OS = overall survival; PORT = postoperative radiotherapy; RT = radiotherapy; TNM = tumor-node-metastasis.

advantage. In addition, a retrospective review by Liu et al.[949] specifically on maxillary sinus ACC supports the role of surgery followed by postoperative RT. The use of postoperative RT was guided mainly by the presence of positive margins, which was present in up to 63% to 85% of the cases.[946–948,952] Patients who received only surgical treatment were those who had negative margins and those who received RT alone had severely advanced tumor stage, for unresectable palliative care or because they were unfit for surgery. Because radiation improves survival in patients with ACC outside the sinonasal tract,[956,957] it may be of benefit for sinonasal tract ACC; although it is noted that 96% of ACC tumors respond to radiation, the recurrence rate after RT as definitive therapy has been reported as high as 94%.[958,959] Although these data are not specific to sinonasal tract ACC, they support the notion that surgery should play a key role in the management of sinonasal tract ACC.

In contraposition, Thompson et al.[938] found that RT when combined with surgery does not seem to significantly alter overall patient outcome ($p = 0.545$), but may result in longer DFS. Husain et al.,[950] in a systematic review that consolidated 454 patients, found similar survival rates between the surgery with RT group (68.4%) and the surgery alone group (63.2%), but lower in the RT alone group (42.1%). These findings were also supported by a meta-analysis by Amit et al., (10) who found no added outcome benefit from adjuvant therapy. Margin status, PNI, skull base, dural, and orbit compromise should also be considered in the treatment plan. Michel et al.[951] and Amit et al.[943] found that positive margins lower 5-year OS and DFS; however, Thompson et al.[938] did not find this to be a significant risk factor for DSS and DFS ($p = 0.128$). Wiseman et al.[948] found that patients with positive margins experienced higher local recurrence rates when compared to patients with negative margins (41.7 vs 22.2%, respectively, $p = 0.34$). Furthermore, the presence of local recurrence was a poor 5-year OS prognostic factor ($p = 0.05$). Although the impact of positive margins on DSS and OS is variable, most of the literature agrees on the negative impact it has on local recurrence.

The impact of PNI, skull base, dural, and orbit involvement on recurrence and survival is limited because of the limited literature available on sinonasal tract ACC. Skull-base invasion has been identified as a significant factor for OS and DSS when compared with no skull-base invasion ($p = 0.029$ and $p = 0.031$, respectively).[946] The role of PNI on local recurrence and survival is still a manner of debate. Because of sinonasal tract ACC proximity to important neurovascular structures, so far the question still remains if local recurrence is due to positive margins or PNI. One can conclude that compromise of important neurovascular structures, such as the skull base and orbit, will impact local recurrence rate and, this way, indirectly impact survival.

The current evidence available does not support the routine use of postoperative RT (Recommendation C) and it should be considered on a case-by-case basis taking into account the margin status, tumor stage, and location.

Salivary gland neoplasms respond poorly to chemotherapy, and adjuvant concurrent chemoradiation therapy is currently not recommended, but can be considered for advanced-stage disease, nonresectable tumors, or palliation. The Radiation Therapy Oncology Group (RTOG) 1008 is investigating whether systemic therapy in combination with RT has any role in this disease, although this is for non–sinonasal tract ACC.[960]

Because of the low incidence of this disease, randomized data is completely absent. Treatment outcomes for open and endoscopic approaches for sinonasal tract ACC are limited[961,962] because the majority of reports only document surgery without specifying long-term results. Michel et al.,[951] in a cohort of 25 patients with sinonasal tract ACC, found no significant difference in 5-year OS or 5-year DFS between endoscopic and open surgery; however, they only had 4 T2 exclusively endoscopic cases, so both small numbers and selection bias are issues. Nonetheless, negative margin status, should apply to endoscopic techniques and should be the goal for ESBS.

VIII.D.2. *Recurrence, outcomes, and prognosis after sinonasal tract ACC*

Recurrences for sinonasal tract ACC are frequent (30%)[950] and occur late, sometimes many years after initial management. Patients with sinonasal tract ACC require lifelong follow-up. The following characteristics, when present, predict an increased incidence of recurrence: multiple areas of tumor involvement, advanced disease stage (stage IV), skull-base involvement, PNI, bone invasion, and lymphovascular invasion.

Given the scarcity of sinonasal tract ACC, the majority of reports on demographic and survival data are limited to retrospective systematic and single-institutional reviews. Survival rates for sinonasal tract ACC have been reported in a few studies. Liu et al.[949] reported a 5-year survival rate of 65.2% in a series of 80 patients with ACC of the maxillary sinus. Wiseman et al.[948] in patients with sinonasal tract ACC, the 5-year, 10-year, and 15-year OS rates were 65%, 55%, and 28%, respectively. Wei et al.[955] and Zhang et al.,[954] in 2 articles published in Chinese, based on 2 series of 40 patients and 80 patients with sinonasal tract ACC, reported 5-year OS rates of 76.9% and 64%, respectively. Amit et al.,[941] in a cohort of 98 patients with sinonasal tract ACC, found an OS and DSS of 64% and 65%, respectively. In a meta-analysis the 5-year OS and DSS of a 520-patient cohort with sinonasal tract ACC were 62% (range, 25% to 81%) and 67% (range, 40% to 86%), respectively.[943]

Tumor location has a pivotal impact on survival because of the proximity to important neurovascular structures. Sinonasal tract ACC is more frequent in the maxillary sinus and nasal cavity, followed by the ethmoid and sphenoid sinus.[938,941,943,948,950] Amit et al.[943] found a DSS rate of 83% and 64% for the nasal cavity and maxillary sinus, respectively, whereas ethmoid or sphenoid sinus involvement

resulted in a DSS of 25% ($p < 0.001$; hazard ratio [HR] 7.7; 95% CI, 1.7 to 23.5). This may be explained by the close proximity of the ethmoid and sphenoid sinuses to the orbit and skull base, because skull base involvement is associated with lower OS. Thompson et al.[938] found a survival average of 6.5 years for patients with skull-base involvement, compared to 12.1 years from those without ($p = 0.005$). In addition to this, 80.8% with skull-base involvement were dead of disease compared to 41.7% without skull-base involvement. Furthermore, positive/close tumor margins are significantly more associated with poorer OS than negative tumor margins (69% vs 27%, respectively, $p < 0.04$, HR 3.1).[943] Although it is possible that proximity of sinonasal tract ACC to the skull base and other vital structures limits the impact of PNI on survival, its presence is associated with positive margins. Even when surgical margins may be negative, it has been suggested skip lesions along nerve trunks may invalidate a negative margin.[941,942,963] The existence of skip lesions in large nerve PNI from cutaneous SCC has been challenged, but no such data exists on ACC.[964] In addition to tumor origin; positive lymph node, metastasis, and age (>70 years) are also considered independent predictors of outcome (OS and DSS).[943,952] Sinonasal tract ACC is associated with the lowest rate of distant metastases, but has the poorest outcome when compared to non–sinonasal tract ACC.[933] Although lung is the more common, bone and brain metastasies behave more aggressively.[941]

Extensive surgical planning is necessary to obtain the highest chance of a clear surgical margin. Surgical approach must be based upon tumor location, patient desire, and surgeons' experience/preference. In general, optimal treatment in the management of sinonasal tract ACC should be surgical resection with negative margins. The use of postoperative RT must be decided on a case-by-case base (skull base, dural, or orbital compromise). Patients with positive margins should be treated with postoperative RT.[948,953]

- Aggregate Grade of Evidence: C (Level 2a: 2 studies, Level 4: 4 studies).
- Benefit: Surgery with negative margins improves overall 5-year survival and DSS.
- Harm: Surgical complications and morbidity are largely related to the approach and tumor primary site. The addition of RT can possibly result in both temporary and long-term morbidity.
- Cost: Moderate direct costs from surgery. The addition of RT increases cost; complications increase costs (eg, wound dehiscence, flap failure, osteoradionecrosis).
- Benefit-Harm Assessment: Primary surgery is beneficial in the management of sinonasal tract ACC. The preponderance of benefit over harm has not been demonstrated for postoperative RT or its avoidance. Benefits are largely theoretical and should be balanced against the significant RT morbidity.
- Value Judgments: It is important to understand radiation nuances specific to skull-base areas when considering postoperative RT. Characteristics affecting prognosis such as tumor location (eg, maxillary sinus vs sphenoclival or ethmoid sinus), tumor histology (eg, solid vs cribiform), margin status, and TNM disease stage should be taken into account.
- Policy Level: Option
- Intervention: Primary surgery should be considered in all patients. Postoperative RT should be considered on a case-by-case basis for patients with sinonasal tract ACC. Current literature does not support its routine usage. Primary radiation, with the possible addition of concurrent chemotherapy, should be reserved for those patients with unresectable disease and patients who are not surgical candidates.

VIII.E. Endoscopic nasopharyngectomy

Surgical management of nasopharyngeal tumors is challenging due to the restricted anatomy and difficult access. Nasopharyngectomy is typically indicated in cases of residual or recurrent local nasopharyngeal carcinoma (NPC), but may also be used to treat epidermoid carcinomas, lymphoepitheliomas, adenoid cystic carcinomas, adenocarcinomas, mucoepidermoid carcinomas, and sarcomas of the nasopharynx.[965,966] Nasopharyngectomy is traditionally performed using an open approach such as a maxillary swing, midface degloving, transpalatal approach, or transinfratemporal fossa approach.[967–969] However, such techniques risk significant morbidities including oronasal fistula, palatal incompetence, trismus, numbness, facial scarring, and carotid rupture.[970]

First reported in 2005, experience with endoscopic nasopharyngectomy (ENP) is increasing.[971] Best described in patients with recurrent NPC, the endoscopic approach includes adequate visualization of the tumor cavity through the nasal cavity and oral cavity, complete surgical resection to negative margins, and identification of critical neurovascular structures such as the ICA. The endonasal approach is attractive because of the avoidance of an external scar, perceived reduction of functional deficits, and improved visualization afforded by the high endoscopic magnification.

A limited number of anatomic cadaver studies and expert opinion reports have described the approach to ENP.[965,966,971–980] Most reports focus on recurrent NPC. There is no standardized procedure and the endoscopic surgical plan must be customized for the individual patient's tumor. For small tumors confined to the posterior nasopharyngeal wall, a posterior septectomy can be performed to visualize the floor of the sphenoid sinus and the posterior wall. This can be extended superiorly to include the anterior wall and floor of the sphenoid sinus with removal of the intersphenoidal septum. For larger tumors with more lateral extension, the surgeon can perform an endoscopic medial maxillectomy with removal of the inferior turbinate, medial maxillary wall, and/or nasolacrimal duct. Access to the nasopharynx and adjacent structures can be achieved by removal of the posterior wall of the maxillary antrum, ligating the sphenopalatine artery and associated vasculature, clearing the tissue of the pterygopalatine fossa, and

removing the medial and lateral pterygoid plates. This exposes the cartilaginous Eustachian tube, which can be removed. The limits of resectability are poorly defined and debatable, but some authors cite the clivus posterosuperiorly, lateral pterygoid plate laterally, inferior turbinate anteriorly, and the level of the soft palate inferiorly.[976–980] The parapharyngeal ICA is at risk during dissection after removal of the pterygoid plates and is the oncologic limit of dissection. Intracranial invasion is not typically addressed with an endoscopic approach. Identification of key surgical landmarks and their relationship to the ICA is critical to minimize the risk of injury.[979–981] Stereotactic image-guided navigation is commonly used during the operation.

Tumor resection can be achieved with sharp dissection, electrocautery, or laser.[973,982] En bloc resection of tumors is difficult or impossible in most cases given the narrow confines of the nasopharynx limiting working space. The resection area can be left open to heal secondarily, or a number of local rotational flaps can be utilized for coverage.[974,975,983–985] Prior preoperative and postoperative radiation considerations should be taken into account when planning reconstruction. However, there is no definitive evidence that flap coverage of the defect helps prevent osteoradionecrosis.[975,985]

Patient selection is critical for the success of ENP. Extent of the tumor must be determined prior to deciding the approach. Preoperatively, patients should undergo a thorough workup including both imaging and flexible nasopharyngoscopy to delineate the tumor's location and extent. The likelihood of successful surgical excision diminishes with increasing tumor size and lateral extension. Locoregional disease factors include significant parapharyngeal space extension, ICA involvement, involvement of the bony skull base beyond the clivus, significant dural involvement, cavernous sinus involvement, and brain invasion. The extent of parapharyngeal space involvement that precludes resection has not been well studied, although Chen et al.[982] reported that 29% of patients with tumors in the superficial parapharyngeal space recurred compared to no recurrences in patients with T1 disease.

There have only been a small number of publications on the literature studying the results of ENP. Yoshizaki et al.[971] first reported on the use of ENP in 5 patients. Four patients had recurrent T2 (rT2) NPC, whereas 1 patient had sinonasal malignant melanoma. Four of the 5 cases were successfully resected, while the fifth patient with rT2 disease had massive parapharyngeal extension not amenable to resection. There were no major complications. Chen et al.[972] published their experience with 6 patients who underwent ENP for recurrent T1 (rT1) and rT2 NPC. There were no intraoperative complications in this study. The local control rate was 83.3% at 29 months. One patient died of osteoradionecrosis causing significant bleeding 19 months after surgery. Ko et al.[973] reported on the use of endoscopic titanyl-phosphate (KTP) laser nasopharyngectomy in 28 patients with rT1 and rT2 disease. Two-year OS was 59.4%, and 2-year DFS was 57.6%. Rohaizam et al.[986] reported on a series of 6 patients with rT1 NPC. They had no recurrences or deaths in a follow-up period of 3 to 14 months. Castelnuovo et al.,[987] in 2009, looked at 4 patients with rT1, 1 patient with rT2, and 3 patients with recurrent T3 (rT3) disease undergoing ENP. With a mean follow-up of 28 months, there were no recurrences in patients with rT1 or rT2 disease. Two of the patients with rT3 disease were alive, whereas 1 was dead of disease. Chen et al.[972] reported on a series of 37 patients with disease ranging from rT1 to rT3 NPC. With a median follow-up of 24 months, 2-year OS was 86.2%, local relapse-free survival was 86.3%, and progression-free survival was 82.6%. Tay et al.[988] studied 6 patients with locally-contained nasopharyngeal tumors undergoing ENP and found a mean DFS and OS of 90.7 months. Castelnuovo et al.[989] updated their previously reported series in 2013 and looked at intraperative and postoperative complications in a larger group of patients with early-stage recurrent NPC (rNPC) undergoing ENP. They found no major complications in their series of 36 patients. Nine patients experienced minor complications including headache, numbness of hard palate, otorrhea, and temporary postoperative masticatory impairment.

In 2012, Ho et al.[975] examined 13 patients with early-stage rNPC and found 2-year local DFS and OS rates of 69.2% and 100%, respectively. There was a 52.6% rate of minor complications. Otitis media with effusion was the most common complication (30%) in the 15-person cohort after postoperative crusting (100%). Mild epistaxis occurred in 1 case. In 2014, Hsu et al.[980] reported on a group of 9 patients with rT1 to rT3 tumors and found a 2-year survival rate of 100%, 2-year disease-free rate of 80%, and no significant complications.

Recently, Vlantis et al.[985] conducted a systematic review of the ENP literature along with a pooled analysis of 300 patients who underwent ENP for rNPC. The pooled analysis found a local recurrence rate of 20.1%, a DSS rate of 85.8%, and an OS rate of 82.9%. The study also revealed 20 major postoperative complications in the literature. There were 15 cases of osteoradionecrosis, 2 cases of flap necrosis, 1 hypoglossal nerve palsy, 1 intracranial infection, and 1 case of velopharyngeal insufficiency.

Only 1 recent study has looked at the use of ENP in patients with only locally advanced disease. Wong et al.[990] recently reported on a series of 15 patients with rT3 and rT4 disease who underwent ENP and suggested it was a safe and effective option. The study included patients with advanced disease as defined by tumor extent rather than volume, and excluded those with tumors that crossed dura. There were no serious complications, and there was an overall reported 2-year survival of 66.7%. However, this conclusion is limited by the retrospective study design and small sample size.

No studies have directly compared ENP to traditional open approaches. In 2014, Na'ara et al.[991] performed a meta-analysis of the literature on treatment of rNPC over a 22-year period and determined prognostic factors associated with outcomes. Within the study, they performed

a survival analysis according to surgical approach on 84 patients. They found a statistically significant difference in the 5-year OS rate between the open approach patients (49%) and the endoscopic approach group (70%). In a subgroup analysis, endoscopic and open approaches had no significant effect upon survival for early-stage disease (rT1 and rT2); however, the endoscopic approach had a statistically significant survival advantage compared to open approaches for rT3 and rT4 tumors (66% vs 12%, respectively).[27,991]

A few studies have compared ENP to re-irradiation for rNPC. Zou et al.,[992] reported on a retrospective cohort study comparing patients who underwent intensity-modulated RT (IMRT), conventional RT, and ENP. In patients with rT1 to rT2 disease, both IMRT and ENP resulted in better OS than conventional RT. ENP was superior to IMRT in terms of OS (79.2% vs 62.1%, $p = 0.007$). However, there was no difference in survival among patients with rT3 to rT4 disease (29.8% vs 16.8%, respectively, $p = 0.351$). In You et al.'s[993] study, ENP was found to be superior to IMRT for OS (77.1% vs 55.5%, $p = 0.003$), QOL conservation as defined by the mean global health status score (57.6 vs 29.8, $p < 0.001$), and decrease in post-treatment complications (12.5% vs 65.3%, $p < 0.001$).

Current available data suggests that ENP is a reasonable option for patients with rT1 and rT2 disease. Although there is lack of long-term follow up data, 2-yearand 5-year survival rates suggest that there is a relatively good short-term survival for patients with minimal complications after ENP in appropriately selected patient. There is insufficient evidence to support the expansion of ENP to patients with later stage rT3 and rT4, except in possibly some select cases (see Table VIII.E).

- Aggregate Grade of Evidence: C (Level 3a: 1 study; Level 3b: 2 study; Level 4: 11 studies)
- Benefit: ENP is a reasonable and safe option for the treatment of rT1 and rT2 NPC tumors with acceptable complication rates and good survival. Although no studies have directly compared ENP with traditional open approaches, endoscopy may reduce functional and cosmetic morbidities inherently associated with open approaches.
- Harm: Potential harm of the endoscopic approach includes insufficient removal of residual or recurrent disease. This is in addition to the well-described risks associated with endoscopic approaches to the skull base, including bleeding, infection, and damage to surrounding structures such as the orbit, brain, and nerves.
- Cost: No studies have examined the cost of ENP. Potentially, ENP may lead to shorter operative time, faster recovery, and shorter hospital length of stay, which may translate to lower costs.
- Benefit-Harm Assessment: Preponderance of benefit over harm for early-stage rT1 and rT2 nasopharyngeal cancers.
- Value Judgments: ENP appears to result in outcomes that are comparable to those from traditional open approaches in patients with rT1 and rT2 recurrent or persistent nasopharyngeal cancer; however, there have been no studies directly comparing the 2. All studies to date suggest that for select patients with disease in this area, ENP is safe, results in lower surgical morbidity, and provides a good rate of local control and survival. There is little evidence supporting the use of ENP for patients with rT3 and rT4 tumors.
- Policy Level: Recommendation
- Intervention: ENP is a reasonable option in patients with locally-confined recurrent or persistent nasopharyngeal SCC that reduces morbidity compared to open approaches and provides good disease control and survival rates.

IX. Clival tumors

IX.A. Clival chordoma

Multiple open approaches are used to address lesions of the clivus. The relative anatomic inaccessibility of this region in conjunction with critical adjacent structures has made surgical management challenging, and only in recent decades with the further refinement of techniques have less invasive approaches for this region, including EEA, been employed.

The clivus is located behind the nasopharynx and the body of the sphenoid and can be categorized into 3 parts: the upper, middle, and lower clivus. The lower clivus is below the sphenoid sinus floor, the middle portion spans from the sphenoid sinus floor inferiorly to the sellar floor superiorly, and the upper portion is from the sellar floor to the dorsum sella.[994] There are numerous critical neurovascular structures adjacent to the clivus, including the ICA; brainstem (ie, the pons), the vertebral arteries; the basilar artery; CNs III, IV, V, and VI; and the lower CNs inferiorly. Furthermore, the clivus is adjacent to the sella and associated structures, including the optic chiasm. The intimate proximity of these critical structures makes an anatomic understanding of common lesions and surgical approaches paramount.

Lesions of the clivus encompass a broad differential diagnosis, with chondrosarcomas and chordomas representing the majority of these lesions, with the latter being the most common. Comprised of physaliferous cells theoretically derived from the notochord (with a "soap bubble" appearance on histology), chordomas represent a low-grade malignancy with significant potential for functional deficits because of the crucial structures adjacent to the clivus.[995,996] Patients often present with discrete symptoms from CN deficits, commonly CN VI palsy, nonspecific complaints including headaches, or can have lesions detected incidentally on imaging studies. Certain radiologic features can assist diagnosis; eg, chordomas tend to be more midline, with T2 hyperintensity on MRI, and can have cystic/lytic components best illustrated on CT, whereas

TABLE VIII.E. ENP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Vlantis[985]	2017	3a	Systematic review with pooled analysis	Patients who underwent ENP for rNPC	Survival rate, complications	Local recurrence rate 20.1%, disease-related death rate 14.2%, all cause mortality 17.1%
Na'ara[991]	2014	3a	Systematic review with meta-analysis	Patients undergoing salvage surgery for rNPC	Prognostic factors associated with outcomes after surgery	Statistically significant 5-year OS advantage for endoscopic vs open approach
You[993]	2015	3b	Case-control	ENP vs IMRT for patients with rT1-T2 rNPC	Survival, morbidity, long term oncologic results, treatment-related complications, QOL	Statistically significant increase in survival, QOL, decrease in posttreatment complications for ENP
Zou[992]	2015	3b	Case control	ENP vs IMRT vs conventional RT for rNPC	Survival	Better survival for ENP compared to IMRT
Wong[990]	2017	4	Case series	Patients with rT3 and rT4 NPC undergoing ENP	Survival, complication rates	2-Year OS 66.7%, DFS 40%, no severe operative complications
Castelnuovo[989]	2013	4	Case series	Patients with early stage rNPC undergoing ENP	Intraoperative and postoperative complications, survival	No serious intraoperative or postoperative complications
Hsu[980]	2014	4	Case series	9 Patients with rT1–rT3 tumors	Survival, complications	2-Year survival rate of 100%, 2-year DFS rate of 90%, no significant complications
Ho[975]	2012	4	Case series	13 Patients with rT1–rT3 rNPC	Survival and recurrence rates, complications, intraoperative blood loss	2-Year local DFS and OS rates of 69.2% and 100%, overall minor complication rate 52.6%, no major complications
Castelnuovo[987]	2010	4	Case series	Patients with rT1, rT2, and rT3 disease undergoing ENP	Survival, recurrence	No recurrences in patients with rT1 and rT2 disease, 2 patients alive with rT3 disease with a third dead on follow-up
Tay[988]	2009	4	Case series	6 Patients with locally contained nasopharyngeal tumors undergoing ENP	Survival	Mean DFS and OS 90.7 months
Chen[982]	2009	4	Case series	37 Patients with rT1, rT2 and rT3 disease undergoing ENP	Survival	2-Year OS 84.2%, local relapse-free survival of 86.3% and progression-free survival of 82.6%
Rohaizam[986]	2009	4	Case series	6 Patients with rT1 disease undergoing ENP	Recurrence	No recurrences after 3–14 months
Ko[973]	2009	4	Case series	Use of KTP laser ENP in 28 patients with rT1 and rT2 NPC	Survival	2-Year OS of 59.4, 2-year DFS of 57.6%
Chen[972]	2007	4	Case series	6 Patients with rT1 and rT2 NPC that underwent ENP	Survival, recurrence and complications	No complications, only 1 recurrence at 33 months
Yoshizaki[971]	2005	4	Case series	4 Patients with rT2 NPC, 1 patient with sinonasal melanoma who underwent ENP	Complications	No complications, successful resection in 4 of 5 cases

ENP = endoscopic nasopharyngectomy; DFS = disease-free survival; IMRT = intensity-modulated radiation therapy; KTP = potassium titanyl phosphate; NPC = nasopharyngeal carcinoma; OS = overall survival; QOL = quality of life; rNPC = recurrent nasopharyngeal carcinoma; RT = radiation therapy; rT1 = recurrent T1 disease; rT2 = recurrent T2 disease; rT3 = recurrent T3 disease.

chondrosarcomas tend to be paramedian and may be partially calcified.[997–1001] Nevertheless, pathologic specimen is generally needed for a definitive diagnosis.

At centers with appropriate expertise, clival chordomas are largely amenable to endoscopic endonasal resection when surgical intervention is considered. There are several factors (detailed later in this section) that come into play when considering this approach, including the laterality of the tumor and surgeon experience. Preoperatively, an evaluation of the CNs is critical. In addition to conventional preoperative imaging such as CT and MRI, many authors recommend obtaining angiography, preferably CT angiography, because it is less invasive and offers information regarding vessel involvement, bony involvement, craniocervical junction stability, and resectability.

The primary goal of surgical resection is the complete resection of tumor and the involved bone and extracompartmental disease extension. The surgical steps for endoscopic endonasal resection certainly differ by institution and surgeon preference, but in general are as follows. Bilateral wide sphenoidotomies are performed, taking care not to injure the sphenopalatine artery, which supplies the pedicles for vascularized NSFs for skull-base reconstruction. After elevation of an NSF (usually unilateral) and placement away from the surgical site, the sphenoid rostrum is removed. Sellar bone is drilled away, exposing the dura, and the clivus bone is drilled medial to the vidian nerves bilaterally just below the second genu of the carotid arteries.[996] The ICAs are avoided using several strategies, including knowledge of the location of the vidian nerve, neuronavigation, Doppler, and carefully removing bone with a diamond burr rather than a cutting bur.[996,1002] Clival drilling continues at the clivus until the dura is exposed, and if dural opening is necessary, it is done so in the midline to avoid CN VI injury. If a lesion involves the lower clivus, mucosa and soft tissues of the nasopharynx are raised prior to further bony removal. Further nuances are dictated by the extent of the lesion and goals of surgical resection.

The EBR in the next section is intended to disseminate knowledge about outcomes and other clinical considerations relating to patients undergoing endonasal endoscopic resection of clival chordomas. Following the ICAR:ESBS protocols, 111 articles were initially identified with 89 excluded because of the following reasons: anatomic/cadaveric study (7), case report (15), not about clival chordoma (39), no endoscopic approaches (4), non-English (9), review paper (9), skull-base reconstruction techniques manuscript (4), and overlapping/duplicate cohort (3). The bibliographies of the 22 publications meeting inclusion criteria were searched, resulting in the addition of 2 publications. Included publications are detailed in Table IX.A.1.

Three publications from which data were not included in our aggregate numbers are included in Table IX.A.2: 1 of these publications is a systematic review and meta-analysis[1027] and is described separately to avoid double-counting patients; another focuses on tumor seeding rates and also involves the same patient population as patients in another analysis; and another contains a cohort already contained in 1 of the included manuscripts.

IX.A.1. *Outcomes of EEA for clival chordoma*

The majority of included studies evaluated outcomes for these patients; however, most conclusions were limited by a modest follow-up period. In fact, only 6 of the included analyses had follow-up periods averaging greater than 2 years, even though chordomas both in the skull base and elsewhere have been known to recur several years after initial management. Among studies with longer follow-up periods, recurrences did occur in several patients. Tan et al.'s[1015] review of 14 patients who underwent EEAs for clival chordomas had a mean follow-up of 41.5 months, with 2 reported recurrences. One of these patients died of recurrence whereas another patient underwent further adjuvant IMRT.

Shidoh et al.[1013] reported their experience with 18 clival chordomas, including 9 performed using an endoscopic endonasal technique and the other 9 performed using a transpalatal/pharyngeal technique. Median operating room time and hospitalization length was shorter among the endonasal cohort, with improved postoperative oral intake in this group as well. On the other hand, surgical complications were noted to be higher among the endoscopic endonasal patients, mainly caused by aggressive management of subdural invasion. Importantly, case selection was affected by lesion location (ie, upper clivus vs lower lesions), making any comparisons among this modest cohort somewhat confounded. Nearly all other included analyses were retrospective series examining solely EEAs rather than comparison among different techniques. Additionally, the lack of a standardized stating system further limits comparison between surgical techniques.

As a result of modest sample sizes and the LOE among these studies (predominantly Level 4 LOE), a review of these series may not be optimal for judging outcomes and comparisons, and further higher-quality prospective comparisons will likely prove invaluable. Another strategy for evaluating outcomes may be using population-based resources, such as the SEER database. One SEER analysis examining skull-base chordomas noted that patients undergoing resection had a greater 10-year survival (61.4%) than those receiving primary radiation (44.8%), although differences among surgical approaches were not differentiated in this study.[1029] Skull-base chordomas have been noted in other SEER analyses to have significantly lower survival than that of other clival lesions such as chondrosarcoma.[1030] However, these population databases cannot differentiate between surgical approaches or extent of surgery.

Table IX.A.1, Table IX.A.2, and Table IX.A.3 offer a summary of clinical details and conclusions.

The literature focusing on endoscopic resection of chordomas is comprised predominantly of single-institution

TABLE IX.A.1. Summary of evidence for endoscopic endonasal resection of clival chordomas

Study	Year	LOE	Design	Study groups	Clinical endpoint(s)	Conclusion
Arbolay[1003]	2009	4	Retrospective review	Invasive adenomas (4), clival chordomas (2), craniopharyngioma (2), astrocytoma (1), pituitary adenoma (3)	GTR in 66.7% of cases	EEA to the clivus is feasible
Frank[1004]	2006	4	Retrospective review	9 Chordoma, 2 chondrosarcoma	3 Patients died of chordoma; 1 patient experienced 2 recurrences	EEAs are feasible in the surgical management of aggressive cranial base tumors, including chordomas and chondrosarcomas of the clivus
Chibbaro[1005]	2014	4	Prospective review	54 EEAs for skull-base chordomas	88% GTR rate among newly diagnosed; 65% overall GTR rate	The EEA management of skull-base chordomas has a gradual learning curve that once acquired offers similar or better resection rates compared to traditional approaches with less morbidity
Fraser[1006]	2010	4	Retrospective review	10 Chordoma	GTR or NTR in 90% of patients in which maximal resection was the goal	The endonasal endoscopic transclival approach represents a less invasive and more direct approach than a transcranial approach to treat certain moderate-sized midline skull-base chordomas. Large tumors with significant extension lateral to the carotid artery may not be suitable for this approach.
Garzaro[1007]	2016	4	Retrospective review	9 Chordoma	GTR in 66.6%	When dural opening is required, 3D vision allowed an accurate intradural sharp dissection and a precise repair of the skull base.
Holzmann[1008]	2010	4	Retrospective review	13 Chordoma	Radical or near total removal in 92.3%	The transnasal transclival approach provides an elegant alternative to classical approaches to clival lesions especially for midline tumor locations. For large tumors iMRI is of significant help. Dural reconstruction of large defects emerged as the greatest challenge of this technique even for experienced endoscopic surgeons.
Hwang[1009]	2007	4	Retrospective review	3 Chordoma	All 3 patients with near total removal	The neuronavigation image-guided transsphenoidal approach is a viable, minimally invasive alternative for surgical treatment of clival tumors.
Koutourousiou[1010]	2012	4	Retrospective review	60 EEAs for 50 cranial base chordomas (35 primary, 25 recurrent/persistent)	GTR rate of 66.7%.	EEA is an alternative for cranial base chordomas, with minimal morbidity and high success of GTR when performed by experienced surgeons.
Messerer[1011]	2016	4	Retrospective review	3 Chordoma	GTR in all chordomas	EEAs allow direct access to the skull base, limiting the incidence of neurological morbidities. For midline epidural clival tumors, this approach allows a total excision and also offers excellent access to the clival component intradural lesions. A combined approach permits good tumor control with minimal complications.

(*Continued*)

TABLE IX.A.1. Continued

Study	Year	LOE	Design	Study groups	Clinical endpoint(s)	Conclusion
Ramm-Petersen[1012]	2016	3	Retrospective cohort	10 Chordoma (6 EEA, 4 observation)	Total or gross total resection in 4 of 6 patients (66.7%)	The endoscopic transsphenoidal approach is a valid, minimally invasive alternative for the treatment of clival chordoma. In selected patients a wait-and-scan strategy can be considered.
Shidoh[1013]	2014	3	Retrospective cohort	9 EEA, 9 transoral/transpalatal	GTR in 3 cases in EEA group, 1 case in transoral group	Surgical complications are higher in endoscopic endonasal approaches than the transoral/transoropharyngeal cohort, mainly caused by aggressive management of subdural invasion among EEAs. Postoperative PO intake and operating room time is shorter among individuals who underwent endoscopic endonasal approaches for clival chordomas.
Solares[1014]	2010	4	Retrospective review	19 EEA to sphenoclival region		This study demonstrates that transnasal endoscopic access to the sphenoclival region is technically feasible and allows successful surgical extirpation of tumors with a low complication rate and acceptable patient outcomes.
Tan[1015]	2012	4	Retrospective review	7 Primary chordomas, 7 recurrent chordomas	Macroscopic resection rates in primary and revision groups were 71% and 29%, respectively	Endoscopic resection of clival chordomas is a safe and viable alternative to the traditional open approach. The nasoseptal flap is an excellent method of obtaining a watertight skull-base closure. Furthermore, this series highlighted the fact that the primary attempt at surgery offers the best chance to achieve a total resection.
Taniguchi[1016]	2012	4	Retrospective review	4 Chordomas extending into retro-carotid space	100% GTR	Though a longer follow-up is needed to evaluate its effectiveness in long-term tumor control, the surgical maneuver using the side-viewing endoscope is effective for removing laterally extended clival chordomas.
Vellutini Ede[1017]	2014	4	Retrospective review	38 EEAs for clival lesions	GTR in 48% of patients with indications for GTR	Endoscopic transnasal surgery is an alternative approach to treatment of clivus lesions, and, in expert hands, this technique can obtain good results. Lateral extension and previous treatment were factors that could make the surgery more difficult. Intradural extension did not limit the radicality of the removal.
Zhang[1018]	2008	4	Retrospective review	9 EEAs for clival lesions	Total removal in 6 chordoma and 1 chondrosarcoma	EEA: Provides better visualization of the deeper anatomical structures in the skull base and affords a means to "look around corners." This approach promises a simple and rapid access to the clivus. It is both a safe and efficient procedure.
Hong Jiang[1019]	2008	4	Retrospective review	9 EEA for upper/mid-clival chordomas	7 of 9 achieved GTR (77.8%)	The endoscopic approaches developed for treatment of chordomas according to the different clival location provide the possibility for more complete tumor

(*Continued*)

TABLE IX.A.1. Continued

Study	Year	LOE	Design	Study groups	Clinical endpoint(s)	Conclusion
						resection with maximal preservation of anatomic structures and reduction of the overall incidence of complications.
Zoli[1020]	2018	4	Retrospective review	65 Patients who underwent 80 EEAs	58.7% GTR	The EEA was associated with a high rate of tumor removal and symptom control, with low morbidity and preservation of a good QOL. These results allow for a satisfactory overall survival rate, particularly after GTR and for primary surgery. Considering these results, the authors believe that an EEA can be a helpful tool in chordoma surgery, achieving a good balance between as much tumor removal as possible and the preservation of an acceptable patient QOL.
Dehdashti[1021]	2008	4	Retrospective review	12 Chordoma	GTR in 58%	The EEA is a valid minimally invasive alternative for the treatment of centrally located clival chordomas or as an adjunct for the central part of chordomas with lateral extension. The early results of this technique indicate at least equivalency to more extensive open approaches, and its versatility may widen the horizon of surgical management of these aggressive lesions. The challenge with the CSF leakage is being addressed with novel local flap repair techniques. This approach should be in the armamentarium of cranial base surgeons as an option in the management of clival chordomas.
Fraser[1022]	2010	4	Retrospective review	17 EEAs for clival lesions	> 95% Resection for 11 of 12 cases (92%) in which it was the surgical goal	The endonasal endoscopic transclival approach provides a minimal-access approach to the ventral midline posterior fossa skull-base. The risk of CSF leak is low if appropriate closure techniques are applied.
Saito[1023]	2012	4	Retrospective review	6 Chordomas	GTR in 3 cases (50%)	The endoscopic endonasal transclival approach allows an appropriate extent of resection with acceptable complication rates in comparison with other approaches. In our series, the accomplishment of gross total removal was associated with the relationship between the tumors and surrounding structures, such as the pituitary gland and the cavernous portion of the ICA.
Jho[443]	2001	4	Retrospective review	160 Transsphenoidal resections	5 of 7 Clival chordomas with GTR	Endoscopic endonasal transsphenoidal surgery in this series resulted with comparable surgical outcomes to conventional microscopic transsphenoidal surgery. Patients' quick recovery, short hospital stays, and minimal postoperative discomfort have been observed.

(*Continued*)

TABLE IX.A.1. Continued

Study	Year	LOE	Design	Study groups	Clinical endpoint(s)	Conclusion
Solares[1024]	2005	4	Retrospective review	6 EEAs for clival lesions		The transnasal endoscopic management of clival lesions is a viable option to traditional open approaches with acceptable morbidity and mortality. The use of computer-aided surgery further minimizes surgical risks while maximizing tumor resection.
Kim[1025]	2018	4	Retrospective review	42 EEAs for clival lesions	GTR in 66.7%	An EEA can provide favorable clinical and surgical outcomes. However, the tumor laterality should be considered as a potential obstacle to total removal.

3D = 3-dimensional; CSF = cerebrospinal fluid; EEA = endoscopic endonasal approach; GTR = gross total resection; ICA = internal carotid artery; iMRI = intraperative magnetic resonance imaging; LOE = level of evidence; NTR = near-total resection; PO = per os; QOL = quality of life.

TABLE IX.A.2. Additional publications: summary of evidence for endoscopic endonasal resection of clival chordomas*

Study	Year	LOE	Design	Conclusion
Fernandes Cabral[1026]	2018	4	Retrospective review	Iatrogenic seeding during EES for clival chordomas is likely a result of decreased visualization during tumor removal combined with mucosal trauma. Tumors with more aggressive biology at likely at a higher risk for seeding and recurrence.
Labidi[1027]	2016	1	Systematic review and meta-analysis (clival chordoma, all approaches)	There was a 5-year progression free survival and overall survival of 49.9% and 73.9%, respectively, reported in clival chordoma series published between 2006 and 2016. The GTR rate in these studies was 39.9%, with reduced recurrence with complete resection. Although anterior midline approaches may allow for higher GTR rates and lesser morbidity, their impact of long-term survival and disease control remains largely unknown.
Stippler[1028]	2009	4	Retrospective review	Endoscopic endonasal resection of cranial base chordomas is safe once adequate experience is gained with the technique. This approach provides the potential for, at the least, similar resections compared with traditional cranial base approaches while potentially limiting morbidity.

*The patient population in these publications overlapped with already included publications, thus these figures were not included in overall numbers reported in the present analysis.
EES = endoscopic endonasal surgery; LOE = level of evidence; GTR = gross total resection.

case series, with widely varying follow-up times and heterogeneous outcome measures (eg, not all publications offered recurrence and mortality data). These issues highlight the need for higher-quality multi-institutional series, and at some point, more prospectively designed analyses in an attempt to facilitate patient and physician decision-making. As the skull-base community acquires more experience with EEAs to clival chordomas, a clearer picture will likely emerge pertaining to the incidence of neurovascular complications, impact of endoscopic resection on QOL, and survival. A relatively modest rate of neurovascular complications, including cerebrovascular accident, paralysis, and CN palsy, was reported among analyses included (detailed in Section IX.A.2.). Nonetheless, the intimate proximity of critical structures necessitates the inclusion of these risks in a comprehensive preoperative informed consent process, because perceived deficits in informed consent have been raised in litigation related to skull-base surgery.[1031]

IX.A.2. *Neurovascular complications associated with EEA for clival chordoma*

A comprehensive knowledge of skull-base anatomy is requisite for the safe performance of endoscopic clival surgery, because injury to adjacent structures harbors the potential for devastating neurologic sequelae. Several analyses have suggested an association with the extent of resection and

TABLE IX.A.3. Neurovascular complications of EEAs for clival chordoma

Study	Year	Study sample	Number of EEA chordoma resections	Neurovascular complications
Arbolay[1003]	2009	Invasive adenomas (4), clival chordomas (2), craniopharyngioma (2), astrocytoma (1), pituitary adenoma (3)	2	
Chibbaro[1005]	2013	54 EEAs for skull base chordomas	54	ICA pseudoaneurysm, death
Frank[1004]	2006	9 Chordoma, 2 chondrosarcoma	9	1 ICA injury
Fraser[1006]		10 Chordoma	10	
Garzaro[1007]	2016	9 Chordoma (3D-guided system)	9	1 Transient CN VI palsy
Holzmann[1008]	2010	13 Chordoma	13	
Hwang[1009]	2007	3 Chordoma	3	1 Postoperative hydrocephalus
Koutourousiou[1010]	2012	60 EEAs for 50 cranial base chordomas (35 primary, 25 recurrent/persistent)	60	CN palsy (4), carotid injury (2), hematoma (1), pontine hemorrhage (1)
Messerer[1011]	2016	3 Chordoma	3	
Ramm-Pettersen[1012]	2017	10 Chordoma (6 EEA, 4 obs.)	6	
Shidoh[1013]	2014	9 EEA, 9 transoral/transpalatal		1 Pharyngeal fistula; 1 hydrocephalus; 1 brainstem infarction
Solares[1014]	2010	19 EEA to sphenoclival region	4	
Tan[1015]	2012	7 Primary chordomas, 7 recurrent chordomas	14	1 Hydrocephalus, 1 brainstem bleed, 1 basilar artery injury, 1 transient CN III palsy
Taniguchi[1016]	2012	4 Chordomas extending into retro-carotid space	4	1 CN VI injury
Vellutini Ede[1017]	2014	38 EEAs for clival lesions	24	1 CVA leading to death
Zhang[1018]	2008	9 EEAs for clival lesions	7	1 Subarachnoid hemorrhage
Hong Jiang[1019]	2008	9 EEA for upper/mid-clival chordomas	9	
Zoli[1020]	2018	65 Patients who underwent 80 EEAs	80	5 Transient CN VI palsies (6.2%); 2 internal carotid artery injuries (2.5%); 3 patients (3.8%) with permanent neurological deficits due to a postoperative hematoma (1.2%) causing hemiparesis, and 2 permanent ophthalmoplegias (2.5%).
Dehdashti[1021]	2008	12 Chordoma	12	1 Hemiparesis
Fraser[1022]	2010	17 EEAs for clival lesions	8	
Saito[1023]	2012	6 Chordomas	6	1 Brainstem infarction and hydrocephalus
Jho[443]	2001	160 Transsphenoidal resections	7	
Solares[1024]	2005	6 EEAs for clival lesions	3	
Kim[1025]	2018	42 EEAs for clival lesions	37	1 CN VI injury

3D = 3-dimensional; CN = cranial nerve; CVA = cerebrovascular accident ; ICA = internal carotid artery; EEA = endoscopic endonasal approach.

degree of complications encountered; these are discussed further in Section IX.A.5 Prognostic factors including GTR in clival chordoma. Several neurovascular complications were identified among the series analyzed. In addition to being familiar with technical pearls to prevent these injuries, it is important to include these possibilities in a preoperative comprehensive informed consent discussion. Out of 395 endoscopic endonasal resections for chordomas included, there was a 7.8% rate of significant neurovascular complications, including stroke, hydrocephalus, brainstem injury, and CN injury. Importantly, this encompassed a 2.8% rate of stroke and major vessel injury, including injuries to the ICA and basilar arteries. A variety of strategies can be employed to minimize risks to these structures. During the initial endoscopic approach, identifying the Vidian nerves bilaterally and drilling down the clivus along this facilitates identification of the second genu of the ICAs at the foramen lacerum.[996,1002]

Palsy of the CNs controlling eye movements, particularly CN VI, is a common presenting feature. These nerves are also at increased risk of injury during surgical intervention. In cases requiring dural incision, it is important for incisions to begin medially in order to prevent CN VI injury at the intradural segment. Out of 281 EEAs for clival chordomas, there was a 3.1% rate of new onset postoperative abducens nerve palsy. All but 3 of these injuries were transient, making the permanent rate of abducens nerve injury 0.8%. Hence, it is important to include this possible risk in a preoperative discussion of risks, as well as relaying that most of these injuries are transient.

Another sequela (not necessarily a complication) surgeons should be aware of is the potential for atlanto-occipital instability due to tumor invasion of the craniovertebral junction structures. In a single-institution retrospective review specifically investigating this sequela among patients undergoing EEAs for lower clival lesions, 3.3% of patients required arthrodesis (the majority after combined endoscopic and open approaches).[1032] The degree of occipital condyle involvement by tumor invasion or subsequent iatrogenic resection was associated with subsequent occipitocervical instability and the use of combined approaches ultimately necessitated atlanto-occipital fixation. Clival resection alone did not lead to instability.

IX.A.3. *Patterns of recurrence and seeding after EEA for clival chordoma*

Of 18 analyses with individual patient data providing sufficient details about recurrence, 39 patients (17.3%) were noted to have recurrent disease detected during their surgical follow-up periods. Of course, follow-up time varies considerably among series in which this information was available, ranging from 5.9 months to 91 months; hence, taken together, these data may not be optimal for judging recurrence rates. What has been established is that chordomas generally grow slowly, and recurrence rates may not necessarily stabilize after 5 years. In 1 of the larger datasets, encompassing aggregate patient data from 80 endoscopic endonasal resections, Zoli et al.[1020] reported 24 patients (40%) presenting with concern for recurrence and/or residual tumor (several recurred multiple times), with a median time of recurrence at 20.5 months. Interestingly, 22 patients experienced regrowth after a partial resection, and only 4 had recurrence as demonstrated on MRI after GTR. Ultimately, 26.2% of patients in Zoli et al.[1020] passed away from tumor progression. It is important to understand these results come from a larger cohort of 80 surgeries, and contrast them with many of the smaller available series with limited follow-up. In dataset of Koutourousiou et al.[1010] encompassing 60 patients, 14 patients (23.3%) demonstrated either growth of residual tumor or recurrence, undergoing revision surgery. Chibbaro et al.[1005] represented another large series of skull-base chordomas resected endoscopically, reporting a 11% recurrence rate. Both a greater extent of intradural extension on preoperative MRI as well as postoperative residual tumor on early postoperative MRI had significant associations with early recurrence and subsequent progression. One of the main points of controversy within many series includes discussion of the appropriate indications for choosing a purely EEA; there is a general consensus agreeing on the utility of this approach for midline lesions, but in lesions with more lateral extension as well as lesions of the lower clivus, decisions of whether to undergo endoscopic approaches varied and appear to be a function of each individual center's experience with this approach. As the skull-base community acquires more experience with longer-term follow-up of clival chordoma patients who have undergone EEAs, these data will likely be revisited.

There have been several reports with recurrence in which authors believe seeding along the surgical pathway may have played a role, particularly in open cases.[1033–1039] It can be difficult to attribute a recurrence to "seeding" and no definitive consensus has emerged regarding this; however, it has been suggested that minimally invasive techniques such as the EEA may limit seeding.[1037] In a large series, specifically examining iatrogenic seeding following 173 endoscopic endonasal resections for skull-base chordomas, Fernandes Cabral et al.[1026] noted a 1.2% rate of seeding.

IX.A.4. *Reconstruction after EEA for clival chordoma*

One of the initial concerns with EEA for clival lesions was the ability to address CSF leaks. With greater experience and subsequent technical innovations, this has become less of an issue, because CSF leak rates with endoscopic techniques have decreased significantly. An important difference in the surgical management of clival lesions is that these defects tend to be significantly larger than those for other ventral skull-base locations and involve the higher-risk posterior fossa. Furthermore, extra care must be taken to avoid overpacking of reconstructive materials, because compression of the brainstem as well as the surrounding

critical neurovascular structures have the potential for devastating consequences. The level of detail provided for closure and CSF leak rates varied tremendously in the series included. For example, numerous series encompassed various types of clival lesions, but did not differentiate the CSF leak rate for each pathology. Of the 17 series that did report sufficient details there was an 11.8% postoperative CSF leak rate after EEA resection of chordomas. Twelve of these series reported individual patient data in a manner allowing for evaluation of the relationship between extent of resection and postoperative leak rates. There was a 20.3% postoperative CSF leak rate among patients who underwent GTR compared to an 8.7% leak rate among patients who underwent a less than total resection.

In addition to extent of resection, several other factors may be associated with an increased risk for postoperative CSF leak. For example, there is the possibility that intradural clival defects likely harbor a greater risk of postoperative CSF leak, although data was reported inconsistently among these series and this assertion was not supported as strongly as the relationship with extent of resection. Another potential factor deals with surgeon experience with EEAs for clival lesions. Koutourousiou et al.[1010] notes strong evidence for the presence of a learning curve, with a 27.3% postoperative CSF leak rate dropping to 15.8% upon comparison of consecutive 4-year periods.

Skull-base reconstruction is further detailed in later sections (see Section X.A. Vascular reconstruction and Section X.B. Free-graft reconstruction). Briefly, nearly all authors in the included analyses advocate multilayer closure. The vast majority of authors advocated the use of vascularized, pedicled flaps, specifically an NSF, in cases with dural defect. Furthermore, a large proportion of authors also support using it more routinely in endoscopic resection of clival lesions. Intradural clival lesions are also associated with a 17% incidence of postoperative pontine encephalocele, a radiographic finding that could limit radiation dosing to the surrounding area and is dramatically reduced by the use of fat in the reconstruction.[1040] In the 16 analyses in which sufficient detail was provided, 7 author groups advocated use of fibrin sealants, while 9 made no mention of the use of these products. This issue is further detailed in Section XII.C. Perioperative and postoperative management in ESBS.

IX.A.5. *Prognostic factors including GTR in clival chordoma*

A variety of factors have been suggested to correlate with long-term prognosis, and population-based resources have previously evaluated these relationships. Focusing on skull-base chordomas, 1 SEER analysis reported larger tumor size and older age as negative predictors of survival.[1030] In another analysis examining these lesions, positive predictors of survival included patients who underwent surgical resection, younger age, and management in a higher-volume institution.[1029]

GTR has been associated with improved outcomes and decreased recurrence in multiple older series predating the popularization of endoscopic approaches. In an older series from the pre-endoscopic era examining chondrosarcoma and chordoma patients, patients with more extensive resections (either total resection or NTR) had a significantly greater 5-year recurrence-free survival rate vs those with partial resections (84% vs 64%).[1041] With regard to the individual series included in this EBR, follow-up times were inconsistent and often short-term, allowing only limited conclusions. Nonetheless, numerous series reported GTR or near total resection as being associated with fewer recurrences and greater survival. As noted in Section IX.A.3. Patterns of recurrence and seeding after EEA for clival chordoma, Chibbaro et al.[1005] noted the absence of postoperative residual tumor on early postoperative MRI to have a significant association with not developing recurrence. Numerous series, including those with microscopic or lateral approaches as well as authors reporting experiences with endoscopic approaches, have concluded that extent of resection has a strong association with decreased recurrence and increased survival.[1010,1041–1044] For the 17 series in which individual patient data detailing the extent of resection was available, the rate of GTR was 64.5%.

In 1 of the larger detailed retrospective reviews reporting aggregate patient data, Zoli et al.[1020] explored outcomes of 65 patients who underwent a total of 80 EEAs for clival chordomas. GTR was noted in 58.7% of cases; the extent of tumor removal and having primary (rather than recurrent) lesions were both correlated with longer survival. Primary procedures, lesions located in the upper two-thirds of the clivus, and extradural lesions were noted to have an association with a greater likelihood of GTR.[1020] In another series of 60 cranial base chordomas, the GTR rate was 66.7%, although this was heavily influenced by whether this was a primary surgery vs surgery in a previously treated patient (82.9% GTR vs 44% GTR, respectively).[1010]

There are several practical issues to consider with regard to the extent of resection performed. Importantly, the degree of tumor extension around adjacent nerves and blood vessels sometimes dictates the degree to which a safe resection can be achieved. Greater rates of GTR and decreased complication rates have been suggested to be a function of surgical team experience.[1010]

IX.A.6. *Adjuvant therapy for clival chordoma*

Despite being a low-grade lesion, clival chordoma resection has a high potential for significant morbidity and even death due to involvement of surrounding critical structures. Although GTR is the goal, several factors including the potential injury to critical neurovascular structures must be balanced with this benefit. Particularly in lesions with extension lateral to the ICAs, this goal of total resection may require a variety of surgical approaches and multimodality treatment. Although the relative rarity of skull-base chordomas is at least in part responsible for a lack of high-quality

prospective trials, there is a general consensus that adjuvant radiation may play a role in disease control.[1045–1047] In contrast, the role of adjuvant chemotherapy and immunotherapy are largely undefined and not routinely used.

Among the studies with individual patient data in which adjuvant therapy was discussed, 52.0% of patients who underwent EEAs underwent adjuvant RT. Furthermore, these radiation regimens differed by series and even within series, making an understanding of their differences important for practitioners involved in the care of these patients. Conventional external beam RT was used among several patients in the analyses included, but other radiation modalities were adopted more frequently, including IMRT, stereotactic radiosurgery, and proton beam therapy. In general, proton beam RT is employed when critical unaffected structures are located directly adjacent to tumors.[1047,1048] Importantly, there is a pronounced dose decrease beyond targeted tissue,[1045] which minimizes damage to surrounding critical skull-base structures including the brainstem and CN VI. Among series in which specific radiation modality was detailed, a plurality (46.5%) of patients underwent adjuvant proton beam RT. A recent systematic review has suggested that proton beam therapy likely has higher local control and survival than other radiation modalities for clival chordomas, although trials with direct comparison are needed to further solidify this into a consensus.[1047] The primary disadvantages of proton beam therapy include a lack of availability and cost. Increasing experience with its use in clival chordomas will further define the role of this modality and its role in adjuvant treatment.

Conclusion

The EEA can be utilized in midline chordomas of the clivus in skull-base centers with sufficient experience and expertise. Patient selection is critical and may be complementary to open approaches. GTR is the goal of treatment with adjuvant RT to minimize recurrence.

- Aggregate Grade of Evidence: C/D (Level 3: 2 studies; Level 4: 22 studies)
- Benefit: EEAs to the clival region offer an opportunity for decreased surgical morbidity for midline lesions of the clivus, because numerous single-institution series have demonstrated this to be a feasible approach with simple and rapid access.
- Harm: There is a modest potential for significant neurovascular complications with use of the EEA for clival chordoma, although direct comparisons to traditional open approaches are lacking in the literature. Surgeons and patients should be familiar with the potential for brainstem injury, vascular injury, and the potential for transient and permanent injury to CN VI. Although there is a consensus that GTR is associated with decreased recurrence, extensive resection may also be associated with a greater postoperative CSF leak rate.
- Cost: No studies directly evaluating the cost for treatment of clival chordomas were identified.
- Benefit-Harm Assessment: Direct comparison between the open approach and EEA are lacking, and similar risks for neurovascular injuries are present. The direct corridor with minimal approach morbidity favors EEA while the increased risk of postoperative CSF leak is noted with this subsite.
- Policy Level:
  - Recommendation: The EEA can be utilized in midline chordomas of the clivus in skull-base centers with sufficient expertise and experience
  - Option: The EEA is feasible, including in conjunction with an open approach, for certain chordomas with lateral extension as well as those of the lower clivus.
- Intervention: Clival chordoma may be treated with EEAs as part of a multidisciplinary approach to the treatment of these lesions.

IX.B. Chondrosarcoma

Chondrosarcomas are rare bony lesions that can arise in the skull base from degenerated chondroid cells.[1049] They constitute approximately 0.15% of all intracranial tumors and 6% of tumors located in the skull base.[1050] Skull-base chondrosarcoma represent 2% of all chondrosarcomas and are typically located close to the synchondroses.[1049]

Recently, technical advances in endoscopic surgery, especially in terms of closure and skull-base reconstruction with the use of vascularized mucosal flaps,[273] have allowed the median endonasal corridor to be used in the management of skull-base chondrosarcoma. Skull-base chondrosarcomas originating in the median and paramedian location are the ideal candidate to be managed though the EEA.

Our objective was to analyze the current literature through the ICAR:ESBS methodology and summarize the current surgical results with endoscopic endonasal surgery for primary chondrosarcomas of the skull base. We excluded publications with data concerning chondrosarcomas undistinguishable from that of other lesions or series not presenting surgical technique and outcome data. Only the most recently published version of duplicates or updated surgical series were included in the analysis. Following the ICAR:ESBE methodology, 25 articles, including 10 case reports, were thus included in our analysis.

IX.B.1. *Outcomes of endoscopic endonasal surgery for chondrosarcoma*

The evidentiary table (see Table IX.B) summarizes the design and conclusion(s) of the included studies, excluding case reports. Only retrospective case series and case reports were identified, with a corresponding level of evidence according to the Oxford LOE classification of 4 and 5, respectively. Among the included studies, only 3 were focused solely on ESBS for skull-base chondrosarcoma,[1054,1055,1059,1060] with 3 additional studies including also chordoma cases along with chondrosarcoma operated through an ESBS.[1004,1018,1025] The studies published by Carlson et al.,[1056] Cho et al.,[1053] and Raza

TABLE IX.B. Evidence for ESBS for chondrosarcoma

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Castelnuovo[1051]	2005	4	Case series	Consecutive series of ESBS for sphenoid sinus pathology	1. Treatment-related outcome	1 Chondrosarcoma with GTR and no postoperative morbidity
Frank[1004]	2006	4	Case series	Consecutive series of chordoma (9) or chondrosarcoma (2) treated with ESBS at 1 institution	1. Treatment-related outcome	A radical resection was achieved in both chondrosarcoma cases. No postoperative morbidity
Tami[1052]	2006	4	Case series	Consecutive series of ESBS for lesions of the sphenoid lateral recess (8 patients, including 1 chondrosarcoma)	1. Treatment-related outcome	GTR, no complication
Cho[1053]	2008	4	Case series	Consecutive series of chondroid lesions with 11 chondrosarcoma (including 2 treated with ESBS) at 1 institution	1. Treatment-related outcome 2. OS and PFS 3. Functional outcome	1. 3 GTR in chondrosarcoma (none with ESBS) 2. OS rates at 3 and 5 years were 100.0%, and the PFS rate at 3 and 5 years was 88.9 and 80.0% 3. 5 patients with no symptoms and 6 with nondisabling symptoms
Zhang[1018]	2008	4	Case series	Consecutive series of chondroid lesions with 2 chondrosarcoma at one institution	1. Treatment-related outcome	1 Chondrosarcoma with STR and no postoperative morbidity
Mesquita Filho[1054]	2014	4	Case series	Consecutive series of chondrosarcoma treated with ESBS (5 cases)	1. Treatment-related outcome	2 GTR, 3 NTR 2 Patients had staged surgeries No new neurological deficit, no CSF leak
Vellutini Ede[1017]	2014	4	Case series	Consecutive series of ESBS for clival and paraclival tumors (38 patients, including 2 chondrosarcoma)	1. Treatment-related outcome	1 GTR, 1 STR. 1 CN VI palsy postop
Moussazadeh[1055]	2015	4	Multicentric case series	Consecutive series of chondrosarcoma treated with ESBS (8 cases)	1. Treatment-related outcome	5 GTR, 2 NTR and 1 STR. 1 postoperative CSF leak "Extended endonasal corridors to the skull base, [. . .], are well suited for addressing paramedian lesions such as chondrosarcomas"
Carlson[1056]	2016	4	Multicentric case series	1. Primary chondrosarcoma of the petroclival junction (47 cases, including 5 ESBS) 2. Recurrent chondrosarcoma of the petroclival junction (17 cases, including 3 ESBS)	1. Treatment-related outcome 2. OS and PFS	1. 1 Carotid-injury and 1 surgical revision for CSF leak after ESBS 2. The 1-year, 3-year, 5-year, and 10-year PFS rate for all 45 patients who underwent surgery with or without adjuvant radiation therapy was 97%, 89%, 70%, and 56%, respectively.
Patrona[907]	2017	4	Case series	1. Consecutive series of ESBS for nonmeningioma, nonpituitary lesions involving the cavernous sinus (15 cases, including 3 chondrosarcoma)	1. Treatment-related outcome 2. Identification of factors associated with GTR of the cavernous sinus extension	1. 1 GTR, 2 STR. Improvement of presenting CN palsy in all 3 cases but new CN III and CN V palsy in 1 case 2. In the overall series, extent of resection within the chondrosarcoma; GTR was accomplished in 55% of

(*Continued*)

TABLE IX.B. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
						1. tumors with Knosp-Steiner Grade 1 to 2 and in 16.6% of tumors with Knosp-Steiner Grades 3 to 4, respectively. GTR was achieved in 55% of the tumors with ICA encasement <75% and in 14.3% of lesions with ICA encasement >75%.
Messerer[1011]	2016	4	Case series	1. Consecutive series of ESBS for clival and paraclival tumors (11 patients, including 1 chondrosarcoma)	1. Treatment-related outcome	STR, no complication
Raza[1058]	2017	4	Case series	1. Consecutive series of chondrosarcoma (37 patients including 9 ESBS)	1. Treatment-related outcome 2. OS and PFS	1. Patients operated through an ESBS not distinguishable but GTR in 62% or the cohort. The 30-day complication rate was 16% but no new neurological deficit was seen. 2. 32% local recurrence rate at a median of 37 months after the index surgery. The 5-year PFS was 0% with STR vs 67% in GTR
Kim[1025]	2018	4	Case series	1. Consecutive series of chondroid lesions with 5 chondrosarcoma treated with ESBS at 1 institution	1. Treatment-related outcome 2. Identification of factors associated with GTR	1. 3 GTR and 2 STR in chondrosarcoma. No postoperative morbidity 2. Lateral extension of the chondrosarcoma was found to be associated with reduced GTR rates
Vaz-Guimaraes[1059]	2017	4	Case series	1. Consecutive series of chondrosarcoma treated with ESBS (35 cases)	1. Treatment-related outcome 2. Identification of factors associated with GTR 3. Disease-specific survival and PFS	1. 22 GTR (62.9%), 11 NTR (31.4%), and 2 STR (5.7%) Among the 19 patients with CN palsy, 11 improved (57.9%) and 8 remained unchanged (42.1%). 6 CSF leak (17%), 5 permanent new CN deficits (14%), 2 meningitis (6%), 1 ICA injury 2. Factors associated with incomplete resection were tumor volume, involvement of the middle fossa, cavernous sinus, and CPA 3. The average follow-up time was 44.6 ± 31 months. 7 patients (22.6%) had local tumor recurrence/progression. Disease-specific survival at 3 and 5 years were 91.1% and 90.5%, respectively. The cumulative recurrence-free survival rate was of 83.7% and 80.8% at 3 and 5 years, respectively.

(*Continued*)

TABLE IX.B. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Hasegawa[1060]	2018	4	Case series	1. Consecutive series of chondrosarcoma treated with ESBS (19 cases)	1. Treatment-related outcome 2. PFS	1. 15 GTR (78.9%), 2 subtotal (10.5%) and 2 PR (10.5%). 1 CSF leak and 3 transient abducens nerve palsy (15.8%) 2. The overall actuarial tumor control rates at 3 and 5 years were 92.9% (median follow-up of 47 months)

CSF = cerebrospinal fluid; CPA = cerebellopontine angle; ESBS = endoscopic skull-base surgery; GTR = gross total resection; ICA = internal carotid artery; LOE = level of evidence; NTR = near-total resection; OS = overall survival; PFS = progression free survival; PR = partial resection; STR = subtotal resection.

et al.[1058] were consecutive clinical series of skull-base chondrosarcomas that included a number of patients operated through an EEA. The remaining 5 studies were consecutive clinical series of patients who had an ESBS for a variety of pathology centered on a specific anatomical region (ie, the cavernous sinus, the clival and paraclival area, etc.).[1011,1017,1051,1052,1057]

XI.B.1.a. Endoscopic endonasal surgery series in chondrosarcoma. Vaz-Guimaraes et al.[1059] have presented the largest clinical series of skull-base chondrosarcoma resected through an ESBS, with 35 such cases. In his cohort study, 26 patients had a single surgery and the remaining 9 patients had multiple surgical stages (4 patients had multiples ESBSs and 5 had a combination of ESBS and open approaches). GTR was achieved in 22 cases (62.9%), NTR (>90% resection) in 11 cases (31.4%), and STR (<90% resection) in 2 cases (5.7%). Among the 19 patients that had a preoperative CN palsy, 11 improved (57.9%) and 8 remained unchanged (42.1%). The complications from this series included 6 CSF leaks (17%), as well as 5 permanent new CN deficits (14%), 2 cases of meningitis (6%), and 1 ICA injury. Factors associated with incomplete resection were tumor volume (with a cutoff volume of 26.2 cm^3), involvement of the middle fossa, cavernous sinus, and cerebellopontine angle (CPA). GTR rates were similar in patients who underwent only ESBS (63.4%) and patients who required a combination of endoscopic and open approaches (60%) ($p = 0.999$). After an average follow-up time of 44.6 ± 31 months, 7 patients (22.6%) presented local tumor recurrence or progression. DSS at 3 and 5 years was 91.1% and 90.5%, respectively. The cumulative recurrence-free survival rate was 83.7% and 80.8% at 3 and 5 years, respectively. Hasegawa et al.[1060] reported on a series of 19 patients with skull-base chondrosarcoma operated exclusively through an ESBS (although 6 patients had previous transcranial surgeries). In this series, GTR was obtained in 15 cases (78.9%), while subtotal resection (>90% resection) was obtained in 2 cases (10.5%) and partial resection (PR) (<90% resection) was obtained in 2 cases (10.5%). Only 1 CSF leak was observed in this series and the only additional complications reported were 3 occurrences of transient abducens nerve palsy (15.8%). The outcome of preoperative neurological deficits was not reported in this study. The overall actuarial tumor control rates at 3 and 5 years were 92.9% (with a median follow up of 47 months).

Moussazadeh et al.[1055] have reported their clinical series of ESBS in chondrosarcoma with 8 such cases operated in 2 neurosurgical centers. In this study, the authors report 5 GTRs (62.5%) and 2 NTRs (25%) and very few postoperative complications. Only 1 patient presented a postoperative CSF leak and no new neurological deficit was found. In fact, 6 patients had improvement of their preoperative CN deficits. Duration of follow-up and recurrence rate are not provided in this study. Mesquita et al.[1054] report similar findings in their series of 5 ESBSs for chondrosarcoma extending predominantly toward the posterior fossa and the CPA, with 2 GTRs and 3 NTRs, although 2 of the NTRs were achieved after additional surgical stages. In this study, no postoperative complication was recorded, including no CSF leak. In 3 patients out of 5 that presented preoperative symptoms which may be attributed to CN deficits, complete or partial improvement of the presenting deficit(s) was reported. No recurrence nor residual tumor progression were observed during follow-up (mean duration, 14.8 ± 12.1 months).

IX.B.1.b. Endoscopic endonasal surgery series for chondroid tumors in the clivus. Among the earliest reports, a study by the Bologna group reported on a series of cases treated through an EEA that included 9 chordomas and 2 chondrosarcomas.[1004] In the 2 chondrosarcoma cases, which were both located in the clivus and had an extension toward the cavernous sinus, the resection was complete and no complication was recorded (follow-up of 27 and 38 months without evidence of tumor recurrence). One of the 2 patients had recovery of a CN VI palsy wheras no improvement was reported for a lower CN palsy in the

second patient. Zhang et al.[1018] also reported on 2 patients with chondrosarcoma that were resected though an ESBS with 1 GTR and 1 STR (no recurrence after 39 months and stable disease after 14 months, respectively). More recently Kim et al.[1025] have analyzed their series of chondroid lesions that were approached though an ESBS. In this study, GTR was achieved in 3 of 5 cases of chondrosarcoma and no postoperative morbidity is reported in this subgroup. Interestingly, this group studied analyzed preoperative factors that could be associated with achieving GTR in their series, which also included 37 chordomas. Lateral extension of the tumor (beyond a tangent plane between the cavernous ICA, paraclival ICA, cisternal portion of the trigeminal nerve, and hypoglossal canal) was found to be associated with reduced GTR rates on both univariate (OR 6.25; 95% CI, 1.51 to 25.86; $p = 0.011$) and multivariate analysis (OR 41.16; 95% CI, 1.12 to 1512.65; $p = 0.043$). In the whole cohort including 5 chondrosarcomas and 37 chordomas, there were 8 recurrences (19.0%) during the mean follow-up of 32.7 months (range, 1.0 to 81.7 months).

Two publications reported clinical results on the surgical treatment of a mixture of lesions located in the clivus and paraclival area. In a series of 38 patients with such lesions, including 2 chondrosarcoma and 26 chordoma, Vellutini Ede et al.[1017] obtained 1 GTR and 1 STR in chondrosarcoma cases, with 1 patient developing a new CN VI palsy postoperatively. Duration of follow-up and recurrence rate are not provided in this study. The authors conclude that EEA is an effective alternative for treatment of patients with clivus tumors of any origin. Messerer et al.[1011] have reached similar conclusions in a series of 11 cases of clival and paraclival pathology, including 1 chondrosarcoma case (STR, no complication, lost at follow-up after 6 months). They state, "The [EEA] is the most direct route to access the ventral midline skull base."

IX.B.1.c. Chondrosarcomas isolated to the sphenoid sinus. Castelnuovo et al.[1051] were the first group to present a case of chondrosarcoma resected through an EEA. This case was among a clinical series of sphenoid sinus lesions treated with ESBS. In this clinical case, the patient presented with sudden visual deterioration, a deficit that improved after GTR of the tumor. The patient did not suffer any complication and was disease-free at the last follow-up, 56 months postoperatively. Another study focused on ESBS for lesions of the sphenoid sinus, more specifically in the lateral recess of the sinus,[1052] with only 1 chondrosarcoma in a series of 8 cases. The resection was complete and no complication is reported in this case. Follow-up duration was 35 months with no evidence of disease recurrence. In both of these publications, the authors conclude that the EEA is a safe and effective surgical route for pathology centered in the sphenoid sinus or the lateral sphenoid recess.

IX.B.1.d. Endoscopic endonasal surgery for chondrosarcomas involving the cavernous sinus. In their study focusing on lesions involving the cavernous sinus, Patrona et al.[1057] discuss surgical outcomes in a series of 15 cases, including 3 chondrosarcomas. In this study, GTR resection was performed in 1 chondrosarcoma case and STR in 2 cases. All 3 had improvement or resolution of their presenting CN palsy; although, in 1 case, there was resolution of a preoperative CN VI palsy but new deficits of CN III and IV. Duration of follow-up is not provided for the chondrosarcomas, but there was tumor progression in 1 case during the follow-up period. These authors also propose that the degree of internal carotid encasement and the Knosp-Steiner grade might predict the ability to achieve GTR. This, however, is supported only by the absolute difference in GTR rates obtained between the varying degree of carotid encasement, and Knosp-Steiner grade and statistical significance is not reported.

IX.B.1.e. Endoscopic endonasal surgery as part of multimodal therapy for chondrosarcoma. The last 3 included studies describe relatively large clinical series of skull-base chondrosarcoma treated by a multimodal approach (multiple surgical techniques with or without RT). In the largest such series, Carlson et al.[1056] discuss 47 cases of primary chondrosarcoma including 5 treated with ESBS and 17 cases of recurrent chondrosarcoma, including 3 treated with ESBS, in 4 neurosurgical centers. In their series, the GTR rate was 27% and there was 1 carotid injury and 1 CSF leak among the patients that had ESBS, but no neurological deficit is reported at 30 days after the index surgery. The authors also report outcome data, with a PFS at 1 year, 3 years, 5 years, and 10 years for all 45 patients who underwent surgery for primary chondrosarcoma with or without adjuvant RT of 97%, 89%, 70%, and 56%, respectively. In a similar single-institutional clinical outcomes study, Raza et al.[1058] report on 37 consecutive chondrosarcoma cases, including 9 ESBS. In their study, surgical outcomes of patients operated with ESBS were not distinguishable from other surgical approaches. The GTR rate was 62% in the whole cohort. The 30-day complication rate was 16% but no new neurological deficit was seen. The local recurrence rate was found to be 32% at a median of 37 months after the index surgery. The 5-year PFS was 0% with STR vs 67% with GTR. The authors further discuss the role of adjuvant therapy, including RT. In this study, the authors propose that indications for RT should be made based on histological subtype and grade. In this series of patients, there was no progression of residual grade 1 chondrosarcoma, whereas adjuvant RT provided a significant benefit on local disease control for grades 2 and 3. In a study including both chordoma and chondrosarcoma, Cho et al.[1053] reported on clinical and functional outcomes. Among 11 chondrosarcoma cases, GTR was achieved in 3 cases although there were no GTRs in either of the 2 ESBS cases. The OS rates at 3 years and 5 years were both 100.0%. The PFS rate

at 3 years and 5 years were 88.9 and 80.0%, respectively. From the functional standpoint, the 11 patients operated for a skull-base chondrosarcoma fared well, with 5 patients having no symptoms and 6 with nondisabling symptoms at the last follow-up.

IX.B.1.f. Case reports on endoscopic endonasal surgery for chondrosarcoma. Ten case reports on the application of the EEA for the surgical treatment of skull-base chondrosarcomas were found.[1061–1070] Out of a total of 12 patients, GTR was achieved in 5 cases. In 2 patients, a postoperative CSF leak[1061,1070] occurred, with 2 cases of meningitis[1067,1070] recorded. The sole new neurological deficit was a de novo CN VI palsy.[1070]

IX.B.2. *Factors influencing GTR and CN outcomes in chondrosarcoma*

Although no studies have demonstrated the superiority of ESBS for the treatment of chondrosarcoma compared to traditional surgical techniques, a relatively high GTR rate was reported, ranging between 40% and 78.9% (63% in the largest series). In fact, ESBS is probably a useful addition to the surgical armamentarium for the treatment of skull-base chondrosarcoma and might allow satisfactory tumor resection or decompression in appropriately selected cases. Some authors have reported the successful use of a staged surgical strategy combining an EEA and a transcranial approach to achieve GTR.[1058,1060]

Factors associated with a lower GTR rate were larger tumor volume and extension into the middle fossa, cavernous sinus, or CPA.[1059] Likewise, in a mixed cohort of clival tumors (chordomas and chondrosarcomas) resected through an ESBS, tumors located medial to a plane tangent to the cavernous ICA, paraclival ICA, cisternal portion of the trigeminal nerve, and hypoglossal canal were found to be associated with increased GTR rates.[1025]

Analysis of the reported tumor control data is limited by short follow-up (only 1 study reporting a mean duration of follow-up >60 months) and a low number of patients in each cohort. Nonetheless, PFS rates reported in the included series are comparable to previous studies on skull-base chondrosarcomas (70 to 81% at 5 years).[1053,1056,1060]

The use of the endonasal corridor in these tumors located in or around the midline has the potential to reduce postoperative CN morbidity. In the larger studies included in this review, the rate of new postoperative CN deficit was low. On the contrary, a significant proportion of patients actually had improvement of their preoperative CN deficits.[1054,1055,1057,1060] However, this review is limited by significant heterogeneity among the included studies. Moreover, the majority of the publications included in this systematic review are case reports or surgical series with a limited number of patients (only 7 publications reporting on 5 or more patients with chondrosarcoma treated through an ESBS). These small series and case reports introduce significant selection and publication biases. Moreover, definitions of the extent of resection classification were not provided in many of the included studies, making comparison and inference subject to a significant information bias. Finally, because of the heterogeneity in reporting, there was a high rate of missing data, especially in the rates of cranial neuropathy recovery, duration of follow-up, and tumor control rates.

Conclusion

In this systematic review, we have found that there is no high-level evidence on the subject of endoscopic endonasal surgery in skull-base chondrosarcoma. The current evidence, all of which is derived from case series (LOE 4) and case reports (LOE 5), supports ESBS as an option in the treatment of chondrosarcoma.

- Aggregate Grade of Evidence: D (Level 4: 14 studies; Level 5: 10 studies)
- Benefit: Although no studies have demonstrated a direct benefit of ESBS for the treatment of chondrosarcoma compared to traditional surgical techniques, the use of the median corridor in these tumors located in or around the midline can result in a relatively high GTR rate and has the potential to reduce postoperative CN morbidity. There is no evidence that allows assessment of the GTR rate as compared to standard surgical techniques. However, the ESBS is probably better suited in some chondrosarcomas, especially those centered on or near the midline and/or extending toward the sphenoid sinus, the cavernous sinus, and the clival area.
- Harm: Potential harm of the technique include the risk of CSF leak, new CN morbidity, and reduced sinonasal QOL.
- Cost: Although no study has examined the issue of cost related to ESBS in chondrosarcoma, reduced CN morbidity might potentially translate into lower costs in the long-term. On the other hand, increased equipment costs that might be associated with EEAs needs to be considered.
- Benefits-Harm Assessment: In the case series reviewed, the CSF leak rate was relatively low, as was the rate of new postoperative CN deficit. In fact, a significant proportion of patients actually benefited from improvement of their preoperative CN deficits. There is no evidence that ESBS would provide increased GTR rates, but recent large clinical series have shown that it can be part of a multimodal strategy in the treatment of skull-base chondrosarcoma. In 1 study included in the present review, tumor laterality was found to be associated with reduced GTR rates in a cohort of clival tumors (chordomas and chondrosarcomas).
- Value-Judgment: There is no significant argument for or against the use of ESBS for chondrosarcoma in the current literature. Studies to date have mostly shown that it is a rational surgical approach for chondrosarcoma, because these tumors tend to be located near or at the

midline. Traditionally, EEAs have been burdened by a high risk of CSF leak. However, results reported in the clinical series reviewed were encouraging. This might be explained in part by the fact that, in many cases, chondrosarcomas are purely extradural lesions.

- Policy Level: Option
- Intervention: EES is likely a reasonable option for skull-base chondrosarcomas, especially those that are located at or near the midline.

X. Reconstruction

X.A. Vascular reconstruction

Optimal endoscopic reconstruction of skull-base defects remains an area of ongoing evolution. Similar to reconstructive techniques used in open surgical cases, endoscopic repairs must achieve multiple goals: re-establishing the separation between the sterile cranial vault and the microbe-colonized sinonasal cavity; preventing CSF transgression across the skull-base defect; and filling the void created by tumor extirpation. Inconsistency in achieving successful skull-base reconstruction was 1 of the final obstacles preventing widespread adoption of ESBS.[1071] Rates of CSF leaks from early reconstructive efforts, often using free grafts, were reported in excess of 30%.[273] However, with the introduction of vascularized tissue flaps,[273] the rate of postoperative CSF leak has dropped significantly, with groups reporting leak rates of 3.1% to 8.3%.[477,1072–1074] The adoption and successful implementation of the pedicled NSF proved to be a watershed event for the progression of the discipline of ESBS.[273] The breadth of vascularized reconstructive options has continued to expand to include local pedicled flaps, regional pedicled flaps, and distal free-tissue transfer flaps. Herein, we provide an overview of types of vascular flaps, discuss the evidence supporting vascular flap reconstruction, and review the major complications and limitations of these repairs.

X.A.1. *Types of vascular flaps*

The NSF is the dominant vascular flap used in skull-base reconstruction because of an ideal central location, robust vascular supply, ample coverage area, and acceptable donor-site morbidity. The origins of the NSF can be traced to a description by Hirsh[1075] in 1952,whereas in 1966 Montgomery[1076] detailed the NSF as a useful technique to prevent CSF rhinorrhea following pituitary tumor resection. The broad adoption of the NSF in endoscopic surgery, however, is credited to Hadad et al.,[273] who in 2006 described the NSF as a means to reconstruct large dural defects after expanded ESBS. Prior to this publication, only 9% of endoscopic CSF leak repairs used vascularized flaps,[52] but today the NSF has become 1 of the primary techniques for vascularized repair of endoscopic skull-base defects.

The majority of literature addressing the utility of vascularized flaps in skull-base reconstruction has focused on local flaps, namely the NSF, owing to its widespread adoption and extensive reporting of outcomes by many institutions. Numerous alternatives to the NSF have been described, including other local flaps, as well as regional and distal vascularized flaps (Table X.A.1).

In situations where NSF reconstruction is not an option, other local flaps such as turbinate, lateral nasal wall, or nasal floor flaps have been described as viable substitutes, drawing their blood supply from branches of the sphenopalatine artery or ethmoidal arteries. However, the current LOE describing the application of these flaps is limited to retrospective case series (Table X.A.1).

Regional and distal flaps offer alternative reconstructive options to local flaps, but again the available literature on outcomes of these options is limited to case series and case reports. Of the regional flaps, the pericranial flap is heralded as perhaps the most versatile, with a long history of use in reconstructing anterior skull-base defects[1099] and recently having been adapted for endoscopic harvest and reconstruction.[1089] Additional regional flaps include the temporoparietal fascia flap and the buccal fat pad flap,[984] which are based on the superficial temporal and internal maxillary arteries, respectively. These regional flap options, although less accessible than the NSF, are versatile options for closure of skull-base defects where an NSF flap may not be available. A case series review of skull-base closure techniques performed at a tertiary academic medical center demonstrated a 10% rate of utilization of secondary flaps; the postoperative CSF leak rate among secondary flap reconstructions was 3.6%, comparable to rates observed with NSF reconstructions.[858]

Distal flaps in the form of free-tissue transfer exist mainly as options in dire circumstances, where defect size, location, or limitations in vascular supply preclude the use of more readily accessible tissue. Publications regarding the applicability of free flaps in endoscopic skull-base reconstruction have been limited to a few case reports[858] and a descriptive cadaveric study. The relative paucity of literature regarding these flaps likely reflects narrow indications for the use of free flaps in endoscopic skull-base reconstruction, because successful repair of most skull-base defects can be achieved using less morbid reconstructive options.

X.A.2. *Outcomes with vascularized flap reconstruction*

To date, there have been no randomized clinical trials to determine the efficacy of vascular flaps. The best evidence exists in 2 systematic reviews and 2 case series reports that compare vascular flap and nonvascularized reconstruction in ESBS; the primary clinical outcome assessed in all studies was the rate of postoperative CSF leak. A systematic review by Harvey et al.[477] compared data on CSF leak rates in patients aggregated from 12 articles describing vascular reconstruction, 17 describing free-graft repair, and 9

TABLE X.A.1. Summary of vascularized flaps for ESBS

Tissue	Artery pedicle	Highest level of evidence
Nasoseptal (NSF) [including numerous modifications, including rescue, bilateral Janus, and extended][273, 1078, 1079]	Posterior septal artery (from SPA)	Historical control study
Inferior turbinate (ITF)[431, 1080, 1081]	Inferior turbinate artery	Multiple case series
Middle turbinate (MTF)[1082, 1083]	Middle turbinate artery	Case series
Anterior septal (ASF)[1084]	Anterior ethmoidal artery	Case series
Anterior lateral nasal wall flap (ALNWF)[1085]	Facial and anterior ethmoidal arteries	Case series
Posterior lateral nasal wall flap (PLNWF)[1086]	SPA	Case series
Turbinal flap (superior and middle turbinate) (TF)[1087]	Ethmoidal artery system	Case series
Septal flip flap (SFF)[1088]	Septal branches of ethmoidal arteries	Case series
Nasal floor (NFF)[1089]	Septal branches of the SPA	Case series
Pericranial (PCF)[432, 1090]	Supraorbital and supratrochlear arteries	Multiple case series
Temporoparietal fascial (TPF)[859, 1091]	Superficial temporal artery	Case series
Palatal (PF)[1092]	Greater palatine artery	Case series
Buccal fat pad (BFP)[985]	Distal internal maxillary artery	Case series
Facial buccinator flap (FBF)[1093]	Facial artery	Case series
Facial artery musculomucosal flap (FAMM)[1094]	Facial artery	Case series
Occipital galeopericranial flap (OGF)[1095]	Occipital artery	Case series
Fascia lata free flap (FLFP)[1096]	Ascending branch of lateral femoral circumflex artery	Cadaveric study
Omental free flap (OFF)[1097]	Gastroepiploic artery	Case report
Adipofascial radial forearm free flap (ARFF)[1098]	Radial artery	Case report
Fibula free flap (FFF)[1099]	Peroneal artery	Case report

ESBS = endoscopic skull-base surgery; SPA = sphenopalatine artery.

detailing mixed reconstruction. CSF leaks were experienced in 6.7% (19/238) of patients undergoing vascular repair compared to 15.6% (51/326) of patients undergoing free-graft repair.[477] A subsequent systematic review by Soudry et al.[242] reported a postoperative CSF leak rate of 8.5% (57/673) for all repair types. The authors included data from 74 patients across 5 studies, in which CSF leaks were found in 0% (0/10) of vascular flap repairs, vs 7.8% (5/64) of free graft repairs (see Table X.A.2).

Two case series also compared outcomes of vascularized vs free-graft repair of skull-base defects. In a multi-institutional case series, Karnezis et al.[1100] demonstrated a significantly lower rate of postoperative CSF leaks among patients undergoing vascular flap repairs (7.5%, 16/212) compared to patients repaired with free grafts (14.5%, 20/138). Additionally, Horiguchi et al.[1077] reported a single institution's skull-base repair outcomes before and after the adoption of vascular reconstruction. Before the adoption of vascular flap repair, the rate of postoperative CSF leaks was 27.3% (3/11) of patients with free-graft repair; after adoption of vascular repair in 2008, the rate of CSF leaks dropped to 9.5% (2/21) of patients.

X.A.2.a. Determinants of outcome. Numerous paradigms have been proposed for determining the need for vascularized reconstruction of skull-base defects. The following clinical considerations are among the most common criteria for determining the indications for vascular flap reconstruction: severity of intraoperative CSF leak, site of defect, size of defect, and mechanism of defect.[241, 1100, 1104–1108]

X.A.2.b. Severity of CSF leak: high-flow vs low-flow. Severity of intraoperative CSF leak is the prevailing factor used in determining the necessity of a vascular flap. High-flow leaks are created when resections involve intra-arachnoid dissection, specifically those resulting in direct communication with a cistern or the third ventricle. Low flow leaks may occur when only a small segment of arachnoid is violated or in anterior cranial fossa defects abutting the frontal lobe. Although there has been some debate regarding the potential subjectivity inherent to estimating actual CSF flow rates,[1074] expert opinion has converged around the notion that high-flow leaks are more likely than low-flow leaks to require vascularized tissue reconstruction.

TABLE X.A.2. Evidence for vascularized reconstruction in ESBS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Soudry[242]	2014	3a	Systematic review	1. High-flow vs low-flow CSF leaks 2. Site of skull-base defect	CSF leak	1. Overall success rate of skull-base reconstruction at 92% without CSF leak 2. In cases of high-flow intraoperative CSF leak, vascularized pedicled flaps resulted in improved rates (94% vs 82%)
Harvey[477]	2012	3a	Systematic review and meta-analysis	1. Free graft repair 2. Vascularized reconstruction	CSF leak	1. Overall CSF leak rate was 11.5% (70/609) 2. Free grafts had a 15.6% leak rate (51/326) 3. Vascularized reconstruction had a 6.7% leak rate (19/283)
Karnezis[1100]	2016	4	Case series	1. NSF 2. No NSF	CSF leak	1. In patients with an intraoperative leak, use of vascularized septal flaps reduced the occurrence of postoperative leak (OR = 0.431, $p = 0.027$) 2. Only factor to improve postoperative CSF leak rates, once an intraoperative leak identified, was NSF reconstruction
Horiguchi[1077]	2010	3b	Case control	1. Nonvascular flap repair 2. Vascular flap repair	CSF leak	1. Before the adoption of vascular flap repair (2005–2008), rate of postoperative CSF leaks was 27.3% (3/11) patients with free graft repair 2. After adoption of vascular repair (2008-2009), the rate of CSF leaks dropped to 9.5% (2/21) patients
Dehdashti[241]	2016	4	Case series	1. Multilayered repair without nasoseptal flap 2. Repair including NSF	CSF leak	Among patients with high-flow leaks repaired with multilayered closure without an NSF, 18% (7/39) experienced postoperative CSF leak, whereas repair with an NSF had a 4% (2/50) CSF leak rate
Gruss[1074]	2014	4	Case series	Patients who underwent skull-base defect repair using an NSF	CSF leak	Increased risk of septal flap failure and subsequent CSF leak in central skull-base cases (16%) compared to the anterior skull base (4%) ($p = 0.047$)
Greig[1101]	2016	2a	Systematic review	Patients undergoing endoscopic endonasal approaches to the anterior skull base	Olfaction	1. Elevation of NSF may lead to transient olfactory loss 2. Monopolar electrocautery for mucosal incisions may increase the risk of olfactory impairment
Tam[1102]	2012	1b	RCT	1. HB flaps raised and placed for sellar floor defects 2. Reconstruction with synthetic or non-autologous materials	Subjective assessment of olfaction via preoperative and 6 months postoperative UPSIT	1. Both flap and no flap groups demonstrated a significant decrease in UPSIT scores at 6 months postoperatively 2. Patients undergoing HB flap reconstruction had an average of 19.6% reduction in UPSIT scores, which was significantly different from the 9.1% change in those not undergoing HB flap reconstruction
Kim[1103]	2013	3b	Case control	1. NSFs raised and placed for sellar floor defects	Preoperative and postoperative butanol threshold test	1. Olfactory impairment is not common after use of the NSF 2. Use of cold knife for superior incision reduces tissue damage, which may have an impact olfaction

CSF = cerebrospinal fluid; HB = Hadad-Bassagasteguy; LOE = level of evidence; NSF = nasoseptal flap; OR = odds ratio; RCT = randomized controlled trial; UPSIT = University of Pennsylvania Smell Identification Test.

Several publications offer evidence to support this hypothesis. The systematic review by Soudry et al.[242] demonstrated that among cases of high-flow skull-base defects, postoperative CSF leaks occurred in 5.8% (5/86) of cases repaired by vascularized flaps, compared to 18% (20/111) of cases repaired by free grafts. For cases involving low-flow leaks, closure success was nearly equivalent between vascularized (100%; 10/10 patients) and free mucosal repair (92%; 59/64 patients) techniques. Subsequent reports have further characterized postoperative CSF leak rates based on intraoperative severity. Dehdashti et al.[241] reported outcomes of a clinical protocol in which the complexity of skull-base repair was escalated according to CSF leak severity. Among patients with skull-base and dural defects resulting in severe intraoperative CSF leaks, patients who underwent reconstruction with vascularized flaps experienced a postoperative leak rate of 4% (2/50) compared to a postoperative CSF leak rate of 18% (7/39) in those patients undergoing nonvascular reconstruction. In a series of skull-base procedures with high-volume CSF leaks, McCoul et al.[1072] reported a 4.9% postoperative leak rate (5/102) when reconstructing with an NSF compared to a 9% (7/78) rate when repairing with a free graft.

X.A.2.c. Site of defect. Resection of suprasellar and posterior fossa tumors is associated with more complex resections and higher-flow leaks, and therefore may benefit from vascular flap reconstruction. In reporting their extensive institutional experience, Kassam et al.[227] underscored the importance of vascular reconstruction for tumors involving the suprasellar region and planum sphenoidale. Prior to the adoption of the NSF, their reported postoperative CSF leak rate was 58%, whereas the rate was reduced to 5.56% (1/18) after integrating the use of an NSF into their practice. In a 2017 review by Fraser et al.,[233] posterior fossa tumors required vascular reconstruction more frequently (92%, 48/52) than anterior skull-base tumors (80%, 243/304) or sellar tumors (62%, 161/259). The use of a vascular flap was associated with a significantly lower postoperative leakage rate (13.2%, 62/468) than when a free graft was used (27.9%, 41/147).

Certain tumor types may be associated with higher rates of CSF leak. A recent review of risk factors associated with postoperative CSF leaks found that patients with chondroid tumors, meningiomas, and craniopharyngiomas experienced higher rates of CSF leak, without a statistically significant difference in leak rates between these lesions.[233] The observed correlation may, however, have been confounded by the predilection of some tumors to develop at certain anatomic sites that may carry inherent risks of higher-flow leaks. Specific recommendations for skull-base reconstruction based on site of defect are provided in a separate section within this consensus statement (Section XI.A.2.a. Site of defect).

X.A.2.d. Size of defect. Small (<1 cm^2) skull-base defects are reliably closed in over 90% of cases using multilayered free grafts, obviating the need for vascularized flap reconstruction.[52,477] Larger dural defects, specifically those ≥ 2 cm^2, are more likely to experience a postoperative CSF leak and thus benefit from the added support of vascularized flap reconstruction.[1074]

X.A.2.e. Mechanism of defect. The majority of skull-base defects requiring vascular repair are iatrogenic in nature, resulting from endoscopic extirpation of tumors. Other etiologies include congenital and traumatic. In a series of endoscopically-repaired congenital meningoencephaloceles, Rawal et al.[1109] reported a lower rate of recurrence (4.8%) with vascular flap reconstruction compared to all other repair techniques (12.7%). Traumatic skull-base defects, when repaired with vascular flaps, have also been shown to have improved rates of closure, approaching a 0% CSF leak rate.[30,1110,1111]

X.A.2.f. Pediatric indications. Early reports raised concerns that the NSF may have limited utility in pediatric skull-base reconstruction because of reduced septal surface area and diminished range of flap rotation.[1112] However, subsequent reports have described adequate coverage and pedicle length in sellar skull-base reconstructions in patients between the ages of 5 and 17 years[1113] and in suprasellar skull-base reconstructions in children as young as 3 years of age.[1114] Despite the use of vascularized flaps, repair of skull-base defects in the pediatric population remains a challenge. In the largest case series reported to date, Stapleton et al.[1115] detailed 47 reconstructions after ESBS among patients ages 1 month to 18 years. The rate of postoperative CSF leak among patients with vascularized flap repair (28%, 10/36) was not statistically different from the rate of leak in patients reconstructed without the use of a flap (9%, 1/11, $p = 0.41$). The authors cited selection bias toward the increased use of vascularized flaps in cases with larger skull-base defects or higher-flow leaks that might account for the discrepant outcomes.

X.A.3. *Complications and limitations with vascularized flap reconstruction*

Overall, the scope of complications associated with local and regional vascular flaps generally fall within 3 categories: flap integrity, recipient site complications, and donor-site complications.[227,1116,1117] A review of institutional complications by Soudry et al.[1116] revealed an overall complication rate of 27% (33/121) associated with NSF elevation and use, in which the majority of complications involved donor-site morbidity.

Flap integrity may be affected by technical challenges encountered during flap elevation. Prominent septal deviations, large septal spurs, and prior septal surgery can contribute to heightened difficulty during flap elevation,

potentially increasing the likelihood of flap laceration or tearing. Despite these potential risks to the flap, a recent review suggested that prior septoplasty or transseptal endoscopic surgery does not appear to increase the likelihood of flap laceration during the harvesting process. Moreover, small lacerations do not appear to impart an increased risk for postoperative CSF leak.[1118] Additionally, delaying flap elevation until the completion of the case (often described as a "rescue" flap) or the re-use of a previously placed NSF during revision cases appears to have minimal impact on flap failure rates and postoperative CSF leak rates.[1119–1121]

The viability of the vascularized flap and the recipient skull-base defect site may be adversely affected by exogenous factors, such as prior RT. Reported rates of postoperative CSF leak among patients undergoing vascular flap repair in the setting of previous RT range from 8.1% to 28.6%.[1073,1100,1122–1124] Although these studies suggested a moderately increased risk of postoperative CSF leak despite vascular flap application, a case series compiled by Gruss et al.[1074] observed no difference in postoperative CSF leak rate after vascular flap repairs between patients with a history of RT (5.4%, 2/37) and patients with no prior RT (9.5%, 8/84).

Other potential recipient site complications include incorrect orientation of the mucosal surface of the flap against the skull-base defect, delayed mucocele formation under the flap,[1125,1126] and a risk for misinterpretation of the vascular reconstruction as disease persistence or recurrence on surveillance imaging.[1127,1128]

Complications involving the donor site can cause considerable impairment in sinonasal QOL, most commonly relating to prolonged nasal crusting and impaired olfaction. Remucosalization of the denuded septum can be expected to take up to 90 days,[1129] and within this period, nasal crusting at the donor site is an expected aspect of normal wound healing. Prolonged crusting beyond 3 months may reflect incomplete re-epithelialization or impaired viability of the septal bone or cartilage. Patients undergoing an NSF did not actually have a significantly longer time to absence of crusting (median time, 104 days) compared to those without NSF (median time, 98 days).[1129] Crusting and other nasal donor-site morbidity may be improved with adjacent mucosal graft transfer techniques,[1130] or a reverse rotation flap using mucosa from the posterior aspect of the contralateral septum.[1131,1132]

ESBS with or without the elevation of an NSF often leads to transient reduction in olfaction; however, the reported impact on olfaction varies considerably among studies.[1101] A randomized controlled trial by Tam et al.[1102] demonstrated that patients undergoing endoscopic pituitary surgery, regardless of NSF use, experienced a significant decrease in University of Pennsylvania Smell Identification Test (UPSIT) scores at 6 months postoperation. However, those patients undergoing NSF had a nearly 20% reduction in UPSIT score at 6 months compared to their preoperative score, whereas patients without flaps had only a 9% reduction in this time frame. Rotenberg et al.[1133] reported that patients undergoing NSF reconstruction had a mean preoperative UPSIT value of 37.2 (normosmia) and mean postoperative UPSIT value of 30.8 (moderate hyposmia) at their 6-month follow-up visit. In contrast, Chaaban et al.[1134] reported no significant difference in mean preoperative UPSIT scores vs 3-month postoperative UPSIT scores among patients undergoing endoscopic pituitary surgery (31.3 vs 30.5), and no significant difference in preoperative vs 3-month postoperative UPSIT scores in patients with NSF (29.4 vs 28.9). Overall, the preponderance of evidence suggests that raising an NSF has at least a transient impact on olfaction; however, the heterogeneity of reported outcomes limits the development of a clear consensus on this topic.

The structural integrity of the nasal septum may be compromised in a notable percentage of patients undergoing septal flap reconstruction. Septal perforation has been reported at rates approaching 14%,[1116] whereas nasal dorsum collapse has been reported in nearly 16% of cases.[1117]

Of note, the rate of complications appears to decrease with increasing surgeon experience. This finding is particularly true for postoperative CSF leak rates. In an early review of their vascular flap reconstruction outcomes, Kassam et al.[274] reported a 33% leak rate in their first 25 repairs, which declined to a leak rate of 4% in their subsequent 50 patients. Similarly, Horiguchi et al.[1077] reported a 12.2% leak rate in their first 90 procedures, which dropped to 2.3% in their subsequent 42 procedures. Mascarenhas et al.[1135] detailed 4 leaks in their initial 63 patients undergoing vascular flap reconstruction, and none in their subsequent 63 patients.

- Aggregate Grade of Evidence: B (Level 2a: 2 studies, Level 4: 3 studies)
- Benefit: Vascular flaps appear to reduce the incidence of postoperative CSF leaks in repair of skull-base defects
- Harm: Moderate harm, mainly sinonasal QOL due to donor-site morbidity, particularly the possibility of postoperative olfactory impairment
- Cost: Low
- Benefit-Harm Assessment: Strong benefit of flap placement over mild reduction in QOL symptoms
- Value Judgment: Vascular flaps appear to reduce CSF leaks and improve overall outcomes for endoscopic repair of skull-base defects
- Policy Level: Strong recommendation for the use of vascular flap
- Intervention: When performing endoscopic repair of skull-base defects, vascular flaps appear to reduce the rates of postoperative CSF leakage, most notably in cases of high-flow leaks (intra-arachnoid), cases involving craniopharyngiomas and meningiomas, cases involving the posterior cranial fossa, clivus, or regions at the limit of endoscopic resection where repairs are more complex, and cases with dural defects ≥ 1 cm^2

X.B. Free-graft reconstruction

Because EEA is becoming the standard of care for the treatment of various skull-base disease processes, the need to standardize reconstruction has become evident. The primary goal for reconstruction, regardless of pathology, is to separate the intracranial space from the access corridor, the nasal cavity, and paranasal sinuses. Separation of these compartments with a watertight seal eliminates egress of CSF and potentially life-threatening complications including ascending meningitis, intracranial abscess, encephalitis, meningoencephalocele, and tension pneumocephalus.[52,1136]

Wigand[1137] first described endoscopic repair of an ethmoidal roof defect for CSF rhinorrhea using a free mucosal graft in 1981. Since then, the most common forms of reconstruction have come to involve the use of a free, or nonvascularized graft, or a vascularized pedicled flap. Free grafts have been used alone in single or multilayer fashion or in combination with vascularized pedicled flaps.

X.B.1. *Types of free grafts*

Free grafts are divided into autologous grafts and allografts. Autologous free grafts include fat, temporalis fascia, fascia lata, and more commonly, nasal free-mucosal grafts. Septal bone and cartilage have also been described as part of a multilayer reconstruction.[1138] Popular allografts include acellular human cadaveric dermis (Alloderm; Lifecell Corporation, Branchburg, NJ), acellular porcine intestines (Biodesign-Cook Medical, Bloomington, IN), and collagen matrix materials such as DuraGen (Integra Lifescience Corporation, Plainsboro, NJ).

Free mucosal grafts are frequently derived from the middle turbinate, which is often completely or partially resected as part of the EEA. Other sites include the inferior turbinate, nasal septum, and nasal floor, while taking care to preserve olfactory epithelium. Advantages of free mucosal grafts are that they generally have low nasal morbidity and are straightforward to obtain.[1139] In cases where tumor spread within the nasal cavity can limit pedicle dependent flaps, often, free mucosal grafts can still be feasibly harvested because they can be obtained from multiple locations. Harvested intranasally, they do not require a separate incision or surgical site as is necessary with harvesting fat or fascia. Care should be taken to ensure that these grafts are only used as an onlay with the mucosal epithelial surface facing intranasally to avoid mucocele formation.[1140] Nonmucosal or non-epithelium–containing autologous grafts and allografts can be used as either inlay or onlay grafts.

Grafting technique can range from a simple onlay graft skull-base reconstruction to a combined inlay-onlay or gasket seal closure with or without a vascularized flap.[428] The chosen technique depends on a variety of factors, discussed below (Section X.B.2.a. Decision-making considerations for free-graft reconstruction). Inlay graft materials should consist of materials without epithelial surfaces such as fascia, bone, or fat, as well as collagen matrix materials.

The graft should be larger than the defect so that it may rest on the bony ledges of the defect.[1141] Historically, free bone grafts had been used as an inlay to support the soft tissues of the brain. However, if postoperative RT is necessary, they are prone to osteoradionecrosis and can take longer to heal compared to other graft materials.[1142] If used, free bone grafts should be combined with a vascularized onlay graft.[1143]

Onlay grafts can be used in a single or multilayer fashion and should encompass the entire bony rim of the defect with an adequate margin to account for contraction. Free grafts generally lose about one-fifth of their size during the healing process so starting with a graft that is at least 1.25 times the size of the defect is advised.[1144] Small graft size, especially for an onlay graft, is a common reason for postoperative CSF leak.[1145]

X.B.2. *Outcomes with free-graft reconstruction*

To date, there are 2 systematic reviews that include comparison of free grafts with vascularized flaps in skull-base reconstruction and rates of postoperative CSF leak. The most recent review was published in 2014 by Soudry et al.[242] The study included a total of 673 patients, who were analyzed with regard to intraoperative CSF leak (none 141, low-flow 74, and high-flow 218) and location of defect (anterior cranial fossa, sella, clivus, and tuberculum). The reconstruction techniques within each of these categories were analyzed, with the postoperative CSF leak rate as the clinical endpoint. The success rate was defined as no postoperatove CSF leak. The overall leak rate was 8.5% (57/673).

In the group with no observed intraoperative leak, there was no postoperative leak regardless of closure. In the low-flow leak group, there was no observed difference between the success rates based on the technique or material used for closure (layered free grafts 92% and vascular flaps 100%). In the high-flow group, 107 patients were reconstructed with vascular flaps with or without a free graft, which achieved a 94% success rate compared with 111 with multilayered free grafts and an 82% success rate. Low-flow leaks were generally limited to sellar and parasellar defects, whereas high-flow leaks were identified in all subsites. Although no formal statistical analysis was mentioned, the authors considered both methods of reconstruction to be equally successful in the low-flow group, while acknowledging there may be a difference in the high-flow group, with vascularized reconstruction having the better outcome. The authors concluded that in cases of no observed intraoperative leak and in low-flow intraoperative leaks, free grafting technique success rates are comparable to vascular flap–reconstructed rates. However, in cases of high-flow intraoperative leaks, the use of a vascular flap is superior to free grafts alone.

Overall success rates with regard to location of defect were as follows: anterior cranial fossa 92%, sella 93%, clivus 80%, and tuberculum sella 100% (data limited and unclear for tuberculum location). Free grafts were

comparable to vascular flap in all locations except for the clivus, where the success rate was only 60% for free grafts alone, but 75% to 100% with a vascularized flap. There was also a fairly large range noted in the anterior cranial fossa location for free grafts (67-93%). This may reflect surgeon familiarity with effective grafting techniques, and how to accomplish a circumferential watertight seal, or variations in defect size, and not so much a failure of free grafts in achieving a good closure.

Based on location, clival defects showed more success with vascular flap. Although the data were limited for tuberculum defects, theoretically the clivus and tuberculum are at increased risk of high-flow leaks because they are closer to the arachnoid cisterns and intracranial ventricles. Therefore, the use of a vascular flap in these defect locations is recommended.[242]

Harvey et al.[477] published a systematic review and meta-analysis in 2012 of endoscopic endonasal reconstructions, specifically looking at large skull-base defects. The Medline, Embase, and Cochrane databases were searched and 609 cases with large dural defects were included in the study and compared based on reconstruction with free grafts or vascularized flaps. The overall CSF leak rate was 11.5%. A total of 326 defects were reconstructed with free grafts, with a 15.6% leak rate, whereas 283 cases were reconstructed with a vascularized flap, resulting in a 6.7% leak rate. The authors concluded that a vascularized flap is indicated for large dural defects. This analysis corroborates earlier studies that reported a >90% success rate with small defects (<1 cm) with multilayered free grafts,[52,1146] and that larger defects (>3cm) repaired with free grafts have a higher CSF leak rate as compared to similar repairs in smaller defects.[1147]

X.B.2.a. Decision-making considerations for free-graft reconstruction. A reconstruction algorithm based on defect location and quality of intraoperative CSF leak was developed in 2010 after a prospective study of 150 cases and an additional 75 cases reviewed from the literature, all of which were repaired using vascular flaps, specifically NSFs.[1104] The authors evaluated tumor size, location, size of defect, and quality of intraoperative leak (high-flow vs low-flow). This study was included in the previous systematic reviews but is worth examining alone because applicable recommendations and trends are seen. The overall leak rate after NSF reconstruction in 150 patients at the primary institution was 4.0% (6/150). In 59 cases with a high-flow intraoperative leak, 4 of 59 (6.7%) developed a postoperative leak. These occurred among the following pathologies: olfactory groove meningioma, pituitary macroadenoma, craniopharyngioma, and clival chordoma. Alternatively, the postoperative leak rate was 2.1% (2/91) in the 91 cases where a low-flow intraoperative, or "weeping" CSF leak was noted.[1104] Low-flow leaks generally occur when dura is opened, as can occur in a thinned diaphragma or transcribriform skull-base defects, without the disruption of the basilar or suprasellar arachnoid cisterns and/or ventricles.[1104]

In the algorithm, the authors proposed that if there is a low-flow leak, then defect site and size (small <1 cm, large >2 cm) should guide whether a free-graft reconstruction alone is adequate or the use of a vascularized flap is required. In a high-flow leak, defect site alone guides the reconstruction. High-flow intraoperative leaks with AlloDerm reconstruction resulted in a 30% postoperative leak rate at best, but has been found to be as high as 50%. Vascularized tissue for larger and more complex skull-base defects is the preferred option.[1104] Again, their discrepancy with others in the literature may reflect surgical technique or patient factors such as obesity, and not as much the material used. However, every surgeon must find a material and technique that works best for him or her.

In sellar defects, the size of the defect matters as this corresponds to the availability of a bony defect rim, which can be limited by the optic nerve and parasellar carotid. If there is no bony ledge, reconstruction with purely free grafts is difficult, and a vascularized flap is advised.[1104] Interestingly, they found that the size of the tumor does not directly correlate with the presence or quality of intraoperative CSF leak. The most predictive factor in the occurrence of an intraoperative CSF leak is the violation of the arachnoid cisterns and the size of the dural defect.[1104]

Patient risk factors, particularly BMI, should also be considered when deciding on reconstruction technique. Elevated BMI has been found to be a risk factor for postoperative leak in sellar defects in pituitary surgery[1148] and was later found to be a significant risk factor when analyzed in conjunction with high-flow intraoperative CSF leaks regardless of defect location when compared to normal-weight patients.[233] Free-graft reconstructions alone should be avoided in these cases. Fraser et al.[233] concluded that a vascularized flap should be used in all patients with a BMI >25 kg/m^2 in the presence of an intraoperative CSF leak regardless of location. They found that the use of a vascularized flap significantly decreased the CSF leak rate in patients with BMI >25 kg/m^2 when compared to free grafts. The postoperative CSF leak rate was also decreased in normal-weight patients, when comparing vascularized flaps to free-graft reconstruction; however, it did not reach statistical significance. Additionally, their data correlates with previous studies in which posterior fossa tumors had the highest CSF leak rate.

X.B.2.b. Free grafts for anterior skull-base. Reconstruction of the anterior skull-base (ASB) including large defects >2 cm, using free grafting techniques has been consistently reported as successful.[859,1149] In a retrospective review comparing outcomes of transnasal endoscopically resected ASB tumors that were reconstructed with free grafts (primarily AlloDerm) with open craniofacial resection and reconstruction of ASB defects with vascular flaps or free flaps, there was no statistically significant difference in rates

of major or minor complications. More specifically, in the 34 patients who underwent transnasal endoscopic resection, only 1 developed a postoperative CSF leak (2.9%).[1149]

All of these effectively reconstructed ASB defects have been done so with AlloDerm or tissue-banked freeze-dried dura alone, using an inlay-overlay technique. In this technique, the central portion of the AlloDerm graft is placed intracranially as an "inlay," with the margins of the graft extending intranasally to overlay the bone surrounding the defect. Typically, an expandable yet absorbable material such as surgicel/gelfoam cylinders are tucked circumferentially into the pocket that is created, thereby securing the inlay portion of the graft from pulling away from the bony margins of the orbit, sphenoid planum, and posterior frontal sinus. The weight of the brain against the reconstruction further holds the graft in place by providing downward pressure to the periphery of the graft.[859] In the inlay-overlay technique, a bony rim is necessary and mucosa from the rim must be removed so the graft may lie directly on bone to aid revascularization.[1150] A vascular flap can still be used as a second layer to provide mucosal coverage, but is not necessary to achieve a watertight closure.

X.B.2.c. Free grafts for sellar reconstruction. In recent years, there have been several studies to examine the role of free-graft reconstruction particularly in sellar defects after endoscopic endonasal pituitary surgery as a de-escalated alternative to vascularized pedicled flaps.[244,1151,1152] In a retrospective review of 73 sellar defects reconstructed with layered avascular free grafts, Roxbury et al.[1151] observed an overall leak rate of 6.85% and found high-flow intraoperative leak to be a significant predictor of failure. Of note in their study, 7.9% had nasal crusting, which is the most common nasal morbidity associated with EEA,[1129] and there was no difference in crusting between allograft and mucosal graft reconstruction. In sellar defects with low-flow intraoperative CSF leaks, layered free-graft reconstruction is a good alternative to NSF and has decreased nasal donor-site morbidity.[1151]

In a prospective study examining 50 consecutive endonasal pituitary adenoma resections, free middle-turbinate mucosal grafts were found to be an adequate reconstruction option with no postoperative CSF leaks in 32 cases (9 microadenomas and 23 macroadenomas, 3 observed intraoperative leaks). Of the 50 cases, 12 were excluded in which a macroadenoma >3 cm was present and a high-flow intraoperative CSF leak was anticipated. The authors concluded that a free middle-turbinate mucosal graft is a good alternative for sellar defect reconstruction after pituitary surgery for microadenomas and macroadenomas <3 cm with no or low-flow intraoperative CSF leak.[1152]

Another set of 50 consecutive sellar defects (47 macroadenoma, 3 microadenoma, 40% with intraoperative CSF leak) after endoscopic pituitary adenoma surgery reconstructed with a collagen dural inlay graft and nasal floor free-mucosal overlay graft had no postoperative CSF leaks. Near complete remucosalization from the nasal floor donor site was noted at 1 month with no significant difference in preoperative and postoperative 22-item Sino-Nasal Outcome Test (SNOT-22) scores.[244] These findings support the use of free-graft reconstruction in sellar defects after pituitary surgery.

X.B.3. *QOL considerations*

Because endonasal techniques are becoming the norm, the attention has shifted from not only minimizing major postoperative complications that result from a failure to separate the intracranial cavity from the nasal cavity, but also a recognition of postoperative nasal morbidity and QOL. Free grafts, including free mucosal grafts harvested intranasally, have limited nasal morbidity, but must be used in the appropriate situations to minimize and avoid the potentially costly complication of CSF leak.

Summary

In summary, there are several factors that should be considered when determining the use of free grafts in reconstructing skull-base defects. These include defect size, location, presence or absence of intraoperative CSF leak, quality of CSF leak (high-flow vs low-flow), tumor pathology, patient risk factors, prior or future RT, and presence of bony rim around defects (see Table X.B).

Free-graft reconstruction alone may be useful in cases of no intraoperative CSF leak or low-flow CSF leaks with small (<1 cm) defect size, achieving success rates upward of 90%.[52,242,1146] The location of the defect and tumor pathology coincide in determining the likelihood of CSF leak as well as anticipated flow rate of CSF leak. Posterior fossa tumors with clival defects should not be repaired with free grafts alone because these generally produce a high-flow leak given their proximity to the cisterns. Meningiomas and craniopharyngiomas often require significant dural and arachnoid dissection and their location, often in the suprasellar region (or clivus for posterior fossa meningiomas), will result in a high-flow leak. Free grafts alone should also be avoided in these situations. Finally, surgeons must find a material and technique that works best for them, with equal or better success rates to those published in the literature. The overriding goal is achieving a circumferential watertight seal, regardless of material used.

Patient risk factors, including obesity, intracranial hypertension, previous and future RT, should also deter from free-graft reconstruction alone. In these situations, a vascularized flap is more appropriate.

- Aggregate Grade of Evidence: C (Level 4: 10 studies).
- Benefit: Although there is no evidence to support the direct benefit of free grafts in the reconstruction of skull-base defects, they are straightforward to harvest (or easily stocked and available), generally have low donor-site

TABLE X.B. FG repair for endoscopic SB defects

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Soudry[242]	2014	4	Systematic review of case series - PubMed - SCOPUS - Cochrane English Human ≥5 Patients 1. EEA SB resection 2. SB recon techniques and outcomes	n = 673 Intraoperative CSF flow: - None - Low-flow - High-flow Location of defect: - Anterior cranial fossa - Sella - Clivus - Tuberculum	Postoperative leak rate Overall rate 8.5% (57/673) Intraoperative CSF flow: —None 141 No postoperative leak regardless of closure Low-flow 74 —64 Layered FG 92% —10 Vascular flap 100% High-flow 218 —107 Vascular flap ± FG 94% —111 multilayered FG 82% Location of defect: Anterior cranial fossa (92%) —FG 67% to 93% —Vascular flap 96% to 100% Sella (93%) —FG 87% to 100% —Vascular flap 94% to 100% Clivus (80%) —FG 60% —Vascular flap 75% to 100% Tuberculum (100%) —FG and vascular flap but limited/unclear data	No leak or low-flow: - FG = vascular flap - High flow: vascular flap > FG Location: - Clivus: vascular flap >FG
Harvey[477]	2012	4	Systematic review and meta-analysis endoscopic endonasal reconstruction of large SB defects —Medline —Embase —Cochrane	n = 609 Large dural defects Reconstruction: —Vascularized —Free graft	Postoperative CSF leak rate Overall rate of CSF leak 11.5% 326 FG reconstruction 15.6% leak rate 283 Vascularized reconstruction 6.7% leak rate	Vascularized flap for large dural defects
Fishpool[1152]	2017	4	Prospective consecutive cohort	n = 50 sellar defects; 12 excluded (macroadenoma >3 cm or high-flow leak anticipated—NSF harvested) Free MT graft = 32 9 Microadenoma 23 Macroadenoma 3 Intraoperative leaks	Postoperative CSF leak rate Rhinologic morbidity No postoperative leaks Mean SNOT-22 was 31.9 at 6 weeks and 23.4 at 6 months ($p = 0.001$)	Free MT graft reconstruction is an option in sellar defects s/p resection of microadenomas and macroadenomas <3 cm with low-flow intraoperative CSF leaks.
Peris-Celda[244]	2017	4	Retrospective review	n = 50 consecutive sellar defects repaired with collagen dural graft inlay + nasal floor free mucosal graft overlay No LD SNOT-22 preoperation, 1 month, 3 months	Postoperative leak rate SNOT-22 47 Macroadenoma 3 Microadenoma 40% Intraoperative leaks No postoperative leaks Near total or complete re-mucosalization of donor site at 1 month No significant difference in preoperative and 1 month SNOT-22	FG reconstruction using an allograft inlay with a free mucosal graft overlay is an option for reconstruction of sellar defects after pituitary surgery. The nasal floor is a donor site option for free mucosal grafts with decreased nasal morbidity.

(*Continued*)

TABLE X.B. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Fraser[1153]	2018	4	Retrospective review	n = 615 patients Demographics Defect location Reconstruction technique Tumor pathology LD	Postoperative CSF leak Overall leak 16.7% —BMI >25: 18.7% —Normal BMI: 11.5% Posterior fossa—32.6% Anterior skull base—21.0% Sellar/suprasellar—9.9% vascular flap—13.5% Free graft—27.8% BMI >25: 15.0% with vascular flap and 29.5% with FG. Statistically significant. Normal BMI—21.9% with vascular flap, 9.2% with FG. Not statistically significant	Posterior fossa lesions have the highest postoperative CSF leak rate. BMI >25 has a higher postoperative CSF leak rate. Using a vascular flap in patients with BMI >25 decreased postoperative CSF leak rate when compared with FG. Gender and perioperative LD did not affect leak rate.
Roxbury[1151]	2016	4	Retrospective review	n = 73 sellar defects repaired with layered FG	Postoperative CSF leak Nasal morbidity Overall leak rate 6.85% 7.9% with persistent crusting No difference in crusting between allografts and mucosal grafts.	In sellar defects with low-flow intraoperative CSF leaks, layered FG reconstruction is a good alternative to NSF and has decreased nasal morbidity. High-flow intraoperative leaks are a predictor of failure with FG reconstruction.
Wood[1149]	2012	4	Retrospective review	n = 34 endoscopic ASB resections repaired with AlloDerm n = 48 open craniofacial resections repaired with vascular flap/free flaps	Perioperative and oncologic outcomes including major and minor complications	No statistically significant difference in complication rates. Repair of ASB with AlloDerm is an effective technique.
Patel[1104]	2010	4	Prospective case series	166 Dural defects reconstruction rate of CSF leak	Postoperative CSF leak FG in low flow: 90% success FG in high flow: 50% to 70% success NSF in 150 defects 59 High-flow: 6.7% leak rate 91 Low-flow: 2.1% leak rate	Anterior/sellar – NSF, pericranial flap High-flow leaks and clival/posterior fossa defects – NSF (or another vascular flap)
Germani[859]	2007	4	Retrospective review	n = 56 ASB defects repaired with FGs Dural defect size —Small (<0.4 cm) —Intermediate (0.4–2.0 cm) —Large (>2.0 cm) Primary graft material	Success of graft take Major/minor complications 16/55 Large defects Alloderm 30/55 97% Graft take 0% and 3.3% Major and minor complications Non-Alloderm 25/55 92% graft take 4% and 12% Major and minor complications	No difference in complication rates based on type of repair and defect size. Can use Alloderm to repair ASB, including large defects >2 cm
Leong[1154]	2006	4	Retrospective review	n = 14 ASB defects repaired with multilayer FG closer 10 Intraoperative leaks LD in 7 cases	Postoperative CSF leak 0/14 Leaks at mean follow-up of 18 months	Layered FG reconstruction may be a good option in ASB defects. LD confounding

ASB = anterior skull base; BMI = body mass index; CSF = cerebrospinal fluid; EEA = endoscopic endonasal approach; FG = free graft; LD = lumbar drainage; LOE = level of evidence; MT = middle turbinate; NSF = nasoseptal flap; s/p = status post; SB = skull base; SNOT-22 = 22-item Sino-Nasal Outcome Test.

morbidity, and have been shown to have low rhinologic morbidity when obtained from the nasal cavity.

- Harm: The potential harm of using free grafts to reconstruct skull-base defects is the development of a CSF leak and its sequelae, when used in inappropriate cases, or applied incorrectly to achieve a watertight seal.
- Cost: No studies have compared the cost of free-graft reconstruction alone with vascularized tissue reconstruction, but theoretically the additional material cost of allografts may be considered. The additional operative time taken to harvest autologous free grafts has not been studied when compared to the time taken to harvest tissue for a vascularized reconstruction; neither has its translation to surgical costs. Theoretically, obtaining free grafts may take slightly less time than harvesting a vascularized pedicled flap, although in experienced hands and depending on the type of graft or flap, this can be nearly equal.
- Benefit-Harm Assessment: The potential harm in development of a postoperative CSF leak and its clinical sequelae considerably outweighs the marginal benefit of using free grafts alone in the inappropriate case selection.
- Value Judgements: Free-graft reconstruction techniques provide clinical outcomes that are similar to vascularized tissue reconstruction in small anterior skull-base and sellar defects cases with no intraoperative or low-flow leaks. In large defects with high-flow leaks, especially in the clivus, vascularized pedicled flaps are recommended. Although there is evidence against the use of free grafts alone in the latter situation, there is no significant evidence against using vascularized tissue in the former. In overweight or obese patients undergoing skull-base resections and/or those with a history of prior RT or need for future RT, vascularized tissue reconstruction is favored.

  It is important to consider the possibility of technical bias in the literature. It is common for surgeons to use the technique they are most comfortable with, which often coincides with methods learned during their training. Institutions trained in a particular method will continue to encourage the use of that proven method, establishing a dominant procedure within their organization. Together, this breeds technical bias in the literature because institutions with high volumes of skull-base procedures that favor certain reconstruction practices will skew the outcomes results in favor of their reconstruction methods.

  Furthermore, the reasoning for using vascularized tissue is often unexplained. Its use as a primary closure layer as opposed to simply aiding in mucosal healing is unclear in most of these studies. Most would agree that mucosal coverage, especially with vascularized tissue, as a second layer (full or partial coverage) would expedite healing. This would bias the literature, especially in ASB defects, toward using vascularized tissue. Ultimately, any technique and material, whether it consists of free grafts, vascularized tissue, or a combination thereof, used to achieve a circumferential watertight seal, will be successful. In middle or posterior cranial fossa defects with high-flow leaks, this often translates to a multilayered reconstruction.

- Policy Level: Option
- Intervention: In normal-weight patients without prior RT or need for future RT and in those with small skull-base defects with the presence of a bony rim and no observed intraoperative leak or low-flow leaks, reconstruction with free grafts alone is a viable option.

X.C. LD after ESBS

Postoperative CSF leak is 1 of the complications that can occur following ESBS, with a variable percentage of incidence according to the pertinent literature. A variety of techniques have been described to reduce the rate of postoperative CSF leaks, including the use of multilayer closures with synthetic and autologous materials, the vascularized NSF, and the use of buttresses such as a Foley balloon. Techniques for reconstruction and materials have substantially evolved over the past decades and, as the landscape of skull-base surgery reconstruction techniques continues to change, so does the attitude on LD usage in the setting of CSF leak repair.

The insertion of a drain into the lumbar subarachnoid cistern diverts CSF and may reduce the risk of a postoperative CSF leak following cranial base procedures. The goal of CSF drainage from the lumbar subarachnoid space is to provide a controlled, low-resistance egress of CSF in the immediate postoperative period. This allows initial healing to occur under decreased tension and, theoretically, lowers the chance of persistent CSF fistula. Although lumbar drains are often used for these important purposes, there is no set standard for their use in endoscopic skull-base tumor resection and reconstruction. Currently, the available evidence for the use of lumbar drains in skull-base surgery is of poor quality.

A total of 15 studies met the inclusion and exclusion criteria.[233,234,241,266,478,1104,1148,1155–1161] Overall, the evidence level was low with the majority of studies comprising level 4 evidence (Table X.C.1).

After review of these full-text articles, 8 were removed secondary to reporting an unspecified number of lumbar drains, duplicate data sources, excluding repaired CSF leaks, addressing only secondary CSF leaks, or not using contemporary reconstructive techniques. This left 7 studies to be included in this review. Accordingly, all 7 studies were reviewed.

Notably, there was a lack of prospective studies whereas 2 recent meta-analysis were identified.[131,268] In addition, there was significant variability in the pathology treated and the defects repaired within each study and also between studies.

TABLE X.C.1. Evidence for LD after ESBS

Study	Year	LOE	Study design	Study group with LD protocol	Primary endpoint	Conclusion
Patel[1104]	2010	4	Retrospective case series and literature review	134 Patients with lumbar drain placed after repair (not in operating room)	Endoscopic skull base reconstructive options and limitations	Comprehensive overview of the endoscopic reconstructive options
Dlouhy[1148]	2012	4	Retrospective analysis	92 Patients	Role of the BMI in postoperative CSF leak after EES	Elevated BMI is an independent predictor of postoperative CSF leak after an endonasal endoscopic transsphenoidal approach
Eloy[478]	2013	4	Retrospective review over a 2-year period	10 Patients	Triple-layer reconstruction technique as effective in reconstructing large ASB defects	The triple-layer reconstruction technique is effective
Garcia-Navarro[234]	2013	4	Prospectively acquired database of a case series	46 patients Lumber drains were left in place for 24–48 hours and opened intermittently at a rate of 5 mL/hour	Gasket seal role in extended endonasal endoscopic skull-base surgery	Gasket seal closure is a reliable long-term effective method for achieving watertight closure of the cranial base
Ivan[266]	2014	4	Retrospective case series	98 Patients Lumbar drain may be left in place for 3 to 5 days draining 10–20 mL/hour	Postoperative CSF leak after expanded endoscopic endonasal surgery	In expanded endoscopic transsphenoidal surgeries, abnormal preoperative BMI remains an important preoperative predictor for postoperative CSF leak and infection
Martinez-Capoccioni[1157]	2015	4	Retrospective case series	25 Patients CSF drainage was maintained for 72 hours at 5–10 mL/hour	Spontaneous CSF leaks in the ASB. Role of the lumbar drain plus acetazolamide therapy	This study indicates that treating underlying intracranial hypertension coupled with endoscopic repair can provide high success rates approaching those of other etiologies of CSF leaks
Yang[1159]	2015	4	Retrospective chart review	20 Patients	Endoscopic endonasal treatment of pituitary apoplexy	The endoscopic endonasal transsphenoidal approach is an effective modality to treat pituitary apoplexy with a high rate of GTR and minimal risk
Hu[1158]	2015	3	Non-randomized controlled cohort	33 Patients in 2 cohorts 1. Single technique group2) Combined technique group (include gasket seal) 2. A lumbar drain was placed for continuous CSF drainage with a volume of 150 mL daily	Role of the combined use of a Gasket seal closure and vascularized pedicle nasoseptal flap	LD after the operation is a necessary auxiliary method.
Zhan[1155]	2015	4	Retrospectively reviewed	33 Patients	Effectiveness of continuous LD for management of postoperative CSF leaks	Placement of LD may not be necessary for the management of low-flow postoperative CSF leak

(*Continued*)

TABLE X.C.1. Continued

Study	Year	LOE	Study design	Study group with LD protocol	Primary endpoint	Conclusion
					after endoscopic endonasal transsphenoidal approach for resection of pituitary adenoma	after using endoscopic endonasal transsphenoidal approach to pituitary adenoma
Zhan[1155]	2015	4	Retrospective review (pediatric patients)	11 Patients	EEA for pituitary adenomas	EETA provides a safe and effective surgical option with low morbidity and mortality in pediatric patients
Fraser[1153]	2018	4	Retrospective review of patients	615 Patients	Determine risk factors for the development of a postoperative CSF leak after an EEA for resection of skull-base tumors	Use of a pedicled vascularized may be associated with reduced risk of a CSF leak, particularly in overweight patients
Dehdashti[241]	2016	4	Retrospective analysis	180 Patients	Repair protocol for EES	Routine prophylactic lumbar drain placement in all type III leak and reconstructions
Wilson[1161]	2018	4	Retrospective review of a prospectively acquired database	135 Patients	Endoscopic pituitary surgery in the elderly	The use of a lumbar drain or lumbar punctures should be weighed against the risk of subdural hematoma in patients with preexisting atrophy
Negm[1160]	2017	4	Prospectively collected database of a consecutive series	42 Patients with LD rate of 5 mL/hour for 1 day Comparing: 1. Endoscopic endonasal technique 2. Microscopic endonasal technique	Specific sites of residual or recurrent tumor after different transsphenoidal approaches	Endonasal endoscopic reoperation offers excellent results for residual or recurrent tumors and should be considered before radiation therapy, particularly for symptomatic patients
Cohen[1156]	2018	4	Prospectively acquired database of EESs	25 Patients	Role of the LD in patient with elevated BMI and endonasal surgery for suprasellar meningiomas	A lumbar drain may be useful to prevent postoperative CSF leak, particularly in patients with elevated BMI.

ASB = anterior skull base; BMI = body mass index; CSF = cerebrospinal fluid; EEA = endoscopic endonasal approach; EES = endoscopic endonasal surgery; EETA = endoscopic endonasal (transnasal) transsphenoidal approach; ESBS = endoscopic skull-base surgery; GTR = gross total resection; LD = lumbar drainage; LOE = level of evidence.

A total of 1131 cases of ESBS with involvement of lumbar drains as adjunctive procedure for reconstruction were found and revised (Table X.C.2). A meta-analysis was performed to determine the equivalency of a CSF leak between the pooled data with and without a lumbar drain. Among these studies, the average OR for postoperative CSF leak for patients without a lumbar drain relative to patients with a lumbar drain was 1.1455 (95% CI, 0.7954 to 1.6496), thus confirming that there is insufficient evidence to suggest that adjunctive LD significantly reduces the rate of postoperative CSF leak following EES. The literature summary for an EBRR is provided in Table X.C.1.

Since the advent of the pedicled NSF, largely considered the workhorse for endoscopic skull-base reconstruction, multiple studies have shown that lumbar drains may not be needed even in the challenging settings of high-flow CSF fistulae and large skull-base defects. Nonetheless, the precise indications for perioperative CSF diversion remain unclear and controversial.

Analysis of the data of literature suggests that there was no statistically significant difference in the rate of CSF leak with respect to the use of lumbar drains. Indeed, the overall OR of the analyzed studies is very close to the neutral effect of the LD (OR = 1.1455).

Furthermore, it has to be stressed that the articles included in this review did not report adequate relationships between pathology and CSF leak rates. All reported some aspect of the pathology included in the data but did not report pathology-specific postoperative CSF leak rates based on LD utility. This led us to conclude that the data were

TABLE X.C.2. Summary of the effect of LD after endoscopic endonasal skull-base surgery

			No LD		LD				
Study	Year	Total patients (weight)	CSF leak	No CSF leak	CSF leak	No CSF leak	Odds ratio	95% CI	*p*
Patel[1104]	2010	134 (11.85)	2	93	4	51	3.6471	0.6456–20.6011	0.143
Garcia-Navarro[234]	2013	46 (4.07)	1	14	1	30	0.4667	0.0272–8.0156	0.599
Ivan[266]	2014	98 (8.67)	3	30	8	57	1.4035	0.3466–5.6838	0.634
Zhan[1155]	2015	33 (2.92)	1	14	1	17	0.8235	0.0471–14.3901	0.894
Fraser[1153]	2016	615 (54.38)	71	397	32	115	1.5559	0.9763–2.4797	0.063
Dehdashti[241]	2016	180 (15.91)	2	89	9	80	5.0063	1.0502–23.8638	0.043
Cohen[1156]	2017	25 (2.21)	2	0	0	23	0.0043	0.0001–0.2649	0.009
Overall	–	1131 (100)	82	637	55	373	1.1455	0.7954–1.6496	0.465

CI = confidence interval; CSF = cerebrospinal fluid; LD = lumbar drainage.

insufficient to make any evidence-based comments with respect to LD usage and CSF leak rates as they correlate to pathologic diagnosis, and, given the heterogeneity, prohibited any clinically practical conclusions to be drawn.

Additionally, it should be noted that the published literature is not controlled and therefore selection bias may be significant between patients with LD and those without. More complex tumors and reconstructions are more likely to have been included in the LD group; without controlled data the net potential benefit and harm cannot be fully known. LD is still part of the toolbox for the skull-base surgeon in the postoperative period, especially for the most complex intradural defects.

However, it has to be stressed that a recent prospective and randomized control trial for lumbar drain placement after endoscopic endonasal skull-base surgery, in subjects who were at a high risk for postoperative CSF leak, highlighted that prophylactic lumbar drain placement lowered the rate of postoperative CSF leak.[1162]

Finally, it has to be highlighted that as with any procedure, lumbar drain placement has inherent complications. Most of these risks are minor and can be managed with minimal consequence to the patient. The complication rate associated with LD has been calculated as 5% for minor and 3% for major complications, according to a recent meta-analysis and systematic review that evaluated the need for lumbar drains in contemporary skull-base reconstruction after resection of skull-base tumors.[268] A common minor risk includes headache, which can occur during active CSF diversion and may require an epidural blood patch.[1163] More significant reported complications include meningitis, tension pneumocephalus, subdural hemorrhage, and uncal herniation. All of these complications are rare but potentially fatal.

- Aggregate Grade of Evidence: C (Level 4: 7 studies)
- Benefit: Provides a controlled, low-resistance egress of CSF in the immediate postoperative period
- Harm: Minor risk: Headaches; Significant risks: meningitis, tension pneumocephalus, subdural hemorrhage, uncal herniation
- Cost: Surgical procedure or intervention that may be performed in another setting, hospital stays, and management
- Benefit-Harm Assessment: Balance of benefit and harm
- Value Judgment: No statistically significant difference in the rate of overall CSF leak with respect to the use of LD after ESBS
- Policy Level: Optional use of LD after ESBS
- Intervention: Lumbar drain placement before and/or after ESBS may be used during ESBS

XI. Complications

XI.A. Risk factors for postoperative CSF leaks

CSF leaks can be broadly classified into 3 categories: traumatic, spontaneous (idiopathic), and postoperative. Management principles of traumatic and spontaneous CSF rhinorrhea are covered in detail elsewhere (Section III. Primary CSF rhinorrhea). Further breakdown, based on

characteristics of the defect, assists to delineate the management strategy of intraoperative and postoperative CSF rhinorrhea. Factors such as defect size, location (anterior fossa, posterior fossa, sella turcica, etc.), and flow (direct connection with cisterns or ventricles) warrant careful consideration.

Reconstituting a barrier between the cranial and nasal compartments is of paramount importance to avoid intracranial infectious complications such as postoperative meningitis, which has been associated with significant morbidity and mortality. In a recent systematic review, Lai et al.[1164] demonstrated that the risk of meningitis is directly related to postoperative CSF leaks with an OR of 92. In the absence of a CSF leak, the risk of meningitis and intracranial infectious complications approached zero. Failure to close a surgical skull-base defect has been associated with up to 21% incidence of meningitis along with increased rate of reoperations and major complications.[1108] Therefore, sealing of an intraoperative CSF leak is regarded as the most important component of skull-base reconstruction.

In recent decades, a wide variety of reconstructive techniques have been described, ranging from free autologous and allogenic grafts (Section X.B. Free-graft reconstruction) to pedicled locoregional flaps (Section X.A. Vascular reconstruction) and even microvascular free flaps. In addition to an appropriate reconstructive technique, the identification of patient and surgical risk factors associated with reconstructive failure are critical considerations.

Several reviews have been published over the last 5 years with respect to reconstructive approaches, risk factors, and management outcomes for skull-base defects. Thus, this EBRR focused on systematic reviews, metanalyses, and randomized controlled data, while providing a contemporary review of the newest data in skull-base reconstruction. Although there is a relative paucity of such data, all level 1, 2, or 3 articles were included, whereas level 4 data was limited to publications newer than 2012, because data prior to this would have been captured in the included systematic reviews. Following the ICAR:ESBS methodology and detailed bibliography review of included papers, 42 articles were selected for final inclusion in the EBRR. These articles represent the highest-quality and most contemporary data on risk factors and outcomes in skull-base reconstruction (see Table XI.A.1).

XI.A.1. *Preoperative risk factors influencing reconstructive outcomes*

XI.A.1.a. BMI. Spontaneous CSF rhinorrhea has been associated with intracranial hypertension. In turn, several studies have highlighted a linear correlation between obesity and intracranial hypertension.[1180] Thus, it has been speculated that obesity is a risk factor for reconstructive failure after skull-base interventions, presumably related to elevated intracranial pressures. One contemporary study, by Fraser et al.,[233] evaluated the risk of postoperative CSF leak in relation to radiographic signs of intracranial hypertension. They retrospectively evaluated the incidence of CSF leak, evaluating with respect to several preoperative risk factors in a series of 615 patients with intradural lesions. Preoperative hydrocephalus (in 35 patients) was significantly associated with postoperative CSF leaks, and many of these patients required CSF diversion with shunt placement. In addition, they looked at BMI independently, and demonstrated the incidence of CSF leak to be significantly higher in overweight and obese patients compared to those with normal BMI (18.8% vs 11.6%, $p = 0.04$).[233] Karnezis et al.[1100] retrospectively evaluated over 1000 patients with sellar lesions (craniopharyngioma and pituitary adenomas) from 7 different institutions and demonstrated a significantly higher postoperative CSF leak in patients with high BMI. A similar review of nearly 1000 patients with sellar lesions by Boling et al.[1174] similarly showed a significant increase in CSF leak rates with BMI >30. This finding has been further confirmed by Dlouhy et al.[1148] and Ivan et al.[266]. Cohen et al.[1156] also showed that elevated BMI was associated with postoperative CSF leak after resection of suprasellar meningioma in a small study. Two small retrospective studies[1115,1177] failed to clearly show this relationship; however, their combined sample size was 72 patients and included pediatric patients and highly variable pathology. One further component to this relationship between BMI and skull-base reconstruction is a potential further role for obstructive sleep apnea (OSA).[1180] However, the overlap between obesity and OSA has not been properly evaluated with respect to reconstructive failures.

- Aggregate Grade of Evidence: D (Level 4: 8 studies)
- Summary Statement: Consistent evidence demonstrates that high BMI is associated with reconstructive failure and postoperative CSF leak

XI.A.1.b. Age. Several contemporary Level 4 retrospective reviews have evaluated the effect of age on skull-base repair outcomes. Overall, results from the largest series have been mixed, with no clear evidence for age predicting postoperative leaks. Jeon et al.[1167] evaluated 95 patients with large dural defects and found no correlation between patient age and postoperative reconstructive outcome. Fraser et al.[233] reported a series including 615 patients with intradural pathology, in which the average age of patients without postoperative leaks was not statistically different from those with (50.4 vs 50.0 years; $p = 0.899$). Thawani et al.[1170] similarly demonstrated no correlation between age and postoperative leak in a retrospective review of 203 patients with sellar and parasellar lesions. Zhou et al.[240] reported similar results after reviewing their experience with nearly 500 patients with pituitary lesions. Similar results were demonstrated by Gruss et al.[1074] and Mortuaire et al.[1177]

Stapleton et al.[1115] reviewed 55 pediatric skull-base patients and showed CSF leak rates were higher in ages 5 to

TABLE XI.A.1. Risk factors for postoperative CSF leak after ESBS

Study	Year	LOE	Study design	Study groups (number)	Subsite(s) studied	Risk factors evaluated	Conclusions
Gardner[1162]	2017	1b	Randomized controlled trial	RCT on postoperative CSF leak rates or patients undergoing EEA receiving lumbar drain postoperatively (85) vs no lumbar drain (85)	Endonasal, high flow leaks (anterior fossa, posterior fossa and suprasellar)	• Lumbar drain	• Study was terminated due to significant increase in postop CSF leak rates seen in patients without prophylactic lumbar drain use • 21% Without LD, 8% with LD • Details of patient demographics, defects and reconstruction not yet published
Shriver[1165]	2016	2a	Systematic review	SR of endonasal (92) vs transoral odontoidectomy (1238)	Odontoid	• Comparative complications between transoral and transnasal resection	• 5.2% Postop CSF leak with endonasal approach—this was higher but not statistically significant compared to transoral approaches
Oakley[64]	2016	2a	EBRR	Evidence based review on management for all types of CSF leak	Endoscopic endonasal	• Prophylactic antibiotics • Reconstructive technique • Lumbar drain	• Prophylactic antibiotics do not significantly reduce meningitis rates: option (largely traumatic CSF leak patients) • Lumbar drainage does not appear to contribute to successful repair: option • Neither fat, bone grafts, or allografts show clear benefit in repair success: option • Vascularized reconstruction demonstrates improved success compared to free grafts particularly for high-flow and larger defects: option
Przybylowski[1166]	2017	2b	Cohort study	Revision pituitary surgery (50) vs matched primary pituitary surgery (46)	Sellar	• Revision surgery	• Postoperative leak rate was not significantly different between revision and primary cases (2% vs 6%) • 50% of postoperative leaks managed conservatively
Turel[463]	2016	3a	Systematic review	SR of level III and IV studies on outcomes of endoscopic tuberculum sellae meningioma resection (150)	Parasellar	• Overall postop leak rate	• 15.3% Overall CSF leak rate
Lai[1164]	2014	3a	Systematic review	SR evaluating meningitis rates and CSF leak rates after expanded approaches (2005)	Endoscopic endonasal	• Anterior vs posterior fossa • Overall leak rates and associated meningitis	• 1.8% Rate of meningitis, strongly associated with leaks • 13.4% Overall CSF leak rate • 13% of Postoperative leaks developed meningitis • No difference between anterior and posterior (clival) fossae
Soudry[242]	2014	3a	Systematic review	SR evaluating vascular vs free graft reconstruction of surgical skull-base defects (673)	Endoscopic endonasal	• Location, flow rate • Lumbar drain • Revision • Reconstructive technique	• High-flow defects had higher overall rates of postoperative CSF leak. Vascular flaps were significantly better (6% vs 18% failure) • Sellar (7%), anterior fossa (8%) and posterior fossa (20%) leak rates • 38% of postoperative leaks were managed conservatively
Clark[464]	2013	3a	Systematic review	Comparison of EEA (49) vs transcranial (412) tuberculum sella meningioma resection	Parasellar	• Overall EEA postop leak rate	• 21% Postoperative CSF leak rate

(*Continued*)

TABLE XI.A.1. Continued

Study	Year	LOE	Study design	Study groups (number)	Subsite(s) studied	Risk factors evaluated	Conclusions
Harvey[477]	2012	3a	Systematic review	SR of patients with large dural defects (endonasal craniotomy) using free (326) and vascular (283) reconstruction	Endoscopic endonasal	• Reconstructive technique	• Overall CSF leak rate 11.5% • 15.6% with free graft, 6.7% with vascularized graft • Significantly reduced postoperative CSF leak rates when using vascularized reconstruction
D'Anza[268]	2016	3a	Systemic review	SR evaluating the utility of perioperative lumbar drain in preventing postop CSF leak (376)	Endoscopic endonasal	• Preoperative or intraoperative lumbar drain	• No significant difference in postoperative CSF leak rates when utilizing lumbar drain • 15/174 (8.6%) Postoperative leak with lumbar drain, 6/202 (3.97%) without
Jeon[1167]	2017	4	Retrospective case series	High-flow leak (95)	Endoscopic endonasal	• Reconstruction type • Gender • Age • Tumor type • Location [anterior, central, clivus]	• Overall leak rate: 14.6% • Only male gender was borderline significant risk factor
Chibbaro[1168]	2017	4	Retrospective case series	Craniocervical junction decompression (14)	Odontoid	• N/A	• Overall CSF leak 0%
Pereira[258]	2017	4	Retrospective case series	Sellar tumors with various reconstructive materials and sealants (250 total)	Sella	• Lumbar drain • Duraseal and Tisseal	• Overall CSF Leak 5.2% • Lumbar drain and different sealants do not influence leak rates
Fraser[233]	2018	4	Retrospective case series	All EEA patients with intradural pathology (615)	Clivus, anterior fossa, and sellar/parasellar	• Sex, BMI, demographics • Reconstructive technique • Hydrocephalus • Lumbar drain • Tumor pathology • Year of surgery	• Defect subsite significantly affected CSF leak rate (clivus > anterior fossa > sella) • Decreased experience, elevated BMI, hydrocephalus, and free graft reconstruction all increased CSF leak rates.
Zwagerman[1169]	2018	4	Retrospective case series	Craniocervical junction decompression (34)	Odontoid	• Intraoperative and postop CSF leak	• 2/34 Patients with intraoperative leak, 1/34 with postop leak
Thawani[1170]	2017	4	Retrospective case series	Endoscopic pituitary macroadenoma complications and relationships (203)	Sellar/parasellar	• Intraoperative and postoperative CSF leak • Lumbar drain • Reconstruction method • Revision, Radiation, tumor size	• Leak rates: 40% (intraop) and 10% (postop) • Intraoperative leak strongly correlated to postop leak • Gross total resection increased risk of leak • Revision, radiation, lumbar drain and reconstructive method were not risk factors
Shikary[1171]	2017	4	Retrospective case series	Operative experience (case number) compared to outcomes and complications (202)	Sellar/parasellar	• Intraoperative and postoperative CSF leak • Sinonasal crusting and complications	• Postop CSF leak significantly reduced with increased experience (plateau around 100 cases) • Overall postoperative leak 2.9%
Zhou[240]	2017	4	Retrospective case series	Factors influencing primarily intraoperative CSF leak (492)	Sellar	• Gender, diabetes • Revision surgery • Tumor consistency, Knosp grade, and tumor type	• Revision status, tenacious adenomas, and larger adenomas (25 mm) predicted intraoperative leak

(*Continued*)

TABLE XI.A.1. Continued

Study	Year	LOE	Study design	Study groups (number)	Subsite(s) studied	Risk factors evaluated	Conclusions
Stapleton[1115]	2017	4	Retrospective case series	Pediatric patients with pituitary lesions, craniopharyngioma and chordoma (55)	Sellar/parasellar, clival	• Age, BMI • Lumbar drain • Reconstruction t type • Tumor type/location	• No significant difference was observed in any of the risk factors evaluated, including reconstruction type, BMI, or lumbar drain use
Kshettry[1172]	2016	4	Comparative retrospective case series	Endoscopic craniopharyngiomas from 2005 to 2019 (20) vs 2010 to 2015 (23)	Sellar/parasellar	• Surgical and clinical outcomes compared between early and late group	• CSF leak was significantly more common in the early cohort (40%) compared to late cohort (4%), although nasoseptal flaps were not routinely used in the early cohort.
Karnezis[1100]	2016	4	Multi-institutional retrospective case series	Endoscopic pituitary adenoma and craniopharyngiomas at multiple centers (1161)	Sellar/parasellar	• Demographics, comorbidity • Tumor extension • Reconstructive technique and lumbar drain • Intraoperative vs postoperative leak	• Patients with postoperative leak showed higher BMI (34 vs 30.1) and lower overall age (46 vs 52) • Craniopharyngiomas and prior radiation had increased postoperative leak rates • Tumors extending outside the sella and intraventricular extension demonstrated higher leak rates • Nasoseptal flaps, but not lumbar drain, decreased postoperative leak rates once intraoperative leak was identified
Shahangian[1108]	2017	4	Multi-institutional retrospective case series	Multicenter review of patients with no intraoperative leak (1533), successful repair (452), and failed repair (112)	Anterior, middle, and posterior fossa	• Factors influencing failed intraoperative leak repair • Lumbar drain, technique, tumor characteristics	• Intraoperative leak increased risk of postoperative leak • Pituitary adenoma had lowest leak repair failure, craniopharyngioma and meningioma were highest • Pedicled flaps increased repair rate, while lumbar drain did not • Significant morbidity was associated with failed repair: DVT (8%), 30 day readmission (52%), meningitis (21%) and reoperation (75%)
Fomichev[1173]	2016	4	Retrospective case series	Outcomes review on suprasellar craniopharyngiomas (136)	Parasellar	• Postoperative leak rates, rates of meningitis and factors influencing	• 8.8% Postoperative CSF leak rate • Not influenced by reconstruction type • Influenced by surgeon experience
Magro[270]	2016	4	Retrospective case series	Complications in nonfunctioning macroadenoma resection (300)	Sellar	• Overall leak rates and reconstructive techniques	• Overall postoperative CSF leak rate 2.7% • Postoperative leaks were strongly associated with intraoperative leaks and diabetes insipidus • Rigid reconstruction (titanium mesh or medpore) improved leak rates
Boling[1174]	2016	4	Retrospective case series	Multicenter review of risk factors for morbidity after endoscopic pituitary surgery (982)	Sellar/suprasellar	• Demographics, comorbidities, functional status • Revision, radiation • Tumor size and extension	• 5.5% Overall postop CSF leak • Intraventricular extension was the greatest predictor of postop leak • Younger age, BMI >30, and female gender were all associated with increased leak rates
Ivan[266]	2015	4	Retrospective case series	Patients with any tumor or pathology extending beyond the sella: risk factors for leak and meningitis (98)	Endoscopic endonasal	• Demographics, comorbidities, BMI • Revision, radiation • Tumor pathology	• Overall 11% postoperative CSF leak rate • On univariate analysis, older age, elevated BMI and combined open/endoscopic cases predicted leak

(*Continued*)

TABLE XI.A.1. Continued

Study	Year	LOE	Study design	Study groups (number)	Subsite(s) studied	Risk factors evaluated	Conclusions
							• Prophylactic lumbar drain, revision status, tumor pathology, comorbidities, and tumor extension did not affect CSF leak rates
Gruss[1074]	2014	4	Retrospective case series	Risk factors for postoperative CSF leak after nasoseptal flap (121)	Endoscopic endonasal	• Demographics, pathology • Revision, radiation • Defect size, tumor location • Lumbar drain	• Overall 8.3% postoperative leak rate • Central/clival skull-base defects, and those >2.0 cm demonstrated significantly higher leak rates • No other factors significantly predicted CSF leak
Song[1175]	2014	4	Retrospective case series	Outcomes in patients with tumors extending beyond the sella (30)	Parasellar	• Overall leak rate	• 10% Overall postoperative CSF leak rate
Paluzzi[252]	2014	4	Retrospective case series	Outcomes in pituitary adenomas (555)	Sellar	• Overall leak rate and nasoseptal vs free graft reconstruction	• 5% Overall CSF leak rate • Improved from 11.5% to 2.9% after implementing nasoseptal flap
Mascarenhas[1135]	2014	4	Retrospective case series	Outcomes in trans-planum/transtubercular high-flow CSF leak cases (122)	Parasellar	• Overall rate • Reconstruction type	• 3.1% Overall CSF leak rate • Improvement in leak rates seen with addition of nasoseptal flap
Eloy[1176]	2012	4	Retrospective case series	Comparing outcomes with nasoseptal flap reconstruction of high flow sellar (37) vs expanded (32) skull base defects	Endoscopic endonasal	• Overall rates	• 0% (sellar) and 3.1% (expanded) rates of postop CSF leak
Dlouhy[1148]	2012	4	Retrospective case series	CSF leak rates compared to BMI in EEA of sellar lesions (96)	Sellar	• BMI • Age	• 13.5% Overall postoperative CSF leak rate • Increased BMI, intraoperative leak, and younger age were statistically associated with postoperative leak • For every 5- kg/m^2 increase in BMI, odds of leak increased 1.61
Caballero[132]	2012	4	Retrospective case series	All patients undergoing endoscopic CSF leak repair (any etiology) and comparison of outcomes with (68) and without (37) lumbar drain	Endoscopic endonasal	• Lumbar drain • Etiology of leak	• No improvement in postoperative leak rates with lumbar drain • Subgroup analysis of iatrogenic leaks showed no difference in endoscopic repair outcomes with or without lumbar drain
Mortuaire[1177]	2012	4	Retrospective case series	Outcomes after endoscopic anterior and middle fossa tumor resection (17)	Endoscopic endonasal	• Age, gender • BMI • Size	• Overall rate was 29.4% • Leak rate was not influenced by age, gender, BMI or tumor size
Cavallo[1178]	2013	4	Retrospective case series	Outcomes on revision endoscopic pituitary patients (59)	Sellar	• Postoperative CSF leak rate	• Overall CSF leak rate 2.5% (comparable to general rates of primary sellar tumors)
Negm[1160]	2017	4	Retrospective case series	Outcomes in revision endoscopic pituitary patients	Sellar	• Postoperative CSF leak	• Overall CSF leak rate 2.4% (comparable to general rates of primary sellar tumors)
Cutler[1179]	2013	4	Retrospective case series	Outcomes after endoscopic transclival approaches (19)	Posterior fossa	• Postoperative CSF leak rate	• 19% (2/19) Reconstructive failure

BMI = body mass index; CSF = cerebrospinal fluid; DVT = deep vein thrombosis; EBRR = evidence-based review with recommendations; EEA = endoscopic endonasal approach; ESBS = endoscopic skull-base surgery; LD = lumbar drainage; LOE = level of evidence; RCT = randomized controlled trial; SR = systematic review.

10 years and 16+ years, but their study is limited by small sample sizes at each quartile. However, Karnezis et al.[1100] and Boling et al.[1174] demonstrated that a younger age was significantly associated with reconstructive failure, though their data set may have overlapped. This was also seen by Dlouhy et al.[1148] in a small series of 96 patients with sellar lesions. Conversely, Ivan et al.[266] showed that older patients were at increased risk of postoperative leak.

- Aggregate Grade of Evidence: D (Level 4: 11 studies)
- Summary Statement: Available evidence demonstrates no association between patient age and reconstructive failure.

XI.A.1.c. Gender. Similar to age, gender was evaluated in many of these retrospective studies with respect to the risk of postoperative CSF leak. Several studies failed to show evidence that gender influences the reconstructive outcome.[233,240,266,1170,1177] Nonetheless, pooled data from 6 institutions suggested that female gender was an independent predictor of postoperative CSF leak in a multivariate analysis.[1174] Conversely, Dlouhy et al.[1148] and Jeon et al.[1167] showed a strong trend toward the association of male gender with postoperative CSF leak.

- Aggregate Grade of Evidence: D (Level 4: 8 studies)
- Summary Statement: Collective data suggests that gender is not associated with reconstructive failure.

XI.A.1.d. Revision surgery. Several studies have evaluated the effect of revision skull-base surgery on reconstructive outcomes. Przybylowski et al.,[1166] in a comparison of 50 patients requiring revision pituitary surgery and matched for tumor characteristics and demographics to 46 patients with primary pituitary surgery, demonstrated no difference in postoperative leak rates. Furthermore, the revision surgery cohort had a lower failure rate (2% vs 6%). Other retrospective reviews also demonstrated no increased risk of postoperative CSF leak in revision surgery.[266,1074,1170,1174] However, Zhou et al.[240] retrospectively reviewed nearly 500 pituitary surgeries and showed that revision surgery was associated with increased risk of intraoperative CSF leak (30% vs 16%). Nonetheless, their data did not appear to predict postoperative leak. Cavallo et al.[1178] reviewed 59 revision pituitary endoscopic surgeries, demonstrating an overall postoperative CSF leak rate of 2.5%. Similarly, Negm et al.[1160] reported a 2.4% postoperative CSF leak rate in a retrospective review of 41 endoscopic pituitary surgeries. Although these were not directly compared to primary pituitary surgeries, these rates are well within the range of other reports addressing sellar lesions. Overall, the evidence suggests that revision surgery is not associated with an increased risk for postoperative CSF leak. One must note, however, that most of the literature pertains to pituitary surgeries.

- Aggregate Grade of Evidence: C (Level 3: 1 study, Level 4: 7 studies)
- Summary Statement: Data suggests that revision surgery involves no increased risk of postoperative CSF leak. However, the data does not account for revision cases with intraoperative leaks in which traditional reconstructive options were not available due to prior operations, and most data pertains to pituitary surgeries.

XI.A.1.e. Prior RT. A small cohort of retrospective studies evaluated the effects of RT on reconstructive outcomes. Thawani et al.,[1170] who retrospectively reviewed over 200 consecutive pituitary patients, with an overall leak rate of 10%, noted that prior irradiation was not a predictor of postoperative CSF leaks. Similarly, Ivan et al.[266] demonstrated no significant increase of postoperative CSF leak rates in patients with prior RT/chemotherapy (18% vs 10%, $p = 0.48$). Gruss et al.[1074] assessed prior irradiation in their review of 121 patients with NSF reconstruction at multiple subsites and showed no difference of CSF leak rates in the 31% of patients who had received RT ($p = 0.72$). Conversely, Karnezis et al.[1100] retrospectively studied endoscopic pituitary patients from 7 institutions (n = 1161) and demonstrated a 28% postoperative leak rate in patients with prior irradiation (albeit only 14 patients) compared to 5.6% of patients without prior irradiation ($p = 0.007$). Shahangian et al.[1108] evaluated 70 patients with prior irradiation compared to the remaining 2000 patients in their multicenter review and demonstrated a significant increase in failed CSF leak repair.

- Aggregate Grade of Evidence: D (Level 4: 5 studies)
- Summary Statement: Available data demonstrates no clear consensus, with 3 studies that were underpowered showing no effect while 2 larger multicenter studies demonstrated an increased risk of reconstructive failure in patients with previous irradiation.

XI.A.2. *Operative factors influencing reconstructive outcomes*

XI.A.2.a. Site of defect. Over the last decade, many studies, including a handful of systematic reviews and large retrospective series, have evaluated the effect of subsite on the incidence of reconstructive failure for oncologic endoscopic skull-base defects. The data from this EBRR is summarized below (see Table XI.A.2).

Sella turcica

A systematic review by Soudry et al.,[242] in 2014, nicely summarized 22 studies aggregating information on postoperative CSF leaks after ESBS. Compiled data from 104 patients suggested that sellar defects were associated with a 7% incidence of reconstructive failure. There are several contemporary retrospective studies that add further data on reconstructive outcomes. Pereira et al.[258] evaluated

TABLE XI.A.2. Modern pooled reconstructive failure rates based on site of defect

Site of defect	Total number of patients	Number of postoperative CSF leaks	% Reconstructive failure
Sella	3091	148	4.8
Parasellar (tuberculum, suprasellar)	1121	101	9
Anterior fossa (cribriform, planum)	1175	153	13
Clivus (posterior fossa)	299	57	19.1
Odontoid (craniocervical junction)	140	6	4.2

CSF = cerebrospinal fluid.

250 primarily sellar defect reconstructions using various tissue sealants and lumbar drain use. Although diversion and sealants seemed to have no impact, the overall CSF leak rate was 5.2% for primarily sellar tumors. The matched cohort by Przybylowski et al.[1166] on revision vs primary pituitary surgery showed overall leak rates of 4% (combined cohort). Dlouhy et al.[1148] demonstrated a 13.5% rate of reconstructive failure for primarily sellar pathologies. Zhou et al.[240] demonstrated a 1.3% rate of postoperative leak after sellar surgeries; however, only 17.5% of patients were noted to have intraoperative leaks. Karnezis et al.[1100] compiled a large multicenter data set on pituitary pathologies and demonstrated a 5.9% postoperative CSF leak rate. Other data highlights postoperative leaks for sellar pathologies at 2.7%,[270] 5%,[252] and 0%.[1176] The range of postoperative CSF leak of the compiled data spans from 0% to 13.5%. Aggregating this data demonstrates a 4.8% rate of postoperative CSF leak for sellar pathologies in 3091 patients. Notably, each of the above studies (excluding Eloy et al.[1176]) highlight outcomes for all sellar tumors, not just sellar tumors with intraoperative leak or dural exposure. Thawani et al.[1170] confirmed the intuitively high correlation between intraoperative and postoperative leak.

Parasellar (tuberculum, suprasellar, cavernous sinus)

There is some evidence to suggest that pituitary tumors extending beyond the sella are likely associated with a higher rate of reconstructive failure. In addition, there is some data that highlight an increased CSF leak rate in patients with parasellar meningiomas. In a recent systematic review, Turel et al.[463] identified 150 patients with tuberculum sella meningiomas with an overall postoperative CSF leak rate of 15.3%. Similarly, in another systematic review, Clark et al.[464] identified 49 patients who had undergone endoscopic resection of tuberculum meningiomas, showing a 21% rate of postoperative CSF leaks. Evaluating suprasellar craniopharyngiomas, Fomichev et al.[1173] showed an 8.8% reconstructive failure rate in 136 patients. Mascarenhas et al.[1135] looked at transplanum/transtuberculum approaches and highlighted a 3.1% postoperative CSF leak rate.

Notably, many combined sellar and parasellar lesions or pituitary tumors with extrasellar extension into a single subsite. Fraser et al.[233] combined all sellar and parasellar pathologies in their retrospective review of 259 patients showing a 10% CSF leak rate. Importantly, their study specifically excluded isolated sellar pathologies that did not have intraoperative leaks. This is a very important point, because some authors provide an overall CSF leak rate; thus including patients who never had a dural breach, which greatly diminishes the true rate of postoperative failure.

Similarly, Thawani et al.[1170] also combined all sellar and parasellar pathologies in 203 patients with an overall 40% intraoperative leak rate and 10% postoperative leak rate, whereas Shikary et al.[1171] highlighted a 2.9% postoperative CSF leak rate in 202 combined sellar/parasellar tumors. Only 15% of the tumors were isolated intrasellar lesions, which is why this data was included in the parasellar category. However, they did not distinguish between intradural or extradural tumors and only 5.5% of patients had an intraoperative leak identified. Nevertheless, aggregating this data reveals 1121 patients with a 9.0% overall reconstructive failure rate for parasellar pathologies.

Anterior cranial fossa (cribriform, planum sphenoidale)

There are few contemporary studies that highlight reconstructive outcomes specifically for anterior fossa defects, although recent systematic reviews are available. Soudry et al.'s[242] systematic review identified 142 patients with an 8% reconstructive failure rate. Lai et al.,[1164] in evaluating postoperative meningitis rates for endoscopic endonasal skull-base patients, performed a systematic review and identified 664 patients with an 11.3% rate of postoperative CSF leak. Fraser et al.'s[233] retrospective review highlighted a 20.7% leak rate in 304 anterior fossa tumors with intradural extension. Jeon et al.'s[1167] small retrospective review highlighted a 14.3% reconstructive failure rate in 14 patients with anterior fossa defects. Gruss et al.[1074] demonstrated a 4% leak rate in 51 patients. Aggregated, this data represents a 13% reconstructive failure in 1175 patients with anterior fossa defects.

Posterior cranial fossa (clivus)

Clival defects have been regarded as the highest risk location for postoperative CSF leak due in part to the fact that opening of the prepontine cistern creates high CSF flow rates and that the incidence of intradural lesions is high. In a systematic review, Lai et al.[1164] demonstrated a 16.5% reconstructive failure rate in 97 patients with clival defects. Soudry et al.'s[242] systematic review identified 4 studies with a total of 51 patients and a 20% reconstructive failure

rate. A handful of retrospective reviews have also highlighted rates of CSF leak for transclival surgeries, particularly dealing with the resection of chordomas. These studies report rates of reconstructive failure of 32.7% (17/52),[233] 15.7% (8/51),[1074] 19% (2/19),[1179] 6.7% (1/15),[1181] and 21% (3/14),[1015] respectively. Aggregating this data reveals a 19.1% rate of reconstructive failure for a total of 299 patients with clival defects.

Craniocervical junction (odontoid)
There was limited data available on the reconstructive outcomes for transodontoid approaches to the craniocervical junction. Notably, most lesions in this area are extradural (basilar invagination, rheumatoid pannus, etc.); thus, it is difficult to distinguish from the literature the true rates of reconstructive failure. Furthermore, most traditional pedicled flaps (eg, NSF, pericranial flap) do not easily reach this region. Zwagerman et al.[1169] reported on 34 patients undergoing decompression of the craniocervical junction. Only 1 patient developed a postoperative CSF leak; however, only 2 patients had intraoperative leaks. Chibbaro et al.[1168] reported on 14 patients, of whom only 2 had intraoperative leaks, both successfully repaired. Shriver et al.[1165] performed a systematic review comparing transoral to endonasal odontoidectomy. In the endonasal group, they reported a 5.2% rate of CSF leak in the 92 patients identified, although the number of patients with dural defects was not noted. Collectively, this represents a 4.2% rate of postoperative CSF leak from 3 studies and a total of 140 patients undergoing decompression of the craniocervical junction. It should be noted that postoperative CSF leaks appear to be highly contingent on a dural breach at this location, which is uncommon.

- Aggregate Grade of Evidence: C (Level 3: 4 studies, Level 4: 25 studies)
- Summary Statement: Pooled data suggests that sellar defects have the lowest rate of postoperative CSF leak (4.8%) followed by parasellar defects (9.0%) and anterior fossa defects (13.0%). Posterior fossa/clival defects are associated with the highest rate of reconstructive failure at 19% (Table XI.A.2). Each of these values is statistically significant (chi-square test).

XI.A.2.b. Surgeon experience. Not surprisingly, surgeon experience has been suggested as a significant factor contributing to the success of an endoscopic reconstruction. Most retrospective studies have demonstrated that CSF leaks are more common in the early endoscopic experience compared to later in the surgeon's career.[233,1172,1173] Shikary et al.[1171] specifically looked at operative experience and showed that CSF leak rates appeared to plateau at around 100 surgical cases of experience. Surgeon experience certainly contributes to reconstructive success, though this data is likely confounded by the development of improved reconstructive strategies (vascularized grafts, less invasive approaches, etc.) during many of these study periods.

- Aggregate Grade of Evidence: D (Level 4: 4 studies)
- Summary Statement: Increased surgeon experience likely confers improvements in skull-base reconstruction with decreased postoperative CSF leaks.

XI.A.2.c. Tumor histopathology. Heterogeneous data has been published regarding various tumor features that may influence rates of reconstructive failure. Craniopharyngiomas have been associated with increased postoperative CSF leak rates compared to pituitary adenomas in some studies,[1100,1108] but not in others.[233,266] Across expanded skull-base defects, there is no clear evidence of any specific tumor pathology predicting reconstructive failure.[233,266,1074,1115,1167] No studies have fully evaluated histology while controlling for the extent of surgical defect. For example, chordoma is primarily found in the clivus, and thus would likely have a different leak profile than pituitary adenomas.

- Aggregate Grade of Evidence: D (Level 4: 8 studies)
- Summary Statement: Aggregate data suggests there is no *independent* influence on postoperative CSF leak rates by tumor histopathology, although craniopharyngiomas demonstrate mixed results compared to pituitary adenomas. The primary challenge remains the confounding association between tumor pathology, location, and extent, for which it is very difficult to provide adequate controls.

XI.A.2.d. Intraoperative CSF flow and reconstructive technique. CSF defect flow has been repeatedly implicated as a risk factor for skull-base reconstructive failure. A high-flow leak has generally been described as any defect in direct communication with a ventricle or cistern.[1123] There was a recent EBRR published in 2015 that evaluated the utility of vascularized vs free-tissue reconstruction[64] for CSF leaks. Notably, this review covered skull-base defects of all etiologies (spontaneous, traumatic, surgical). In this EBR, Oakley et al.[64] evaluated 39 studies on a wide variety of topics. With a grade of evidence C, they concluded that large defects and high-flow leaks have the best outcome with vascular flaps and suggested high-flow intraoperative leaks were significantly more likely to develop postoperative leaks. Much of this data was summarized in a previous systematic review by Soudry et al.,[242] who specifically evaluated high-flow vs low-flow CSF leaks and endoscopic reconstructive success. In their review, they identified 74 patients with "low-flow" CSF leaks with a 93% reconstructive success overall (independent of reconstructive technique). Of the 218 patients with high-flow CSF leak, overall successful repair was 87%, and this was significantly worse when a free-tissue graft (ie, avascular) was used for reconstruction. Findings further supporting the

risk of high-flow leaks have been demonstrated in several other studies.[1073,1100,1174]

Prior to this, a landmark systematic review by Harvey et al.[477] reviewed free-tissue graft vs vascularized flap reconstruction of large dural defects in 38 studies and demonstrated that vascularized flap reconstruction was superior to free-graft reconstruction (6.7% vs 15.6% postoperative CSF leak). Although the utility of vascularized reconstruction has been generally accepted, there have been a handful of studies published since Oakley et al.'s[64] EBRR confirming this finding. Roxbury et al.[1151] retrospectively reviewed a layered free-graft reconstruction for 37 sellar defects. Although most patients were successfully reconstructed with free-tissue grafts, they noted a significant correlation between high-flow leaks (3rd ventricle or arachnoid cistern exposed) and free-graft reconstruction failure ($p = 0.01$). Fraser et al.[233] similarly noted free-graft reconstruction was associated with reconstructive failure (13.2% vs 27.9% failure). Similar findings were also noted by Karnezis et al.[1100] and Shahangian et al.[1108] Conversely, Jeon et al.[1167] evaluated 95 high-flow skull-base defects repaired with NSF (57 patients) or layered free graft (38 patients), but noted no difference in postoperative CSF leak rates. Similar findings were noted by Stapleton et al.[1115] and Thawani et al.,[1170] though most of these patients had sellar defects with likely low-flow intraoperative leaks.

- Aggregate Grade of Evidence: C (Level 2: 1 study, Level 3: 2 studies, Level 4: 6 studies)
- Benefit: Vascular skull-base reconstructions seem to improve reconstructive outcomes for high-flow or large defects. Free-graft and vascular reconstructions appear equally effective in smaller, low-flow defects.
- Harm: Potential donor-site morbidity (anosmia, crusting), increased operative time for graft elevation
- Cost: Mildly increased operative time
- Benefit-harm assessment: Benefits for vascularized reconstruction outweigh harms for high-flow or large defects.
- Value Judgment: Surgeon preference and experience
- Recommendation Level: recommend against routine use of free-graft reconstruction for large, high-flow skull-base defects. Option for reconstruction of smaller or low-flow defects.
- Intervention: Free-graft vs vascularized flap reconstruction of skull-base defects

XI.A.2.e. Lumbar drain. CSF diversion is frequently utilized in endoscopic skull-base reconstruction with lumbar drains. However, the utility of lumbar drains in preventing postoperative CSF leaks has been questioned by multiple studies. In Oakley et al.'s[64] EBRR, 19 studies on the utility of LD were reviewed, including a meta-analysis in 2000[52] and a randomized controlled trial in 2013.[136] All of these studies, as well as nearly a dozen additional retrospective studies, showed that routine use of lumbar drains did not reduce postoperative CSF leak rates.[64] However, it should be noted that these studies largely included CSF leaks from a wide variety of etiologies, including spontaneous and traumatic leaks. Notably, there was some evidence of benefit in patients with intracranial hypertension. Since this publication, D'Anza et al.[268] performed a meta-analysis specifically evaluating reconstructive success after endoscopic skull-base tumor resection. They identified 5 papers with a total of 376 patients, and demonstrated no difference in patients utilizing preoperative/intraoperative lumbar drain (8.6% postoperative leak rate) compared to those in whom no lumbar drain was utilized (4.0%). Although the data trended toward worse reconstructive outcomes with lumbar drain use, it is worth noting that these are retrospective reviews, likely with significant bias. Presumably, lumbar drains were likely used more frequently when the surgical team was more concerned about postoperative leak (ie, inadequate reconstruction or high-risk patients). A handful of recent retrospective series were also identified since this meta-analysis, all of which showed no influence on postoperative CSF leak rates with the use of perioperative lumbar drain.[233,258,1100,1115,1170]

In spite of the seemingly overwhelming evidence suggesting prophylactic LD does not reduce postoperative CSF leak rates, a recent randomized controlled trial was performed for ESBS with 170 patients enrolled (85 with prophylactic lumbar drain).[233] The study was terminated early due to a significant increase in postoperative CSF leak rates when LD was not utilized. This data has not been fully published, and thus the details of the study parameters are not disclosed. However, this study is unique in that it only included patients with high-flow CSF leaks following skull-base tumor resection. Cohen et al.[1156] also recently highlighted increased reconstructive failure rates in patients who did not receive prophylactic LD for suprasellar meningioma resection. Both reconstructive failures were obese and could not receive LD, and both developed postoperative leaks, while the other 23 patients received LD and had no leaks.

- Aggregate Grade of Evidence: C (Level 1: 1 study; Level 2: 3 studies; Level 4: 7 studies)
- Benefit: Diversion of CSF decreases pressure on the skull-base reconstruction[1182,1183]
- Harm: Complications associated with LD (3% major, 5% minor); including meningitis, headache, additional wound, pneumocephalus, or epidural hematoma.[1184]
- Cost: Increased cost due to prolonged length of stay in patients with LD
- Benefit-harm Assessment: No evidence of benefit in published data with significant associated risks of complications related to LD. However, unpublished data on recent RCT may provide level 1 evidence that lumbar drains do reduce CSF leak rates in selected high-flow leak situations.
- Value Judgement: None
- Recommendation Level: Recommend against *routine* use of LD for skull-base reconstruction, particularly in smaller, low-flow defects. It remains an option in

conditions including large defects, high-flow defects, and revision repairs. Randomized data, when published, may provide more information.
- Intervention: Prophylactic use of LD for CSF diversion after skull-base resection and reconstruction.

XI.A.3. *Management of postoperative CSF leak*

Despite the constellation of data collected, there have been limited reports properly summarizing the management strategies for patients who do develop postoperative CSF leaks. The primary strategy distinction is deciding when to pursue a conservative management strategy (lumbar drain, bed rest, etc.) vs operative re-exploration and revision repair. Soudry et al.'s[242] systematic review highlighted that 38% of patients in the studies they reviewed were managed conservatively, while 62% were taken back to the operating room. Przybylowski et al.[1166] noted 2 of their 4 patients with postoperative leaks were managed conservatively. Although both studies demonstrate that conservative management can be successful, they do not define what factors influence that decision. There were no studies identified in this review that highlight when to pursue conservative management vs operative re-exploration.

- Aggregate Grade of Evidence: Very limited evidence exists and therefore no evidence-based recommendation can be made. However, early re-exploration could be considered to prevent further infectious complications such as meningitis.

XI.B. Management of carotid artery injury

A potentially devastating complication in ESBS is injury of the ICA.[1185,1186] Fortunately, ICA injury is relatively uncommon and large series of EEAs suggest an incidence of 0.016% to 1%.[221,1187–1191] However, the mortality from endonasal ICA injury may reach up to 10%, emphasizing the importance of an effective management strategy.[1192] Although open microscopic skull-base approaches may allow direct repair, the restricted endonasal surgical corridor requires alternative strategies for repair and definitive management.[1185,1193–1195] Given that ICA injury is a relatively rare complication in ESBS, the development of an evidence-based treatment strategy is difficult. In this section, we discuss the available literature regarding injury of the ICA in endoscopic endonasal surgery to provide the overall level of evidence regarding its management.

The general strategies employed for the management of ICA injury consist of recognizing that an ICA injury has occurred, determining the location of injury, controlling the hemorrhage within the surgical field by local packing and compression, endovascular repair or vessel occlusion, and/or vascular bypass.[1185,1186,1192,1195,1196] Reported injuries to the ICA have mainly occurred during the stages of cranial base exposure and tumor resection, and to a lesser degree in the final stages of hemostasis and cranial base repair.[1192] Among the series of functional endoscopic sinus cases, ICA injury most commonly occurred during sphenoidotomy procedures.[1192] Sudden high-flow arterial bleeding should raise concern of injury to the ICA.[1195] Identification of the injury site may be a challenge given the constricted surgical space and the need to keep the endoscope clean to maintain adequate visualization. Multiple retrospective studies have recommended a 2-surgeon approach because it may be beneficial to introduce an additional suction into the field, diverting blood from the endoscope and maintaining visualization.[1188,1197,1198] The most commonly reported ICA segment injured is the C4 (parasellar) segment; however, the C2 (petrous), C3 (paraclival), and C5 (paraclinoidal) segments have also been reported.[1192] The left ICA may be more commonly injured, possibly because most surgeons are right-handed.[1192] In cases where the instrument that caused the injury was reported, multiple instruments have been implicated, including the microdebrider, Kerrison punch, drills, Blakesley and Thru-Cut forceps, ring curette, and suction instruments such as ultrasonic aspirator.[1192,1199]

Once the injury site has been identified, initial control of the hemorrhage is attempted with packing and compression.[1185,1192,1195] Packing materials reported for initial hemostatic control include gauze, oxidized cellulose ([Surgicel™ (Ethicon, Inc.; Somerville, NJ)], cottonoids/cotton strips, Surgifoam™ (Ethicon, Inc.; Somerville, NJ), and Merocel (Medtronic Inc., Minneapolis, MN) nasal packs with balloon tamponade.[1188,1190,1197,1200,1201] The most frequently reported packing material is gauze.[1192,1198] These initial methods are usually geared toward providing temporary hemostasis while enabling subsequent implementation of more permanent hemostatic measures. Weidenbecher et al.[1202] also recommended the use of bilateral common carotid compression during initial hemostasis. Other authors have reported achievement of direct intraoperative permanent hemostasis using bipolar cautery, endoscopic aneurysm clip placement, or packing with muscle fascia graft.[1185,1188,1195,1198,1203] Bipolar cautery and endoscopic aneurysm clip placement have both been used for either sealing the injury defect or for intraoperative sacrifice of the ICA.[227,965,1181,1188] The use of crushed muscle graft has been advocated by several authors for hemostasis.[1188,1198,1202,1203] Reported sites for muscle harvest include the abdominal rectus, sternocleidomastoid, or temporalis muscle.[1194]

While the surgeons obtain hemostasis, authors recommended assistance from anesthesia with resuscitation of the patient, maintaining normotension, or even controlled hypertension, to maintain cerebral perfusion.[1185,1195] In addition, adenosine-induced cardiac arrest can be used as it is in aneurysm surgery for brief control of hemorrhage.[1188] However, outcomes of these maneuvers have not been specifically evaluated regarding with endonasal ICA injury. Administration of heparin to avoid cerebral embolic events during vessel manipulation has been mentioned, but there is no literature to support this intervention.[1185,1195] The use

of somatosensory evoked potentials and electroencephalography monitoring to help guide whether the ICA can be sacrificed intraoperatively without stroke-related morbidity has been suggested.[1188,1194,1195]

Because there is limited clinical data on endoscopic ICA injury repair in humans, several authors have developed animal models as a surrogate to assess efficacy of intraoperative repair methods.[1186,1198,1204–1207] Valentine used a sheep model to compare crushed muscle with other hemostatic techniques and found muscle superior to oxidized cellulose Floseal® (Baxter, Deerfield, IL) and Chitosan gel (Surgi Shield; D. med, Seoul, Korea).[1186,1204] The parameters they evaluated were the rate of reaching primary hemostasis, blood loss, and animal survival.[1205] In that study, they also showed vascular control with the use of U-clip anastomotic devices; however, these are no longer commercially available. In a subsequent study utilizing the sheep model, Padhye et al.[1206] compared crushed muscle with bipolar cautery and aneurysm clip application. They showed both the muscle and endoscopic clip to be superior to bipolar coagulation in achieving primary and long-term hemostasis. There was a lower rate of pseudoaneurysm formation with clipping, but carotid patency rates were superior with crushed muscle. Using the same study design, Padhye et al.[1207] later compared the Anastoclip Device with the prior mentioned methods and found decreased blood loss and time to hemostasis with good rates of ICA patency. Endoscopic clip placement requires significant exposure of the injured carotid segment, which may not always be feasible and requires considerable technical skill, likely the reason that use of other packing methods is more commonly reported.[1185,1188,1192]

Whether temporary or permanent repair was attempted endonasally, most reported cases subsequently underwent catheter-angiography.[1188,1190–1192,1195,1198,1202] Angiography was used to determine the degree of injury, adequacy of repair, and determine need for subsequent endovascular or open repair.[1188,1192,1208,1209] Although some reported cases showed adequate ICA integrity after endonasal repair, angiography demonstrated a significant rate of ICA pathology.[1186,1192 1209] The most common pathology reported as a consequence of endoscopic ICA injury was pseudoaneurysm formation. Additional vascular abnormalities identified angiographically included carotid cavernous fistula, ICA occlusion, active extravasation, stenosis, dissection, and middle cerebral artery (MCA) thromboembolus requiring thrombectomy[1192,1208,1209] or heparinization.[1188]

The methods reported for endovascular repair are vessel sacrifice, lesion embolization, and endoluminal reconstruction.[1185,1188,1192,1209] Although many authors recommend preservation of the ICA, in most reports the ICA was sacrificed with accepted risk of neurological sequelae.[1192,1209] In their review, Sylvester et al.[1209] found a 21.7% risk of permanent neurological deficit following ICA endovascular sacrifice. Assessment of collateral flow by angiogram or with balloon test occlusion (BTO) is recommended. However, there is a reported 0.4% stroke related to these procedures and 4.7% incidence of stroke despite passing these tests.[1209,1210] Several authors have reported attempts at embolizing the pseudoaneurysm with or without the use of a stent, as well as endoluminal reconstruction with covered stents or flow diverters; however, these procedures are complicated by technical difficulties including the tortuosity of the ICA segments involved, and the requirement for antiplatelet agents postoperatively in the setting of acute hemorrhage.[1198,1209] For cases with poor collateral circulation that were not suitable for a vessel-preserving endovascular repair, extracranial-to-intracranial bypass has been reported as an option. Rangel-Castilla et al.[1196] reported a series of 4 patients with ICA injury during endoscopic surgery who were treated with ICA bypass and achieved a modified Rankin scale score of either 0 or 1 at time of follow-up. Significant questions remain, however, about the practicality of efficient bypass in the setting of active ischemia.

Although delayed postoperative vascular imaging is typically recommended for follow-up after ICA injury, the exact modality and timing of the imaging is inconsistent among studies.[1185,1186,1188,1192,1194,1198,1199,1211] Postoperative vascular studies were mostly recommended for cases without sacrifice of the ICA or negative initial cerebral angiogram.[1198] There have been reports of delayed development of ICA pathology and these were usually reported within 1 month after initial injury, suggesting close follow-up is warranted during the first month despite an initial negative angiogram.[1190,1198,1200,1201,1212] For cases where a follow-up imaging modality was specified, a variety of modalities including angiography, CT angiography, and MR angiography have all been reported.[1188,1192] Gardner et al.[1188] recommended a formal angiogram within 1 week, followed by CT angiogram or formal angiogram in the subsequent month and then within 3 to 6 months. Padhye et al.[1198] recommended a 1-week postoperative angiogram, then repeated angiograms at 6 weeks, 3 months, and 1 year. Buerke et al.[1211] advocated the use of MR angiography in the postoperative period as a noninvasive method of delayed vascular assessment.

Given the potential for debilitating outcome and limited means for repair, it is paramount to avoid ICA injury during endonasal procedures. Knowledge of anatomical landmarks, recognition of risk factors, increased surgeon experience, and intraoperative strategies may help avoid ICA injury.[227,1198] Dehiscent bone over the ICA is found in 4% to 22% of anatomic specimens, and in 88% of cases the thin bony wall overlying the ICA is <0.5 mm thick.[1202,1213] Morphometric studies have shown anatomical landmarks correlating with segments of the ICA.[1185,1195,1214] An anatomic and radiographic study by Fernandez-Miranda et al.[1215] showed that intrasphenoidal septations most commonly attach to the ICA canal. Although there has not been any clinical study directly correlating sinus or ICA anatomy with risk of ICA injury, some endonasal surgical approaches may carry increased risk. In the series by Gardner et al.,[1188] the rates of ICA injury

TABLE XI.B.1. Evidence for the management of carotid artery injury in ESBS—clinical

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Romero[1199]	2017	4	Case series	ICA injury (1) in series of 800 cases of ESBS	Management and outcome of vascular injury	Vessel sacrifice most reliable method of definitive repair with low risk of stroke.
Chin[1192]	2016	4	SR of case series/reports	ICA injury in endoscopic endonasal surgery	Relevant patient, surgical, hemostasis, and outcome variables	Incidence of reported cases of ICA injury is low. Left-sided injuries to the cavernous segment occurred more frequently. No consensus regarding intraoperative image guidance and postoperative follow-up could be made.
Dolati[1217]	2016	4	Case series	25 Patients with pituitary tumor that underwent transsphenoidal resection with 3-T segmented MRI for navigation.	Correlation with intraoperative confirmation with navigation wand and Doppler	Image-based preoperative vascular and neural element segmentation can potentially assist less-experienced neurosurgeons in preventing vascular and neural injury during TSS.
Sylvester[1209]	2016	4	Case series	ICA injury out of 576 transsphenoidal pituitary cases that underwent endovascular treatment with literature review.	Hemostasis and outcome of different endovascular strategies	Endovascular treatments of vessel sacrifice, coil embolization, and endoluminal reconstruction offer a tailored approach to ICA injury. Vessel preservation should always be considered. Endovascular treatment algorithm presented.
Zhang[1191]	2016	4	Case series	(2) ICA Injury in ESBS 2978 tumor + 8863 inflammatory	Hemostasis and outcome after injury	ICA injury infrequent. Oxidized cellulose as option for hemostasis as its easily accessible and pliable. Further reconstruction with fascia lata and fat graft.
Padhye[1203]	2015	4	Case series	(8) ICA injury in ESBS with Vascular Injuries Workshop–trained surgeons	Hemostasis and outcome after injury	Vascular Injury Workshop–trained surgeons were able to control ICA injury without morbidity/mortality of patients. Muscle graft effective for primary hemostasis; low risk of delayed ICA pathology
Little[1181]	2014	4	Case series	49 Patients that underwent 55 transclival surgeries; 1 ICA injury	Outcomes after transclival approaches	Important to consider size and lateral extension of the lesion relative to the ICA, preoperative surgical intent, and an experienced surgical and interventional team. One ICA injury in 55 procedures (rate of 2% of transclival approaches)
Rangel-Castilla[1196]	2014	4	Case series	(4) Endoscopic ICA Injuries with final repair with EC-IC bypass	Outcome with modified Rankin Scale Score of 0-1; patency of bypasses	In cases where endovascular means of ICA repair not feasible, EC-IC bypass is an option.
Kalinin[1190]	2013	4	Case series	(4) ICA injury in ESBS out of 3000 patient with adenomas	Hemostasis and outcome after injury	ICA injury is rare but potentially fatal. Ability to identify midline using anatomical structures is important. Endovascular repair is dependent on good collateral flow and tortuosity of ICA
Gardner[1188]	2013	4	Case series	(7) ICA injury out of 2015 ESBS	Hemostasis and outcome after injury	ICA injury infrequent. Vessel preservation difficult. Chondroid tumors higher risk.

(*Continued*)

TABLE XI.B.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Berker[221]	2012	4	Case series	570 Patients and 624 ESBS; (1) ICA injury patient	Outcomes and complications after endoscopic pituitary surgery	Low rate of complications for endoscopic pituitary surgery
Gondim[1189]	2011	4	Case series	301 Patients endoscopic resection of pituitary adenomas; 3 ICA injuries	Outcomes after procedure	Cases of parasellar extension pose higher risk of ICA injury. Use of intraoperative Doppler and neuronavigation recommended, especially for redo-surgery.
Kassam[227]	2011	4	Case series	800 Patients that underwent ESBS; 2 ICA injuries reported	Outcomes in large series of ESBS	ICA injury risk not a contraindication for ESBS. Incremental experience in ESBS may help avoid injury as well as improve its management.
Zada[1216]	2010	4	Case series	169 Patients with acromegaly; 1 ICA injury	Outcomes and complications after endoscopic pituitary surgery	Acromegalics have anatomical changes in the caliber and tortuosity of the ICA that may increase risk of injury in endoscopic surgery
Liu and Di[1218]	2009	4	Case series	10 Patients that underwent endoscopic biopsy cavernous sinus lesions; 1 ICA injury	Outcomes after procedure	Intraoperative control may be achieved with placement of clips proximal and distal to rupture site. Consider covering exposed ICA with fat to avoid post-operative rupture.
Dusick[1219]	2007	4	Case series	114 Procedures (2 ICA injuries) undergoing ESBS without use of Doppler vs 511 procedures with use of Doppler	Vascular injury with or without use of Doppler	Cavernous carotid localization with Doppler probe before dural opening and dural opening with hook-blade can help minimize ICA injury risk.
Weidenbecher[1202]	2005	4	Case series	(4) ICA injuries in functional ESS	Hemostasis and outcomes after injury	Bilateral common carotid compression may control hemorrhage. Use of muscle graft with tamponade for primary hemostasis
Cavallo[1187]	2004	4	Case series	250 Patients with vascular complications after ESBS; 1 ICA injury	Outcomes after vascular complications	Neurosurgeons that perform endoscopic pituitary surgery should have interventional radiology as modern use of endovascular techniques may control hemorrhagic complications less invasively.
Hudgins[1220]	1992	4	Case series	150 Patients that underwent FESS; 1 ICA injury	Outcomes after FESS complications.	Radiographic evaluation of severe intraoperative or postoperative bleeding in sphenoid surgery should include angiography and should be prepared for BTO.
AlQahtani[1185]	2016	5	Expert opinion	None		Preoperative planning as well as execution of an effective plan of action with multidisciplinary team is crucial to minimize consequences. After hemorrhage control, endovascular evaluation for permanent repair as needed, followed by close clinical and radiographic monitoring to prevent early or late complications is recommended.

(*Continued*)

TABLE XI.B.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Gardner[1194]	2016	5	Expert opinion	None		Knowledge of ICA landmarks, use of intraoperative vascular evaluation, and recognizing tumors that pose greater risk helps to avoid injury. Treatment algorithm presented.
Cobb[1221]	2015	5	Case report	1. ICA Injury in endoscopic endonasal resection of osteoblastoma	Hemostasis and outcome after injury	Balloon-assisted repair of lacerated ICA
Mortimer[1212]	2015	5	Case series	1. ICA injury in ESBS in acromegalic patient	Outcome and endovascular repair after injury	Normal angiogram soon after transsphenoidal surgery complicated by ICA injury does not exclude subsequent development of pseudoaneurysm.
Nerva[1222]	2015	5	Case series	2. ICA injuries in ESBS treated with flow diverter	ICA repair and outcome with Modified Rankin Scale Score	Flow diverters are useful for repair of iatrogenic pseudoaneurysm but should weigh the risk of dual antiplatelet therapy.
Smith[1223]	2015	5	Case series	1. ICA injury in Series of ACTH-positive staining tumors	Outcome after resection and injury	ICA injury is a potential yet uncommon complication in ACTH-secreting adenomas
Dedmon[1224]	2014	5	Case report	1. Patient with endonasal extruded coils after embolization of pseudoaneurysm due to ICA injury in ESS	Outcome after repair	Complications of iatrogenic ICA injury endovascular repair can happen thus patients should be carefully monitored.
Padhye[1198]	2014	5	Expert opinion	None		Optimal preoperative assessment with preoperative planning, skilled operative maneuvers to achieve hemostasis, and postoperative assessments and comprehensive management of potential complications will result in the best possible outcome for the patient.
Shakir[1225]	2014	5	Case report	1. ICA injury in ESBS treated with flow diverter and covered stent	Hemostasis and outcome after injury and repair	Successful use of combined covered stent and flow diverters to treat active ICA injury.
Iacoangeli[1197]	2013	5	Case report	1. ICA injury in ESBS for giant cell tumor	Hemostasis and outcome after injury	Control of ICA bleeding may be challenging with endoscope. Significant experience, coordination, teamwork, and surgical tricks needed to maintain surgical view and hemostasis.
Golinelli[1201]	2012	5	Case series	2. ICA injuries in ESS	Hemostasis and outcome after injury	Angiography recommended if profuse bleeding in sphenoid surgery. Noninvasive delayed radiological follow-up recommended to identify subsequent ICA pseudoaneurysm.
Al Sheibani[965]	2011	5	Case series	20 Patients that underwent endoscopic transpterygoid nasopharyngectomy; 1 ICA injury	Hemostasis and outcome after injury and approach	Control with endoscopic clip and final repair with endovascular coils.
Valentine[1204]	2011	5	Expert opinion	None		Recognition of patient risk factors may prevent ICA injury. A 2-surgeon is more effective for hemorrhage control. Packing with attempt to not occlude the ICA with multiple agents and endovascular treatments are available. It is important to recognize ICA injuries may manifest in delayed fashion.

(*Continued*)

TABLE XI.B.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Pawar[1226]	2010	5	Case report	1. Delayed ICA injury in patient with sphenoid mucocele	Hemostasis and outcome after repair of injury	Proximity of ICA place them at risk for injury in sphenoid mucoceles. Suspect ICA injury if delayed epitasis in sphenoid mucocele.
Solares[1195]	2010	5	Expert opinion	None		Training in ESBS as well as knowledge of ICA anatomy from endonasal perspective help prevent its injury.
Biswas[1200]	2009	5	Case report	1. ICA injury in recurrent sinus malignant melanoma	Hemostasis and outcome after injury	Suspect ICA injury if profuse bleeding seen during sphenoid sinus surgery. Early diagnosis and treatment to expedite endovascular intervention.
Cathelinaud[1227]	2008	5	Case report	1. ICA injury in functional ESS	Hemostasis and outcome after injury	ICA injury success relies on close collaboration between anesthesiologist, ENT and IR.
Buerke[1211]	2007	5	Case report	1. ICA injury in functional ESS	Control and repair of ICA injury	3D TOF MRA as tool for routine follow up in suspicion of ICA injury
Pepper[1228]	2007	5	Case series	1. ICA injury in ESS	Hemostasis and outcomes	Having a treatment algorithm involving cooperation between ER physicians, ENT, and IRs optimizes the treatment and efficiency of hemostasis of ICA injury
Koitschev[1229]	2006	5	Case series	1. ICA injury in ESS	Hemostasis and outcomes after injury	Immediate interdisciplinary management by the otolaryngologist and interventional radiologist is critical for improved outcome. Endovascular occlusion of the source of bleeding is the treatment of choice, with coils or balloons.
Cappabianca[1230]	2001	5	Case report	ICA injury in acromegalic patient	Hemostasis and outcomes after injury	Endovascular treatment can be preferred to direct surgical approach due to lower morbidity and mortality with attempt for complete exclusion of lesion while preserving the ICA.
Park[1231]	1998	5	Case report	ICA injury in FESS	Hemostasis and outcomes after injury	If no good primary control and good collateral flow on BTO, ICA sacrifice with detachable coils as means for control
Isenberg[1232]	1994	5	Case report	ICA injury in FESS	Hemostasis and outcomes after injury	If no good primary control and good collateral flow on BTO, ICA sacrifice with detachable balloons may provide final repair with low risk of major neurological deficit.

ACTH = adrenocorticotropic hormone; BTO = balloon test occlusion; EC-IC = extracranial–intracranial; ENT = ear-nose-throat; ER = emergency room; ESBS = endoscopic skull-base surgery; ESS = endoscopic sinus surgery; FESS = functional endoscopic sinus surgery; ICA = internal carotid artery; IR = interventional radiologist; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; SR = systematic review; TOF = time-of-flight; TSS = transsphenoidal surgery.

were subdivided by approach, revealing 0.3% (3/1004 cases) for transsellar approaches and 0.9% (4/534 cases) for transclival/transpterygoid approaches. Although the rates of ICA injury based on approach were not found to be statistically significant in their study, the authors suggest that approaches approximating the paraclival and petrous segments of the ICA carry a higher risk of injury. Additionally, the risk of ICA injury may also be related to the pathology treated using these approaches. When analyzing pathology types, they also found higher incidence of ICA injury with chondroid tumors, reaching 2% (3/142 cases).[1188] Other pathologies reported as having an increased risk of ICA injury are GH-secreting pituitary adenomas, because they may have tortuous ICA and complex sphenoid sinus anatomy.[1216] Previous surgery, previous RT, chemotherapy, and prior treatment with bromocriptine for pituitary tumors have also been linked to ICA injury.[1185,1188,1198] Identifying cases that may represent a higher risk of ICA injury may guide the surgeons to establish goals and strategies of surgery preoperatively or utilize additional tests, such as BTO or vascular imaging studies to aid during surgery.[1185,1188,1194,1209] (see Table XI.B.1).

Intraoperative adjuncts reported to avoid ICA injury include intraoperative neuronavigation and micro-Doppler ultrasound.[1189,1202,1219] However, their use has been inconsistently described in published cases of ICA injury. In

their systematic review, Chin et al.[1192] showed that the use of intraoperative image guidance was rarely reported. In the series by Gondim et al.,[1189] the authors reported that all 3 of their cases of carotid injury occurred before their routine use of Doppler and intraoperative neuronavigation. In their series of 631 procedures, Dusick et al.[1219] report that their 2 carotid injuries occurred prior to use of micro-Doppler. A prospective validation study by Dolati et al.[1217] showed correlation of ICA location confirmed by micro-Doppler with vascular segmentation on preoperative MRI used for intraoperative navigation. In their series of 25 patients, no injury was reported. Although the use of both intraoperative neuronavigation and micro-Doppler may be beneficial to avoid ICA injury and is recommended by many experts, no direct correlation with their use and a decreased risk of ICA injury can be made.

In addition to avoidance of ICA injury, an increased preparedness for its management may improve outcomes after a carotid artery injury.[1198] To achieve this goal, several endonasal carotid injury models have been developed.[1204,1233–1236] These include the previously mentioned sheep model, perfusion-based cadaveric models, and noncadaveric synthetic models. Studies assessing the surgeon's feeling of preparedness, timing of vascular control, and volume of blood loss after a workshop of carotid artery injury indicate that these models may help to more effectively manage this rare complication (see Table XI.B.2).

Only 1 clinical study has suggested improved control of ICA injury following the use of simulator models.[1203]

- Aggregate Grade of Evidence: C (Level 4: 19 studies; Level 5: 23 studies)

XI.C. Nasal morbidity following ESBS

Improved, more prominent utilization of endoscopic techniques has permitted safe and minimally invasive access to skull-base pathologies. However, adequate use of the endoscopic transnasal corridor often involves wide access to accommodate the endoscope and multiple instruments simultaneously and to fully access the entire ventral skull-base. To this end, normal, nonpathologic anatomic structures, such as the inferior, middle, and superior turbinates, the nasal septum, and the paranasal sinuses, at times bilaterally, are dissected or resected to provide access.

As a result of this, significant sinonasal morbidity may result from endonasal management of skull-base pathologies, creating a new problem to avoid the previous transcranial ones. Furthermore, many patients require adjunctive therapies such as chemotherapy and RT, which additionally produce morbid changes of the sinonasal tract, a full discussion of which is beyond the scope of this section. Focusing on surgery-dependent sequelae, negative effects include the realms of olfaction, nasal crusting and obstruction, nasal structure, and mucosal function.

XI.C.1. *Olfaction outcomes following ESBS*

Especially with transnasal approaches to reach suprasellar or anterior cranial base pathologies, as well as those requiring harvest of a pedicled NSF, nasal mucosa containing olfactory epithelium is frequently at risk for disruption or thermal injury. The first report of olfactory loss following ESBS came from Rotenburg et al.,[1133] where a cohort of 17 patients all reported subjective smell loss (and tested objectively for it) postoperatively. One systematic review estimates olfactory dysfunction to be present in 26.7% of cases.[1238] A randomized controlled study of 20 patients by Tam et al.[1102] demonstrated diminished olfaction following endoscopic pituitary surgery, with worse olfaction in those patients who were reconstructed with an NSF. Also, in a retrospective review of 226 patients who underwent endoscopic transnasal, transsphenoidal surgery involving posterior septectomy and NSF use, Kim et al.[1239] found that patients experienced both objective and subjective olfactory dysfunction at 6 months postoperatively. Table XIC.1 reviews the evidence surrounding olfactory outcomes following ESBS.

The recommendations below have been thoroughly reviewed by Greig et al.,[1101] who have composed the only high-level systematic review on the topic.

Several technical modifications have been proposed for smell preservation in endoscopic sinus and skull-base surgery. Perhaps the most commonly utilized is resection of only the inferior one-half to one-third of the superior turbinate when accessing the natural ostium of the sphenoid sinus, which generally has a low probability of containing olfactory neurons.[1251] A similar technique involves "straddling" the superior turbinate, moving it laterally and medially but preserving its natural structure, when accessing the sphenoid sinus.[1252] More recently, Harvey et al.[1243] described a distinct appearance of the "olfactory strip" located on the nasal septum opposite the superior turbinate and the superior half of the middle turbinate, and excluding this portion of the septal mucosa from the NSF resulted in smell preservation in a cohort of 98 patients. Upadhyay et al.[1246] further explored this modification in a study involving 42 patients who had purposeful sparing of the olfactory strip, and found that smell preservation was universal, though more pronounced in those patients reconstructed without an NSF.

If possible, a unilateral approach with preservation of the septal mucosa on the contralateral side can be considered. Sowerby et al.[1249] reported no changes in olfactory function following unilateral endoscopic transsellar approach in a cohort of 22 patients. Tajudeen et al.[843] reported a series of 14 patients with unilateral esthesioneuroblastomas who underwent unilateral resection followed by radiation therapy, with 6 (43%) patients having some smell preservation following treatment completion. Youssef et al.[487] reported a similar outcome in a patient who had an olfactory groove meningioma. The same can be accomplished through a transseptal approach, which Hong et al.[1245]

TABLE XI.B.2. Evidence for the management of carotid artery injury in ESBS—non-clinical

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Muto[1234]	2017	N/A	Synthetic carotid injury model	5 Surgical trainees	Self-assessment questionnaires on surgical skills and self-confidence	Model eliminates ethical, legal, religious, and biohazard problems associated with animal and cadaveric models.
Pacca[1236]	2017	N/A	5 Perfused cadaveric heads	Residents and fellows under senior surgeon guidance	6-Point questionnaire after simulation.	Live cadaver models may provide real life-like experience with major vessel injury and improve current training for management of this form of injury.
Ciporen[1233]	2017	N/A	Cadaveric perfused model	Early (3) and second (7) learner groups in simulated ICA injury	Simulation assessment, blood loss and performance metric data	Perfusion model helped learners optimized technique for ICA injury management.
Padhye[1207]	2015	N/A	Live sheep model	8 Sheep ICA linear carotid injuries treated with AnastoClip device	Primary hemostasis, procedure time, blood loss, pseudoaneurysm formation, patency on follow-up MRI	Direct vessel closure as an effective option for control of ICA injury, allowing normal carotid flow and low risk of pseudoaneurysm formation.
Padhye[1206]	2014	N/A	Live sheep model	27 Sheep with standardized ICA injuries treated with bipolar, muscle, and aneurysm clip.	Primary and time to hemostasis, blood loss, pseudoaneurysm, carotid patency	Crushed muscle patch and aneurysm clip are viable options with short and long-term benefits.
Pham[1235]	2014	N/A	8 Perfused cadaveric heads	Neurosurgical and junior faculty trainees.	5-Point questionnaire to assess pretraining and posttraining confidence scores	Strategies and techniques for rapid hemostasis, endoscope manipulation, suction, and packing can be rehearsed with this model.
Speelman[1237]	2013	N/A	Live porcine model	Jugular and carotid progressively larger standardized injuries in 7 pigs	Hemostasis	Porcine model effective in simulating surgical scenario. Crushed muscle patch effective for arterial injuries of 3 mm and aneurysm clips of 5 mm and on.
Valentine[1205]	2011	N/A	Live sheep model	20 Sheep with standardized ICA injuries treated with 5 different hemostatic techniques	Time to hemostasis, time MAP >55 mmHg, blood loss, and survival time	Muscle patch and U-Clip anastomotic device significantly improved survival, reduced blood loss, and achieved primary hemostasis with vascular patency
Valentine and Wormald[1204]	2011	N/A	Live sheep model	Anesthetized live sheep	Physiologic parameters during standardized injury to carotid	Model replicates the endoscopic surgical field of an ICA injury with potential to train surgeons.
Valentine and Wormald[1186]	2011	N/A	Live sheep model	Anesthetized live sheep; 42 endoscopic carotid and 25 venous injuries	Obtaining surgical field control.	Controlling the field relies on surgical team cooperation, careful endoscope maneuvering, and appropriate suction selection.

ICA = internal carotid artery; ESS = endoscopic sinus surgery; FESS = functional endoscopic sinus surgery; LOE = level of evidence; MAP = mean arterial pressure; MRI = magnetic resonance imaging; N/A = not applicable.

TABLE XIC.1. Evidence surrounding olfactory outcomes following ESBS

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Tam[1102]	2013	1b	Randomized controlled study	20 Patients underwent endoscopic TNTS for pituitary lesions, of which 10 were reconstructed using nasoseptal flap and the other 10 with synthetic/non-autologous materials	Comparison of preoperative and 6 months postoperative SIT scores	Both groups experienced smell dysfunction postoperatively, but patients who were reconstructed with a nasoseptal flap had worse smell outcomes
Greig[1101]	2016	2a	Systematic review of level 1 studies	10 Studies (2 randomized controlled trials, 6 cohort studies, 2 retrospective case series) examining objective olfactory outcomes following endoscopic anterior skull-base surgery	Objective olfactory outcomes	Nasoseptal flap elevation with or without use may cause impairment in objective olfactory function. Endoscopic sellar and parasellar surgery without nasoseptal flap elevation may lead to a transient olfactory dysfunction. Consider not elevating a nasoseptal flap if the risk for CSF leak is low. Monopolar electrocautery for mucosal flap incisions may increase the risk of olfactory impairment. If a nasoseptal flap is used, consider donor site reconstruction
Alobid[1240]	2013	3b	Case-control study	36 Patients underwent endoscopic TNTS and 14 patients underwent EEA	Comparison of preoperative and 3 months postoperative: 1. VAS scores for sinonasal symptoms 2. Barcelona smell test 3. Saccharin test for mucociliary transport	Both EEA and TNTS patients experienced smell dysfunction. EEA patients had higher loss of smell and posterior nasal discharge, as well as longer mucociliary transport, when compared to TNTS patients
Kahilogullari[1241]	2013	3b	Case-control study	25 Patients underwent endoscopic TNTS (compared to 25 patients who underwent a microscopic approach)	Comparison of preoperative and 1 and 6 months postoperative smell diskettes olfaction test results	3/25 Patients (12%) in endoscopic TNTS group and 18/25 (72%) in microscopic group experienced olfactory dysfunction
Kim[1103]	2013	3b	Case-control study	15 Patients underwent endoscopic TNTS with nasoseptal flap reconstruction, of which the superior flap incision was performed by either cold knife (n = 8) or electrocautery (n = 7)	1. Comparison of preoperative and 6 months postoperative SIT scores 2. Histologic analysis of posterior septal mucosa	1/7 Patients in the electrocautery group experienced olfactory dysfunction, compared to 0/8 in the cold knife group. 20% of the cold knife group and 55.8% (cutting)/76.9% (coagulation) of the electrocautery group demonstrated total olfactory epithelial loss when posterior septal mucosa was analyzed

(*Continued*)

TABLE XI.C.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Hong[1242]	2014	3b	Case-control study	49 Patients underwent endoscopic TNTS, of which the rescue flap was raised with either cold knife (n = 30) or electrocautery (n = 19)	Comparison of preoperative and 3 and 6 months postoperative: 1. SIT scores 2. VAS scores for smell function	Electrocautery group exhibited significantly worse subjective smell function as compared to cold knife group, though there was no significant difference in objective testing
Harvey[1243]	2015	3b	Retrospective cohort study	98 Patients (40 pituitary, 58 tumor) who underwent endoscopic TNTS with reconstruction using nasoseptal flap, with preservation of "olfactory strip"	Comparison of preoperative and 6 months postoperative: 1. SNOT-22 scores 2. NSS scores 3. SIT scores	Preservation of olfactory strip resulted in improved SNOT-22 scores and unchanged NSS scores and objective smell function. Smell function was compared to controls and found to be similar
Hong[1244]	2015	3b	Case-control study	35 Patients underwent endoscopic binarial TNTS (compared to 20 patients who underwent a microscopic approach)	Comparison of preoperative and 3 months postoperative: 1. SIT scores 2. Butanol threshold test 3. VAS scores for smell function 4. ASK scores	Microscopic approach conferred improved ASK scores when compared to endoscopic approach, though smell outcomes were not different
Chaaban[1134]	2015	3b	Case-control study	18 Patients underwent endoscopic TNTS, of which 6 had nasoseptal flap reconstruction	Comparison of preoperative and 3-4 months postoperative SIT scores	No difference in SIT scores before and after surgery in those who did and did not have nasoseptal flap reconstruction
Hong[1245]	2016	3b	Case-control study	30 Patients underwent endoscopic TNTS as compared to 51 patients who underwent endoscopic transseptal approach to pituitary	Comparison of preoperative, and 1 and 3 months postoperative: 1. SIT scores 2. SNOT-20 scores 3. ASK scores 4. VAS scores for smell function	Patients who underwent modified transseptal approach reported better olfactory outcomes and ASK scores postoperatively compared to standard TNTS approach
Upadhyay[1246]	2017	3b	Case-control study	42 Patients underwent EEA for resection of skull-base tumors with preservation of the olfactory strip, of which 7 had nasoseptal flap reconstruction	Comparison of preoperative, 6 weeks, 3 months and 6 months postoperative SIT scores	With purposeful preservation of the olfactory strip, patients reconstructed with a nasoseptal flap demonstrated worse SIT scores at 6 weeks, which recovered to baseline levels at 6 months. Those who did not have flap reconstruction had no changes in olfaction from baseline
Rotenberg[1133]	2011	4	Prospective case series	17 Patients underwent endoscopic TNTS (middle turbinate preservation) with nasoseptal flap reconstruction	Comparison of preoperative and 6 months postoperative: 1. SIT scores 2. LKES scores 3. Subjective olfactory function	All patients reported olfactory dysfunction, with significantly lower objective olfaction as measured by SIT

(*Continued*)

TABLE XI.C.1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Kim[1247]	2013	4	Retrospective case series	142 Patients underwent endoscopic TNTS (binarial, 4-hand)	Comparison of preoperative and 6 months postoperative: 1. NOSE scores 2. SNOT-20 scores 3. VAS for nasal symptoms	No significant changes in NOSE, SNOT-20, VAS scores before and after surgery, with the exception of worse olfaction postoperatively
Bedrosian[1248]	2013	4	Retrospective case series	85 Patients who underwent endoscopic skull-base surgery	Comparison of preoperative and 1 year postoperative ASK scores	Preoperative smell and taste were worse in the nonpituitary cohort. Smell symptoms worsened in the short term but returned to baseline by 12 months postoperatively
Sowerby[1249]	2013	4	Retrospective case series	22 Patients who underwent endoscopic TNTS (unilateral with middle turbinate resection)	Comparison of preoperative and mean 58 days postoperative: 1. SNOT-22 scores 2. LKES scores 3. SIT scores	91% of patients had smell preservation. No differences between preoperative and postoperative SNOT-22 scores. Slightly worse LKES in early postoperative period
Kim[1239]	2014	4	Retrospective case series	226 Patients who underwent endoscopic TNTS (posterior septectomy) for sellar pathologies	Comparison of preoperative and 6 months postoperative: 1. SIT scores 2. CCCRC scores 3. VAS scores for smell function	Regardless of full nasoseptal flap use or rescue flap elevation, patients experienced significant objective and subjective olfactory dysfunction postoperatively
Tajudeen[843]	2016	4	Retrospective case series	14 Patients underwent unilateral resection of esthesioneuroblastoma followed by radiation therapy	Recurrence rate and comparison of preoperative and long-term postoperative SIT scores (mean follow up 51.7 months)	No recurrences. 6 (43%) patients had smell preservation following treatment, with 2 (14%) patients having normal or mildly reduced smell function
Wessell[1250]	2014	5	Case report	1 Patient underwent unilateral resection of esthesioneuroblastoma with cribriform plate involvement (Kadish C)	Recurrence and SIT score at 18 months	No recurrence, with mild microsomia 18 months postoperatively
Youssef[487]	2016	5	Case report	1 Patient underwent unilateral resection of olfactory groove meningioma	SIT score at 12 months	Microsomia at 12 months postoperatively

ASK = anterior skull base nasal inventory; CCCRC = Connecticut Chemosensory Clinical Research Center Test; EEA = expanded endonasal approach; ESBS = endoscopic skull-base surgery; LKES = Lund-Kennedy endoscopic score; LOE = level of evidence; NOSE = Nasal Obstruction Symptom Evaluation; NSS = nasal symptom score; SIT = smell identification test; SNOT-22 = 22-item Sino-Nasal Outcome Test; TNTS = transnasal transsphenoidal surgery; VAS = visual analog scale.

reports as being associated with better olfaction and QOL outcomes compared to a standard transnasal approach.

Olfactory outcomes as a function of extent of surgery are currently unclear. In a review of 36 patients, Alobid et al.[1240] reported that the EEA tended to produce a greater degree of smell dysfunction when compared to patients who underwent endoscopic transnasal transsphenoidal surgery. Bedrosian et al.[1248] reported improved smell outcomes in endoscopic surgery for pituitary pathologies when compared to other skull-base pathologies. However, the previously quoted study by Upadhyay et al.[1246] reported excellent olfactory outcomes following EEA with preservation of the olfactory strip, suggesting that specific anatomic elements are likely responsible for the differences in outcomes.

There is also some evidence suggesting that cold knife techniques for NSF harvest may improve olfactory

outcomes. This is especially important when making the superior flap incision that borders the olfactory strip. Kim et al.,[1103] in a histologic study of 15 patients undergoing pituitary surgery, found that only 20% of posterior septal mucosal specimens exhibited total olfactory epithelial loss with the cold knife technique compared to >50% for the electrocautery group. Hong et al.[1242] performed a similar study looking at olfaction with either technique following raising of rescue flaps, finding that those in the electrocautery group reported worse subjective smell function postoperatively.

XI.C.2. *Sinonasal QOL following ESBS*

Naturally, instrumentation of the sinonasal tract during transnasal access to skull-base lesions leads to mucosal trauma. In addition, harvesting the NSF involves denuding the septal cartilage and bone of mucoperichondrium and mucoperiosteum, respectively.[273] Thus, it must remucosalize gradually by secondary intention, and this healing response generally produces significant nasal crusting. In a systematic review of sinonasal morbidity following ESBS, the most commonly patient-reported symptoms are nasal crusting (50.8%), nasal discharge (40.4%), nasal obstruction (40.1%), and hyposmia/anosmia (26.7%).[1238] These symptoms tend to be worse in the early postoperative period and improve by 3 to 4 months, though some also report resolution taking up to 6 to 9 months.[1253–1256] Anteriorly located tumors,[1257] complexity (ie, extent of dissection),[1129] and RT[1073] may be associated with increased crusting. Use of the NSF has been associated with worse nasal symptoms in multiple studies,[1258,1259] though the converse, where there is no impact or even a positive effect on QOL, has also been claimed.[1260–1262] Nasal morbidity is ameliorated by postoperative debridement and nasal irrigations, which underscores the important role of follow-up care, often requiring more than 1 postoperative visit.

Table XI.C.2 summarizes the evidence surrounding nasal morbidity as measured by symptomatology and QOL following ESBS.

There are only 2 Level 1 studies on sinonasal-related QOL outcomes following ESBS, both by Little et al.,[283,1263] both studies focused on pituitary lesions. One study found that there was no difference in nasal morbidity and QOL outcomes between microscopic and endoscopic approaches.[1263] The other aimed to identify predictors of sinonasal morbidity, and found that the only negative prognosticator for long-term outcomes was overall health status.[283]

In order to reduce nasal crusting from cartilage exposure, 1 commonly utilized technical modification is the "rescue flap" technique.[1269,1271] Though reported anecdotally to minimize sinonasal morbidity because of septal mucosal preservation, no studies have formally examined this relationship. Other modifications in surgical technique have been described. Thompson et al.[945] reported improvements in postoperative nasal symptom scores with middle turbinate preservation, limiting the approach to transnasal (ie, no dissection of maxillary and sphenoid sinuses), and reducing NSF utilization whenever possible. One may also consider secondary coverage of the exposed cartilage, either in the form of a "reverse flap"[1131,1132] or free mucosal graft,[1272] to promote rapid remucosalization.

XI.C.3. *Nasal structural changes following ESBS*

Based on the available evidence, iatrogenic nasal structural changes following ESBS in the modern era are rare. It is important to emphasize that septectomy may be purposely performed for access and oncologic control, thus making septal perforations a natural sequela of the surgical approach itself or result from tumor resection. Attention to this topic began when Koren et al.[1273] reported a 10% rate of septal perforation associated with endoscopic transnasal transsphenoidal surgery in a cohort of 20 patients, whereas the traditional sublabial approach resulted in a 30% septal perforation rate as well as 2 (10%) patients having nasal tip deprojection. Based on more recent reports, the incidence of structural complications is exceedingly rare. In a series of 328 consecutive patients, Rowan et al.[1117] identified that nasal dorsal collapse, possibly related to devascularization of septal cartilage, was present in 19 (5.8%) patients, while septal perforation occurred in 3 (0.9%) patients, with all complication associated with CSF use. Cheng et al.[1274] had only 1 (0.8%) septal perforation in a cohort of 129 patients who underwent endoscopic transnasal transsphenoidal surgery, whereas Dolci et al.[1275] reported internal nasal valve collapse in 6 (14.6%) patients and no septal perforations in a cohort of 41 endoscopic transnasal transsphenoidal surgery patients. Table XI.C.3 summarizes the existing evidence surrounding nasal structural changes following ESBS.

XI.C.4. *Chronic rhinosinusitis as a sequelae of ESBS*

Intuitively, sinonasal dissection in a previously nondiseased field for access to skull-base lesions may lead to iatrogenic scarring and disruption of mucociliary function, thereby leading to sinusitis. However, there is currently limited evidence that ESBS results in clinically significant sinusitis beyond the postoperative healing period. In a clinical trial of 218 patients, 28 (13%) developed "sinusitis," defined as facial pressure and nasal discharge requiring antibiotic therapy.[283] Though sinonasal symptoms partially contribute to the clinical picture, endoscopy and/or radiographic changes are generally necessary to make the diagnosis of chronic rhinosinusitis. Deconde et al.[1277] examined radiographic changes suggestive of mucosal inflammation following endoscopic transsphenoidal surgery with middle turbinate resection and maxillary antrostomy; they found that there was increased postoperative anterior ethmoid mucosal thickening, and that preservation of native anatomy was associated with a lower incidence of this change. Similarly, Langdon et al.[1278] found, in a cohort

TABLE XI.C.2. Evidence surrounding QOL outcomes, including nasal crusting and obstruction, following ESBS

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Little[283]	2015	1b	Multi-institutional, nonblinded, RCT	218 Patients (111 microscopic, 107 endoscopic) underwent TNTS	Comparison of preoperative and 6 month postoperative: 1. SNOT-22 scores 2. ASK scores 3. SF-8 scores 4. EuroQOL-5D-5L	13% of Patients in endoscopic group developed sinusitis. QOL scores worsened within 2 weeks after surgery, but improved at the 3 month mark. There were no significant differences in QOL outcomes between microscopic and endoscopic approaches.
Little[1263]	2015	1b	Multi-institutional, nonblinded, RCT (subgroup analysis)	100 Patients underwent endoscopic TNTS	Comparison of preoperative and 2 week, 3 and 6 month postoperative: 1. ASK scores 2. SF-8 scores	Predictors of lower QOL at 3 months include sinusitis, advanced age, and absorbable nasal packing use. Health status predicted worse nasal morbidity at 3 and 6 months. Nasal crusting, mucopurulence, and synechia took 16, 6, and 4 weeks to resolve, respectively.
Awad[1238]	2015	3a	Systematic review of case-control studies	7 Studies (5 prospective, 2 retrospective) examining sinonasal morbidity following endoscopic skull-base surgery	1. Incidence of morbidities 2. Intraoperative risk factors 3. Mucocele formation 4. Epistaxis 5. Technical modifications to reduce morbidity 6. Time to resolution 7. QOL	The most common problems are nasal crusting (50.8%), nasal discharge (40.4%), nasal obstruction (40.1%), and hyposmia/anosmia (26.7%), which often resolve within 3 to 4 months. Mucocele formation is more prevalent in children.
Alobid[1259]	2013	3b	Case-control study	55 (38 TNTS, 17 EEA with nasoseptal flap) patients who underwent endoscopic surgery	Comparison of preoperative and 3 month postoperative: 1. SF-36 scores 2. RSOM-31 scores	EEA patients had worse nasal and general QOL symptoms, including worse olfaction, than TNTS patients
Harvey[1260]	2015	3b	Case-control study	118 Patients who underwent endoscopic surgery for sinonasal or skull base tumors, of which 42 were reconstructed with nasoseptal flap	Comparison of preoperative and postoperative: 1. SNOT-22 scores 2. NSS scores	No significant differences in SNOT-22 and NSS scores postoperatively between those who required nasoseptal flaps and those who did not
McCoul[1264]	2015	3b	Case-control study	40 Patients who underwent endoscopic TNTS, of which 18 were reconstructed with nasoseptal flap	Comparison of preoperative and 1.5-month, 3-month, 6-month, and 12-month postoperative: 1. SNOT-22 scores 2. Acoustic rhinometry (compared to normative data)	Cross-sectional areas at the level of the middle turbinate head and body significantly increased after surgery. No significant changes between preoperative and postoperative QOL, even in those patients who had nasoseptal flaps
Jalessi[1258]	2016	3b	Case-control study	106 Patients who underwent endoscopic TNTS for pituitary adenomas, of which 68 were reconstructed with nasoseptal flap	Comparison of preoperative and 1, 3, 6, and 12 month postoperative: 1. SNOT-22 scores 2. "9Q" – nasal congestion, thick nasal discharge, postnasal discharge, sense of taste/smell, runny nose, need for nose	Patients in the nasoseptal flap group exhibited worse 9Q scores and worse sense of taste/smell, both of which returned to baseline at 3 months

(*Continued*)

TABLE XI.C.2. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
					blowing, cough, sneeze, and facial pain/pressurerunny nose, need for nose blowing, cough, sneeze, and facial pain/pressure	
Pant[1262]	2010	4	Retrospective case series	51 Patients who underwent endoscopic skull-base surgery	Incidence of complications and comparison of preoperative and 3-month, 6-month, and 12-month postoperative: 1. SNOT-22 scores 2. ASK scores	Mean duration of nasal crusting was 126 days, which is not affected by use of nasoseptal flap. QOL outcomes worsened on short term but improved over time
Balaker[1254]	2010	4	Retrospective case series	69 Patients who underwent endoscopic TNTS	Comparison of preoperative and early, middle, and late postoperative SNOT-20 scores	Many early symptoms which resolve over time, with near complete resolution at 6 to 9 months postoperatively. Postnasal discharge and thick nasal discharge persist longer
Wang[1265]	2011	4	Retrospective case series	88 Patients who underwent endoscopic TNTS	Comparison of preoperative and postoperative GNPI scores	No significant changes in QOL measures between pre- and postoperative assessments. Only 9% patients had persistent nasal symptoms at final follow-up appointment
de Almeida[1129]	2011	4	Retrospective case series	63 Patients who underwent endoscopic skull-base surgery	Postoperative nasal morbidity	Nasal crusting (98%) and discharge (46%) were most common postoperative symptoms. Surgical complexity (extent of approach) was associated with worse crusting.
Georgalas[1266]	2012	4	Retrospective case series	91 Patients who underwent endoscopic skull-base surgery for benign pathology	Comparison of preoperative and postoperative RSOM-31 scores	Smell and headache were worse in patients reconstructed with nasoseptal flaps, though this recovered over time. Secreting adenomas were independently associated with worse QOL scores
McCoul[1267]	2012	4	Retrospective case series	85 Patients who underwent endoscopic skull-base surgery	Comparison of preoperative and 3-week, 6-week, 12-week; and 6-month postoperative: 1. SNOT-22 scores 2. ASK scores	Endoscopic skull-base surgery improves sinonasal-related QOL on the long run
McCoul[1268]	2012	4	Retrospective case series	66 Patients who underwent endoscopic skull base surgery	Comparison of preoperative and 3-week, 6-week, 12-week; and 6-month postoperative: 1. SNOT-22 scores 2. ASK scores	Site-specific QOL scores improved as compared to baseline scores, with gross total resection being associated with improved outcomes
Rawal[1269]	2012	4	Retrospective case series	26 Patients who underwent endoscopic TNTS with rescue flap incisions, of which 7 were converted into nasoseptal flaps	1. Postoperative CSF leak 2. Septal perforation	No CSF leaks or septal perforations, but no mention of nasal symptoms

(*Continued*)

TABLE XI.C.2. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
de Almeida[1257]	2013	4	Retrospective case series	138 Patients who underwent skull-base surgery, of which 65 underwent an endoscopic approach	Postoperative physical complaints	Anterior tumors tended to produce more nasal symptoms and treatment leads to greater morbidity as compared to central tumors
Gallagher[1256]	2014	4	Retrospective case series	124 Patients who underwent endoscopic anterior skull-base surgery	Comparison of preoperative and postoperative nasal symptoms using a questionnaire	Mild or no nasal crusting was reported by 77% of patients, of which 50% had resolution by 4 months. 71% had no subjective change in smell after surgery.
Thompson[945]	2014	4	Retrospective case series	93 Patients who underwent endoscopic TNTS	Comparison of preoperative and postoperative SNOT-22 scores	Middle turbinate preservation, not performing unnecessary maxillary antrostomies, and limited utilization of the nasoseptal flap led to improved individual SNOT score items reflecting better symptoms
Zimmer[1253]	2014	4	Retrospective case series	37 Patients who underwent endoscopic TNTS	Comparison of preoperative and 1- and 3-month postoperative SNOT-22 scores	Nasal obstruction, olfaction, and postnasal drainage worsened at 1 month, but improved by 3 months postoperatively
McCoul[1270]	2015	4	Retrospective case series	81 Patients who underwent endoscopic TNTS	Comparison of preoperative and 12-week, 6-month, and 1-year postoperative: 1. SNOT-22 scores 2. ASK scores	There was transient worsening of QOL scores in the short term, which improved by 1 year postoperatively. Subtotal resection was the only factor associated with negative QOL outcomes
Hanson[1261]	2015	4	Retrospective case series	36 Patients who underwent endoscopic skull-base surgery with nasoseptal flap reconstruction	Comparison of preoperative and 90-day postoperative: 1. SNOT-20 scores 2. VAS for nasal obstruction, pain, secretions, smell 3. Endoscopic exam 4. Mucociliary clearance	No significant differences in SNOT QOL scores preoperatively and postoperatively, with apparent improvement in nasal obstruction on VAS. Endoscopy scores worsened postoperatively.
Davies[1255]	2017	4	Prospective case series	56 Patients who underwent endoscopic TNTS	Comparison of preoperative and 1-day, 3 days, 2 weeks, 3 months, and 6–12 months postoperative GNPI scores	QOL scores worsen within 2 weeks postoperatively, but improve by 6–12 months. Patients with functioning tumors had worse QOL scores.

EEA = endoscopic endonasal approach; GNPI = General Nasal Patient Inventory; LKES = Lund-Kennedy endoscopic score; NSS = nasal symptom score; QOL = quality of life; RCT = randomized controlled trial; RSOM = Rhinosinusitis Outcome Measure; SF = Short Form Health Survey; SNOT-22 = 22-item Sino-Nasal Outcome Test; TNTS = transnasal transsphenoidal surgery; VAS = visual analog scale.

of 55 patients, that Lund-Mackay scores (an objective measure of radiographic sinusitis) remained elevated 12 months following ESBS, with higher average scores among patients who required NSF reconstruction, but this did not correlate with symptoms. Table XI.C.4 reviews the existing evidence surrounding development of chronic sinusitis following ESBS.

- Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 2a: 1 study; Level 3a: 1 study; Level 3b: 13 studies; Level 4: multiple studies; Table XIC.1, Table XI.C.2, Table XI.C.3, and Table XI.C.4).
- Benefit: Minimization of nasal morbidity is correlated with improved QOL scores and lower incidence of iatrogenic complications.

TABLE XI.C.3. Evidence surrounding nasal structural deformities following ESBS

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Koren[1273]	1999	4	Retrospective case series	40 (20 sublabial, 20 endoscopic) patients who underwent transnasal, transsphenoidal surgery	Incidence of complications	Septal perforation occurred in 2 (10%) and 6 (30%) patients in the endoscopic and sublabial groups, respectively. Sublabial group also had 2 (10%) patients with deprojection of the nasal tip
Heo[1276]	2008	4	Retrospective case series	11 Patients who underwent endoscopic surgery for both chronic rhinosinusitis and pituitary adenoma	Incidence of complications	1 (9%) Patient developed septal perforation
Rowan[1117]	2016	4	Retrospective case series	328 Patients who underwent endoscopic skull-base surgery	Incidence of nasal deformities	Nasal dorsal collapse occurred in 19 (5.8%) patients, while septal perforation occurred in 3 (0.9%) patients. Deformities were associated with nasoseptal flap use and combined endoscopic approaches
Cheng[1274]	2017	4	Retrospective case series	129 Patients who underwent endoscopic transnasal transsphenoidal surgery	Incidence of complications	1 (0.8%) Patient developed septal perforation
Dolci[1275]	2017	4	Retrospective case series	41 Patients who underwent endoscopic skull-base surgery	Incidence of complications	Synechia formation occurred in 8 (19.5%) patients, internal valve collapse in 6 (14.6%), and no septal perforations

ESBS = endoscopic skull-base surgery; LOE = level of evidence.

TABLE XI.C.4. Evidence surrounding clinically significant iatrogenic sinusitis following ESBS

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusions
Deconde[1277]	2014	4	Retrospective case series	51 Patients who underwent endoscopic TNTS	Comparison of preoperative and 3 and 6 month postoperative Lund-Mackay scores	Middle turbinate resection and maxillary antrostomy are associated with increased postoperative mucosal thickening of anterior ethmoids
Langdon[1278]	2016	4	Retrospective case series	55 Patients who underwent ESBS, of which 17 required nasoseptal flap reconstruction	Comparison of preoperative and 3 and 12 month postoperative: 1. Lund-Mackay scores 2. Sinonasal symptoms	Mean Lund-Mackay score increased at 3 and 12 months postoperatively compared to baseline, with increased scores in the nasoseptal flap subgroup. Symptoms were worse postoperatively, however, returned to baseline at 12 months

ESBS = endoscopic skull-base surgery; LOE = level of evidence; TNTS = transnasal transsphenoidal surgery.

- Harm: Nasal morbidity leads to adverse QOL changes, but must be balanced against sufficient endoscopic access, oncologic control, and successful repair of skull-base defects in select cases (eg, CSF leak).
- Cost: No studies have formally assessed the monetary costs of nasal morbidity, but mindfulness on the part of the surgeon will likely decrease patient-related and system-related costs for the management of undesired sequelae.

- Benefit-Harms Assessment: Directed, meticulous endoscopic dissection and preoperative planning will likely improve lesion access, operative time, and minimize nasal morbidity.
- Value Judgments: Potentially worse olfactory outcomes are associated with NSF elevation, thermal (eg, electrocautery) flap elevation techniques, binarial dissection, and dissection of the "olfactory strip." Nasal crusting, discharge, and obstruction are the most common postoperative symptoms. There is generally significant worsening in QOL and symptom scores during the early postoperative period, with return to baseline 3 to 12 months postoperatively. Nasal structural complications are rare following ESBS. Clinically significant sinusitis is also rare in the long term, with radiographic data correlating poorly with symptoms.
- Policy Level: Recommendation
- Intervention: Careful preoperative planning should be undertaken by the surgical team (eg, to assess need for NSF). Whenever possible, minimize unnecessary sinonasal dissection for access to skull-base pathology.

XII. Intraoperative considerations

XII.A. Arterial hemostatic techniques

Arterial injury during ESBS remains 1 of the most challenging circumstances a skull-base surgeon may encounter. This may vary from catastrophic ICA injury to more minor perforator-based bleeding. Surgeons need to have a sound understanding of how they will manage all types of arterial vascular injury during surgery prior to the event, because formulating a management plan during this anxiety-provoking event is difficult or impossible. The management of arterial bleeding during ESBS is largely based upon surgeon-accumulated anecdotal experience without evidence-based guidelines (see Table XIIA).

XII.A.1. *Packing*

XII.A.1.a. Major arterial injury. There are no previously published systematic reviews, clinical guidelines, or RCTs pertaining to the use of nasal packing during endoscopic injury of a major artery during ESBS. Packing with a variety of agents has been recommended for the management of major endoscopic arterial injuries where vessel preservation is required.[1281] There are several papers recommending the use of non-occlusive packing in general for major arterial vascular injuries.[1194] Muscle packing is particularly useful because it is reliable, readily accessible, and quick to acquire. Valentine et al.[1205] were the first to identify its efficacy in a large arterial injury in a prospective RCT utilizing a novel sheep model. The muscle patch is advantageous because it can be used in all cases, regardless of surgical exposure to the injury site.[1203] Donor sites advocated include abdominal rectus, sternocleidomastoid, thigh, or temporalis muscle.[1194,1206] Padhye et al.[1203] investigated the efficacy of the non-occlusive muscle patch in a prospective randomized trial in a sheep model of major endoscopic arterial injury utilizing a linear, stellate, and punch arterial injury. This showed 100% efficacy of the muscle patch in achieving primary hemostasis. A retrospective series of major arterial injury during ESBS has also been published. This showed universal success in achieving hemostasis with the muscle patch in all cases without subsequent neurological injury. There was only 1 pseudoaneurysm from the 9 cases treated with the muscle patch. In several case reports, FloSeal, a gelatin-thrombin hemostatic matrix sealant, has been shown to be effective in endoscopic arterial major injury management when used as a focally applied, topical packing agent.[1279,1280] This must be used with caution, however, because it has the ability to embolize into the parent vessel.

XII.A.1.b. Minor arterial injury. There are no previously published systematic reviews, clinical guidelines, or RCTs pertaining to the use of nasal packing during endoscopic injury of a minor artery during ESBS. There are several case reports of the use of FloSeal as an effective agent in focally applied topical packing.[1279,1280] In addition, Avitene packing with warm saline irrigation or Gelfoam packing has also been recommended for small arterial injuries.[1281–1283]

- Aggregate Grade of Evidence: D (Level 4: 2 studies, Level 5: 7 studies)
- Benefit: Subjective improvement in surgical field, subjective decrease in intraoperative bleeding
- Harm: No specific reports about side-effects; potential increase in blood loss
- Cost: Low
- Benefit-Harm Assessment: Option: Muscle patching appears to be successful in control of bleeding as well as minimization of delayed complications such as pseudoaneurysm development.
- Value Judgments: Effective bleeding control method
- Policy Level: Option
- Intervention: Option

XII.A.2. *Bipolar cautery*

XII.A.2.a. Major arterial injury. There are no previously published systematic reviews, clinical guidelines, or RCTs pertaining to the use of bipolar cautery during endoscopic injury to a major artery during skull-base surgery. With regard to large vascular arterial injuries, the efficacy of bipolar cautery in achieving primary hemostasis has been shown in a sheep model of large vascular injury. In 5 of the 7 cases hemostasis was achieved with bipolar cautery but this resulted in the largest intraoperative blood loss when compared to other hemostatic methods.[1206] A number of authors have reported success using bipolar cautery as an effective option for major arterial vascular injury.[1188,1194,1195,1206,1283] However, Padhye et al.[1206] demonstrated that it was not as reliable at

TABLE XIIA. Evidence for arterial hemostasis techniques

Study	Year	LOE	Study design	Study groups	End points	Conclusion
Padhye[1203]	2015	4	Retrospective cohort	1. Muscle patch	1. Hemostasis 2. Pseudoaneurysm 3. Neurological deficit	Muscle is reliable, 100% hemostasis, 1/9 pseudoaneurysm
Padhye[1206]	2014	N/A Animal Model	RCT	1. Muscle patch 2. Aneurysmal clip 3. Bipolar	1. Hemostasis 2. Pseudoaneurysm 3. Neurological deficit	Muscle and Aneurysmal clip is reliable, low pseudoaneurysm risk
Padhye[1207]	2014	N/A Animal Model	Prospective cohort	1. Anastoclip	1. Hemostasis 2. Pseudoaneurysm 3. Neurological deficit	Anastoclip is reliable, 100% hemostasis, 1/9 pseudoaneurysm
Valentine[1205]	2011	N/A Animal Model	RCT	1. Muscle patch 2. FloSeal 3. Surgicel 4. Chitosan Gel 5. U-clip	1. Hemostasis 2. Blood loss	Muscle patch and U-clip are reliable, 100% hemostasis, less blood loss.
Cappabianca[1279]	2009	4	Retrospective case note review	1. FloSeal	1. Hemostasis	FloSeal was useful for oozing and focal hemorrhage
Reeves[1280]	2011	4	Case study	1. FloSeal	1. Hemostasis	FloSeal was effective

LOE = level of evidence; N/A = not applicable; RCT = randomized controlled trial.

achieving hemostasis when compared to clip and packing techniques, with pseudoaneurysm formation a risk.

XII.A.2.b. Minor arterial injury. There are no previously published systematic reviews, clinical guidelines, or randomized controlled trials pertaining to the use of bipolar cautery during endoscopic injury of a minor artery during endoscopic skull base surgery. Bipolar techniques have been recommended for small artery injury control when the site can be accessed,[1195,1279,1281,1282] with a number of angled tips available for difficult to reach sites.

- Aggregate Grade of Evidence: D (Level 4: 1 study, Level 5: 6 studies)
- Benefit: Subjective improvement in surgical field, subjective decrease in intraoperative bleeding
- Harm: No specific reports about side-effects
- Cost: Low
- Benefit-Harm Assessment: Option
- Value Judgments: Effective bleeding control method but may have increased blood loss associated with control in comparison to packing.
- Policy Level: Option
- Intervention: Option

XII.A.3. *Ligature clips, aneurysmal clips, and anastoclip*

XII.A.3.a. Major arterial injury. There are no previously published systematic reviews, clinical guidelines, or RCTs pertaining to the use of surgical clips during endoscopic major arterial injury during skull-base surgery. The efficacy of aneurysmal clips in primary large vessel hemostasis has been shown in a sheep model of large vascular injury, with all cases achieving hemostasis.[1206] Gardner et al.[1194] and Solares et al.[1195] recommended aneurysmal clips as an effective option for major arterial vascular injury while trying to preserve vascular patency and preservation. The use of a novel AnastoClip vessel closure system has also been shown to be effective in all cases in a sheep model, with only 1 pseudoaneurysm out of 9 cases.[1207] The use of all clip devices, however, does require some level of surgical exposure of the injury site, and may be more technically challenging to apply. In addition, appropriate length, single-shaft clip appliers are needed.

XII.A.3.b. Minor arterial injury. There are no previously published systematic reviews, clinical guidelines, or RCTs pertaining to the use of surgical clips during minor endoscopic arterial injury during skull-base surgery. Endoscopic applied clips have been recommended for small arterial perforators where the artery can be sacrificed.[1281]

- Aggregate Grade of Evidence: D (Level 4: 1 study; Level 5: 3 studies)
- Benefit: Subjective improvement in surgical field, subjective decrease in intraoperative bleeding
- Harm: No specific reports about side effects
- Cost: Low
- Benefit-Harm Assessment: Option
- Value Judgments: Effective bleeding control method
- Policy Level: Option
- Intervention: Option

XII.B. Venous hemostatic techniques

Endoscopic intracranial surgery provides the benefit of a deep-reaching surgery through a minimally invasive access point. The endoscope enables the surgeon to view more while exposing less. The benefits of ESBS have been described throughout this report. An indirect view of the surgical field is 1 of the main challenges of endoscopic surgery. This challenge is especially recognized during attempts at hemostasis. The confines of a smaller access point during ESBS require meticulous hemostasis to not only to reduce surgical morbidity, but to also keep the field of view clear and available for continued surgical momentum. Especially with intraventricular extension, hemostasis is of particular concern to prevent the obstruction of cerebrospinal fluid pathways.

XII.B.1. *Venous hemostatic techniques*

XII.B.1.a. Bipolar cautery. The endoscope permits angled visualization of neural structures that would otherwise not be seen through open surgery. This, however, requires the use of angled instrumentation. Angled bipolar cauterization is a requirement to address hemostasis of venous bleeding viewed by angled endoscopy. Monopolar cautery is not recommended around neurovascular structures due to the heat and electrical transfer to these important functional structures.

Two studies examined the utility of specialized, angled bipolar electrocautery forceps for the use of endoscopic neurosurgical applications.[1283,1284] Kassam et al.[1283] retrospectively reported on their observations of 400 ESBS cases and concluded that angled bipolar forceps, especially with pistol-gripping features, enable the surgeon to maneuver bipolar electrocautery with greater precision and ergonomics. As an aside, their observations also report on their unquantified success with flowable gelatin-thrombin matrix for hemostasis. Kim et al.[1284] report on their experience with 940 cases of transsphenoidal surgery, of which there were 72 patients with significant cavernous sinus bleeding. Of the 72 patients, 67 were managed via angled bipolar cauterization alone. The remaining 5 cases utilized tack-up sutures for dural repair after angled bipolar management and packable hemostastic agents had failed to achieve hemostasis initially. No cases required endovascular management. No cases had postoperative epistaxis or intracranial hemorrhage. Their use of specialized, angled bipolar forceps were described as being practical in reducing hemorrhage from intercavernous sinus bleeding.

XII.B.1.b. Flowable packing. When traditional methods of hemostasis are impractical, impossible, or exhausted, the use of flowable packing can be considered. A variety of flowable packing materials are available in the international market, which can be divided into 2 general groups: gelatin-thrombin matrices or fibrin glues. The flowable gelatin-thrombin matrix utilizes the principle of granulized gelatin to adhere to the vessel and thrombin to facilitate coagulation, which is in the form of a flowable, prohemostatic sealant. Fibrin glues come in different varieties, though the general components are fibrinogen and thrombin. When combined, these 2 components mimic the final stage of the human coagulation cascade. Fibrin glues, however, have not been approved for neurosurgical use in the United States, thus their use in neurosurgical applications have been off-label and should only be used with caution.

Although these mechanisms of operative hemostasis have been used for many years, the use of flowable hemostatic agents in neurosurgical applications has been cautiously studied. The sensitive microenvironment of the central nervous system, the unforgiving consequences of cerebral venous and sinus thrombosis, and the concern for impediments of CSF flow within the ventricular system are all valid concerns for the safety of these agents for hemostasis.

Studies on the use of the different fibrin glues for intracranial venous hemostasis were limited to a case series and a case report.[1285,1286] Sekhar et al.[1285] reported on their institutional series of 86 retrospective cases in which fibrin glue was used for venous hemostasis. Their report observed 2 cases of temporal lobe venous infarction and brainstem edema following injection of the fibrin glue into the superior petrosal sinus. There were no reports of adverse events when fibrin glue was injected in other intracranial venous structures. Tavanaiepour et al.[1286] reported on a case where fibrin glue was used for cavernous sinus hemostasis with a resultant sensory trigeminal nerve deficit, likely from compressive effects. The off-label use of fibrin glue in neurosurgical applications should be done with care and caution.

The utility of gelatin-thrombin matrix as a flowable hemostatic sealant has been confirmed in many surgical trials. However, none included neurosurgical applications with the consideration of neurosurgical safety. Several observational and retrospective studies have been published, which demonstrate its efficacy for intracranial surgery.[1279,1287–1290] Ellegala et al.[1287] report on a series of 20 patients with significant sellar bleeding during transsphenoidal surgeries. In all 20 patients, flowable gelatin-thrombin matrix was successful in obtaining hemostasis. Fiss et al.[1289] reported on their retrospective review of 7 patients with significant bleeding from intracranial surgery and noted that 5 of the 7 obtained hemostasis following flowable gelatin-thrombin matrix placement. The remaining 2 required other additional means of hemostasis, which was eventually achieved. Cappabianca et al.[1279] performed a prospective analysis of 29 patients who required the use of flowable gelatin-thrombin matrix for significant endoscopic endonasal bleeding, all of which obtained immediate successful hemostasis. Bedi et al.[1288] confirmed successful hemostasis with their prospective analysis of 39 patients undergoing endoscopic endonasal neurosurgical procedures. Gazzeri et al.[1290] has the largest prospective analysis to date, which examined 153 cranial surgery

patients and confirmed the utility of flowable gelatin-thrombin matrix in intracranial applications. Four of their 153 patients suffered delayed-hemorrhages; however, 2 of these cases were for intracerebral hemorrhage surgery and the other 2 were for malignant glioma surgery. No complications attributable to the flowable gelatin-thrombin matrix were reported in any of the above studies.[1279,1287–1290]

XII.B.1.c. Warm water irrigation. The use of warm saline irrigation for hemostasis has been advocated in anecdotal teachings; however, very few studies have been performed to formally demonstrate its efficacy. Several studies have shown its efficacy in the nasal mucosa, but the milieu of the cerebrum and intracranial compartments are vastly different. Although the mechanisms for hemostasis are unclear, several hypotheses believe it may be due to induced interstitial edema and compression of leaky vessels, thereby decreasing blood flow and luminal blood pressure, leading to stasis and subsequent hemostasis.[1291] Others suggest that water/saline may dilute physiologic anticoagulants and induce an imbalance that favors coagulation.[1292] It has also been theorized that irrigation of 40°C or greater optimized coagulation cascade enzyme function. Kassam et al.'s[1283] case series with warm water irrigation found that saline that is "warm to the touch" has been effective in irrigation in their experience. In contrast, 46°C was noted to be the threshold for efficacy for hemostasis, albeit in a study on the nasal mucosa for epistaxis, not cerebrum.[1291] A mouse study by Fujita et al.[1293] demonstrated that the type of irrigation matters. Head-to-head trials of normal saline, lactated Ringer's solution, and artificial CSF (ACF-95) were used to irrigate induced injuries to the mouse's parietal lobe. All irrigation materials were kept at room temperature (23.1°C to 23.8°C). After irrigating for 10 minutes at 100 mL/hour, bleeding points were counted. The results of this study have shown that ACF-95 was superior to normal saline in obtaining hemostasis. ACF-95 and lactated Ringer's were not statistically different in obtaining hemostasis. They concluded that the elements within ACF-95 and lactated Ringer's—and not in normal saline—aided in hemostasis, specifically calcium and potassium. In a second part of their experiment, a head-to-head trial of normal saline vs normal saline with the addition of potassium and calcium was carried out, confirming the statistical benefit of the added elements.

Summary

Although highly powered, RCTs are lacking, case series and expert opinions have demonstrated the safety and utility of flowable packing agents and bipolar cautery for venous hemostasis in intracranial endoscopic surgery. Warm saline irrigation has been demonstrated to be effective, but mechanisms are still unclear and there is a likelihood that other irrigation may be more effective (see Table XII.B).

- Aggregate Grade of Evidence:
  - Fibrin-based flowable hemostatic agent: D (Level 4: 2 studies)
  - Flowable gelatin-thrombin matrix hemostatic agent: C (Level 3b: 3 studies; Level 4: 2 studies)
  - Specialized bipolar cautery: C (Level 3b: 1 study; Level 4: 1 study)
  - Warm irrigation: C (Level 3b: 1 study; Level 3a: 1 study)
- Benefit: Rapid control of intraoperative bleeding.
- Harm: Especially in the fibrin glue literature, reports of venous thromboembolism and compressive injuries to the CNs within the cavernous sinus. Warm saline irrigation does not immediately induce hemostasis, and a time and blood-loss element could play a role in the selection of hemostatic technique.
- Cost: There is a cost associated with all flowable hemostatic agents and specialized, angled bipolar forceps with different degrees of angulation, length, and gripping mechanism. The cost of warm saline irrigation is nominal.
- Benefit-Harm Assessment: Balance of risk and benefits.
- Value Judgments: For the majority of endoscopic intracranial cases, the use of bipolar electrocautery has been appropriate for venous hemostasis. However, flowable hemostatic agents can be used in settings where bipolar cautery is impractical, impossible, or exhausted. In other settings, warm saline irrigation can be just as effective, cheaper, and more available than manufactured hemostatic agents.
- Policy Level: Option
- Intervention: When bleeding cannot be controlled by bipolar cautery, flowable hemostatic agents and profuse warm saline irrigation can be used to help achieve hemostasis. The use of fibrin glue applications has not been approved in the United States and should be used with caution and with recognition of the previously published complications.

XII.C. Perioperative and postoperative management in ESBS

The surgical management of skull-base lesions through EEA is founded on operative techniques, instrumentation, and technologies. A variety of surgical adjuncts are increasingly available with the general goal of optimizing outcomes in the perioperative period. This section focuses on 3 such adjuncts including antibiotics, tissue sealants, and nasal packing. Judicious use of antibiotics is an important consideration given the inherently contaminated nature of the paranasal sinuses and potential intracranial infectious sequela from surgery. The use of antibiotics, however, is tempered by potential side effects and complications and conflicting studies. Tissue sealants and nasal packing are commonly used as final layers in skull-base reconstruction with the theoretical goal of supporting the repair site and assisting with hemostasis. Understanding

TABLE XII.B. Evidence for use of specialized bipolar cautery, flowable hemostatic packing, and warm irrigation in intracranial neurosurgical applications

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Cappabianca[1279]	2009	3b	Prospective case series	29 Undergoing endoscopic endonasal procedures where flowable gelatin-thrombin matrix was used.	Complication rate; clinical outcomes	Gelatin matrix + thrombin is effective and safe.
Bedi[1288]	2011	3b	Prospective case series	39 Undergoing endonasal, endoscopic sellar and suprasellar tumors.	Complication rate; clinical outcomes	Gelatin matrix + thrombin is effective and safe.
Gazzeri[1294]	2011	3b	Prospective case series	153 Undergoing cranial surgery.	Complication rate; clinical outcomes	Gelatin matrix + thrombin is effective, but 4 patients had delayed hemorrhages or re-bleeds.
Kim[1284]	2009	3b	Prospective case series	72 Undergoing transsphenoidal surgery who had significant intercavernous sinus bleeding.	Complication rate; clinical outcomes	The use of angled bipolar forceps are preferred in addressing sinus bleeding in endonasal applications.
Sekhar[1285]	2007	4	Retrospective case series	86 Undergoing intracranial surgery with significant venous bleeding where fibrin glue was utilized.	Complication rate; clinical outcomes	Fibrin glue is effective in hemostasis, but 2 events of venous thromboembolism occurred with fibrin glue injection of the superior petrosal sinus.
Tavanaiepour[1286]	2015	4	Case report	1 Undergoing intracranial surgery with cavernous sinus bleeding	Complication	Fibrin glue is effective, but this case report demonstrated a cranial nerve V deficit, probably from compression by the fibrin glue.
Ellegala[1287]	2002	4	Retrospective case series	20 Undergoing surgery where vigorous bleeding was encountered and traditional methods of hemostasis failed. Flowable gelatin-thrombin matrix was used in all cases.	Complication rate; clinical outcomes	Gelatin matrix + thrombin is effective and safe.
Fiss[1289]	2007	4	Retrospective case series	5 Undergoing intracranial surgery with significant venous or sinus bleeding where flowable gelatin-thrombin matrix was used in all cases.	Complication rate; clinical outcomes	Gelatin matrix + thrombin is effective and safe.
Kassam[1283]	2005	4	Observational	400 Patients who underwent endoscopic neurosurgery.	Complication rate; clinical outcomes	The use of angled bipolar forceps with pistol-grip mechanisms are preferred in addressing venous bleeding in endonasal applications. Warm saline irrigation that is "warm to the touch" is effective in venous hemostasis
Fujita[1293]	2010	N/A	Mouse study	6 Mice in each group, 8 groups total	Quantifiable bleeding points	ACF-95 was superior to normal saline in hemostasis. ACF-95 and lactated ringers were equivalent in efficacy. Normal saline with the addition of calcium and potassium were superior to normal saline alone.

LOE = level of evidence; N/A = not applicable.

the literature allows for an evidence-based approach for their use.

XII.C.1 Perioperative antibiotics

EEAs to the skull base utilize corridors through the nasal cavity and paranasal sinuses to reach the sterile intracranial cavity. The presence of a normal sinonasal microbiome[1295] and, in patients with sinusitis, pathogenic bacteria, conveys a theoretical risk of postoperative intracranial infection with these procedures. However, the risk of postoperative meningitis is low[1164] and antibiotic use has several risks, including adverse effects and allergic reactions to the medication, disruption of the normal gastrointestinal flora resulting in infectious colitis (*Clostridium difficile*), and development of drug-resistant organisms. Therefore, understanding the available evidence for antibiotic prophylaxis in ESBS is important to guide judicious perioperative protocols.

Prior to the regular utilization of ESBS, 3 studies evaluated the role of antibiotics in open and microscopic approaches to the skull base.[54,1296,1297] Because the 3 studies covered procedures that were inherently different from endonasal surgery in addition to other study limitations (eg, single institutions, nonrandomized), it is difficult to draw conclusions that can extrapolate to ESBS. It appears, however, that the risk of meningitis with microscopic transsphenoidal surgery is low (0.7%) when a single antibiotic (cefuroxime) is given 30 minutes prior to surgery and 8 hours after the first dose.[1297]

There have been 4 studies evaluating the role of antibiotics in ESBS over the past decade.[1298–1301] All of these studies are single institutional, nonrandomized and include a variety of skull-base approaches and pathologies. Three were retrospective[1298,1300,1301] and 1 was prospective.[1299] The studies looked at a median of 162 pathologies (range, 90-2032 pathologies), of which 80.5% were microadenoma, macroadenoma, or craniopharyngioma (standard deviation [SD] 10.1; range, 71% to 94%) with the remainder representing an assortment of anterior skull-base pathologies. Two of the studies did not have exclusion criteria,[1298,1299] the other 2 studies excluded patients felt to be at elevated risk of postoperative complications.[1300,1301] In addition, there was a systematic review of open, microscopic, and endoscopic approaches to the skull base,[1302] which included the studies listed here that had been published at that time.[54,1296–1299] However, the authors were not able to perform a meta-analysis given the heterogeneity of the studies.

The antibiotic protocols reported in the purely endoscopic studies varied. Three of the studies used a single antibiotic: cefazolin,[1299–1301] or ampicillin/sulbactam,[1301] with vancomycin, clindamycin, or clarithromycin reserved for patients with sensitivities to the first-choice agent. Orlando et al.[1298] primarily utilized amikacin with either ceftazidime or ceftriaxone. The earlier studies had antibiotic durations for 1 to 3 days,[1298,1299] whereas the more recent studies gave antibiotics 30 minutes prior to surgery with or without a single postoperative dose 6 to 8 hours after surgery.[1300,1301] The majority of the reviewed studies did not mention postoperative nasal packing. When mentioned, the authors did not specify the type of packing or duration of packing. Additionally, the use of nasal packing was not assessed as an independent factor for outcomes including infectious complications. The 2016 systematic review by Rosen et al.[1302] did not find any evidence linking the use of nasal packing or the duration of nasal packing to infectious complications or duration of antibiotics.

Interestingly, the rate of postoperative bacterial meningitis is lower among the studies of endoscopic approaches to the skull base (mean, 0.31%; SD, 0.36; range, 0% to 0.69%) relative to those evaluating open approaches (mean, 3.15%; SD, 1.63; range, 2% to 4.3%), although statistical comparison is not feasible. Among the studies of endoscopic skull-base procedures, only 1 looked at factors associated with postoperative meningitis, and found significantly higher rates among patients with a postoperative CSF leak (OR, 20.79; 95% CI, 5.64 to 76.63; $p < 0.001$), as well as those with malignant pathology (OR, 8.31; 95% CI, 1.180 to 36.81; $p = 0.020$).[1301] No studies were able to identify an association between postoperative meningitis and choice of antibiotic agent or antibiotic duration. None of the studies looked at complications from the antibiotics.

There are several limitations to the available literature. The nonrandomized nature of these studies as well as a lack of a nonantibiotic control arm precludes any definite conclusions. In addition, there are many potentially confounding variables, including patient comorbidities, extent of surgery, types of skull-base pathology, use of LD, differences in surgical technique, and postoperative care, any of which may influence rates of postoperative complications. Although a major factor driving the decision of antibiotic choice is the risks associated with unnecessary antibiotic usage, none of the studies report antibiotic-related complications. Finally, because meningitis after ESBS has a low incidence, a properly powered, randomized study would require an impractically large number of patients.

In conclusion, the literature for perioperative antibiotics in ESBS is limited and does not allow for definitive conclusions regarding the safety and impact of antibiotics on postoperative infectious complications. The studies do suggest a low rate of meningitis with short-term perioperative antibiotics, which may be an option for ESBS. A higher rate of infectious complications in patients with postoperative CSF leak and those undergoing surgery for malignancy may indicate a preferential role of antibiotics in these settings. Additional research is required to elucidate this question.

- Aggregate Grade of Evidence: C
- Summary: The overall evidence is limited. Antibiotics more likely to benefit patients with postoperative CSF leak and those undergoing surgery for malignancy

XII.C.2. *Tissue sealants*

Successful reconstruction of the skull base is an essential aspect of ESBS. Although a variety of techniques and materials have been described, the primary common objective is to prevent a postoperative CSF leak. In this regard, tissue sealants are frequently used as a final step of the reconstruction.

There are several commercially available tissue sealants that have been evaluated with in vitro and in vivo models. Fibrin-based sealants stimulate the final phase of the coagulation cascade by combining thrombin and fibrinogen. Beriplast P (CSL-Behring, Tokyo, Japan) has been studied with in vitro experiments utilizing synthetic materials and has been shown to withstand an average pressure of 32 cm H_20 ten minutes after application and more than 40 cm H_20 of pressure after 24 hours.[1303] This ability to withstand pressure increases as the ratio of fibrinogen to thrombin increases.[1304] Another fibrin-based sealant, Tisseel (Baxter Inc., Mississauga, ON, Canada) has been evaluated both in vitro[1305] and in vivo,[1306] showing improved graft adherence and overall increased ability to withstand burst pressure compared to the control arm (14.9 ± 1.5 vs 3.9 ± 0.7 psi; $p < 0.001$).

There are several non–fibrin-based tissue sealants available. Bioglue (Cryolife Inc., Kennesaw, GA) is a tissue glue made of bovine serum albumin and glutaraldehyde which crosslink when combined in a special applicator. Duraseal (Integra LifeSciences Corporation, Plainsboro, NJ) is a synthetic polyethylene glycol dural sealant that is designed to hold dura closed for 4 to 8 weeks while healing occurs. There have been 2 in vitro studies comparing the various tissue sealants. Utilizing a pressure chamber system with cadaveric dural samples, a gain in leak pressure compared to dural substitute was noted for all studied sealants, with higher pressures for the fibrin sealant Tachosil (Nycomed, Linz, Austria) and Duraseal compared to Bioglue and Tissucol (Baxter AG, Vienna, Austria) (+22.22 mmHg, +23.53 mmHg, +12.19 mmHg, and +3.28 mmHg, respectively; $p = 0.001$).[1307] Another study evaluating the use of Tisseel and Duraseal in combination with various grafting materials found that overall, the tissue sealants were able to withstand similar burst pressures, but that the combination of Tisseel and pig pericranium formed the strongest barrier to leak when compared to any combination of Tisseel or Duraseal and Alloderm, Durasis, or Pericranium (12.5 mmHg Alloderm and Duraseal; 21.8 mmHg Durasis and Duraseal; 44.7 mmHg Pericranium and Duraseal; 30.6 mmHg Alloderm and Tisseel; 15.8 mmHg Durasis and Tisseel; 95.5 mmHg Pericranium and Tisseel; $p < 0.0001$).[1308]

Prior to the era of advanced ESBS, several studies evaluated the use of fibrin-based sealants used in place of autologous tissues such as fat or muscle in microsurgical approaches to the sella and parasellar regions. These found comparable rates of postoperative CSF leak compared to earlier studies that did not use fibrin sealants. Van Velthoven et al.[1309] retrospectively reviewed 126 patients who underwent microsurgical resection of sellar pathology and had the sella reconstructed with pieces of septal bone in addition to Beriplast fibrin glue. Two of the 15 patients with intraoperative CSF leak developed postoperative CSF rhinorrhea. Seda et al.[1310] retrospectively evaluated 567 patients who underwent microsurgical resection of pituitary or sellar tumors. In the 64 patients who developed intraoperative CSF leak, a fibrin glue (Beriplast) was used to fill the intrasellar space, and only 1 of these patients suffered from a postoperative CSF leak. Although these were single-cohort studies, their rates of postoperative CSF leak were similar to prior studies utilizing autologous tissue for sellar reconstruction (1.5-9.6%).[1311–1324]

There have been several retrospective clinical studies evaluating fibrin-based sealants in ESBS as part of a multilayered skull-base reconstruction in cases in which an intraoperative CSF leak was encountered. Cappabianca et al.[1324] found that the combined use of the fibrin sealant Tissucol and collagen fleece (Tissufleece E; Baxter AG, Vienna, Austria) resulted in a lower rate of postoperative CSF leak compared to Tissucol use alone (0% vs 12.5%). Yano et al.[1325] found significantly lower rates when a sheet of polyglactin acid was used in addition to the fibrin-based sealant Bolheal (Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan), with or without autologous fat used to fill the sellar defect. When fibrin glue only was used, the leak rate was 33.3%, which compared to 26.7% when a mucosal patch was used with fat, 5.9% when a mucosal patch was used without fat, and 0% when a polyglycolic acid (PGA) sheet was used with fibrin glue. Cappabianca et al.[246] reviewed their experience with 40 cases in which Tisseel was used as a part of a multilayered skull-base reconstruction instead of abdominal fat with no postoperative CSF leaks. The same group later reported successfully using Tisseel in 9 awake patients with CSF leaks in the early postoperative period after ESBS, 4 of whom also had a lumbar drain placed.[1326]

Bioglue and Duraseal have also been evaluated in retrospective clinical studies. Bioglue has been shown in single-institutional case series to be a useful adjunct in skull-base reconstruction. In a prospective single-cohort study of 32 patients who underwent microsurgical resection of lesions in the sellar region, the skull-base defect was reconstructed with autologous abdominal fat, autologous bone fragments from the sphenoid, and Bioglue, and there were no cases of postoperative CSF leak.[1327] In a larger retrospective single-cohort study of 124 patients who underwent microsurgical resection of pituitary tumors, 124 (44%) developed an intraoperative leak and all skull-base defects were reconstructed with BioGlue and collagen sponge with or without titanium mesh buttress or abdominal fat graft. The rate of postoperative CSF leak was 1.6%, which compared favorably to prior studies.[1328] Although there is a theoretical concern regarding the glutaraldehyde component causing damage to neurologic tissue, this has not been reported, likely because of the several layers of repair between brain parenchyma and the Bioglue. Nevertheless, it carries a warning for nerve toxicity and tissue necrosis. Duraseal

was evaluated in a small retrospective study of 5 patients undergoing ESBS in which an intraoperative CSF leak was encountered, with similar rates of postoperative CSF leak compared to Tisseel.[1329]

There are several potential drawbacks to using a tissue sealant. Most of the fibrin-based sealants (Beriplast, Tisseel, Tissucol, Tachosil, and Bolheal) are made from pooled donor human plasma with additional equine collagen (Tachosil), whereas Bioglue contains bovine proteins, incurring the risk exist of transmitting various blood-borne viruses, prion disease, or allergic reaction to the foreign proteins. These risks are minimized if autologous blood is utilized, such as with Vivostat (Vivostat A/S, Alleroed, Denmark).[1330,1331] Additionally, the use of tissue sealants does increase surgical costs.[1332] Moreover, the additional benefit of using a tissue sealant in a multilayered reconstruction with a vascularized NSF is unclear. In a retrospective study of 74 patients with high-flow intraoperative CSF leaks repaired with multilayered reconstruction utilizing an NSF, no difference was found in the rates of postoperative CSF leak between those that used a tissue sealant (Duraseal or a fibrin-based sealant) and those that did not.[1333] Finally, none of these products are U.S. Food and Drug Administration (FDA)-approved for ESBS.

In conclusion, although it appears that tissue sealants increase the ability to withstand pressure based on data from in vivo and in vitro studies, the evidence to support their use in ESBS is limited to small, single-institution, retrospective studies. Drawing definitive conclusions from these studies is limited given the significant flaws in study design, including sample size, heterogenous patient and tumor variables, and variety of reconstruction materials and techniques. It is therefore difficult to determine the optimal role for tissue sealants. In cases where an intraoperative CSF leak is encountered, the cumulative clinical experience supports the need for a robust multilayered reconstruction with meticulous surgical technique. Although use of tissue sealants may be an appropriate adjunct in skull-base reconstruction, further research is required to understand the indications and benefits.

- Aggregate Grade of Evidence: D
- Summary: Evidence is limited. Option as an adjunct in multilayered skull-base reconstruction to potentially reduce rate of postoperative CSF leak.

XII.C.3. *Nasal packing*

Nasal packing is often used to line the nasal and sinus cavities at the conclusion of ESBS. Theoretical benefits for nasal packing include hemostasis, support and decrease the risk of migration of the skull-base reconstructive materials, stenting of the sinonasal outflow tracts, and providing a barrier between the intracranial cavity and the external environment. However, it is unclear if these potential benefits outweigh the theoretical risks and limitations, including infection risk, synechia formation, patient discomfort, and additional costs.

There are several different types of packing material that may be used. Absorbable packing, such as Nasopore (Stryker, Kalamazoo, MI), gelfoam (Pfizer Inc., New York, NY), and Merogel (Medtronic, Minneapolis, MN) may be used but often require saline irrigation and office debridement for complete removal. The use of nonabsorbable packing products, including Telfa (Kendall Company, Walpole, MA) and Merocel sponges (Medtronic, Minneapolis, MN) has been reported,[1072,1135] but requires removal and antibiotic prophylaxis. Use of an inflatable balloon to fill a large cavitary defect and support the skull-base repair has also been described as part of a strategy to reduce postoperative CSF leak.[227] However, none of these studies specifically reported the indications and impact on outcomes of the packing. Moreover, several other large series do not mention nasal packing,[252,1073,1104,1334–1336] whereas 1 of the largest studies, with over 1000 patients, reported not using nasal packing unless copious bleeding was encountered.[1337]

In a study of 100 endoscopic transsphenoidal surgeries for pituitary lesions, Little et al.[1263] evaluated determinants of sinonasal QOL as measured by the Anterior Skull Base Nasal Inventory-12, with nasal packing being 1 of the studied variables. In this prospectively enrolled cohort, nasal splints were used in 13%, absorbable nasal packing was used in 20%, and nonabsorbable nasal packing was used in 8%. Use of nasal splints or nasal packing was not determined based on any specific indication or algorithm, but rather at the discretion of the surgeon. The authors found that nasal splints decreased the sinonasal QOL at 2 weeks and that the use of absorbable nasal packing decreased sinonasal QOL at 3 months. In this study, the other outcomes possibly affected by nasal packing, including postoperative bleeding and CSF leak, were not reported.

In conclusion, a variety of nasal packings may be used as a complement to skull-base surgery. The decision to use and the type of packing used is likely based on surgeon preference. Although both theoretical benefits and deterrents for use of packing in this setting exist, the scientific literature investigating this issue is not adequate to make any definitive conclusion. Current common practice includes the use of some type of packing following skull-base reconstruction with intraoperative CSF leak, but further research is required to determine the role of packing in the setting of ESBS.

- Aggregate Grade of Evidence: D
- Summary: The evidence is limited. Option as an adjunct based largely on surgeon preference that may help with hemostasis, decreased risk of migration of other reconstructive materials, and stenting of sinonasal outflow tracts.

XII.D. Imaging techniques for ESBS

This section reviews the evidence for imaging in the preoperative, intraoperative, and postoperative periods of endoscopic, endonasal anterior skull-base tumor surgery. The

challenge with this review is the lack of RCTs evaluating imaging techniques. Nonetheless, it appears that developments in imaging have been an integral part of ESBS, but this EBR focuses on cohort studies with appropriate comparison groups. Cohort studies included were retrospective unless otherwise specified.

XII.D.1. *Preoperative imaging for intraoperative stereotactic guidance and navigation*

Evidence for imaging for the initial diagnosis of skull-base tumors is not discussed in this review. Instead, it focuses on the role of preoperative imaging coupled to computer navigation platforms as a surgical adjunct. Image guidance is endorsed by The American Academy of Otolaryngology–Head and Neck Surgery, specifically in pathologies involving the skull base.

Intraoperative fluoroscopy was routinely utilized for navigation in transsphenoidal surgery since it was popularized in the 1960s by Jules Hardy.[1338] However, multiplanar navigation with preoperative imaging has largely supplanted fluoroscopy in current clinical practice.[229]

XII.D.1.a. CT. The search for stereotactic navigation with multiplanar preoperative imaging identified 347 papers, with only 1 cohort study comparing stereotaxy to a control group without stereotaxy.[1339] In this study for recurrent, nonfunctioning pituitary adenomas, Lasio et al.[1339] evaluated the role of preoperative CT for navigation. There was no difference in morbidity or mortality between cases with navigation (n = 11) vs those without (n = 8). GTR was obtained in 82% vs 75% of patients, respectively. Although setup time was extended by 13 minutes, operative time was reduced in the navigation group by 36 minutes. This study showed equivalence of clinical outcomes, and does not necessarily provide support for CT navigation.

In an analysis of a nationwide database by Chung et al.[1340] on transsphenoidal approaches to neoplastic pituitary pathologies, CT-guided cases (n = 1768) when compared to those without image guidance (n = 45,446) had lower CSF leak rates (6.4% vs 8.9%), length of stay (2.9 vs 3.7 days), and cost. There was no difference in mortality. An important limitation of this study is that the database used did not differentiate endoscopic vs microscopic approaches, revision cases, or intraoperative vs postoperative CSF leaks during the index admission. Nevertheless, given the large size of this study, the results do provide support for CT navigation during surgery for pituitary neoplasms.

There were also 3 cohort studies comparing this technique to standard fluoroscopy. Patel et al.[1341] demonstrated in patients with sellar lesions undergoing endoscopic surgery that there was no difference in adverse events between CT guidance and fluoroscopy with respect to residual tumor, CSF leak, DI, and hemorrhage. Time in the operating room was equivalent for both treatment groups. In another cohort study for sellar lesions, Jagannathan et al.[1342] found that operating room time was actually shorter in the CT guidance group (microscope vs endoscope not specified). Eboli et al.[1343] similarly reported in a cohort of patients undergoing microscopic surgery, some with adjunctive endoscopy, decreased operating room time in the image guidance group (MRI co-registered to CT) compared to in the intraoperative fluoroscopy group.

In conclusion, CT is the most commonly-utilized adjunct in endoscopic transsphenoidal surgery across neurosurgical centers.[229] Intuitively, navigation is most helpful in cases of (1) distortion of surgical landmarks by the pathology or prior surgery; (2) anatomical variations as in, eg, a poorly pneumatized sphenoid sinus or medially placed carotid arteries; or (3) large, aggressive tumors invading or displacing surrounding neurovascular structures.

XII.D.1.b. MRI. The literature search did not show any studies comparing MR guidance to a control group without sterotaxy. However, MR guidance has been compared to other methods of stereotaxy. Jagannathan et al.[1342] compared stereotaxy for sellar lesions with preoperative MRI, preoperative CT, or preincisional fluoroscopy. Although there was a decreased rate of CSF leaks in the MR guidance group, there were no statistically significant differences in the rate of complications, which also included visual changes and vascular injury. On the contrary, in the abovementioned nationwide database analysis by Chung et al.,[1340] the MR guidance group (n = 1228) had the highest CSF leak rate, length of stay, and cost relative to the CT guidance or control groups. These results are difficult to interpret given that the database used did not include information on the size and location of treated lesions and therefore may have represented a selection bias. Moreover, a potential confounder was that the MR group had more chronic medical comorbidities prior to surgery.

The role of preoperative MRI for navigation, particularly as a solo modality, may be limited by the fact that the ESBS is primarily based on bony landmarks, for which CT is the preferred study. Literature search did not reveal any head-to-head comparisons of registration accuracy for CT vs MRI. Because these modalities provide complementary information, navigation with CT-MRI fused images can be of benefit, particularly in cases where the MRI obtained is not of navigation quality.[1343]

XII.D.2. *Intraoperative imaging for extent of resection*

Because the approach to skull-base lesions is largely based on bony landmarks, navigation based on preoperative imaging has been incorporated into practice successfully. However, this approach cannot be used to assess the extent of resection because not only the tumor, but also the surrounding neurovascular tissue is subject to shift throughout surgery. Therefore, intraoperative imaging with various modalities has been used to provide immediate feedback to the surgeon regarding extent of resection, as well as

imminent postoperative complications, eg, bleeding. In this section, we review intraoperative imaging with CT, MRI, ultrasonography, and fluorescent dyes for the purpose of assessing extent of resection.

XII.D.2.a. CT. The search on intraoperative CT (iCT) led to 17 studies, none of which compared iCT to a control. One cohort study studied the effects of iCT in addition to endoscopy, compared to resection with the microscope without iCT, and hence was not included in this review.[1344] There was 1 case series for pituitary adenomas by Mori et al.,[1345] in which iCT with contrast was performed when tumor removal was thought to be complete or no longer possible using the endoscope. The authors found that the results of iCT led to further resection in 25% of their cases. Overall, there is limited evidence to support the use of iCT in evaluating the extent of resection.

XII.D.2.b. MRI. Intraoperative MRI (iMRI) has been much more widely used to evaluate extent of resection, with 89 identified studies, only 2 of which were cohort studies.

The 2 cohort studies compared the rate of GTR after surgical resection with or without iMRI. In a matched cohort study of microsurgery for nonfunctioning pituitary adenomas, Berkmann et al.[172] found that use of low-field (0.15-T) iMRI was associated with a higher rate of GTR in the iMRI group (85%; n = 60) compared to the control (69%; n = 32). In another cohort study of microsurgery for sellar lesions conducted by Coburger et al.,[1346] high-field (1.5-T) iMRI was associated with a significantly higher GTR of 91% in the iMRI group (n = 44) compared to 73% in the control group (n = 51), including only those patients in whom the goal was GTR. In cases where subtotal resection was the goal, intrasellar remnant was found at a higher rate in the control group (57%; n = 14) vs the iMRI group (18%; n = 27).

One concern with more aggressive resections enabled by iMRI is an increased risk of complications due to harm to the surrounding normal tissue. In the cohort study by Berkmann et al.,[172] in spite of more extensive resections in the iMRI group, postoperative hypopituitarism was actually lower at 29% compared to 45% in the control group. In the other cohort study by Coburger et al.,[1346] there was no difference in complication rates, which included visual change, hemorrhage, CSF leak, postoperative epistaxis, and mucocele formation.

The clinical significance of this increased rate of GTR is unclear. Berkmann et al.[172] showed that no patient from the iMRI group required additional interventions during a follow-up period of 3.2 years, whereas 13% of patients in the control group required additional interventions. In the study by Coburger et al.,[1346] a more direct Kaplan-Meier analyses was performed, but there was no difference in progression-free survival between the 2 groups over 2 years. There was also no difference in biochemical remission rates in the subset of patients with functioning pituitary adenomas in the latter study.

Interpretation of iMRI requires a significant amount of experience, which presents a significant challenge for establishing its role in surgical decision-making. There have been several studies evaluating the sensitivity and specificity of iMRI for the detection of residual tumor.[172,1347–1353] Accuracy was assessed using the postoperative MRI (obtained 72 hours to 6 months after surgery) as the gold standard, when resorption of blood and reduction of peritumoral edema have taken place. Sensitivity was ≥90% for high-field iMRI, but had a wide range for low-field iMRI (32-100%). Specificity was 100% for high-field iMRI, but likewise had a wide range for low-field iMRI (63-100%).

In summary, although the above data is encouraging, wide adoption of iMRI has been prohibited by its cost, increase in workflow complexity, and prolonged operating room time. Coburger et al.[1346] found that operating room time was nearly 3-fold longer in the iMRI group at 158 minutes vs 58 in the control. In a case series by Gerlach et al.,[1353] operating room time was nearly 2-fold longer at 117 minutes compared to 78 minutes in a historical cohort. Because of the low specificity of iMRI reported in the literature, the Congress of Neurological Surgeons does not endorse use of iMRI for resection control for nonfunctioning pituitary adenomas.[1354]

Both cohort studies cited above (Berkmann et al.[172] and Coburger et al.[1346]) were based on microscopic approaches. However, the current search did identify 13 case series of endoscopic approaches with iMRI, demonstrating the feasibility of combining these technologies. Depending on the proximity of the MRI machine to the operating room, the surgeon must assess whether all equipment remains functional within the magnetic field of the MRI, including the screen on which endoscopic images are displayed.[294]

XII.D.2.c. Ultrasonography. Ultrasonography has the advantage of providing truly real-time image guidance of soft tissue anatomy, ie, tumor and vasculature, and has been widely utilized,[229] in particular to avoid catastrophic vascular injuries.[1219] In spite of its cost and time efficiency, in our ultrasonography search leading to 63 studies, none compared this technique to a control group. At present, ultrasonography cannot be recommended for degree of resection assessment.

XII.D.2.d. Fluorescent dyes. Intraoperative imaging with nonspecific (tissue perfusion) or specific (physiologic) dyes has also been utilized for resection control in neurosurgery. Intraoperative fluorescence imaging has the advantage of being truly real-time, while having the potential to reach unprecedented levels of accuracy. This search on the evidence for intraoperative dyes was limited to case series

and only allows for preliminary data given the nascency of the technique.

5-Aminolevulinic acid (5-ALA) has been studied extensively in malignant gliomas, and has been demonstrated to improve GTR and progression-free survival.[1355] A feasibility study of 5-ALA for pituitary lesions has been conducted by Eljamel et al.[1356] Its use specifically for pituitary adenomas, however, is limited because adenomas exhibit a low rate of 5-ALA–induced fluorescence (8%).[1357] Indocyanine green (ICG), a near-infrared (NIR) fluorescent dye, has been used to delineate perisellar vascular anatomy in 1 case series,[1358] and to distinguish sellar lesions from surrounding parenchyma in 2 case series.[1359,1360] In the latter 2 studies, adenoma fluorescence was noted to have lower signal than that of the surrounding normal pituitary gland.

Preliminary work with OTL38, a folate analog conjugated to an analog of ICG, for pituitary adenomas suggests that it may be possible to delineate tumor margins with a high degree of sensitivity and specificity, specifically in adenomas with high folate receptor α expression.[1361] OTL38 functions in the NIR spectrum because of its conjugation with an ICG analog, and has the additional advantage of being a tumor-specific dye, like 5-ALA.

There is little evidence so far to support the use of fluorescent dyes for resection control, but it may have significant utility in the future.

XII.D.3. *Postoperative imaging for CSF leak identification*

The clinical utility of immediate postoperative imaging (within 24 to 72 hours) to identify complications, and either immediate or follow-up postoperative imaging to detect residual disease, is of relevance in all of neurosurgical oncology. This section focuses on imaging for postoperative CSF leaks, which remain the most common complication following ESBS. A recent meta-analysis showed a leak rate of 2% in endoscopic transsphenoidal surgery for pituitary lesions.[1362] CSF leaks are more common in surgery that extends beyond the parasellar region, with a large series on endoscopic resection of various anterior skull-base neoplasms reporting a rate of 15.9%.[227] Another meta-analysis in endoscopic anterior skull-base surgery showed rates as high as 25% for meningiomas and 22% for chordomas.[1363]

A literature search showed 106 studies on the role of postoperative imaging in the identification and localization of CSF leaks; however, evidence was limited to expert opinion. In general, CSF leaks are primarily diagnosed by clinical findings, eg, headache, rhinorrhea, or otorrhea, in addition to laboratory tests, eg, β-2-transferrin. Utilized imaging modalities include CT, MRI, and CT/MRI cisternography.[1364] Even in the absence of clinical findings, serial postoperative CTs that show increasing pneumocephalus are the most convincing evidence of a CSF fistula.

Use of vascularized flap reconstructions has been associated with a lower leak rate of 6.7% compared to 15.6% with free grafts in a meta-analysis of patients undergoing endoscopic repair of skull-base defects.[477] CSF leak rates have been observed to decrease over time in 2 case series of endoscopic resection of sellar lesions, which the authors note may be in part due to the adoption and further development of vascularized flaps.[274,364] MR features of vascularized flaps may be predictive of CSF leaks. Post-operative enhancement of the flap, although suggestive of preserved vascularity, was not associated with CSF leak rates.[1365] Non-enhancing gaps in the area of reconstruction or displacement of the enhancing flap, suggestive of incomplete coverage of the bony defect, have the potential to be associated with CSF leaks.[1366]

Conclusion

Development of perioperative imaging techniques and clinical studies of their treatment effects are undoubtedly paramount to improve the safety and efficacy of endoscopic, endonasal anterior skull-base surgery. Stereotaxy with preoperative CT is widely utilized in part because of its superior multiplanar depiction of bony anatomy. Extent of resection evaluation with iMRI has been studied by many groups, but prevalent adoption of this technique may be hindered by the prohibitive financial and structural investments requisite for its use, in addition to difficulty in its interpretation. Fluorescent dyes have the potential to provide unprecedented levels of real-time feedback; however, results are preliminary. CSF leaks, which remain the most common morbidity of anterior skull-base surgery, continue to be largely a clinical diagnosis. In summary, further studies are required to establish imaging techniques as standard of care.

XII.E. Role of intraoperative neurophysiology

Since the introduction of transsphenoidal surgery by Schloffer in 1907 and its renaissance in 1960 combined with visualization technological advancements,[231] ESBS has been used to access a very large area of the ventral skull-base to remove tumors, with decreased morbidity and mortality.[426,1367] Intraoperative neurophysiologic monitoring (IONM) in skull-base surgery, which can be grouped into monitoring and mapping techniques, is used to identify and preserve neural structures in a difficult/distorted surgical terrain. Monitoring techniques such as somatosensory evoked potentials (SSEP), free-running electromyography (fEMG) of motor CNs, and transcranial motor-evoked potentials (TMEP) of corticospinal and corticobulbar tracts are used to continuously monitor the integrity of brainstem and CNs during the surgical procedures. Mapping techniques using triggered EMG (tEMG) resulting in compound muscle action potentials (CMAPs) are particularly useful to identify and avoid injury to CNs. These techniques have been used alone or in combination based on the neurovascular structures at risk during ESBS. This section provides a review of the literature and summarizes the

current knowledge on the techniques, utilities, and alarm criteria of various IONM modalities utilized in ESBS.

SSEPs can be obtained by stimulating the mixed peripheral nerves (eg, median, tibial) during ESBS, and the evoked response obtained from the brainstem and the primary contralateral somatosensory cortex can be utilized to monitor the integrity of dorsal columns of spinal cord, medial lemniscus in the brainstem, and its connections to the thalamus and primary sensory cortex. In a large series of 976 consecutive patients who underwent continuous SSEP monitoring during ESBS surgery, significant SSEP changes could identify impending risk to neurovascular structures at risk and prevent permanent neurological deficits.[1368] Table XII.E outlines the techniques of various IONM techniques including SSEPs. Significant changes in SSEPs represent a 50% drop in amplitude and/or 10% change in latency.[1369–1372] In this series, the incidence of significant changes in SSEP during ESBS was 20 in 976 (2%) and the incidence of new postoperative neurological deficits was 5 in 976 (0.5%). The majority (15/20) of SSEP changes were reversed during ESBS based on the information provided to the surgical team, with no postoperative neurological deficits. However, patients with irreversible changes in SSEPs during ESBS eventually had postoperative hemiparesis. In 2 patients, who did not have changes in SSEPs and who had postoperative hemiparesis, the etiology was a lacunar stroke, which could not have been identified utilizing SSEPs. Based on animal studies, significant SSEP changes represent an "electrical failure" without any structural disruption to the cellular structures, which occurs as a result of decrease in cerebral or brainstem perfusion.[1373,1374] This change temporally precedes "ion pump failure" at the cellular level which leads to cellular swelling and eventually to cell death or infarction. Thus, interventions addressed to reverse the significant SSEP changes by increasing perfusion, modifying or pausing the surgical procedure, might prevent neuronal death or infarction in some cases. Resection of tumors in petroclival and brainstem regions and vascular tumors such as cavernomas and hemangioblastomas are most likely to result in SSEP changes due to nerve traction and vascular injury, respectively.[1375–1377] ICA injury is an uncommon and underreported complication of ESBS surgery. In many cases, this can only be effectively addressed by sacrificing the vessel,[1188] usually without any neurological sequelae. Real-time SSEP monitoring during ESBS can provide information about the adequacy of cerebral perfusion and guide the surgical team in evaluating the techniques that can be employed to preserve or sacrifice the vessel. It is also worthwhile to note that though SSEPs are more affected by inhalational than intravenous anesthetic agents,[1378,1379] adequate continuous real-time monitoring can be reliably performed under steady-state inhalational anesthetic regimen.

CNs can be continuously monitored during tumor removal using EES by fEMG. Significant fEMG activity can be seen secondary to unintended activation of muscles supplied by a CN during ESBS. They are characterized as spikes, bursts, and neurotonic discharges based on the frequency and amplitude of EMG discharges.[1380–1382] fEMG activity secondary to irrigation of the surgical field, lighter levels of anesthesia, or mechanical movement of the electrodesis are not considered significant.[1383] Neurotonic fEMG discharges are sudden onset, irregular, high-amplitude, and high-frequency discharges (>200 Hz) of longer duration (>30 seconds) indicating potential CN injury.[1380] Single-institutional experience of fEMG monitoring during ESBS from 696 extraocular CNs (CN III, IV, VI)[1384] and 342 lower CNs (CN VII, IX, X, XI, XII) indicate that fEMG activity is seen in 12% of the extraocular CNs and 18% of lower CNs, indicating that fEMG is very sensitive in identifying the location of the CN during surgery.[1385] Patients who underwent repeat procedures or previous radiation surgery had increased incidence of fEMG activity due to the presence of adhesions. Although fEMG may be used to avoid damage to neural structures by identifying neural structures, it has limited value in predicting postoperative CN function.[1384,1386] The absence of fEMG activity can sometimes provide a false sense of security about the location and proximity of the CNs during ESBS. It is important to note that if a CN is abruptly transected, there may be only brief or no EMG activity.[1387] It has been suggested that the use of the tEMG technique can identify and detect CN deficits.

tEMG activity is a CMAP response that is obtained by direct stimulation of CNs at the base of the skull during ESBS and recorded by electrodes placed in the muscles supplied by the CN. These responses can be characterized based on the latency, amplitude, and threshold of the current stimulation.[1388] Studies involving traditional skull-base approaches and the use of facial nerve monitoring with tEMG have noted that changes in stimulation threshold, onset latency, and CMAP amplitude can be predictors of postoperative CN function.[1386,1389–1391] Loss or change of previously recorded CMAP threshold proximal to the tumor during ESBS indicate transection of a nerve during surgery.[1390] The significant challenge in CMAP response for CNs is lack of normative data for the onset latency and amplitude during the ESBS or conventional skull-base approach to determine significant changes. Based on published reports on conventional skull-base surgery and University of Pittsburgh experience during ESBS (unpublished data, University of Pittsburgh, Thirumala P, Gardner P, Wang E, Snyderman C), monitoring extraocular CNs is particularly useful in surgeries of the clivus, cavernous sinus, pons, and midbrain; trigeminal nerve in surgeries involving Meckel's cave and the infratemporal fossa; and facial nerve and lower CNs in surgeries involving the petroclival region.[1377,1385,1392,1393]

The utility of TMEP in identifying damage to motor tracts has been demonstrated in various intracranial and spinal surgeries.[1394–1398] The data on use of transcranial electrical corticospinal and corticobulbar MEP[1399–1403] is limited to conventional skull-base surgery. It has been suggested that corticobulbar MEP amplitude changes have been

TABLE XII.E. Recording techniques of IONM modalities

IONM modality	Stimulating electrode placement	Recording electrodes	Specifications	Alarm criteria
SSEP	Subdermal needle electrodes Median N: cathode between tendons of palmaris longus and flexor carpi radialis; anode 2 cm distal to the wrist crease Ulnar N: cathode between tendons of flexor digitorum superficialis and flexor carpi ulnaris; anode 2 cm distal to the wrist crease Posterior tibial N: cathode on posterior portion of medial malleolus; anode 2 cm distal to the cathode	Subdermal needle electrodes positioned according to International 10-20 system Ulnar/median: CP3 or CP4; Posterior tibial N: CPz for cortical recordings C2 for subcortical recording All sites are referenced to Fz	Pulse duration: 0.3 ms Frequency: 2–5 Hz Intensity: 25–45 mA for UL; 35–50 mA for LL Recording epoch: 50 ms for UL; 100 msec for LL Bandpass filters: 30–300 Hz for cortical recordings; 30–1000 Hz for subcortical recordings Recordings are averaged over 128 or 256 trilas	50% Drop in amplitude and/or 10% change in latency
Transcranial MEP	Corkscrew or subdermal needle electrodes Corticospinal: Left hemisphere: C1 anode/C2 cathode and C3 anode/Cz cathode Right hemisphere: C2 anode/C1 cathode and C4 anode/Cz cathode Corticobulbar: C3/C4 anode and Cz cathode	Positioned at bilateral abductor pollicis brevis or first interdigitorum muscles and tibialis anterior or abductor hallucis muscles	Multipulsed (3–9) train of square wave constant voltage stimuli of 50 to 75 μsec duration with an interstimulus interval of 1–4 ms. Stimulation may result in brief movement and surgery needs to be paused. Insert tongue bite to avoid injury during twitching Recording epoch: 100 ms Bandpass filters: 10–3000 Hz for corticospinal MEP; 10–100 Hz for corticobulbar MEP	Complete disappearance or >50% drop in amplitude or increase in stimulation intensity of more than 20 mA to elicit a response
fEMG	—	Subdermal or intramuscular needle electrodes in superior/inferior rectus (III N), superior oblique (IV N), lateral rectus (VI N), masseter/temporalis (V N), orbicularis oculi (VII N), soft palate (IX N), surface mounted electrode on ET tube over vocal cords (X N), trapezius (XI N), tongue (XII N)	Bandpass filter: 10–3000 Hz Gain: 50–200 μV	Sudden onset, irregular, high-amplitude, and high-frequency neurotonic discharges (train activity on loudspeaker monitoring)
CMAP	Monopolar stimulation: For probing proximity to neural structures. Cathodal stimulation using fine tipped stimulator with anodal electrode on the frontozygomatic bone. Bipolar stimulation widely used to identify a nerve assess stimulus threshold and CMAP amplitude	Needle or wire electrodes positioned as in fEMG and 1 or more muscles on the contralateral side for corticospinal tract assessment	Rectangular pulses of 0.2 msec duration Frequency: 1–3 Hz constant current stimulation Intensity: 0.5–3 mA for ocular motor nerves; 0.1–0.3 mA for other cranial nerves and small increments are made to find the point of lowest threshold Recording epoch: 20–50 ms	Decrease in amplitude responses or increased stimulation threshold

CMAP = compound muscle action potential; ET = endotracheal tube; fEMG = free running electromyography; IONM = intraoperative nerve monitoring; LL = lower level; SSEP = somatosensory evoked potential; UL = upper level.

correlated with postoperative nerve function. In large tumors that encompass CNs completely, corticobulbar MEP maybe more helpful than tEMG during initial tumor debulking because it can provide information about the integrity of the CNs before obtaining tEMG response via direct stimulation. Although not performed widely, corticospinal MEP has the potential to serve as a useful adjunct in monitoring corticospinal changes during petroclival tumor resection.[1377]

As ESBS gains wider acceptance because of its direct and minimally invasive approach, neurophysiological monitoring can improve the identification and possibly prevention of neurovascular deficits. Advances in neuromonitoring techniques have been proven to be cost effective and positively impact the QOL by preserving CN and long-tract function[1404] in conventional skull-base surgeries. A comprehensive approach to neurophysiological monitoring utilizing the modalities based on the neurovascular structures at risk can be similarly valuable. This approach should be undertaken with a clear understanding of limitations and benefits of each monitoring modality. Future research on the use of tMEPs, cortibulbar, and corticospinal MEPs to evaluate the integrity of the neural pathways may be beneficial.

XIII. Cost utility of ESBS

Over the past 2 decades, rapid expansion of EEA has emerged in the treatment of sinonasal and skull-base tumors. In the early to mid-1990s, the endoscope was successfully employed for endonasal transsphenoidal approaches to the sella.[1405] Since then, numerous systematic reviews and meta-analyses have been performed, comparing and reporting the surgical efficacy and effectiveness of both microscopic and endoscopic transsphenoidal approaches.[1406–1408] These advancements led to expansion of the use of the endoscope for resection of other types of skull-base lesions beyond the sella, including benign and malignant skull-base tumors.

Due to this proliferation of endoscopic approaches to the skull base, it is important to consider the utilization of healthcare resources being used to supplant traditional techniques.[1409] Decisions to implement or compensate novel treatment algorithms/techniques are increasingly contingent on cost-effectiveness analyses. These methods are used to weigh the cost-effectiveness of novel techniques so that policy makers, physicians, and patients can compare the costs and health outcomes of interventions to determine which intervention or policy is optimal based on society's willingness to pay.[1408,1410,1411]

When critically appraising economic decision analyses and cost comparisons studies, it is imperative to understand the importance of the use of sensitivity analyses. Estimates of cost, outcomes, and other variables routinely utilized in a cost analysis are subject to some ambiguity and/or variability. Consequently, a sensitivity analysis should be performed to assess the plausible deviations in the variables that are considered to have significant uncertainty and that would ultimately affect the results of the analysis.[1412] Other attributes of cost analyses that should be included to improve the quality of the data produced are as follows: reporting specific comparators (1 intervention vs another), discussing the perspective of the cost analysis (society, third-party payers, hospital, etc.), accounting of direct and indirect costs, as well as consideration of the time horizon of the study (costs change and accrue differently over time). Additional factors that improve the methodology include: reporting of whether average or marginal costs are being considered, considering discounting (how passage of time alters value of costs—including inflation), and the type of modeling being used for the analysis.[1412]

The current published literature on the cost-effectiveness of ESBS is in its infancy, with all data having been published between 2006 and 2017 (Table XIII).

Analogous to the early applications of the endoscope used to approach the skull base, the vast majority of the current cost data report those associated with transsphenoidal sellar approaches, primarily between the use of microscopic and endoscopic techniques.[282,1408,1409,1411,1413–1416] Other studies have examined costs associated with endoscopic endonasal resection of meningiomas, sinonasal malignancies, as well as intra-arachnoidal pathology.[1417–1419] One study assessed the costs associated with ESBS in the pediatric population.[1420]

Although the current data are not robust, it appears that the best early literature on cost indicate a cost benefit for performing EEA over microscopic approaches for sellar pathology (Table XIII). Oosmanally et al.[1411] was 1 of the first authors to report that EEA was less costly than the microscopic approach (cost difference per patient per procedure of $5582 for EEA and $9567 for microscopic approach). However, a major weakness of this study was not patient outcomes or QOL metrics between the procedures in their analysis.[1411] Shortly thereafter, Rudmik et al.[1408] incorporated the procedural cost data from Oosmanally et al.[1411] to perform the most complete cost analyses to date by determining the incremental cost-effectiveness ratio (ICER, a commonly equation used in economic analyses that provides vital information to resource allocation decision makers) for the 2 approaches. Rudmik et al.[1408] reported that EEA was more cost-effective $17,244.63 with 24.30 quality-adjusted life years (QALYs) compared to the microscopic approach $23,756.60 with 24.20 QALYs from a third party-payer perspective. One other level 1 study by Jethwa et al.[1413] reported the cost-effectiveness of either microscopic approach or EEA vs medical therapy in the management of prolactinomas from a third party-payer perspective. They found that microscopic approach was most cost-effective at 5 years whereas EEA was most cost-effective at 10 years. Interestingly, medical therapy was found to be most costly at both time horizons. The authors concluded that EEA was the most cost-effective treatment strategy in the long term.[1413] Other authors have reported

TABLE XIII. Cost utility of ESBS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Rudmik[1408]	2015	1b	Markov decision tree economic evaluation from 3rd party payer perspective	EEA vs MA for pituitary adenomas	1. Cost per QALY	1. EEA is more cost-effective $17,244.63 with 24.30 QALYs compared to the MA $23,756.60 with 24.20 QALYs.
Oosmanally[1411]	2011	1c	Comparative cost analysis with sensitivity analysis of contributing variables	EEA vs MA (SLTS) for pituitary adenomas	1. Real cost 2. Sensitivity of variables contributing to cost	1. EEA is less costly than SLTS at an academic medical center. 2. LOS, nursing care and oerating room time contribute most to overall cost.
Jethwa[1413]	2016	1b	Decision tree economic evaluation from 3rd party payer perspective	EEA vs MA for prolactinomas vs medical therapy	1. Cost-effectiveness at 5 year and 10 year time points	1. MA was most cost-effective at 5 years. 2. EEA was most cost-effective at 10 years. 3. Medical therapy most costly at both time horizons. 4. ICER of $80,235 at 5 years. and $40,737 at 10 years.
Azad[1414]	2017	4	Retrospective observational administrative database study	EEA vs MA for sellar lesions	1. Estimates of cost 2. Clinical outcomes	1. Total index payment was higher for EEA ($32,959) vs MA ($29,977). 2. No difference in long-term payments 3. EEA benefits not seen at population level
Little[282]	2014	4	Comparative cost analysis of hospital charges	EEA vs MA for pituitary lesions	1. Mean hospital charges 2. Variable influencing charges	1. No statistical difference in mean charges between procedures. 2. LOS and Cushing's disease were primary drivers of charges.
McLaughlin[1415]	2014	2c	Activity-based cost analysis	Consecutive patients having endoscopic pituitary surgery after QII	1. Cost of care	1. Most costly parts of care were operating room costs and inpatient care = made >60% of costs 2. Costs related to readmission/reoperation were <5% of care costs.
Eseonu[1416]	2018	4	Comparative cost analysis	EEA vs MA for sellar lesions	1. Inpatient costs 2. QALYs 3. Clinical outcomes	1. EEA was less costly ($19,736) than MA ($22,853). 2. QALY, LOS, and outcomes were similar between approaches.
Little[1409]	2013	4	Retrospective observational database study	Patient undergoing transsphenoidal surgery for Cushing's disease – includes both EEA and MA	1. Mean hospital charges 2. Resource utilization drivers	1. Mean hospital charges were $48,272 ± $32,600. 2. LOS, surgeon volume, hospital characteristics, and postoperative complications had most influence on resource use.

(*Continued*)

TABLE XIII. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Fu[1417]	2017	4	Comparative cost analysis	EEA vs OA for resection of a variety of sinonasal malignancies involving skull base	1. In-hospital costs 2. Complications 3. LOS	1. Free-flaps conferred higher cost, operating room time, and LOS. 2. Surgical approach (EEA vs OA) was not a predictor of any financial outcome. 3. Intuitional protocol mandating ICU admissions may account for lack of cost savings for EEA group.
Gandhoke[1418]	2017	2b	Decision tree economic evaluation from medical center perspective	OA (supraorbital) vs EEA for olfactory grove meningiomas	1. Costs based on GTR and CSF leak rates in author's series and literature for EA	1. OA was less costly ($29,423) than EEA ($83,838)
Morita[1419]	2006	5	Retrospective observational database study	Patients having endoscope used for cisternal pathology and EEA	1. Usefulness of endoscope 2. Clinical outcomes 3. Cost	1. Endoscope can be safely used for microneurosurgical procedures with good outcomes 2. Average cost of use of endoscope per patient was $326
Stapleton[1420]	2015	4	Activity-based cost analysis	Children (ages 1–19) undergoing EEA for skull-base lesions	1. Cost of care 2. Costs comparison of various pathologies	1. Cost of care for EEA in children was $34,056/patient. 2. Angiofibromas were most costly ($59,051) and fibro-osseous were least costly ($10,931/patient).

CSF = cerebrospinal fluid; EEA = endoscopic endonasal approach; ESBS = endoscopic skull-base surgery; GTR = gross total resection; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; LOE = level of evidence; LOS = length of stay; MA = microscopic approach; OA = open approach; QALY = quality-adjusted life-year; QII = quality improvement initiative; SLTS = sublabial transseptal.

the cost-benefit of EEA over other interventions but the level of data is substantially less due to the deficiency of sensitivity analyses.[1416]

In contrast to the above data, several authors have performed level 4 studies that report less favorable cost scenarios for EEAs.[282,1414] Azad et al.[1414] completed a level 4 retrospective, observational administrative database study that reported the total index payment was higher for EEA ($32,959) vs microscopic approach ($29,977) and that EEA benefits were not seen at population level. However, no ICERs or sensitivity analyses were carried out.[1414] Little et al.[282] reported inpatient resource utilization between EEA and the microscopic approach in patients with pituitary lesions and found no statistical difference in mean charges between the 2 procedures.

In terms of resource utilization drivers, most published studies agree that length of hospital stay (LOS), hospital/nursing care, as well as operating room time contribute most to overall costs related to EEAs and microscopic approaches to the pituitary.[282,1409,1411,1415,1416] Other variables reported to influence costs were a diagnosis of Cushing's, surgeon volume, hospital characteristics, and postoperative complications.[282,1409]

The remainder of the available cost literature is quite heterogeneous and is noted to have lower levels of quality (Table XIII). Fu et al.[1417] compared costs EEA vs open approaches for resection of a variety of sinonasal malignancies involving the skull base. They reported that the surgical approach (EEA vs OA) was not a predictor of any financial outcome but with the caveat that institutional protocols of mandating ICU admissions possibly accounted for lack of cost savings for the EEA group.[1417] Morita et al.[1419] simply discussed the cost and safety of utilizing the endoscope for neurosurgical procedures. Stapleton et al.[1420] reported that costs associated with EEA in children was on average $34,056 per patient (angiofibromas were most costly at $59,051 per patient, and FOLs were least costly at $10,931 per patient).

Last, Gandhoke et al.[1418] performed a decision-tree economic evaluation from the medical center perspective comparing supraorbital and EEA with or without craniotomy for OGMs). In contrast to much of the published data, the

authors reported that the supraorbital approach (open) was less costly ($29,423) than EEA ($83,838).[1418] The methods of this analysis were notably criticized by other surgeons from this author's own institution.[1421] The main critiques were the assumption of GTR without consideration of Simpson grade, limited number of patients in model (n = 5), only modeling EEA costs instead of directly comparing costs between the 2 procedures, misclassification of 2 of the tumors as OGMs, which seemed to be better classified as a frontal or orbital roof and planum meningiomas, as well as failure to include branches in the decision tree for NTR without CSF leak or reoperation/additional surgery.[1421]

Healthcare resource utilization will become increasingly important in the future. For this reason, it is critical to understand the how emerging technologies utilize healthcare resources compared to traditional techniques.[282,1411] The available amount of high-quality cost-effectiveness data is limited and the cost-effectiveness of EEA has not been fully elucidated. Future research should include a strong methodological approach in order to provide a comprehensive understanding of the cost-effectiveness of ESBS so that policy makers, physicians, and patients can compare the costs and health outcomes to decide which intervention is optimal.

- Aggregate Grade of Evidence: C (Level 1b: 2 studies; Level 1c: 1 study; Level 2b: 1 study; Level 2c: 1 study; Level 4: 6 studies; Level 5: 1 study)

XIV. Knowledge gaps and research opportunities

ESBS is now a well-accepted surgical approach for numerous pathologies of the skull base. Although there are inherent, unique challenges such as reconstruction and postoperative CSF rhinorrhea, ESBS also has advantages. Whether these advantages result in clinically significant improvement remains an area of important investigation. The ICAR:ESBS document outlines areas where the evidence consistently supports the utilization of this corridor while at the same time, strongly identifying important knowledge gaps that should be the focus of future investigation. Overall, much of the literature is dependent on case series rather than prospectively designed trials. Because of the relative rarity of many of these disease processes, it is likely that multi-institutional collaboration will be critical to explore these questions in a prospective manner. Additionally, standardized methodology for outcomes and reporting are critical for rare diseases to allow for meta-analysis and combining primary data. No such standardized reporting exists for skull-base surgery. Also, reporting with supplements of individual data points allows for direct combinations of series after publication and would increase our abilities to collect data on rare diseases or outcomes. Skull-base surgery has the opportunity to draw on the knowledge base and expertise of multiple different specialties and is thus well suited to address the research opportunities outlined in this section.

XIV.A. Intradural tumors

EEAs to pituitary tumors are the foundation of many of the initial experiences with ESBS, and the success rates associated with this surgical approach are equal to or surpass microscopic approaches in many domains, such as visual improvement and postoperative endocrinopathies. Even the primary drawback of the early experience with endoscopic pituitary resection, CSF rhinorrhea, has been reduced to very low rates. As the primary outcomes continue to improve with experience, secondary outcomes such as mitigation of nasal morbidity have taken on new importance and consideration. Continuing to improve both the primary surgical outcomes as well as these secondary considerations should remain an area of refinement in ESBS.

However, other intracranial and intradural pathologies have much less clarity. The fundamental question of when ESBS should be utilized remains largely based upon expert opinion and logic. Because much of the literature is based upon case series and cohort studies, the decision-making process to utilize this corridor is difficult to derive from the literature. Once this decision has been made, continuing to define the goals of surgery with regard to extent of resection and use of other treatment modalities remains a frontier.

- Appropriate patient selection criteria and indications for ESBS based upon tumor characteristics, anatomy, and symptomatology.
- Balancing treatment modalities as emerging alternative interventions arise.
- Defining risk factors for complications and recurrence.
- Improvement in tumor visualization.
- Defining outcomes by both tumor-specific outcomes (resection grade/percentage) as well as functional and QOL outcomes.

XIV.B. Sinonasal malignancies

Our current knowledge about the treatment of sinonasal malignancies is based on very limited evidence and extrapolation from other head and neck cancers. Certainly, the rarity of the disease process is a significant hurdle in studying these tumors. However, the grouping of all of these tumors into retrospective cohorts based upon their anatomical location limits the ability to provide necessary granularity for examining treatment interventions and predictors of outcome. In addition to a much greater understanding of the biological behavior of these cancers, clearly defining surgical candidates and then primarily endoscopic endonasal surgical candidates is paramount to local tumor control. Given the possibility of delayed recurrences, long-term follow-up from endoscopic resection of sinonasal cancers will continue to be critical.

- Clarification of appropriate surgical candidates based upon tumor type, extent, and surgical approach. This is particularly of interest in regard to orbital extension and salvage surgery after recurrence.

- Optimal treatment protocols for multimodality therapy in each tumor type including type and sequence of interventions and a "personalized" medicine approach based upon genetic and molecular characteristics of cancer.
- Longer-term outcomes for endoscopically resected malignancies in both local and regional/distant recurrences with multi-institutional collaborations to increase power for these rare pathologies.
- Greater elucidation of risk factors for recurrence.
- Multi-institutional collaboration for tumor banking and the identification of molecular prognostic markers.

XIV.C. Clival tumors

Secondary to the limitations of lateral approaches and reduced efficacy of current nonsurgical treatments, clival chordomas and skull-base chondrosarcomas are often surgically treated with an endoscopic transclival approach. Although it is logical to approach these tumors through the nose, the learning curve can be quite significant, and challenges of the anatomy, lateral extension, and reconstruction are not trivial. Inferolateral extension of these lesions remains a clear challenge to the complete resection of these malignancies. Additionally, the reconstructive success noted in many other areas of the skull base is still lagging in the clivus and posterior fossa. Multiple research opportunities exist in this arena.

- Identifying and overcoming the current limitations of the EEA in achieving a GTR of chordoma.
- Appropriate utilization of radiation options including proton beam, intensity modulated RT, and stereotactic radiosurgery.
- Determining the best practices for the reconstruction and CSF diversion of posterior fossa defects.
- Molecular prognostication of clival chordoma.

XIV.D. Reconstruction and complications

The initial primary shortcoming of ESBS, adequate reconstruction and prevention of CSF leaks, has thankfully improved significantly. Certainly, the introduction of vascularized reconstruction has been critical to the expansion of the discipline of ESBS. Despite these advancements, knowledge gaps remain as we balance the need for surgical access and reconstruction with nasal morbidity.

Additionally, as the boundaries of ESBS push forward, the prevention of and ability to manage complications from nasal damage to olfaction and CN weakness to vascular injury is paramount.

- Development of an endonasal reconstructive ladder based upon risk factors of postoperative CSF leak.
- Further evaluation of the incidence of sinonasal complication including olfactory changes associated with ESBS.
- Clarity in the utilization of LD, tissue sealants, and nasal packing to supplement ESBS reconstruction.
- Continued development of high-fidelity and cost-efficient models to simulate ICA injury.

XV. Conclusion

In summary, the authors of ICAR:ESBS have collaborated to outline the current state of the evidence across numerous sinonasal and intradural pathologies, reconstructive options, and complication prevention and management in ESBS. There is clearly a need to improve the LOE in many aspects of ESBS to drive improved patient care. With increasing experience and investigation, more robust EBRs will enhance our understanding of this still young field. Future iterations of this document will hopefully continue to promote the cycle of research, translation to patient care, and further investigation.

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References

1. Jho HD, Carrau RL. Endoscopic endonasal transsphenoidal surgery: experience with 50 patients. *J Neurosurg*. 1997;87:44-51.
2. Papay FA, Maggiano H, Dominquez S, Hassenbusch SJ, Levine HL, Lavertu P. Rigid endoscopic repair of paranasal sinus cerebrospinal fluid fistulas. *Laryngoscope*. 1989;99:1195-1201.
3. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(Suppl 1):S22-S209.
4. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. 2018;8:108-352.
5. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol*. 2011;1:431-437.
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.
7. Oxford Centre for Evidence-Based Medicine (CEBM) – levels of evidence (March 2009). http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009. Accessed May 29, 2019.
8. American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114:874-877.
9. Sharma SD, Kumar G, Bal J, Eweiss A. Endoscopic repair of cerebrospinal fluid rhinorrhoea. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2016;133:187-190.
10. Psaltis AJ, Schlosser RJ, Banks CA, Yawn J, Soler ZM. A systematic review of the endoscopic repair of cerebrospinal fluid leaks. *Otolaryngol Head Neck Surg*. 2012;147:196-203.
11. Ibrahim AA, Okasha M, Elwany S. Endoscopic endonasal multilayer repair of traumatic CSF rhinorrhea. *Eur Arch Otorhinolaryngol*. 2016;273:921-926.
12. Kirtane MV, Gautham K, Upadhyaya SR. Endoscopic CSF rhinorrhea closure: our experience in 267 cases. *Otolaryngol Head Neck Surg*. 2005;132:208-212.
13. Lindstrom DR, Toohill RJ, Loehrl TA, Smith TL. Management of cerebrospinal fluid rhinorrhea: the Medical College of Wisconsin experience. *Laryngoscope*. 2004;114:969-974.
14. Lee DH, Lim SC, Joo YE. Treatment outcomes of endoscopic repairs of sinonasal cerebrospinal fluid leaks. *J Craniofac Surg*. 2011;22:1266-1270.
15. Bumm K, Heupel J, Bozzato A, Iro H, Hornung J. Localization and infliction pattern of iatrogenic skull base defects following endoscopic sinus surgery at a teaching hospital. *Auris Nasus Larynx*. 2009;36:671-676.
16. Singh R, Hazarika P, Nayak DR, Balakrishnan R, Hazarika M, Singh A. Endoscopic repair of cerebrospinal fluid rhinorrhea - Manipal experience.

Indian J Otolaryngol Head Neck Surg. 2009;61:14-18.
17. Lee TJ, Huang CC, Chuang CC, Huang SF. Transnasal endoscopic repair of cerebrospinal fluid rhinorrhea and skull base defect: ten-year experience. *Laryngoscope*. 2004;114:1475-1481.
18. Bhatti SN, Khan SA, Shah R, et al. Transnasal endosocpic repair of cerebrospinal fluid rhinorrhoea. *J Ayub Med Coll Abbottabad*. 2011;23:15-17.
19. Liu P, Wu S, Li Z, Wang B. Surgical strategy for cerebrospinal fluid rhinorrhea repair. *Neurosurgery*. 2010;66(6 Suppl Operative):281-285; discussion 285-286.
20. Virk JS, Elmiyeh B, Saleh HA. Endoscopic management of cerebrospinal fluid rhinorrhea: the charing cross experience. *J Neurol Surg B Skull Base*. 2013;74:61-67.
21. Bell RB, Dierks EJ, Homer L, Potter BE. Management of cerebrospinal fluid leak associated with craniomaxillofacial trauma. *J Oral Maxillofac Surg*. 2004;62:676-684.
22. Yilmazlar S, Arslan E, Kocaeli H, et al. Cerebrospinal fluid leakage complicating skull base fractures: analysis of 81 cases. *Neurosurg Rev*. 2006;29:64-71.
23. Dalgic A, Okay HO, Gezici AR, Daglioglu E, Akdag R, Ergungor MF. An effective and less invasive treatment of post-traumatic cerebrospinal fluid fistula: closed lumbar drainage system. *Minim Invasive Neurosurg*. 2008;51:154-157.
24. Banks CA, Palmer JN, Chiu AG, O'Malley BW Jr, Woodworth BA, Kennedy DW. Endoscopic closure of CSF rhinorrhea: 193 cases over 21 years. *Otolaryngol Head Neck Surg*. 2009;140:826-833.
25. Rodriguez ED, Stanwix MG, Nam AJ, et al. Twenty-six-year experience treating frontal sinus fractures: a novel algorithm based on anatomical fracture pattern and failure of conventional techniques. *Plast Reconstr Surg*. 2008;122:1850-1866.
26. Choi M, Li Y, Shapiro SA, Havlik RJ, Flores RL. A 10-year review of frontal sinus fractures: clinical outcomes of conservative management of posterior table fractures. *Plast Reconstr Surg*. 2012;130:399-406.
27. Gossman DG, Archer SM, Arosarena O. Management of frontal sinus fractures: a review of 96 cases. *Laryngoscope*. 2006;116:1357-1362.
28. Chegini S, Gallighan N, McLeod N, et al. Outcomes of treatment of fractures of the frontal sinus: review from a tertiary multispecialty craniofacial trauma service. *Br J Oral Maxillofac Surg*. 2016;54:801-805.
29. Bell RB, Dierks EJ, Brar P, Potter JK, Potter BE. A protocol for the management of frontal sinus fractures emphasizing sinus preservation. *J Oral Maxillofac Surg*. 2007;65:825-839.
30. Chaaban MR, Conger B, Riley KO, Woodworth BA. Transnasal endoscopic repair of posterior table fractures. *Otolaryngol Head Neck Surg*. 2012;147:1142-1147.
31. Jones V, Virgin F, Riley K, Woodworth BA. Changing paradigms in frontal sinus cerebrospinal fluid leak repair. *Int Forum Allergy Rhinol*. 2012;2:227-232.
32. Woodworth BA, Schlosser RJ, Palmer JN. Endoscopic repair of frontal sinus cerebrospinal fluid leaks. *J Laryngol Otol*. 2005;119:709-713.
33. Grayson JW, Jeyarajan H, Illing EA, Cho DY, Riley KO, Woodworth BA. Changing the surgical dogma in frontal sinus trauma: transnasal endoscopic repair. *Int Forum Allergy Rhinol*. 2017;7:441-449.
34. Shi JB, Chen FH, Fu QL, et al. Frontal sinus cerebrospinal fluid leaks: repair in 15 patients using an endoscopic surgical approach. *ORL J Otorhinolaryngol Relat Spec*. 2010;72:56-62.
35. Illing EA, Woodworth BA. Management of frontal sinus cerebrospinal fluid leaks and encephaloceles. *Otolaryngol Clin North Am*. 2016;49:1035-1050.
36. Conger BT Jr, Riley K, Woodworth BA. The Draf III mucosal grafting technique: a prospective study. *Otolaryngol Head Neck Surg*. 2012;146:664-668.
37. Carter KB Jr, Poetker DM, Rhee JS. Sinus preservation management for frontal sinus fractures in the endoscopic sinus surgery era: a systematic review. *Craniomaxillofac Trauma Reconstr*. 2010;3:141-149.
38. Virgin F, Baranano CF, Riley K, Woodworth BA. Frontal sinus skull base defect repair using the pedicled nasoseptal flap. *Otolaryngol Head Neck Surg*. 2011;145:338-340.
39. Schoentgen C, Henaux PL, Godey B, Jegoux F. Management of post-traumatic cerebrospinal fluid (CSF) leak of anterior skull base: 10 years experience. *Acta Otolaryngol*. 2013;133:944-950.
40. Bernal-Sprekelsen M, Alobid I, Mullol J, Trobat F, Tomas-Barberan M. Closure of cerebrospinal fluid leaks prevents ascending bacterial meningitis. *Rhinology*. 2005;43:277-281.
41. Albu S, Florian IS, Bolboaca SD. The benefit of early lumbar drain insertion in reducing the length of CSF leak in traumatic rhinorrhea. *Clin Neurol Neurosurg*. 2016;142:43-47.
42. Prosser JD, Vender JR, Solares CA. Traumatic cerebrospinal fluid leaks. *Otolaryngol Clin North Am*. 2011;44:857-873, vii.
43. Friedman JA, Ebersold MJ, Quast LM. Post-traumatic cerebrospinal fluid leakage. *World J Surg*. 2001;25:1062-1066.
44. Stankiewicz JA. Cerebrospinal fluid fistula and endoscopic sinus surgery. *Laryngoscope*. 1991;101:250-256.
45. Gosal JS, Gurmey T, Kursa GK, Salunke P, Gupta SK. Is acetazolamide really useful in the management of traumatic cerebrospinal fluid rhinorrhea? *Neurol India*. 2015;63:197-201.
46. Abrishamkar S, Khalighinejad N, Moein P. Analysing the effect of early acetazolamide administration on patients with a high risk of permanent cerebrospinal fluid leakage. *Acta Med Iran*. 2013;51:467-471.
47. Leech PJ, Paterson A. Conservative and operative management for cerebrospinal-fluid leakage after closed head injury. *Lancet*. 1973;1:1013-1016.
48. Bernal-Sprekelsen M, Bleda-Vazquez C, Carrau RL. Ascending meningitis secondary to traumatic cerebrospinal fluid leaks. *Am J Rhinol*. 2000;14:257-259.
49. Sherif C, Di Ieva A, Gibson D, et al. A management algorithm for cerebrospinal fluid leak associated with anterior skull base fractures: detailed clinical and radiological follow-up. *Neurosurg Rev*. 2012;35:227-237; discussion 237-228.
50. Eftekhar B, Ghodsi M, Nejat F, Ketabchi E, Esmaeeli B. Prophylactic administration of ceftriaxone for the prevention of meningitis after traumatic pneumocephalus: results of a clinical trial. *J Neurosurg*. 2004;101:757-761.
51. Eljamel MS. Antibiotic prophylaxis in the management of CSF fistula. *Surg Neurol*. 1998;50:387.
52. Hegazy HM, Carrau RL, Snyderman CH, Kassam A, Zweig J. Transnasal endoscopic repair of cerebrospinal fluid rhinorrhea: a meta-analysis. *Laryngoscope*. 2000;110:1166-1172.
53. Friedman JA, Ebersold MJ, Quast LM. Persistent posttraumatic cerebrospinal fluid leakage. *Neurosurg Focus*. 2000;9:e1.
54. Carrau RL, Snyderman C, Janecka IP, Sekhar L, Sen C, D'Amico F. Antibiotic prophylaxis in cranial base surgery. *Head Neck*. 1991;13:311-317.
55. Clemenza JW, Kaltman SI, Diamond DL. Craniofacial trauma and cerebrospinal fluid leakage: a retrospective clinical study. *J Oral Maxillofac Surg*. 1995;53:1004-1007.
56. Ratilal BO, Costa J, Pappamikail L, Sampaio C. Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. *Cochrane Database Syst Rev*. 2015;(4):CD004884.
57. Villalobos T, Arango C, Kubilis P, Rathore M. Antibiotic prophylaxis after basilar skull fractures: a meta-analysis. *Clin Infect Dis*. 1998;27:364-369.
58. Rathore MH. Do prophylactic antibiotics prevent meningitis after basilar skull fracture? *Pediatr Infect Dis J*. 1991;10:87-88.
59. Eljamel MS. Antibiotic prophylaxis in unrepaired CSF fistulae. *Br J Neurosurg*. 1993;7:501-505.
60. Brodie HA. Prophylactic antibiotics for posttraumatic cerebrospinal fluid fistulae: a meta-analysis. *Arch Otolaryngol Head Neck Surg*. 1997;123:749-752.
61. Demetriades D, Charalambides D, Lakhoo M, Pantanowitz D. Role of prophylactic antibiotics in open and basilar fractures of the skull: a randomized study. *Injury*. 1992;23:377-380.
62. Choi D, Spann R. Traumatic cerebrospinal fluid leakage: risk factors and the use of prophylactic antibiotics. *Br J Neurosurg*. 1996;10:571-575.
63. Rimmer J, Belk C, Lund VJ, Swift A, White P. Immunisations and antibiotics in patients with anterior skull base cerebrospinal fluid leaks. *J Laryngol Otol*. 2014;128:626-629.
64. Oakley GM, Alt JA, Schlosser RJ, Harvey RJ, Orlandi RR. Diagnosis of cerebrospinal fluid rhinorrhea: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2016;6:8-16.
65. MacGee EE, Cauthen JC, Brackett CE. Meningitis following acute traumatic cerebrospinal fluid fistula. *J Neurosurg*. 1970;33:312-316.
66. Frazee RC, Mucha P Jr, Farnell MB, Ebersold MJ. Meningitis after basilar skull fracture: does antibiotic prophylaxis help? *Postgrad Med*. 1988;83:267-268, 273-264.
67. Dagi TF, Meyer FB, Poletti CA. The incidence and prevention of meningitis after basilar skull fracture. *Am J Emerg Med*. 1983;1:295-298.
68. Zrebeet HA, Huang PS. Prophylactic antibiotics in the treatment of fractures at the base of the skull. *Del Med J*. 1986;58:741-748.
69. Wang EW, Vandergrift WA 3rd, Schlosser RJ. Spontaneous CSF Leaks. *Otolaryngol Clin North Am*. 2011;44:845-856, vii.
70. Wise SK, Schlosser RJ. Evaluation of spontaneous nasal cerebrospinal fluid leaks. *Curr Opin Otolaryngol Head Neck Surg*. 2007;15:28-34.
71. Beckhardt RN, Setzen M, Carras R. Primary spontaneous cerebrospinal fluid rhinorrhea. *Otolaryngol Head Neck Surg*. 1991;104:425-432.
72. Centers for Disease Control and Prevention. Adult obesity prevalence maps. 2017; https://www.cdc.gov/obesity/data/prevalence-maps.html. Accessed May 29, 2019.
73. Chen J, Wall M. Epidemiology and risk factors for idiopathic intracranial hypertension. *Int Ophthalmol Clin*. 2014;54:1-11.
74. Nelson RF, Gantz BJ, Hansen MR. The rising incidence of spontaneous cerebrospinal fluid leaks in the United States and the association with obesity and obstructive sleep apnea. *Otol Neurotol*. 2015;36:476-480.
75. Arrer E, Meco C, Oberascher G, Piotrowski W, Albegger K, Patsch W. beta-Trace protein as a marker for cerebrospinal fluid rhinorrhea. *Clin Chem*. 2002;48(6 Pt 1):939-941.
76. McCudden CR, Senior BA, Hainsworth S, et al. Evaluation of high resolution gel beta(2)-transferrin for detection of cerebrospinal fluid leak. *Clin Chem Lab Med*. 2013;51:311-315.
77. Schnabel C, Di Martino E, Gilsbach JM, Riediger D, Gressner AM, Kunz D. Comparison of beta2-transferrin and beta-trace protein for detection of cerebrospinal fluid in nasal and ear fluids. *Clin Chem*. 2004;50:661-663.
78. Bachmann G, Nekic M, Michel O. Clinical experience with beta-trace protein as a marker for cerebrospinal fluid. *Ann Otol Rhinol Laryngol*. 2000;109(12 Pt 1):1099-1102.
79. Daudia A, Biswas D, Jones NS. Risk of meningitis with cerebrospinal fluid rhinorrhea. *Ann Otol Rhinol Laryngol*. 2007;116:902-905.
80. Bedrosian JC, Anand VK, Schwartz TH. The endoscopic endonasal approach to repair of iatrogenic and noniatrogenic cerebrospinal fluid leaks and encephaloceles of the anterior cranial fossa. *World Neurosurg*. 2014;82(6 Suppl):S86-S94.
81. Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH. Endoscopic endonasal versus open repair of anterior skull base CSF leak, meningocele, and encephalocele: a systematic review of outcomes. *J Neurol Surg A Cent Eur Neurosurg*. 2013;74:239-250.
82. Campbell RG, Farquhar D, Zhao N, Chiu AG, Adappa ND, Palmer JN. Cerebrospinal fluid rhinorrhea secondary to idiopathic intracranial hypertension: long-term outcomes of endoscopic repairs. *Am J Rhinol Allergy*. 2016;30:294-300.
83. Schlosser RJ, Bolger WE. Nasal cerebrospinal fluid leaks: critical review and surgical considerations. *Laryngoscope*. 2004;114:255-265.
84. Tahir MZ, Khan MB, Bashir MU, Akhtar S, Bari E. Cerebrospinal fluid rhinorrhea: an institutional perspective from Pakistan. *Surg Neurol Int*. 2011;2:174.
85. Demarco RC, Tamashiro E, Valera FC, Anselmo-Lima WT. Use of a hypodense sodium fluorescein solution for the endoscopic repair of rhinogenic cerebrospinal fluid fistulae. *Am J Rhinol*. 2007;21:184-186.
86. Lanza DC, O'Brien DA, Kennedy DW. Endoscopic repair of cerebrospinal fluid fistulae and encephaloceles. *Laryngoscope*. 1996;106(9 Pt 1):1119-1125.

87. Placantonakis DG, Tabaee A, Anand VK, Hiltzik D, Schwartz TH. Safety of low-dose intrathecal fluorescein in endoscopic cranial base surgery. *Neurosurgery*. 2007;61(3 Suppl):161-165; discussion 165-166.
88. Seth R, Rajasekaran K, Benninger MS, Batra PS. The utility of intrathecal fluorescein in cerebrospinal fluid leak repair. *Otolaryngol Head Neck Surg*. 2010;143:626-632.
89. Saafan ME, Ragab SM, Albirmawy OA. Topical intranasal fluorescein: the missing partner in algorithms of cerebrospinal fluid fistula detection. *Laryngoscope*. 2006;116:1158-1161.
90. Ozturk K, Karabagli H, Bulut S, Egilmez M, Duran M. Is the use of topical fluorescein helpful for management of CSF leakage? *Laryngoscope*. 2012;122:1215-1218.
91. Liu HS, Chen YT, Wang D, et al. The use of topical intranasal fluorescein in endoscopic endonasal repair of cerebrospinal fluid rhinorrhea. *Surg Neurol*. 2009;72:341-345; discussion 346.
92. Banu MA, Kim JH, Shin BJ, Woodworth GF, Anand VK, Schwartz TH. Low-dose intrathecal fluorescein and etiology-based graft choice in endoscopic endonasal closure of CSF leaks. *Clin Neurol Neurosurg*. 2014;116:28-34.
93. Jacob AK, Dilger JA, Hebl JR. Status epilepticus and intrathecal fluorescein: anesthesia providers beware. *Anesth Analg*. 2008;107:229-231.
94. Keerl R, Weber RK, Draf W, Wienke A, Schaefer SD. Use of sodium fluorescein solution for detection of cerebrospinal fluid fistulas: an analysis of 420 administrations and reported complications in Europe and the United States. *Laryngoscope*. 2004;114:266-272.
95. Moseley JI, Carton CA, Stern WE. Spectrum of complications in the use of intrathecal fluorescein. *J Neurosurg*. 1978;48:765-767.
96. Anari S, Waldron M, Carrie S. Delayed absence seizure: a complication of intrathecal fluorescein injection – a case report and literature review. *Auris Nasus Larynx*. 2007;34:515-518.
97. Ommaya AK, Di Chiro G, Baldwin M, Pennybacker JB. Non-traumatic cerebrospinal fluid rhinorrhoea. *J Neurol Neurosurg Psychiatry*. 1968;31:214-225.
98. Schlosser RJ, Bolger WE. Management of multiple spontaneous nasal meningoencephaloceles. *Laryngoscope*. 2002;112:980-985.
99. Schlosser RJ, Wilensky EM, Grady MS, Bolger WE. Elevated intracranial pressures in spontaneous cerebrospinal fluid leaks. *Am J Rhinol*. 2003;17:191-195.
100. Schlosser RJ, Wilensky EM, Grady MS, Palmer JN, Kennedy DW, Bolger WE. Cerebrospinal fluid pressure monitoring after repair of cerebrospinal fluid leaks. *Otolaryngol Head Neck Surg*. 2004;130:443-448.
101. Schlosser RJ, Woodworth BA, Wilensky EM, Grady MS, Bolger WE. Spontaneous cerebrospinal fluid leaks: a variant of benign intracranial hypertension. *Ann Otol Rhinol Laryngol*. 2006;115:495-500.
102. Stevens SM, Rizk HG, Golnik K, et al. Idiopathic intracranial hypertension: contemporary review and implications for the otolaryngologist. *Laryngoscope*. 2018;128:248-256.
103. Aaron G, Doyle J, Vaphiades MS, Riley KO, Woodworth BA. Increased intracranial pressure in spontaneous CSF leak patients is not associated with papilledema. *Otolaryngol Head Neck Surg*. 2014;151:1061-1066.
104. Aaron GP, Illing E, Lambertsen Z, et al. Enlargement of Meckel's cave in patients with spontaneous cerebrospinal fluid leaks. *Int Forum Allergy Rhinol*. 2017;7:421-424.
105. Alexander A, Mathew J, Varghese AM, Ganesan S. Endoscopic repair of CSF fistulae: a ten year experience. *J Clin Diagn Res*. 2016;10:MC01-MC04.
106. Chaaban MR, Illing E, Riley KO, Woodworth BA. Acetazolamide for high intracranial pressure cerebrospinal fluid leaks. *Int Forum Allergy Rhinol*. 2013;3:718-721.
107. Chaaban MR, Illing E, Riley KO, Woodworth BA. Spontaneous cerebrospinal fluid leak repair: a five-year prospective evaluation. *Laryngoscope*. 2014;124:70-75.
108. Quincke H. [About meningitis serosa and related conditions]. Uber Meningitis serosa und verwandte Zustande. *Dtsch Z Nervenheilkd*. 1896;9(3-4):149-168. German.
109. Wall M. Update on idiopathic intracranial hypertension. *Neurol Clin*. 2017;35:45-57.
110. Martinez-Capoccioni G, Serramito-Garcia R, Martin-Bailon M, Garcia-Allut A, Martin-Martin C. Spontaneous cerebrospinal fluid leaks in the anterior skull base secondary to idiopathic intracranial hypertension. *Eur Arch Otorhinolaryngol*. 2017;274:2175-2181.
111. Seth R, Rajasekaran K 3rd, Luong A, Benninger MS, Batra PS. Spontaneous CSF leaks: factors predictive of additional interventions. *Laryngoscope*. 2010;120:2141-2146.
112. Teachey W, Grayson J, Cho DY, Riley KO, Woodworth BA. Intervention for elevated intracranial pressure improves success rate after repair of spontaneous cerebrospinal fluid leaks. *Laryngoscope*. 2017;127:2011-2016.
113. Berdahl JP, Fleischman D, Zaydlarova J, Stinnett S, Allingham RR, Fautsch MP. Body mass index has a linear relationship with cerebrospinal fluid pressure. *Invest Ophthalmol Vis Sci*. 2012;53:1422-1427.
114. Daniels AB, Liu GT, Volpe NJ, et al. Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). *Am J Ophthalmol*. 2007;143:635-641.
115. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology*. 2013;81:1159-1165.
116. Wall M. Idiopathic intracranial hypertension. *Neurol Clin*. 2010;28:593-617.
117. Maralani PJ, Hassanlou M, Torres C, et al. Accuracy of brain imaging in the diagnosis of idiopathic intracranial hypertension. *Clin Radiol*. 2012;67:656-663.
118. Butros SR, Goncalves LF, Thompson D, Agarwal A, Lee HK. Imaging features of idiopathic intracranial hypertension, including a new finding: widening of the foramen ovale. *Acta Radiol*. 2012;53:682-688.
119. Bidot S, Saindane AM, Peragallo JH, Bruce BB, Newman NJ, Biousse V. Brain imaging in idiopathic intracranial hypertension. *J Neuroophthalmol*. 2015;35:400-411.
120. Psaltis AJ, Overton LJ, Thomas WW 3rd, Fox NF, Banks CA, Schlosser RJ. Differences in skull base thickness in patients with spontaneous cerebrospinal fluid leaks. *Am J Rhinol Allergy*. 2014;28:e73-e79.
121. Illing E, Schlosser RJ, Palmer JN, Cure J, Fox N, Woodworth BA. Spontaneous sphenoid lateral recess cerebrospinal fluid leaks arise from intracranial hypertension, not Sternberg's canal. *Int Forum Allergy Rhinol*. 2014;4:246-250.
122. O'Connell BP, Stevens SM, Xiao CC, Meyer TA, Schlosser RJ. Lateral skull base attenuation in patients with anterior cranial fossa spontaneous cerebrospinal fluid leaks. *Otolaryngol Head Neck Surg*. 2016;154:1138-1144.
123. Schlosser RJ, Bolger WE. Significance of empty sella in cerebrospinal fluid leaks. *Otolaryngol Head Neck Surg*. 2003;128:32-38.
124. Woodworth BA, Prince A, Chiu AG, et al. Spontaneous CSF leaks: a paradigm for definitive repair and management of intracranial hypertension. *Otolaryngol Head Neck Surg*. 2008;138:715-720.
125. Naraghi M, Saberi H, Kashfi A. Endonasal endoscopic treatment of parasellar arachnoid cyst: report of a case. *Am J Rhinol*. 2002;16:57-60.
126. NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee, Wall M, McDermott MP, et al. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. *JAMA*. 2014;311:1641-1651.
127. Piper RJ, Kalyvas AV, Young AM, Hughes MA, Jamjoom AA, Fouyas IP. Interventions for idiopathic intracranial hypertension. *Cochrane Database Syst Rev*. 2015;(8):CD003434.
128. Lai LT, Danesh-Meyer HV, Kaye AH. Visual outcomes and headache following interventions for idiopathic intracranial hypertension. *J Clin Neurosci*. 2014;21:1670-1678.
129. Senior BA, Jafri K, Benninger M. Safety and efficacy of endoscopic repair of CSF leaks and encephaloceles: a survey of the members of the American Rhinologic Society. *Am J Rhinol*. 2001;15:21-25.
130. Wise SK, Harvey RJ, Neal JG, Patel SJ, Frankel BM, Schlosser RJ. Factors contributing to failure in endoscopic skull base defect repair. *Am J Rhinol Allergy*. 2009;23:185-191.
131. Ahmed OH, Marcus S, Tauber JR, Wang B, Fang Y, Lebowitz RA. Efficacy of perioperative lumbar drainage following endonasal endoscopic cerebrospinal fluid leak repair. *Otolaryngol Head Neck Surg*. 2017;156:52-60.
132. Caballero N, Bhalla V, Stankiewicz JA, Welch KC. Effect of lumbar drain placement on recurrence of cerebrospinal rhinorrhea after endoscopic repair. *Int Forum Allergy Rhinol*. 2012;2:222-226.
133. Gilat H, Rappaport Z, Yaniv E. Endoscopic transnasal cerebrospinal fluid leak repair: a 10 year experience. *Isr Med Assoc J*. 2011;13:597-600.
134. Meco C, Arrer E, Oberascher G. Efficacy of cerebrospinal fluid fistula repair: sensitive quality control using the beta-trace protein test. *Am J Rhinol*. 2007;21:729-736.
135. Adams AS, Russell PT, Duncavage JA, Chandra RK, Turner JH. Outcomes of endoscopic repair of cerebrospinal fluid rhinorrhea without lumbar drains. *Am J Rhinol Allergy*. 2016;30:424-429.
136. Albu S, Emanuelli E, Trombitas V, Florian IS. Effectiveness of lumbar drains on recurrence rates in endoscopic surgery of cerebrospinal fluid leaks. *Am J Rhinol Allergy*. 2013;27:e190-e194.
137. Phan S, Liao J, Jia F, et al. Laparotomy vs minimally invasive laparoscopic ventriculoperitoneal shunt placement for hydrocephalus: a systematic review and meta-analysis. *Clin Neurol Neurosurg*. 2016;140:26-32.
138. Ferrante E, Ferraroni M, Castrignano T, et al. Nonfunctioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors. *Eur J Endocrinol*. 2006;155:823-829.
139. Laws ER Jr, Thapar K. Pituitary surgery. *Endocrinol Metab Clin North Am*. 1999;28:119-131.
140. Molitch ME. Nonfunctioning pituitary tumors and pituitary incidentalomas. *Endocrinol Metab Clin North Am*. 2008;37:151-171, xi.
141. De Witte O, Carlot S, Devuyst E, Choufani G, Hassid S. Minimally invasive endoscopic unilateral transsphenoidal surgery for pituitary adenomas. *B-ENT*. 2011;7(Suppl 17):27-32.
142. Bokhari AR, Davies MA, Diamond T. Endoscopic transsphenoidal pituitary surgery: a single surgeon experience and the learning curve. *Br J Neurosurg*. 2013;27:44-49.
143. Anderson D, Faber P, Marcovitz S, Hardy J, Lorenzetti D. Pituitary tumors and the ophthalmologist. *Ophthalmology*. 1983;90:1265-1270.
144. Newman SA, Turbin RE, Bodach ME, et al. Congress of Neurological Surgeons systematic review and evidence-based guideline on pretreatment ophthalmology evaluation in patients with suspected nonfunctioning pituitary adenomas. *Neurosurgery*. 2016;79:E530-E532.
145. Hajiabadi M, Alimohamadi M, Fahlbusch R. Decision making for patients with concomitant pituitary macroadenoma and ophthalmologic comorbidity: a clinical controversy. *World Neurosurg*. 2015;84:147-153.
146. Schiefer U, Isbert M, Mikolaschek E, et al. Distribution of scotoma pattern related to chiasmal lesions with special reference to anterior junction syndrome. *Graefes Arch Clin Exp Ophthalmol*. 2004;242:468-477.
147. Clifford-Jones RE, McDonald WI, Landon DN. Chronic optic nerve compression: an experimental study. *Brain*. 1985;108(Pt 1):241-262.
148. Wang X, Neely AJ, McIlwaine GG, Lueck CJ. Multi-scale analysis of optic chiasmal compression by finite element modelling. *J Biomech*. 2014;47:2292-2299.
149. Subei AM, Eggenberger ER. Optical coherence tomography: another useful tool in a neuro-ophthalmologist's armamentarium. *Curr Opin Ophthalmol*. 2009;20:462-466.
150. Garcia T, Sanchez S, Litre CF, et al. Prognostic value of retinal nerve fiber layer thickness for postoperative peripheral visual field recovery in optic chiasm compression. *J Neurosurg*. 2014;121:165-169.
151. Kanamori A, Nakamura M, Matsui N, et al. Optical coherence tomography detects characteristic retinal nerve fiber layer thickness corresponding to band atrophy of the optic discs. *Ophthalmology*. 2004;111:2278-2283.

152. Jacob M, Raverot G, Jouanneau E, et al. Predicting visual outcome after treatment of pituitary adenomas with optical coherence tomography. *Am J Ophthalmol*. 2009;147:64-70.e2.
153. Muskens IS, Zamanipoor Najafabadi AH, Briceno V, et al. Visual outcomes after endoscopic endonasal pituitary adenoma resection: a systematic review and meta-analysis. *Pituitary*. 2017;20:539-552.
154. DeKlotz TR, Chia SH, Lu W, Makambi KH, Aulisi E, Deeb Z. Meta-analysis of endoscopic versus sublabial pituitary surgery. *Laryngoscope*. 2012;122:511-518.
155. Anik I, Anik Y, Koc K, et al. Evaluation of early visual recovery in pituitary macroadenomas after endoscopic endonasal transsphenoidal surgery: quantitative assessment with diffusion tensor imaging (DTI). *Acta Neurochir (Wien)*. 2011;153:831-842.
156. Nakao N, Itakura T. Surgical outcome of the endoscopic endonasal approach for nonfunctioning giant pituitary adenoma. *J Clin Neurosci*. 2011;18:71-75.
157. Thotakura AK, Patibandla MR, Panigrahi MK, Addagada GC. Predictors of visual outcome with transsphenoidal excision of pituitary adenomas having suprasellar extension: a prospective series of 100 cases and brief review of the literature. *Asian J Neurosurg*. 2017;12:1-5.
158. Agrawal D, Mahapatra AK. Visual outcome of blind eyes in pituitary apoplexy after transsphenoidal surgery: a series of 14 eyes. *Surg Neurol*. 2005;63:42-46; discussion 46.
159. Seuk JW, Kim CH, Yang MS, Cheong JH, Kim JM. Visual outcome after transsphenoidal surgery in patients with pituitary apoplexy. *J Korean Neurosurg Soc*. 2011;49:339-344.
160. Chi F, Wang Y, Lin Y, Ge J, Qiu Y, Guo L. A learning curve of endoscopic transsphenoidal surgery for pituitary adenoma. *J Craniofac Surg*. 2013;24:2064-2067.
161. Leach P, Abou-Zeid AH, Kearney T, Davis J, Trainer PJ, Gnanalingham KK. Endoscopic transsphenoidal pituitary surgery: evidence of an operative learning curve. *Neurosurgery*. 2010;67:1205-1212.
162. Cohen AR, Cooper PR, Kupersmith MJ, Flamm ES, Ransohoff J. Visual recovery after transsphenoidal removal of pituitary adenomas. *Neurosurgery*. 1985;17:446-452.
163. Trautmann JC, Laws ER Jr. Visual status after transsphenoidal surgery at the Mayo Clinic, 1971-1982. *Am J Ophthalmol*. 1983;96:200-208.
164. Chabot JD, Chakraborty S, Imbarrato G, Dehdashti AR. Evaluation of outcomes after endoscopic endonasal surgery for large and giant pituitary macroadenoma: a retrospective review of 39 consecutive patients. *World Neurosurg*. 2015;84:978-988.
165. Juraschka K, Khan OH, Godoy BL, et al. Endoscopic endonasal transsphenoidal approach to large and giant pituitary adenomas: institutional experience and predictors of extent of resection. *J Neurosurg*. 2014;121:75-83.
166. Ciric I, Ragin A, Baumgartner C, Pierce D. Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. *Neurosurgery*. 1997;40:225-236; discussion 236-227.
167. Ammirati M, Wei L, Ciric I. Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2013;84:843-849.
168. Regal M, Paramo C, Sierra SM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. *Clin Endocrinol (Oxf)*. 2001;55:735-740.
169. Drange MR, Fram NR, Herman-Bonert V, Melmed S. Pituitary tumor registry: a novel clinical resource. *J Clin Endocrinol Metab*. 2000;85:168-174.
170. Fatemi N, Dusick JR, Mattozo C, et al. Pituitary hormonal loss and recovery after transsphenoidal adenoma removal. *Neurosurgery*. 2008;63:709-718; discussion 718-709.
171. Nomikos P, Ladar C, Fahlbusch R, Buchfelder M. Impact of primary surgery on pituitary function in patients with non-functioning pituitary adenomas—a study on 721 patients. *Acta Neurochir (Wien)*. 2004;146:27-35.
172. Berkmann S, Fandino J, Muller B, Remonda L, Landolt H. Intraoperative MRI and endocrinological outcome of transsphenoidal surgery for non-functioning pituitary adenoma. *Acta Neurochir (Wien)*. 2012;154:639-647.
173. Webb SM, Rigla M, Wagner A, Oliver B, Bartumeus F. Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. *J Clin Endocrinol Metab*. 1999;84:3696-3700.
174. Del Monte P, Foppiani L, Ruelle A, et al. Clinically non-functioning pituitary macroadenomas in the elderly. *Aging Clin Exp Res*. 2007;19:34-40.
175. Higham CE, Johannsson G, Shalet SM. Hypopituitarism. *Lancet*. 2016;388:2403-2415.
176. Arafah BM. Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. *J Clin Endocrinol Metab*. 1986;62:1173-1179.
177. Arafah BM, Prunty D, Ybarra J, Hlavin ML, Selman WR. The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas. *J Clin Endocrinol Metab*. 2000;85:1789-1793.
178. Capatina C, Wass JA. Hypopituitarism: growth hormone and corticotropin deficiency. *Endocrinol Metab Clin North Am*. 2015;44:127-141.
179. Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary apoplexy. *Endocr Rev*. 2015;36:622-645.
180. Marek J, Jezkova J, Hana V, et al. Is it possible to avoid hypopituitarism after irradiation of pituitary adenomas by the Leksell gamma knife? *Eur J Endocrinol*. 2011;164:169-178.
181. Xu Z, Lee Vance M, Schlesinger D, Sheehan JP. Hypopituitarism after stereotactic radiosurgery for pituitary adenomas. *Neurosurgery*. 2013;72:630-637; 636-637.
182. Rolston JD, Blevins LS Jr. Gamma knife radiosurgery for acromegaly. *Int J Endocrinol*. 2012;2012:821579.
183. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101:3888-3921.
184. Fleseriu M, Bodach ME, Tumialan LM, et al. Congress of Neurological Surgeons systematic review and evidence-based guideline for pretreatment endocrine evaluation of patients with nonfunctioning pituitary adenomas. *Neurosurgery*. 2016;79:E527-E529.
185. Di Maio S, Biswas A, Vezina JL, Hardy J, Mohr G. Pre- and postoperative magnetic resonance imaging appearance of the normal residual pituitary gland following macroadenoma resection: clinical implications. *Surg Neurol Int*. 2012;3:67.
186. Arafah BM, Harrington JF, Madhoun ZT, Selman WR. Improvement of pituitary function after surgical decompression for pituitary tumor apoplexy. *J Clin Endocrinol Metab*. 1990;71:323-328.
187. Chanson P, Lepeintre JF, Ducreux D. Management of pituitary apoplexy. *Expert Opin Pharmacother*. 2004;5:1287-1298.
188. Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, Wass JA. Classical pituitary apoplexy: clinical features, management and outcome. *Clin Endocrinol (Oxf)*. 1999;51:181-188.
189. Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J. The clinical and endocrine outcome to trans-sphenoidal microsurgery of nonsecreting pituitary adenomas. *Cancer*. 1991;68:860-866.
190. Jahangiri A, Wagner J, Han SW, et al. Rate and time course of improvement in endocrine function after more than 1000 pituitary operations. *Neurosurgery*. 2014;61(Suppl 1):163-166.
191. Marazuela M, Astigarraga B, Vicente A, et al. Recovery of visual and endocrine function following transsphenoidal surgery of large nonfunctioning pituitary adenomas. *J Endocrinol Invest*. 1994;17:703-707.
192. Yunoue S, Tokimura H, Tominaga A, et al. Transsphenoidal surgical treatment of pituitary adenomas in patients aged 80 years or older. *Neurosurg Rev*. 2014;37:269-276; discussion 276-267.
193. Robenshtok E, Benbassat CA, Hirsch D, et al. Clinical course and outcome of nonfunctioning pituitary adenomas in the elderly compared with younger age groups. *Endocr Pract*. 2014;20:159-164.
194. Liu J, Li C, Xiao Q, et al. Comparison of pituitary adenomas in elderly and younger adults: clinical characteristics, surgical outcomes, and prognosis. *J Am Geriatr Soc*. 2015;63:1924-1930.
195. Carvalho P, Lau E, Carvalho D. Surgery induced hypopituitarism in acromegalic patients: a systematic review and meta-analysis of the results. *Pituitary*. 2015;18(6):844-860.
196. Burman P, Mattsson AF, Johannsson G, et al. Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. *J Clin Endocrinol Metab*. 2013;98:1466-1475.
197. Sherlock M, Ayuk J, Tomlinson JW, et al. Mortality in patients with pituitary disease. *Endocr Rev*. 2010;31:301-342.
198. Baijal V, Gurunadh VS, Palit MG, Sunder S, Thakur PK. Pupil involving complete III N palsy in pituitary adenoma: case report. *Med J Armed Forces India*. 1999;55:69-70.
199. Nawar RN, AbdelMannan D, Selman WR, Arafah BM. Pituitary tumor apoplexy: a review. *J Intensive Care Med*. 2008;23:75-90.
200. Saul RF, Hilliker JK. Third nerve palsy: the presenting sign of a pituitary adenoma in five patients and the only neurological sign in four patients. *J Clin Neuroophthalmol*. 1985;5:185-193.
201. Robert CM Jr, Feigenbaum JA, Stern EW. Ocular palsy occurring with pituitary tumors. *J Neurosurg*. 1973;38:17-19.
202. Abouaf L, Vighetto A, Lebas M. Neuro-ophthalmologic exploration in non-functioning pituitary adenoma. *Ann Endocrinol (Paris)*. 2015;76:210-219.
203. Famularo G, Pozzessere C, Piazza G, De Simone C. Abrupt-onset oculomotor paralysis: an endocrine emergency. *Eur J Emerg Med*. 2001;8:233-236.
204. Lee CC, Cho AS, Carter WA. Emergency department presentation of pituitary apoplexy. *Am J Emerg Med*. 2000;18:328-331.
205. Rossitch E Jr, Carrazana EJ, Black PM. Isolated oculomotor nerve palsy following apoplexy of a pituitary adenoma. *J Neurosurg Sci*. 1992;36:103-105.
206. Lau KK, Joshi SM, Ellamushi H, Afshar F. Isolated bilateral oculomotor nerve palsy in pituitary apoplexy: case report and review. *Br J Neurosurg*. 2007;21:399-402.
207. Bujawansa S, Thondam SK, Steele C, et al. Presentation, management and outcomes in acute pituitary apoplexy: a large single-centre experience from the United Kingdom. *Clin Endocrinol (Oxf)*. 2014;80:419-424.
208. Elsasser Imboden PN, De Tribolet N, Lobrinus A, et al. Apoplexy in pituitary macroadenoma: eight patients presenting in 12 months. *Medicine (Baltimore)*. 2005;84:188-196.
209. Verrees M, Arafah BM, Selman WR. Pituitary tumor apoplexy: characteristics, treatment, and outcomes. *Neurosurg Focus*. 2004;16:E6.
210. Bills DC, Meyer FB, Laws ER Jr, et al. A retrospective analysis of pituitary apoplexy. *Neurosurgery*. 1993;33:602-608; discussion 608-609.
211. Zoli M, Milanese L, Faustini-Fustini M, et al. Endoscopic endonasal surgery for pituitary apoplexy: evidence on a 75-case series from a tertiary care center. *World Neurosurg*. 2017;106:331-338.
212. Tishler RB, Loeffler JS, Lunsford LD, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *Int J Radiat Oncol Biol Phys*. 1993;27:215-221.
213. Leber KA, Bergloff J, Pendl G. Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. *J Neurosurg*. 1998;88:43-50.
214. Chen JC, Giannotta SL, Yu C, Petrovich Z, Levy ML, Apuzzo ML. Radiosurgical management of benign cavernous sinus tumors: dose profiles and acute complications. *Neurosurgery*. 2001;48:1022-1030; discussion 1030-1022.
215. Semple PL, Laws ER Jr. Complications in a contemporary series of patients who underwent transsphenoidal surgery for Cushing's disease. *J Neurosurg*. 1999;91:175-179.
216. Frank G, Pasquini E, Farneti G, et al. The endoscopic versus the traditional approach in pituitary surgery. *Neuroendocrinology*. 2006;83(3-4):240-248.
217. Dehdashti AR, Ganna A, Karabatsou K, Gentili F. Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical

series. *Neurosurgery*. 2008;62:1006-1015; discussion 1015-1007.

218. Gondim JA, Schops M, de Almeida JP, et al. Endoscopic endonasal transsphenoidal surgery: surgical results of 228 pituitary adenomas treated in a pituitary center. *Pituitary*. 2010;13:68-77.
219. Kristof RA, Rother M, Neuloh G, Klingmuller D. Incidence, clinical manifestations, and course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: a prospective observational study. *J Neurosurg*. 2009;111:555-562.
220. Schreckinger M, Walker B, Knepper J, et al. Post-operative diabetes insipidus after endoscopic transsphenoidal surgery. *Pituitary*. 2013;16:445-451.
221. Berker M, Hazer DB, Yucel T, et al. Complications of endoscopic surgery of the pituitary adenomas: analysis of 570 patients and review of the literature. *Pituitary*. 2012;15:288-300.
222. Cote DJ, Alzarea A, Acosta MA, et al. Predictors and rates of delayed symptomatic hyponatremia after transsphenoidal surgery: a systematic review [corrected]. *World Neurosurg*. 2016;88:1-6.
223. Jahangiri A, Wagner J, Tran MT, et al. Factors predicting postoperative hyponatremia and efficacy of hyponatremia management strategies after more than 1000 pituitary operations. *J Neurosurg*. 2013;119:1478-1483.
224. Rajasekaran S, Vanderpump M, Baldeweg S, et al. UK guidelines for the management of pituitary apoplexy. *Clin Endocrinol (Oxf)*. 2011;74:9-20.
225. Tu M, Lu Q, Zhu P, Zheng W. Surgical versus non-surgical treatment for pituitary apoplexy: a systematic review and meta-analysis. *J Neurol Sci*. 2016;370:258-262.
226. Gondim JA, de Albuquerque LAF, Almeida JP, et al. Endoscopic endonasal surgery for treatment of pituitary apoplexy: 16 years of experience in a specialized pituitary center. *World Neurosurg*. 2017;108:137-142.
227. Kassam AB, Prevedello DM, Carrau RL, et al. Endoscopic endonasal skull base surgery: analysis of complications in the authors' initial 800 patients. *J Neurosurg*. 2011;114:1544-1568.
228. Cavallo LM, Frank G, Cappabianca P, et al. The endoscopic endonasal approach for the management of craniopharyngiomas: a series of 103 patients. *J Neurosurg*. 2014;121:100-113.
229. de Divitiis E, Laws ER, Giani U, Iuliano SL, de Divitiis O, Apuzzo ML. The current status of endoscopy in transsphenoidal surgery: an international survey. *World Neurosurg*. 2015;83:447-454.
230. Zhang M, Singh H, Almodovar-Mercado GJ, Anand VK, Schwartz TH. Required reading: the most impactful articles in endoscopic endonasal skull base surgery. *World Neurosurg*. 2016;92:499-512.e2.
231. Wang AJ, Zaidi HA, Laws ED Jr. History of endonasal skull base surgery. *J Neurosurg Sci*. 2016;60:441-453.
232. Berker M, Aghayev K, Yucel T, Hazer DB, Onerci M. Management of cerebrospinal fluid leak during endoscopic pituitary surgery. *Auris Nasus Larynx*. 2013;40:373-378.
233. Fraser S, Gardner PA, Koutourousiou M, et al. Risk factors associated with postoperative cerebrospinal fluid leak after endoscopic endonasal skull base surgery. *J Neurosurg*. 2018;128:1066-1071.
234. Garcia-Navarro V, Anand VK, Schwartz TH. Gasket seal closure for extended endonasal endoscopic skull base surgery: efficacy in a large case series. *World Neurosurg*. 2013;80:563-568.
235. Esposito F, Dusick JR, Fatemi N, Kelly DF. Graded repair of cranial base defects and cerebrospinal fluid leaks in transsphenoidal surgery. *Neurosurgery*. 2007;60(4 Suppl 2):295-303; discussion 303-294.
236. Sciarretta V, Mazzatenta D, Ciarpaglini R, Pasquini E, Farneti G, Frank G. Surgical repair of persisting CSF leaks following standard or extended endoscopic transsphenoidal surgery for pituitary tumor. *Minim Invasive Neurosurg*. 2010;53:55-59.
237. Wang YY, Kearney T, Gnanalingham KK. Low-grade CSF leaks in endoscopic trans-sphenoidal pituitary surgery: efficacy of a simple and fully synthetic repair with a hydrogel sealant. *Acta Neurochir (Wien)*. 2011;153:815-822.
238. Jakimovski D, Bonci G, Attia M, et al. Incidence and significance of intraoperative cerebrospinal fluid leak in endoscopic pituitary surgery using intrathecal fluorescein. *World Neurosurg*. 2014;82(3-4):e513-e523.
239. Park JH, Choi JH, Kim YI, Kim SW, Hong YK. Modified graded repair of cerebrospinal fluid leaks in endoscopic endonasal transsphenoidal surgery. *J Korean Neurosurg Soc*. 2015;58:36-42.
240. Zhou Q, Yang Z, Wang X, et al. Risk factors and management of intraoperative cerebrospinal fluid leaks in endoscopic treatment of pituitary adenoma: analysis of 492 patients. *World Neurosurg*. 2017;101:390-395.
241. Dehdashti AR, Stofko D, Okun J, Obourn C, Kennedy T. Endoscopic endonasal reconstruction of skull base: repair protocol. *J Neurol Surg B Skull Base*. 2016;77:271-278.
242. Soudry E, Turner JH, Nayak JV, Hwang PH. Endoscopic reconstruction of surgically created skull base defects: a systematic review. *Otolaryngol Head Neck Surg*. 2014;150:730-738.
243. Zhang C, Ding X, Lu Y, Hu L, Hu G. Cerebrospinal fluid rhinorrhea following transsphenoidal surgery for pituitary adenoma: experience in a Chinese centre. *Acta Otorhinolaryngol Ital*. 2017;37:303-307.
244. Peris-Celda M, Chaskes M, Lee DD, Kenning TJ, Pinheiro-Neto CD. Optimizing sellar reconstruction after pituitary surgery with free mucosal graft: results from the first 50 consecutive patients. *World Neurosurg*. 2017;101:180-185.
245. Tamasauskas A, Sinkunas K, Draf W, et al. Management of cerebrospinal fluid leak after surgical removal of pituitary adenomas. *Medicina (Kaunas)*. 2008;44:302-307.
246. Cappabianca P, Esposito F, Magro F, et al. Natura abhorret a vacuo—use of fibrin glue as a filler and sealant in neurosurgical "dead spaces": technical note. *Acta Neurochir (Wien)*. 2010;152:897-904.
247. Cho JM, Ahn JY, Chang JH, Kim SH. Prevention of cerebrospinal fluid rhinorrhea after transsphenoidal surgery by collagen fleece coated with fibrin sealant without autologous tissue graft or postoperative lumbar drainage. *Neurosurgery*. 2011;68(1 Suppl Operative):130-136; discussion 136-137.
248. Eloy JA, Kuperan AB, Choudhry OJ, Harirchian S, Liu JK. Efficacy of the pedicled nasoseptal flap without cerebrospinal fluid (CSF) diversion for repair of skull base defects: incidence of postoperative CSF leaks. *Int Forum Allergy Rhinol*. 2012;2:397-401.
249. Gaynor BG, Benveniste RJ, Lieberman S, Casiano R, Morcos JJ. Acellular dermal allograft for sellar repair after transsphenoidal approach to pituitary adenomas. *J Neurol Surg B Skull Base*. 2013;74:155-159.
250. Horridge M, Jesurasa A, Olubajo F, Mirza S, Sinha S. The use of the nasoseptal flap to reduce the rate of post-operative cerebrospinal fluid leaks following endoscopic trans-sphenoidal surgery for pituitary disease. *Br J Neurosurg*. 2013;27:739-741.
251. Iannelli A, Lenzi R, Muscatello L. A useful maneuver to simplify sellar floor repair following endoscopic transnasal pituitary surgery. *J Neurol Surg A Cent Eur Neurosurg*. 2014;75:158-160.
252. Paluzzi A, Fernandez-Miranda JC, Tonya Stefko S, Challinor S, Snyderman CH, Gardner PA. Endoscopic endonasal approach for pituitary adenomas: a series of 555 patients. *Pituitary*. 2014;17:307-319.
253. Hong CK, Kim YB, Hong JB, Lee KS. Sealing of cerebrospinal fluid leakage during conventional transsphenoidal surgery using a fibrin-coated collagen fleece. *J Clin Neurosci*. 2015;22:696-699.
254. Kim EH, Roh TH, Park HH, Moon JH, Hong JB, Kim SH. Direct suture technique of normal gland edge on the incised dura margin to repair the intraoperative cerebrospinal fluid leakage from the arachnoid recess during transsphenoidal pituitary tumor surgery. *Neurosurgery*. 2015;11(Suppl 2):26-31; discussion 31.
255. Liebelt BD, Huang M, Baskin DS. Sellar floor reconstruction with the medpor implant versus autologous bone after transnasal transsphenoidal surgery: outcome in 200 consecutive patients. *World Neurosurg*. 2015;84:240-245.
256. Amano K, Hori T, Kawamata T, Okada Y. Repair and prevention of cerebrospinal fluid leakage in transsphenoidal surgery: a sphenoid sinus mucosa technique. *Neurosurg Rev*. 2016;39:123-131; discussion 131.
257. El Shazly AA, El Wardany MA, Abo El Ezz TA. Sellar repair with autologous muscle and composite septal cartilage grafts for treatment of cerebrospinal fluid leakage following trans-sphenoidal pituitary surgery. *Asian J Neurosurg*. 2016;11:433-439.
258. Pereira EAC, Grandidge CA, Nowak VA, Cudlip SA. Cerebrospinal fluid leaks after transsphenoidal surgery: effect of a polyethylene glycol hydrogel dural sealant. *J Clin Neurosci*. 2017;44:6-10.
259. Han ZL, He DS, Mao ZG, Wang HJ. Cerebrospinal fluid rhinorrhea following trans-sphenoidal pituitary macroadenoma surgery: experience from 592 patients. *Clin Neurol Neurosurg*. 2008;110:570-579.
260. Rabadan AT, Hernandez D, Ruggeri CS. Pituitary tumors: our experience in the prevention of postoperative cerebrospinal fluid leaks after transsphenoidal surgery. *J Neurooncol*. 2009;93:127-131.
261. Yano S, Kawano T, Kudo M, et al. Endoscopic endonasal transsphenoidal approach through the bilateral nostrils for pituitary adenomas. *Neurol Med Chir (Tokyo)*. 2009;49:1-7.
262. Kono Y, Prevedello DM, Snyderman CH, et al. One thousand endoscopic skull base surgical procedures demystifying the infection potential: incidence and description of postoperative meningitis and brain abscesses. *Infect Control Hosp Epidemiol*. 2011;32:77-83.
263. Strychowsky J, Nayan S, Reddy K, Farrokhyar F, Sommer D. Purely endoscopic transsphenoidal surgery versus traditional microsurgery for resection of pituitary adenomas: systematic review. *J Otolaryngol Head Neck Surg*. 2011;40:175-185.
264. Jalessi M, Sharifi G, Mirfallah Layalestani MR, et al. Sellar reconstruction algorithm in endoscopic transsphenoidal pituitary surgery: experience with 240 cases. *Med J Islam Repub Iran*. 2013;27:186-194.
265. Halvorsen H, Ramm-Pettersen J, Josefsen R, et al. Surgical complications after transsphenoidal microscopic and endoscopic surgery for pituitary adenoma: a consecutive series of 506 procedures. *Acta Neurochir (Wien)*. 2014;156:441-449.
266. Ivan ME, Iorgulescu JB, El-Sayed I, et al. Risk factors for postoperative cerebrospinal fluid leak and meningitis after expanded endoscopic endonasal surgery. *J Clin Neurosci*. 2015;22:48-54.
267. Wang F, Zhou T, Wei S, et al. Endoscopic endonasal transsphenoidal surgery of 1,166 pituitary adenomas. *Surg Endosc*. 2015;29:1270-1280.
268. D'Anza B, Tien D, Stokken JK, Recinos PF, Woodard TR, Sindwani R. Role of lumbar drains in contemporary endonasal skull base surgery: meta-analysis and systematic review. *Am J Rhinol Allergy*. 2016;30:430-435.
269. Jang JH, Kim KH, Lee YM, Kim JS, Kim YZ. Surgical results of pure endoscopic endonasal transsphenoidal surgery for 331 pituitary adenomas: a 15-year experience from a single institution. *World Neurosurg*. 2016;96:545-555.
270. Magro E, Graillon T, Lassave J, et al. Complications related to the endoscopic endonasal transsphenoidal approach for nonfunctioning pituitary macroadenomas in 300 consecutive patients. *World Neurosurg*. 2016;89:442-453.
271. Tien DA, Stokken JK, Recinos PF, Woodard TD, Sindwani R. Cerebrospinal fluid diversion in endoscopic skull base reconstruction: an evidence-based approach to the use of lumbar drains. *Otolaryngol Clin North Am*. 2016;49:119-129.
272. Mehta GU, Oldfield EH. Prevention of intraoperative cerebrospinal fluid leaks by lumbar cerebrospinal fluid drainage during surgery for pituitary macroadenomas. *J Neurosurg*. 2012;116:1299-1303.
273. Hadad G, Bassagasteguy L, Carrau RL, et al. A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap. *Laryngoscope*. 2006;116:1882-1886.
274. Kassam AB, Thomas A, Carrau RL, et al. Endoscopic reconstruction of the cranial base using a pedicled nasoseptal flap. *Neurosurgery*. 2008;63(1 Suppl 1):ONS44-ONS52; discussion ONS52-ONS43.
275. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100:2807-2831.
276. Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99:3933-3951.
277. Brucker-Davis F, Oldfield EH, Skarulis MC, Doppman JL, Weintraub BD. Thyrotropin-secreting

pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. *J Clin Endocrinol Metab*. 1999;84:476-486.

278. Kreutzer J, Buslei R, Wallaschofski H, et al. Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. *Eur J Endocrinol*. 2008;158:11-18.
279. Tyrrell JB, Brooks RM, Fitzgerald PA, Cofoid PB, Forsham PH, Wilson CB. Cushing's disease: selective trans-sphenoidal resection of pituitary microadenomas. *N Engl J Med*. 1978;298:753-758.
280. Kreutzer J, Vance ML, Lopes MB, Laws ER Jr. Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. *J Clin Endocrinol Metab*. 2001;86:4072-4077.
281. Mehta GU, Lonser RR. Management of hormone-secreting pituitary adenomas. *Neuro Oncol*. 2017;19:762-773.
282. Little AS, Chapple K, Jahnke H, White WL. Comparative inpatient resource utilization for patients undergoing endoscopic or microscopic transsphenoidal surgery for pituitary lesions. *J Neurosurg*. 2014;121:84-90.
283. Little AS, Kelly DF, Milligan J, et al. Comparison of sinonasal quality of life and health status in patients undergoing microscopic and endoscopic transsphenoidal surgery for pituitary lesions: a prospective cohort study. *J Neurosurg*. 2015;123:799-807.
284. Pledger CL, Elzoghby MA, Oldfield EH, Payne SC, Jane JA Jr. Prospective comparison of sinonasal outcomes after microscopic sublabial or endoscopic endonasal transsphenoidal surgery for nonfunctioning pituitary adenomas. *J Neurosurg*. 2016;125:323-333.
285. Phan K, Xu J, Reddy R, Kalakoti P, Nanda A, Fairhall J. Endoscopic endonasal versus microsurgical transsphenoidal approach for growth hormone-secreting pituitary adenomas-systematic review and meta-analysis. *World Neurosurg*. 2017;97:398-406.
286. Lenzi J, Lapadula G, D'Amico T, et al. Evaluation of trans-sphenoidal surgery in pituitary GH-secreting micro- and macroadenomas: a comparison between microsurgical and endoscopic approach. *J Neurosurg Sci*. 2015;59:11-18.
287. Fathalla H, Cusimano MD, Di Ieva A, et al. Endoscopic versus microscopic approach for surgical treatment of acromegaly. *Neurosurg Rev*. 2015;38:541-548; discussion 548-549.
288. Sarkar S, Rajaratnam S, Chacko G, Chacko AG. Endocrinological outcomes following endoscopic and microscopic transsphenoidal surgery in 113 patients with acromegaly. *Clin Neurol Neurosurg*. 2014;126:190-195.
289. Starke RM, Raper DM, Payne SC, Vance ML, Oldfield EH, Jane JA Jr. Endoscopic vs microsurgical transsphenoidal surgery for acromegaly: outcomes in a concurrent series of patients using modern criteria for remission. *J Clin Endocrinol Metab*. 2013;98:3190-3198.
290. Nomikos P, Buchfelder M, Fahlbusch R. The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. *Eur J Endocrinol*. 2005;152:379-387.
291. Alahmadi H, Cusimano MD, Woo K, et al. Impact of technique on cushing disease outcome using strict remission criteria. *Can J Neurol Sci*. 2013;40:344-341.
292. Cho DY, Liau WR. Comparison of endonasal endoscopic surgery and sublabial microsurgery for prolactinomas. *Surg Neurol*. 2002;58:371-375; discussion 375-376.
293. Zaidi HA, De Los Reyes K, Barkhoudarian G, et al. The utility of high-resolution intraoperative MRI in endoscopic transsphenoidal surgery for pituitary macroadenomas: early experience in the Advanced Multimodality Image Guided Operating Suite. *Neurosurg Focus*. 2016;40:E18.
294. Schwartz TH, Stieg PE, Anand VK. Endoscopic transsphenoidal pituitary surgery with intraoperative magnetic resonance imaging. *Neurosurgery*. 2006;58(1 Suppl):ONS44-ONS51; discussion ONS44-ONS51.
295. Netuka D, Majovsky M, Masopust V, et al. Intraoperative magnetic resonance imaging during endoscopic transsphenoidal surgery of growth hormone-secreting pituitary adenomas. *World Neurosurg*. 2016;91:490-496.
296. Tanei T, Nagatani T, Nakahara N, et al. Use of high-field intraoperative magnetic resonance imaging during endoscopic transsphenoidal surgery for functioning pituitary microadenomas and small adenomas located in the intrasellar region. *Neurol Med Chir (Tokyo)*. 2013;53:501-510.
297. Oldfield EH, Vortmeyer AO. Development of a histological pseudocapsule and its use as a surgical capsule in the excision of pituitary tumors. *J Neurosurg*. 2006;104:7-19.
298. Monteith SJ, Starke RM, Jane JA Jr, Oldfield EH. Use of the histological pseudocapsule in surgery for Cushing disease: rapid postoperative cortisol decline predicting complete tumor resection. *J Neurosurg*. 2012;116:721-727.
299. Ceylan S, Cabuk B, Koc K, Anik I, Vural C. Endoscopic distinction between capsule and pseudocapsule of pituitary adenomas. *Acta Neurochir (Wien)*. 2013;155:1611-1619; discussion 1619.
300. Xie T, Liu T, Zhang X, et al. Time to revive the value of the pseudocapsule in endoscopic endonasal transsphenoidal surgery for growth hormone adenomas. *World Neurosurg*. 2016;89:65-71.
301. Giustina A, Chanson P, Bronstein MD, et al. A consensus on criteria for cure of acromegaly. *J Clin Endocrinol Metab*. 2010;95:3141-3148.
302. Trifanescu R, Ansorge O, Wass JA, Grossman AB, Karavitaki N. Rathke's cleft cysts. *Clin Endocrinol (Oxf)*. 2012;76:151-160.
303. Mendelson ZS, Husain Q, Elmoursi S, Svider PF, Eloy JA, Liu JK. Rathke's cleft cyst recurrence after transsphenoidal surgery: a meta-analysis of 1151 cases. *J Clin Neurosci*. 2014;21:378-385.
304. Madhok R, Prevedello DM, Gardner P, Carrau RL, Snyderman CH, Kassam AB. Endoscopic endonasal resection of Rathke cleft cysts: clinical outcomes and surgical nuances. *J Neurosurg*. 2010;112:1333-1339.
305. Jahangiri A, Potts M, Kunwar S, Blevins L, El-Sayed IH, Aghi MK. Extended endoscopic endonasal approach for suprasellar Rathke's cleft cysts. *J Clin Neurosci*. 2014;21:779-785.
306. Ratha V, Patil S, Karmarkar VS, Shah NJ, Deopujari CE. Surgical management of Rathke cleft cysts. *World Neurosurg*. 2017;107:276-284.
307. Fan J, Peng Y, Qi S, Zhang XA, Qiu B, Pan J. Individualized surgical strategies for Rathke cleft cyst based on cyst location. *J Neurosurg*. 2013;119:1437-1446.
308. Xie T, Hu F, Yu Y, Gu Y, Wang X, Zhang X. Endoscopic endonasal resection of symptomatic Rathke cleft cysts. *J Clin Neurosci*. 2011;18:760-762.
309. Solari D, Cavallo LM, Somma T, et al. Endoscopic endonasal approach in the management of Rathke's cleft cysts. *PLoS One*. 2015;10:e0139609.
310. Frank G, Sciarretta V, Mazzatenta D, Farneti G, Modugno GC, Pasquini E. Transsphenoidal endoscopic approach in the treatment of Rathke's cleft cyst. *Neurosurgery*. 2005;56:124-128; discussion 129.
311. Jane JA Jr, Laws, ER. Craniopharyngioma. *Pituitary*. 2006;9:323-326.
312. Karavitaki N. Management of craniopharyngiomas. *J Endocrinol Invest*. 2014;37:291-228.
313. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM. The descriptive epidemiology of craniopharyngioma. *J Neurosurg*. 1998;89:547-551.
314. Paulus W, Stockel C, Krauss J, Sorensen N, Roggendorf W. Odontogenic classification of craniopharyngiomas: a clinicopathological study of 54 cases. *Histopathology*. 1997;30:172-176.
315. Yasargil MG, Curcic M, Kis M, Siegenthaler G, Teddy PJ, Roth P. Total removal of craniopharyngiomas: approaches and long-term results in 144 patients. *J Neurosurg*. 1990;73:3-11.
316. Samii M, Samii A. Surgical management of craniopharyngiomas. In: Schmidek HH, ed. *Schmidek & Sweet Operative Neurosurgical Techniques: Indications, Methods, and Results*. Philadelphia, PA: W.B. Saunders; 2000:489-502.
317. Van Effenterre R, Boch AL. Craniopharyngioma in adults and children: a study of 122 surgical cases. *J Neurosurg*. 2002;97:3-11.
318. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. *J Neurosurg*. 1999;90:237-250.
319. Gerganov V, Metwali H, Samii A, Fahlbusch R, Samii M. Microsurgical resection of extensive craniopharyngiomas using a frontolateral approach: operative technique and outcome. *J Neurosurg*. 2014;120:559-570.
320. Hofmann BM, Hollig A, Strauss C, Buslei R, Buchfelder M, Fahlbusch R. Results after treatment of craniopharyngiomas: further experiences with 73 patients since 1997. *J Neurosurg*. 2012;116:373-384.
321. Carmel P. Craniopharyngioma: transcranial approaches. In: Apuzzo ML, ed. *Brain Surgery: Complication Avoidance and Management*. Vol 1. New York: Churchill Livingstone; 1993:339-356.
322. Baskin DS, Wilson CB. Surgical management of craniopharyngiomas: a review of 74 cases. *J Neurosurg*. 1986;65:22-27.
323. Aryan HE, Ozgur BM, Jandial R, Levy ML. Subfrontal transbasal approach and technique for resection of craniopharyngioma. *Neurosurg Focus*. 2005;18(6A):E10.
324. Guiot G. Transsphenoidal approach in surgical treatment of pituitary adenomas: general principles and indications in non-functioning adenomas. In: Kohler PO, Ross GT, eds. *Diagnosis and Treatment of Pituitary Adenomas*. Amsterdam, The Netherlands: Excerpta Medica; 1973:159-178.
325. Weiss MH. The transnasal transsphenoidal approach. In: Apuzzo ML, ed. *Surgery of the Third Ventricle*. Baltimore, MD: Williams & Wilkins; 1987:476-494.
326. Laws ER Jr. Transsphenoidal microsurgery in the management of craniopharyngioma. *J Neurosurg*. 1980;52:661-666.
327. Honegger J, Buchfelder M, Fahlbusch R, Daubler B, Dorr HG. Transsphenoidal microsurgery for craniopharyngioma. *Surg Neurol*. 1992;37:189-196.
328. Kaptain GJ, Vincent DA, Sheehan JP, Laws ER Jr. Transsphenoidal approaches for the extracapsular resection of midline suprasellar and anterior cranial base lesions. *Neurosurgery*. 2001;49:94-100; discussion 100-101.
329. Gardner PA, Prevedello DM, Kassam AB, Snyderman CH, Carrau RL, Mintz AH. The evolution of the endonasal approach for craniopharyngiomas. *J Neurosurg*. 2008;108:1043-1047.
330. Cappabianca P, Cavallo LM, Esposito F, de Divcitiis O, Messina A, de Divitiis E. Extended endoscopic endonasal approach to the midline skull base: the evolving role of transsphenoidal surgery. In: Pickard JD, Akalan N, Di Rocco C, Dolenc VV, Lobo Antunes J, Mooij JJA, eds. *Advances and Technical Standards in Neurosurgery*. New York: Springer; 2008:152-199.
331. de Divitiis E, Cappabianca P, Cavallo LM, Esposito F, de Divitiis O, Messina A. Extended endoscopic transsphenoidal approach for extrasellar craniopharyngiomas. *Neurosurgery*. 2007;61(5 Suppl 2):219-227; discussion 228.
332. Kassam A, Snyderman CH, Mintz A, Gardner P, Carrau RL. Expanded endonasal approach: the rostrocaudal axis. Part I. Crista galli to the sella turcica. *Neurosurg Focus*. 2005;19:E3.
333. Kassam AB, Gardner PA, Snyderman CH, Carrau RL, Mintz AH, Prevedello DM. Expanded endonasal approach, a fully endoscopic transnasal approach for the resection of midline suprasellar craniopharyngiomas: a new classification based on the infundibulum. *J Neurosurg*. 2008;108:715-728.
334. Yasargil MG. Craniopharyngiomas. In: Yasargil MG, ed. *Microneurosurgery: Microneurosurgery of CNS Tumors*. Vol IV. Stuttgart, Germany: Georg Thieme Verlag; 1996:205-223.
335. Pascual JM, Prieto R, Carrasco R. Infundibulotuberal or not strictly intraventricular craniopharyngioma: evidence for a major topographical category. *Acta Neurochir (Wien)*. 2011;153:2403-2425; discussion 2426.
336. Steno J, Malacek M, Bizik I. Tumor-third ventricular relationships in supradiaphragmatic craniopharyngiomas: correlation of morphological, magnetic resonance imaging, and operative findings. *Neurosurgery*. 2004;54:1051-1058; discussion 1058-1060.
337. Cavallo LM, Solari D, Esposito F, Cappabianca P. The endoscopic endonasal approach for the management of craniopharyngiomas involving the third ventricle. *Neurosurg Rev*. 2013;36:27-37; discussion 38.
338. Campbell PG, McGettigan B, Luginbuhl A, Yadla S, Rosen M, Evans JJ. Endocrinological and ophthalmological consequences of an initial endonasal

endoscopic approach for resection of craniopharyngiomas. *Neurosurg Focus*. 2010;28:E8.

339. Dehdashti AR, Ganna A, Witterick I, Gentili F. Expanded endoscopic endonasal approach for anterior cranial base and suprasellar lesions: indications and limitations. *Neurosurgery*. 2009;64:677-687; discussion 687-679.
340. Frank G, Pasquini E, Doglietto F, et al. The endoscopic extended transsphenoidal approach for craniopharyngiomas. *Neurosurgery*. 2006;59(1 Suppl 1):ONS75-ONS83; discussion ONS75-ONS83.
341. Jane JA Jr, Kiehna E, Payne SC, Early SV, Laws ER Jr. Early outcomes of endoscopic transsphenoidal surgery for adult craniopharyngiomas. *Neurosurg Focus*. 2010;28:E9.
342. Laufer I, Anand VK, Schwartz TH. Endoscopic, endonasal extended transsphenoidal, transplanum transtuberculum approach for resection of suprasellar lesions. *J Neurosurg*. 2007;106:400-406.
343. Leng LZ, Greenfield JP, Souweidane MM, Anand VK, Schwartz TH. Endoscopic, endonasal resection of craniopharyngiomas: analysis of outcome including extent of resection, cerebrospinal fluid leak, return to preoperative productivity, and body mass index. *Neurosurgery*. 2012;70:110-123; discussion 123-114.
344. Cavallo LM, Prevedello DM, Solari D, et al. Extended endoscopic endonasal transsphenoidal approach for residual or recurrent craniopharyngiomas. *J Neurosurg*. 2009;111:578-589.
345. Ceylan S, Koc K, Anik I. Extended endoscopic approaches for midline skull-base lesions. *Neurosurg Rev*. 2009;32:309-319; discussion 318-309.
346. Patel KS, Raza SM, McCoul ED, et al. Long-term quality of life after endonasal endoscopic resection of adult craniopharyngiomas. *J Neurosurg*. 2015;123:571-580.
347. Kim SK, Kim YH, Park CK, Kim DG, Jung HW. Extended endoscopic endonasal approach for recurrent or residual adult craniopharyngiomas. *Acta Neurochir (Wien)*. 2014;156:1917-1922.
348. Minamida Y, Mikami T, Hashi K, Houkin K. Surgical management of the recurrence and regrowth of craniopharyngiomas. *J Neurosurg*. 2005;103:224-232.
349. Puget S, Garnett M, Wray A, et al. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *J Neurosurg*. 2007;106(1 Suppl):3-12.
350. Chung WY, Pan DH, Shiau CY, Guo WY, Wang LW. Gamma knife radiosurgery for craniopharyngiomas. *J Neurosurg*. 2000;93(Suppl 3):47-56.
351. Kobayashi T, Kida Y, Hasegawa T. Long-term results of gamma knife surgery for craniopharyngioma. *Neurosurg Focus*. 2003;14:e13.
352. Laws ER Jr, Vance ML. Radiosurgery for pituitary tumors and craniopharyngiomas. *Neurosurg Clin N Am*. 1999;10:327-336.
353. Minniti G, Saran F, Traish D, et al. Fractionated stereotactic conformal radiotherapy following conservative surgery in the control of craniopharyngiomas. *Radiother Oncol*. 2007;82:90-95.
354. Schulz-Ertner D, Frank C, Herfarth KK, Rhein B, Wannenmacher M, Debus J. Fractionated stereotactic radiotherapy for craniopharyngiomas. *Int J Radiat Oncol Biol Phys*. 2002;54:1114-1120.
355. Ulfarsson E, Lindquist C, Roberts M, et al. Gamma knife radiosurgery for craniopharyngiomas: long-term results in the first Swedish patients. *J Neurosurg*. 2002;97(5 Suppl):613-622.
356. Weiner HL, Wisoff JH, Rosenberg ME, et al. Craniopharyngiomas: a clinicopathological analysis of factors predictive of recurrence and functional outcome. *Neurosurgery*. 1994;35:1001-1010; discussion 1010-1001.
357. Turel MK, Tsermoulas G, Gonen L, et al. Management and outcome of recurrent adult craniopharyngiomas: an analysis of 42 cases with long-term follow-up. *Neurosurg Focus*. 2016;41:E11.
358. Sughrue ME, Yang I, Kane AJ, et al. Endocrinologic, neurologic, and visual morbidity after treatment for craniopharyngioma. *J Neurooncol*. 2011;101:463-476.
359. Yang I, Sughrue ME, Rutkowski MJ, et al. Craniopharyngioma: a comparison of tumor control with various treatment strategies. *Neurosurg Focus*. 2010;28:E5.
360. Schoenfeld A, Pekmezci M, Barnes MJ, et al. The superiority of conservative resection and adjuvant radiation for craniopharyngiomas. *J Neurooncol*. 2012;108:133-139.
361. Zacharia BE, Bruce SS, Goldstein H, Malone HR, Neugut AI, Bruce JN. Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. *Neuro Oncol*. 2012;14:1070-1078.
362. Koutourousiou M, Gardner PA, Fernandez-Miranda JC, Tyler-Kabara EC, Wang EW, Snyderman CH. Endoscopic endonasal surgery for craniopharyngiomas: surgical outcome in 64 patients. *J Neurosurg*. 2013;119:1194-1207.
363. Dhandapani S, Singh H, Negm HM, et al. Endonasal endoscopic reoperation for residual or recurrent craniopharyngiomas. *J Neurosurg*. 2017;126:418-430.
364. Gardner PA, Kassam AB, Snyderman CH, et al. Outcomes following endoscopic, expanded endonasal resection of suprasellar craniopharyngiomas: a case series. *J Neurosurg*. 2008;109:6-16.
365. Minniti G, Esposito V, Amichetti M, Enrici RM. The role of fractionated radiotherapy and radiosurgery in the management of patients with craniopharyngioma. *Neurosurg Rev*. 2009;32:125-132; discussion 132.
366. Aggarwal A, Fersht N, Brada M. Radiotherapy for craniopharyngioma. *Pituitary*. 2013;16:26-33.
367. Hetelekidis S, Barnes PD, Tao ML, et al. 20-Year experience in childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys*. 1993;27:189-195.
368. Karavitaki N, Brufani C, Warner JT, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf)*. 2005;62:397-409.
369. Merchant TE, Kiehna EN, Sanford RA, et al. Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984-2001. *Int J Radiat Oncol Biol Phys*. 2002;53:533-542.
370. Regine WF, Mohiuddin M, Kramer S. Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. *Radiother Oncol*. 1993;27:13-21.
371. Sainte-Rose C, Puget S, Wray A, et al. Craniopharyngioma: the pendulum of surgical management. *Childs Nerv Syst*. 2005;21(8-9):691-695.
372. Elliott RE, Jane JA Jr, Wisoff JH. Surgical management of craniopharyngiomas in children: meta-analysis and comparison of transcranial and transsphenoidal approaches. *Neurosurgery*. 2011;69:630-643; discussion 643.
373. Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C. Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. *Childs Nerv Syst*. 2005;21(8-9):747-757.
374. Mottolese C, Szathmari A, Berlier P, Hermier M. Craniopharyngiomas: our experience in Lyon. *Childs Nerv Syst*. 2005;21(8-9):790-798.
375. Zuccaro G. Radical resection of craniopharyngioma. *Childs Nerv Syst*. 2005;21(8-9):679-690.
376. Jane JA Jr, Prevedello DM, Alden TD, Laws ER Jr. The transsphenoidal resection of pediatric craniopharyngiomas: a case series. *J Neurosurg Pediatr*. 2010;5:49-60.
377. Tomita T, Bowman RM. Craniopharyngiomas in children: surgical experience at Children's Memorial Hospital. *Childs Nerv Syst*. 2005;21(8-9):729-746.
378. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI. Aggressive surgical management of craniopharyngiomas in children. *J Neurosurg*. 1992;76:47-52.
379. Kim SK, Wang KC, Shin SH, Choe G, Chi JG, Cho BK. Radical excision of pediatric craniopharyngioma: recurrence pattern and prognostic factors. *Childs Nerv Syst*. 2001;17:531-536; discussion 537.
380. Sands SA, Milner JS, Goldberg J, et al. Quality of life and behavioral follow-up study of pediatric survivors of craniopharyngioma. *J Neurosurg*. 2005;103(4 Suppl):302-311.
381. Mallucci C, Pizer B, Blair J, et al. Management of craniopharyngioma: the Liverpool experience following the introduction of the CCLG guidelines. Introducing a new risk assessment grading system. *Childs Nerv Syst*. 2012;28:1181-1192.
382. Di Rocco C, Caldarelli M, Tamburrini G, Massimi L. Surgical management of craniopharyngiomas—experience with a pediatric series. *J Pediatr Endocrinol Metab*. 2006;19(Suppl 1):355-366.
383. Clark AJ, Cage TA, Aranda D, et al. A systematic review of the results of surgery and radiotherapy on tumor control for pediatric craniopharyngioma. *Childs Nerv Syst*. 2013;29:231-238.
384. Locatelli D, Levi D, Rampa F, Pezzotta S, Castelnuovo P. Endoscopic approach for the treatment of relapses in cystic craniopharyngiomas. *Childs Nerv Syst*. 2004;20(11-12):863-867.
385. Fischer EG, Welch K, Shillito J Jr, Winston KR, Tarbell NJ. Craniopharyngiomas in children. Long-term effects of conservative surgical procedures combined with radiation therapy. *J Neurosurg*. 1990;73:534-540.
386. Hussain I, Eloy JA, Carmel PW, Liu JK. Molecular oncogenesis of craniopharyngioma: current and future strategies for the development of targeted therapies. *J Neurosurg*. 2013;119:106-112.
387. Julow J, Lanyi F, Hajda M, et al. Further experiences in the treatment of cystic craniopharyngeomas with yttrium 90 silicate colloid. *Acta Neurochir Suppl (Wien)*. 1988;42:113-119.
388. Lin LL, El Naqa I, Leonard JR, et al. Long-term outcome in children treated for craniopharyngioma with and without radiotherapy. *J Neurosurg Pediatr*. 2008;1:126-130.
389. Munari C, Landre E, Musolino A, Turak B, Habert MO, Chodkiewicz JP. Long term results of stereotactic endocavitary beta irradiation of craniopharyngioma cysts. *J Neurosurg Sci*. 1989;33:99-105.
390. Pollock BE, Lunsford LD, Kondziolka D, Levine G, Flickinger JC. Phosphorus-32 intracavitary irradiation of cystic craniopharyngiomas: current technique and long-term results. *Int J Radiat Oncol Biol Phys*. 1995;33:437-446.
391. Scott RM, Hetelekidis S, Barnes PD, Goumnerova L, Tarbell NJ. Surgery, radiation, and combination therapy in the treatment of childhood craniopharyngioma—a 20-year experience. *Pediatr Neurosurg*. 1994;21(Suppl 1):75-81.
392. Weiss M, Sutton L, Marcial V, et al. The role of radiation therapy in the management of childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys*. 1989;17:1313-1321.
393. Spaziante R, De Divitiis E, Irace C, Cappabianca P, Caputi F. Management of primary or recurring grossly cystic craniopharyngiomas by means of draining systems. Topic review and 6 case reports. *Acta Neurochir (Wien)*. 1989;97(3-4):95-106.
394. Backlund EO. Treatment of craniopharyngiomas: the multimodality approach. *Pediatr Neurosurg*. 1994;21(Suppl 1):82-89.
395. Jeswani S, Nuno M, Wu A, et al. Comparative analysis of outcomes following craniotomy and expanded endoscopic endonasal transsphenoidal resection of craniopharyngioma and related tumors: a single-institution study. *J Neurosurg*. 2016;124:627-638.
396. Kilday JP, Caldarelli M, Massimi L, et al. Intracystic interferon-alpha in pediatric craniopharyngioma patients: an international multicenter assessment on behalf of SIOPE and ISPN. *Neuro Oncol*. 2017;19:1398-1407.
397. Derrey S, Blond S, Reyns N, et al. Management of cystic craniopharyngiomas with stereotactic endocavitary irradiation using colloidal 186Re: a retrospective study of 48 consecutive patients. *Neurosurgery*. 2008;63:1045-1052; discussion 1052-1043.
398. Moon SH, Kim IH, Park SW, et al. Early adjuvant radiotherapy toward long-term survival and better quality of life for craniopharyngiomas—a study in single institute. *Childs Nerv Syst*. 2005;21(8-9):799-807.
399. Hasegawa T, Kondziolka D, Hadjipanayis CG, Lunsford LD. Management of cystic craniopharyngiomas with phosphorus-32 intracavitary irradiation. *Neurosurgery*. 2004;54:813-820; discussion 820-812.
400. Prevedello DM, Solari D, Carrau RL, Gardner P, Kassam AB. Endoscopic endonasal approach for craniopharyngiomas. In: Quinones-Hinojosa A, ed. *Schmideck & Sweet Operative Neurosurgical Techniques. Indications, Methods, and Results*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2012:303-310.
401. Combs SE, Thilmann C, Huber PE, Hoess A, Debus J, Schulz-Ertner D. Achievement of long-term local control in patients with craniopharyngiomas using high precision stereotactic radiotherapy. *Cancer*. 2007;109:2308-2314.

402. Varlotto JM, Flickinger JC, Kondziolka D, Lunsford LD, Deutsch M. External beam irradiation of craniopharyngiomas: long-term analysis of tumor control and morbidity. *Int J Radiat Oncol Biol Phys*. 2002;54:492-499.

403. Cavallo LM, Solari D, Esposito F, Villa A, Minniti G, Cappabianca P. The role of the endoscopic endonasal route in the management of craniopharyngiomas. *World Neurosurg*. 2014;82(6 Suppl):S32-S40.

404. Stripp DC, Maity A, Janss AJ, et al. Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. *Int J Radiat Oncol Biol Phys*. 2004;58:714-720.

405. Chiou SM, Lunsford LD, Niranjan A, Kondziolka D, Flickinger JC. Stereotactic radiosurgery of residual or recurrent craniopharyngioma, after surgery, with or without radiation therapy. *Neuro Oncol*. 2001;3:159-166.

406. Jackson AS, St George EJ, Hayward RJ, Plowman PN. Stereotactic radiosurgery. XVII: Recurrent intrasellar craniopharyngioma. *Br J Neurosurg*. 2003;17:138-143.

407. Iannalfi A, Fragkandrea I, Brock J, Saran F. Radiotherapy in craniopharyngiomas. *Clin Oncol (R Coll Radiol)*. 2013;25:654-667.

408. Veeravagu A, Lee M, Jiang B, Chang SD. The role of radiosurgery in the treatment of craniopharyngiomas. *Neurosurg Focus*. 2010;28:E11.

409. Jeon C, Kim S, Shin HJ, et al. The therapeutic efficacy of fractionated radiotherapy and gamma-knife radiosurgery for craniopharyngiomas. *J Clin Neurosci*. 2011;18:1621-1625.

410. Hukin J, Steinbok P, Lafay-Cousin L, et al. Intracystic bleomycin therapy for craniopharyngioma in children: the Canadian experience. *Cancer*. 2007;109:2124-2131.

411. Julow J, Backlund EO, Lanyi F, et al. Long-term results and late complications after intracavitary yttrium-90 colloid irradiation of recurrent cystic craniopharyngiomas. *Neurosurgery*. 2007;61:288-295; discussion 295-286.

412. Cavalheiro S, Dastoli PA, Silva NS, Toledo S, Lederman H, da Silva MC. Use of interferon alpha in intratumoral chemotherapy for cystic craniopharyngioma. *Childs Nerv Syst*. 2005;21(8-9):719-724.

413. Sekine S, Shibata T, Kokubu A, et al. Craniopharyngiomas of adamantinomatous type harbor beta-catenin gene mutations. *Am J Pathol*. 2002;161:1997-2001.

414. Hofmann BM, Kreutzer J, Saeger W, et al. Nuclear beta-catenin accumulation as reliable marker for the differentiation between cystic craniopharyngiomas and rathke cleft cysts: a clinico-pathologic approach. *Am J Surg Pathol*. 2006;30:1595-1603.

415. Holsken A, Stache C, Schlaffer SM, et al. Adamantinomatous craniopharyngiomas express tumor stem cell markers in cells with activated Wnt signaling: further evidence for the existence of a tumor stem cell niche? *Pituitary*. 2014;17:546-556.

416. Martinez-Gutierrez JC, D'Andrea MR, Cahill DP, Santagata S, Barker FG 2nd, Brastianos PK. Diagnosis and management of craniopharyngiomas in the era of genomics and targeted therapy. *Neurosurg Focus*. 2016;41:E2.

417. Larkin SJ, Ansorge O. Pathology and pathogenesis of craniopharyngiomas. *Pituitary*. 2013;16:9-17.

418. Guadagno E, de Divitiis O, Solari D, et al. Can recurrences be predicted in craniopharyngiomas? beta-catenin coexisting with stem cells markers and p-ATM in a clinicopathologic study of 45 cases. *J Exp Clin Cancer Res*. 2017;36:95.

419. Brastianos PK, Taylor-Weiner A, Manley PE, et al. Exome sequencing identifies BRAF mutations in papillary craniopharyngiomas. *Nat Genet*. 2014;46:161-165.

420. Jung TY, Jung S, Choi JE, Moon KS, Kim IY, Kang SS. Adult craniopharyngiomas: surgical results with a special focus on endocrinological outcomes and recurrence according to pituitary stalk preservation. *J Neurosurg*. 2009;111:572-577.

421. Li K, Lu X, Yang N, Zheng J, Huang B, Li L. Association of pituitary stalk management with endocrine outcomes and recurrence in microsurgery of craniopharyngiomas: a meta-analysis. *Clin Neurol Neurosurg*. 2015;136:20-24.

422. Pratheesh R, Swallow DM, Rajaratnam S, et al. Incidence, predictors and early post-operative course of diabetes insipidus in paediatric craniopharyngioma: a comparison with adults. *Childs Nerv Syst*. 2013;29:941-949.

423. Gonzalez Briceno L, Grill J, Bourdeaut F, et al. Water and electrolyte disorders at long-term post-treatment follow-up in paediatric patients with suprasellar tumours include unexpected persistent cerebral salt-wasting syndrome. *Horm Res Paediatr*. 2014;82:364-371.

424. Moussazadeh N, Prabhu V, Bander ED, et al. Endoscopic endonasal versus open transcranial resection of craniopharyngiomas: a case-matched single-institution analysis. *Neurosurg Focus*. 2016;41:E7.

425. Wannemuehler TJ, Rubel KE, Hendricks BK, et al. Outcomes in transcranial microsurgery versus extended endoscopic endonasal approach for primary resection of adult craniopharyngiomas. *Neurosurg Focus*. 2016;41:E6.

426. Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH. Endoscopic endonasal compared with microscopic transsphenoidal and open transcranial resection of craniopharyngiomas. *World Neurosurg*. 2012;77:329-341.

427. Cavallo LM, Messina A, Esposito F, et al. Skull base reconstruction in the extended endoscopic transsphenoidal approach for suprasellar lesions. *J Neurosurg*. 2007;107:713-720.

428. Leng LZ, Brown S, Anand VK, Schwartz TH. "Gasket-seal" watertight closure in minimal-access endoscopic cranial base surgery. *Neurosurgery*. 2008;62(5 Suppl 2):ONSE342-ONSE343; discussion ONSE343.

429. Tabaee A, Plakantonakis D, Schwartz TH, Anand VK. Reconstruction after endoscopic skull base surgery. In: Anand VK, Schwartz TH, eds. *Practical Endoscopic Skull Base Surgery*. San Diego: Plural Publishing, Inc; 2007:191-202.

430. Fortes FS, Carrau RL, Snyderman CH, et al. The posterior pedicle inferior turbinate flap: a new vascularized flap for skull base reconstruction. *Laryngoscope*. 2007;117:1329-1332.

431. Zanation AM, Snyderman CH, Carrau RL, Kassam AB, Gardner PA, Prevedello DM. Minimally invasive endoscopic pericranial flap: a new method for endonasal skull base reconstruction. *Laryngoscope*. 2009;119:13-18.

432. Pinheiro-Neto CD, Prevedello DM, Carrau RL, et al. Improving the design of the pedicled nasoseptal flap for skull base reconstruction: a radioanatomic study. *Laryngoscope*. 2007;117:1560-1569.

433. Cushing H. Meningiomas arising from the tuberculum sellae. *Arch Ophthalmol*. 1929;1:168-206.

434. Al-Mefty O, Holoubi A, Rifai A, Fox JL. Microsurgical removal of suprasellar meningiomas. *Neurosurgery*. 1985;16:364-372.

435. de Divitiis E, Esposito F, Cappabianca P, Cavallo LM, de Divitiis O. Tuberculum sellae meningiomas: high route or low route? A series of 51 consecutive cases. *Neurosurgery*. 2008;62:556-563; discussion 556-563.

436. de Divitiis E, Mariniello G, Cappabianca P. Suprasellar meningiomas. *Neurosurgery*. 2002;51:851-852; author reply 852.

437. Cushing H. The chiasmal syndrome. *Arch Ophthalmol*. 1930;3:505-551.

438. Palani A, Panigrahi MK, Purohit AK. Tuberculum sellae meningiomas: a series of 41 cases; surgical and ophthalmological outcomes with proposal of a new prognostic scoring system. *J Neurosci Rural Pract*. 2012;3:286-293.

439. Mortazavi MM, Brito da Silva H, Ferreira M Jr, Barber JK, Pridgeon JS, Sekhar LN. Planum sphenoidale and tuberculum sellae meningiomas: operative nuances of a modern surgical technique with outcome and proposal of a new classification system. *World Neurosurg*. 2016;86:270-286.

440. Goel A, Muzumdar D, Desai KI. Tuberculum sellae meningioma: a report on management on the basis of a surgical experience with 70 patients. *Neurosurgery*. 2002;51:1358-1363; discussion 1363-1354.

441. Yasargil MG. Meningiomas. In: Yasargil MG, ed. *Microneurosurgery, Volume IVB: Microneurosurgery of CNS Tumors*. 1st ed. New York: Thieme; 1995:150-151.

442. Ravin JG. The magician with a meningioma. *Arch Ophthalmol*. 2012;130:1317-1321.

443. Jho HD. Endoscopic transsphenoidal surgery. *J Neurooncol*. 2001;54:187-195.

444. de Divitiis E, Esposito F, Cappabianca P, Cavallo LM, de Divitiis O, Esposito I. Endoscopic transnasal resection of anterior cranial fossa meningiomas. *Neurosurg Focus*. 2008;25:E8.

445. Wang Q, Lu XJ, Ji WY, et al. Visual outcome after extended endoscopic endonasal transsphenoidal surgery for tuberculum sellae meningiomas. *World Neurosurg*. 2010;73:694-700.

446. Van Gompel JJ, Frank G, Pasquini E, Zoli M, Hoover J, Lanzino G. Expanded endonasal endoscopic resection of anterior fossa meningiomas: report of 13 cases and meta-analysis of the literature. *Neurosurg Focus*. 2011;30:E15.

447. Ogawa Y, Tominaga T. Extended transsphenoidal approach for tuberculum sellae meningioma—what are the optimum and critical indications? *Acta Neurochir (Wien)*. 2012;154:621-626.

448. Bohman LE, Stein SC, Newman JG, et al. Endoscopic versus open resection of tuberculum sellae meningiomas: a decision analysis. *ORL J Otorhinolaryngol Relat Spec*. 2012;74:255-263.

449. Chowdhury FH, Haque MR, Goel AH, Kawsar KA. Endoscopic endonasal extended transsphenoidal removal of tuberculum sellae meningioma (TSM): an experience of six cases. *Br J Neurosurg*. 2012;26:692-699.

450. Gadgil N, Thomas JG, Takashima M, Yoshor D. Endoscopic resection of tuberculum sellae meningiomas. *J Neurol Surg B Skull Base*. 2013;74:201-210.

451. Koutourousiou M, Fernandez-Miranda JC, Stefko ST, Wang EW, Snyderman CH, Gardner PA. Endoscopic endonasal surgery for suprasellar meningiomas: experience with 75 patients. *J Neurosurg*. 2014;120:1326-1339.

452. Ottenhausen M, Banu MA, Placantonakis DG, et al. Endoscopic endonasal resection of suprasellar meningiomas: the importance of case selection and experience in determining extent of resection, visual improvement, and complications. *World Neurosurg*. 2014;82(3-4):442-449.

453. Ceylan S, Anik I, Koc K, Cabuk B. Extended endoscopic transsphenoidal approach infrachiasmatic corridor. *Neurosurg Rev*. 2015;38:137-147; discussion 147.

454. Hayhurst C, Sughrue ME, Gore PA, Bonney PA, Burks JD, Teo C. Results with expanded endonasal resection of skull base meningiomas technical nuances and approach selection based on an early experience. *Turk Neurosurg*. 2016;26:662-670.

455. Elshazly K, Kshettry VR, Farrell CJ, Nyquist G, Rosen M, Evans JJ. Clinical outcome after endoscopic endonasal resection of tuberculum sella meningiomas. *Oper Neurosurg (Hagerstown)*. 2018;14:494-502.

456. Kitano M, Taneda M, Nakao Y. Postoperative improvement in visual function in patients with tuberculum sellae meningiomas: results of the extended transsphenoidal and transcranial approaches. *J Neurosurg*. 2007;107:337-346.

457. Fatemi N, Dusick JR, de Paiva Neto MA, Malkasian D, Kelly DF. Endonasal versus supraorbital keyhole removal of craniopharyngiomas and tuberculum sellae meningiomas. *Neurosurgery*. 2009;64(5 Suppl 2):269-284; discussion 284-266.

458. Linsler S, Fischer G, Skliarenko V, Stadie A, Oertel J. Endoscopic assisted supraorbital keyhole approach or endoscopic endonasal approach in cases of tuberculum sellae meningioma: which surgical route should be favored? *World Neurosurg*. 2017;104:601-611.

459. Song SW, Kim YH, Kim JW, et al. Outcomes after transcranial and endoscopic endonasal approach for tuberculum meningiomas: a retrospective comparison. *World Neurosurg*. 2018;109:e434-e445.

460. de Divitiis E, Cavallo LM, Esposito F, Stella L, Messina A. Extended endoscopic transsphenoidal approach for tuberculum sellae meningiomas. *Neurosurgery*. 2008;62(6 Suppl 3):1192-1201.

461. Graffeo CS, Dietrich AR, Grobelny B, et al. A panoramic view of the skull base: systematic review of open and endoscopic endonasal approaches to four tumors. *Pituitary*. 2014;17:349-356.

462. Shin M, Kondo K, Saito N. Current status of endoscopic endonasal surgery for skull base meningiomas: review of the literature. *Neurol Med Chir (Tokyo)*. 2015;55:735-743.

463. Turel MK, Tsermoulas G, Reddy D, Andrade-Barazarte H, Zadeh G, Gentili F. Endonasal endoscopic transsphenoidal excision of tuberculum sellae meningiomas: a systematic review. *J Neurosurg Sci*. 2016;60:463-475.

464. Clark AJ, Jahangiri A, Garcia RM, et al. Endoscopic surgery for tuberculum sellae meningiomas: a

systematic review and meta-analysis. *Neurosurg Rev*. 2013;36:349-359.

465. Muskens IS, Briceno V, Ouwehand TL, et al. The endoscopic endonasal approach is not superior to the microscopic transcranial approach for anterior skull base meningiomas—a meta-analysis. *Acta Neurochir (Wien)*. 2018;160:59-75.
466. Mahmoud M, Nader R, Al-Mefty O. Optic canal involvement in tuberculum sellae meningiomas: influence on approach, recurrence, and visual recovery. *Neurosurgery*. 2010;67(3 Suppl Operative):ons108-ons118; discussion ons118-ons109.
467. Obeid F, Al-Mefty O. Recurrence of olfactory groove meningiomas. *Neurosurgery*. 2003;53:534-542; discussion 542-533.
468. Banu MA, Mehta A, Ottenhausen M, et al. Endoscope-assisted endonasal versus supraorbital keyhole resection of olfactory groove meningiomas: comparison and combination of 2 minimally invasive approaches. *J Neurosurg*. 2016;124:605-620.
469. de Almeida JR, Carvalho F, Vaz Guimaraes Filho F, et al. Comparison of endoscopic endonasal and bifrontal craniotomy approaches for olfactory groove meningiomas: a matched pair analysis of outcomes and frontal lobe changes on MRI. *J Clin Neurosci*. 2015;22:1733-1741.
470. Khan OH, Krischek B, Holliman D, et al. Pure endoscopic expanded endonasal approach for olfactory groove and tuberculum sellae meningiomas. *J Clin Neurosci*. 2014;21:927-933.
471. Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH. Endoscopic endonasal versus open transcranial resection of anterior midline skull base meningiomas. *World Neurosurg*. 2012;77(5-6):713-724.
472. Koutourousiou M, Fernandez-Miranda JC, Wang EW, Snyderman CH, Gardner PA. Endoscopic endonasal surgery for olfactory groove meningiomas: outcomes and limitations in 50 patients. *Neurosurg Focus*. 2014;37:E8.
473. Padhye V, Naidoo Y, Alexander H, et al. Endoscopic endonasal resection of anterior skull base meningiomas. *Otolaryngol Head Neck Surg*. 2012;147:575-582.
474. Zhang Q, Wang Z, Guo H, et al. Resection of anterior cranial base meningiomas with intra- and extracranial involvement via a purely endoscopic endonasal approach. *ORL J Otorhinolaryngol Relat Spec*. 2012;74:199-207.
475. Brunworth J, Padhye V, Bassiouni A, et al. Update on endoscopic endonasal resection of skull base meningiomas. *Int Forum Allergy Rhinol*. 2015;5:344-352.
476. Khan OH, Anand VK, Schwartz TH. Endoscopic endonasal resection of skull base meningiomas: the significance of a "cortical cuff" and brain edema compared with careful case selection and surgical experience in predicting morbidity and extent of resection. *Neurosurg Focus*. 2014;37:E7.
477. Harvey RJ, Parmar P, Sacks R, Zanation AM. Endoscopic skull base reconstruction of large dural defects: a systematic review of published evidence. *Laryngoscope*. 2012;122:452-459.
478. Eloy JA, Patel SK, Shukla PA, Smith ML, Choudhry OJ, Liu JK. Triple-layer reconstruction technique for large cribriform defects after endoscopic endonasal resection of anterior skull base tumors. *Int Forum Allergy Rhinol*. 2013;3:204-211.
479. Luginbuhl AJ, Campbell PG, Evans J, Rosen M. Endoscopic repair of high-flow cranial base defects using a bilayer button. *Laryngoscope*. 2010;120:876-880.
480. Fathalla H, Di Ieva A, Lee J, et al. Cerebrospinal fluid leaks in extended endoscopic transsphenoidal surgery: covering all the angles. *Neurosurg Rev*. 2017;40:309-318.
481. Bernat AL, Priola SM, Elsawy A, et al. Recurrence of anterior skull base meningiomas after endoscopic endonasal resection: 10 year experience in a series of 52 endoscopic and transcranial cases. *World Neurosurg*. 2018;120:e107-e113.
482. Eloy JA, Shukla PA, Choudhry OJ, Singh R, Liu JK. Assessment of frontal lobe sagging after endoscopic endonasal transcribriform resection of anterior skull base tumors: is rigid structural reconstruction of the cranial base defect necessary? *Laryngoscope*. 2012;122:2652-2657.
483. Gardner PA, Kassam AB, Thomas A, et al. Endoscopic endonasal resection of anterior cranial base meningiomas. *Neurosurgery*. 2008;63:36-52; discussion 52-34.
484. Jang WY, Jung S, Jung TY, Moon KS, Kim IY. Preservation of olfaction in surgery of olfactory groove meningiomas. *Clin Neurol Neurosurg*. 2013;115:1288-1292.
485. Peris Celda M, Kenning T, Pinheiro-Neto CD. Endoscopic superior ethmoidal approach for anterior cranial base resection: tailoring the approach for maximum exposure with preservation of nasal structures. *World Neurosurg*. 2017;104:311-317.
486. Rosen MR, Rabinowitz MR, Farrell CJ, Schaberg MR, Evans JJ. Septal transposition: a novel technique for preservation of the nasal septum during endoscopic endonasal resection of olfactory groove meningiomas. *Neurosurg Focus*. 2014;37:E6.
487. Youssef AS, Sampath R, Freeman JL, Mattingly JK, Ramakrishnan VR. Unilateral endonasal transcribriform approach with septal transposition for olfactory groove meningioma: can olfaction be preserved? *Acta Neurochir (Wien)*. 2016;158:1965-1972.
488. Nanda A, Javalkar V, Banerjee AD. Petroclival meningiomas: study on outcomes, complications and recurrence rates. *J Neurosurg*. 2011;114:1268-1277.
489. Rhoton AL Jr. The temporal bone and transtemporal approaches. *Neurosurgery*. 2000;47(3 Suppl):S211-S265.
490. Almefty R, Dunn IF, Pravdenkova S, Abolfotoh M, Al-Mefty O. True petroclival meningiomas: results of surgical management. *J Neurosurg*. 2014;120:40-51.
491. Xu F, Karampelas I, Megerian CA, Selman WR, Bambakidis NC. Petroclival meningiomas: an update on surgical approaches, decision making, and treatment results. *Neurosurg Focus*. 2013;35:E11.
492. Aziz KM, Froelich S, Bhatia S, Yu AK, Bricolo A, Hillman T, Sekula RF Jr. Surgical management of petroclival meningiomas. In: Hinojosa A, ed. *Schmidek and Sweet's Operative Technique and Approaches*. 6th ed. Milton, Ontario, Canada: Elsevier; 2012. Pp. 473-485.
493. Hunter JB, Weaver KD, Thompson RC, Wanna GB. Petroclival meningiomas. *Otolaryngol Clin North Am*. 2015;48:477-490.
494. Van Havenbergh T, Carvalho G, Tatagiba M, Plets C, Samii M. Natural history of petroclival meningiomas. *Neurosurgery*. 2003;52:55-62; discussion 62-54.
495. Combs SE, Ganswindt U, Foote RL, Kondziolka D, Tonn JC. State-of-the-art treatment alternatives for base of skull meningiomas: complementing and controversial indications for neurosurgery, stereotactic and robotic based radiosurgery or modern fractionated radiation techniques. *Radiat Oncol*. 2012;7:226.
496. Koutourousiou M, Fernandez-Miranda JC, Vaz-Guimaraes Filho F, et al. Outcomes of endonasal and lateral approaches to petroclival meningiomas. *World Neurosurg*. 2017;99:500-517.
497. Campbell E, Whitfield RD. Posterior fossa meningiomas. *J Neurosurg*. 1948;5:131-153.
498. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. *J Neurol Neurosurg Psychiatry*. 1957;20:22-39.
499. Hunter JB, O'Connell BP, Carlson ML, et al. Tumor progression following petroclival meningioma subtotal resection: a volumetric study. *Oper Neurosurg (Hagerstown)*. 2018;14:215-223.
500. Natarajan SK, Sekhar LN, Schessel D, Morita A. Petroclival meningiomas: multimodality treatment and outcomes at long-term follow-up. *Neurosurgery*. 2007;60:965-979; discussion 979-981.
501. Pirayesh A, Petrakakis I, Raab P, Polemikos M, Krauss JK, Nakamura M. Petroclival meningiomas: magnetic resonance imaging factors predict tumor resectability and clinical outcome. *Clin Neurol Neurosurg*. 2016;147:90-97.
502. Gousias K, Schramm J, Simon M. The Simpson grading revisited: aggressive surgery and its place in modern meningioma management. *J Neurosurg*. 2016;125:551-560.
503. Li D, Hao SY, Wang L, et al. Surgical management and outcomes of petroclival meningiomas: a single-center case series of 259 patients. *Acta Neurochir (Wien)*. 2013;155:1367-1383.
504. Sekhar LN, Swamy NK, Jaiswal V, Rubinstein E, Hirsch WE Jr, Wright DC. Surgical excision of meningiomas involving the clivus: preoperative and intraoperative features as predictors of postoperative functional deterioration. *J Neurosurg*. 1994;81:860-868.
505. Flannery TJ, Kano H, Lunsford LD, et al. Long-term control of petroclival meningiomas through radiosurgery. *J Neurosurg*. 2010;112:957-964.
506. Roche PH, Pellet W, Fuentes S, Thomassin JM, Regis J. Gamma knife radiosurgical management of petroclival meningiomas results and indications. *Acta Neurochir (Wien)*. 2003;145:883-888; discussion 888.
507. Shah AH, Patel N, Raper DM, et al. The role of preoperative embolization for intracranial meningiomas. *J Neurosurg*. 2013;119:364-372.
508. Raper DM, Starke RM, Henderson F Jr, et al. Preoperative embolization of intracranial meningiomas: efficacy, technical considerations, and complications. *AJNR Am J Neuroradiol*. 2014;35:1798-1804.
509. Singla A, Deshaies EM, Melnyk V, et al. Controversies in the role of preoperative embolization in meningioma management. *Neurosurg Focus*. 2013;35:E17.
510. Aihara M, Naito I, Shimizu T, et al. Preoperative embolization of intracranial meningiomas using n-butyl cyanoacrylate. *Neuroradiology*. 2015;57:713-719.
511. Suzuki K, Nagaishi M, Matsumoto Y, et al. Preoperative embolization for skull base meningiomas. *J Neurol Surg B Skull Base*. 2017;78:308-314.
512. Beer-Furlan A, Vellutini EA, Balsalobre L, Stamm AC. Endoscopic endonasal approach to ventral posterior fossa meningiomas: from case selection to surgical management. *Neurosurg Clin N Am*. 2015;26:413-426.
513. Acuna RT. Nasopharyngeal fibroma. *Acta Otolaryngol*. 1973;75:119-126.
514. Lund VJ, Stammberger H, Nicolai P, et al. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. *Rhinol Suppl*. 2010;22:1-143.
515. Boghani Z, Husain Q, Kanumuri VV, et al. Juvenile nasopharyngeal angiofibroma: a systematic review and comparison of endoscopic, endoscopic-assisted, and open resection in 1047 cases. *Laryngoscope*. 2013;123:859-869.
516. Nicolai P, Berlucchi M, Tomenzoli D, et al. Endoscopic surgery for juvenile angiofibroma: when and how. *Laryngoscope*. 2003;113:775-782.
517. Beham A, Beham-Schmid C, Regauer S, Aubock L, Stammberger H. Nasopharyngeal angiofibroma: true neoplasm or vascular malformation? *Adv Anat Pathol*. 2000;7:36-46.
518. Starlinger V, Wendler O, Gramann M, Schick B. Laminin expression in juvenile angiofibroma indicates vessel's early developmental stage. *Acta Otolaryngol*. 2007;127:1310-1315.
519. Schick B, Plinkert PK, Prescher A. [Aetiology of angiofibromas: reflection on their specific vascular component]. *Laryngorhinootologie*. 2002;81:280-284. German.
520. Lopez F, Triantafyllou A, Snyderman CH, et al. Nasal juvenile angiofibroma: current perspectives with emphasis on management. *Head Neck*. 2017;39:1033-1045.
521. Rodriguez DP, Orscheln ES, Koch BL. Masses of the nose, nasal cavity, and nasopharynx in children. *Radiographics*. 2017;37:1704-1730.
522. Khoueir N, Nicolas N, Rohayem Z, Haddad A, Abou Hamad W. Exclusive endoscopic resection of juvenile nasopharyngeal angiofibroma: a systematic review of the literature. *Otolaryngol Head Neck Surg*. 2014;150:350-358.
523. Snyderman CH, Pant H, Carrau RL, Gardner P. A new endoscopic staging system for angiofibromas. *Arch Otolaryngol Head Neck Surg*. 2010;136:588-594.
524. Carrillo JF, Maldonado F, Albores O, Ramirez-Ortega MC, Onate-Ocana LF. Juvenile nasopharyngeal angiofibroma: clinical factors associated with recurrence, and proposal of a staging system. *J Surg Oncol*. 2008;98:75-80.
525. Onerci M, Ogretmenoglu O, Yucel T. Juvenile nasopharyngeal angiofibroma: a revised staging system. *Rhinology*. 2006;44:39-45.
526. Radkowski D, McGill T, Healy GB, Ohlms L, Jones DT. Angiofibroma. Changes in staging and treatment. *Arch Otolaryngol Head Neck Surg*. 1996;122:122-129.
527. Andrews JC, Fisch U, Valavanis A, Aeppli U, Makek MS. The surgical management of extensive

nasopharyngeal angiofibromas with the infratemporal fossa approach. *Laryngoscope*. 1989;99:429-437.

528. Antonelli AR, Cappiello J, Di Lorenzo D, Donajo CA, Nicolai P, Orlandini A. Diagnosis, staging, and treatment of juvenile nasopharyngeal angiofibroma (JNA). *Laryngoscope*. 1987;97:1319-1325.
529. Bremer JW, Neel HB 3rd, DeSanto LW, Jones GC. Angiofibroma: treatment trends in 150 patients during 40 years. *Laryngoscope*. 1986;96:1321-1329.
530. Chandler JR, Goulding R, Moskowitz L, Quencer RM. Nasopharyngeal angiofibromas: staging and management. *Ann Otol Rhinol Laryngol*. 1984;93(4 Pt 1):322-329.
531. Fisch U. The infratemporal fossa approach for nasopharyngeal tumors. *Laryngoscope*. 1983;93:36-44.
532. Sessions RB, Zarin DP, Bryan RN. Juvenile nasopharyngeal angiofibroma. *Am J Dis Child*. 1981;135:535-537.
533. Howard DJ, Lloyd G, Lund V. Recurrence and its avoidance in juvenile angiofibroma. *Laryngoscope*. 2001;111:1509-1511.
534. Dubey SP, Bernhard S. *Juvenile Angiofibroma*. 1st ed. New York: Springer Berlin Heidelberg; 2017.
535. Overdevest JB, Amans MR, Zaki P, Pletcher SD, El-Sayed IH. Patterns of vascularization and surgical morbidity in juvenile nasopharyngeal angiofibroma: a case series, systematic review, and meta-analysis. *Head Neck*. 2018;40:428-443.
536. El Sharkawy AA. Endonasal endoscopic management of juvenile nasopharyngeal angiofibroma without angiographic embolization. *Eur Arch Otorhinolaryngol*. 2013;270:2051-2055.
537. Fonseca AS, Vinhaes E, Boaventura V, et al. Surgical treatment of non-embolized patients with nasoangiofibroma. *Braz J Otorhinolaryngol*. 2008;74:583-587.
538. Borghei P, Baradaranfar MH, Borghei SH, Sokhandon F. Transnasal endoscopic resection of juvenile nasopharyngeal angiofibroma without preoperative embolization. *Ear Nose Throat J*. 2006;85:740-743, 746.
539. Mohammadi M, Saedi B, Basam A. Effect of embolisation on endoscopic resection of angiofibroma. *J Laryngol Otol*. 2010;124:631-635.
540. Janakiram N, Sharma SB, Panicker VB, Srinivas CV. A drastic aftermath of embolisation in juvenile nasopharyngeal angiofibroma. *Indian J Otolaryngol Head Neck Surg*. 2016;68:540-543.
541. Janakiram TN, Sharma SB, Panicker VB. Endoscopic excision of non-embolized juvenile nasopharyngeal angiofibroma: our technique. *Indian J Otolaryngol Head Neck Surg*. 2016;68:263-269.
542. Ramezani A, Haghighatkhah H, Moghadasi H, Taheri MS, Parsafar H. A case of central retinal artery occlusion following embolization procedure for juvenile nasopharyngeal angiofibroma. *Indian J Ophthalmol*. 2010;58:419-421.
543. Nicolai P, Villaret AB, Farina D, et al. Endoscopic surgery for juvenile angiofibroma: a critical review of indications after 46 cases. *Am J Rhinol Allergy*. 2010;24:e67-e72.
544. Robinson S, Patel N, Wormald PJ. Endoscopic management of benign tumors extending into the infratemporal fossa: a two-surgeon transnasal approach. *Laryngoscope*. 2005;115:1818-1822.
545. Cloutier T, Pons Y, Blancal JP, et al. Juvenile nasopharyngeal angiofibroma: does the external approach still make sense? *Otolaryngol Head Neck Surg*. 2012;147:958-963.
546. McLaughlin EJ, Cunningham MJ, Kazahaya K, Hsing J, Kawai K, Adil EA. Endoscopic radiofrequency ablation-assisted resection of juvenile nasopharyngeal angiofibroma: comparison with traditional endoscopic technique. *Otolaryngol Head Neck Surg*. 2016;154:1145-1148.
547. Garofalo P, Pia F, Policarpo M, Tunesi S, Valletti PA. Juvenile nasopharyngeal angiofibroma: comparison between endoscopic and open operative approaches. *J Craniofac Surg*. 2015;26:918-821.
548. Chan KH, Gao D, Fernandez PG, Kingdom TT, Kumpe DA. Juvenile nasopharyngeal angiofibroma: vascular determinates for operative complications and tumor recurrence. *Laryngoscope*. 2014;124:672-677.
549. Huang Y, Liu Z, Wang J, Sun X, Yang L, Wang D. Surgical management of juvenile nasopharyngeal angiofibroma: analysis of 162 cases from 1995 to 2012. *Laryngoscope*. 2014;124:1942-1946.
550. Ballah D, Rabinowitz D, Vossough A, et al. Preoperative angiography and external carotid artery embolization of juvenile nasopharyngeal angiofibromas in a tertiary referral paediatric centre. *Clin Radiol*. 2013;68:1097-1106.
551. Lopez F, Suarez V, Costales M, Suarez C, Llorente JL. Treatment of juvenile angiofibromas: 18-year experience of a single tertiary centre in Spain. *Rhinology*. 2012;50:95-103.
552. Fyrmpas G, Konstantinidis I, Constantinidis J. Endoscopic treatment of juvenile nasopharyngeal angiofibromas: our experience and review of the literature. *Eur Arch Otorhinolaryngol*. 2012;269:523-529.
553. El Morsy SM, Khafagy YW. Transnasal endoscopic management of angiofibroma extending to pterygopalatine and infratemporal fossae. *J Laryngol Otol*. 2011;125:701-705.
554. Baser B, Kothari S, Kinger A. Endoscopic approach to Fisch stage II to III-b juvenile nasopharyngeal angiofibroma. *Indian J Otolaryngol Head Neck Surg*. 2011;63:1-4.
555. Ye L, Zhou X, Li J, Jin J. Coblation-assisted endonasal endoscopic resection of juvenile nasopharyngeal angiofibroma. *J Laryngol Otol*. 2011;125:940-944.
556. Hyun DW, Ryu JH, Kim YS, et al. Treatment outcomes of juvenile nasopharyngeal angiofibroma according to surgical approach. *Int J Pediatr Otorhinolaryngol*. 2011;75:69-73.
557. Wang QY, Chen HH, Lu YY. Comparison of two approaches to the surgical management of juvenile nasopharyngeal angiofibroma stages I and II. *J Otolaryngol Head Neck Surg*. 2011;40:14-18.
558. Bleier BS, Kennedy DW, Palmer JN, Chiu AG, Bloom JD, O'Malley BW Jr. Current management of juvenile nasopharyngeal angiofibroma: a tertiary center experience 1999-2007. *Am J Rhinol Allergy*. 2009;23:328-330.
559. Midilli R, Karci B, Akyildiz S. Juvenile nasopharyngeal angiofibroma: analysis of 42 cases and important aspects of endoscopic approach. *Int J Pediatr Otorhinolaryngol*. 2009;73:401-408.
560. Ardehali MM, Samimi Ardestani SH, Yazdani N, Goodarzi H, Bastaninejad S. Endoscopic approach for excision of juvenile nasopharyngeal angiofibroma: complications and outcomes. *Am J Otolaryngol*. 2010;31:343-349.
561. Hackman T, Snyderman CH, Carrau R, Vescan A, Kassam A. Juvenile nasopharyngeal angiofibroma: the expanded endonasal approach. *Am J Rhinol Allergy*. 2009;23:95-99.
562. Yiotakis I, Eleftheriadou A, Davilis D, et al. Juvenile nasopharyngeal angiofibroma stages I and II: a comparative study of surgical approaches. *Int J Pediatr Otorhinolaryngol*. 2008;72:793-800.
563. Gupta AK, Rajiniganth MG, Gupta AK. Endoscopic approach to juvenile nasopharyngeal angiofibroma: our experience at a tertiary care centre. *J Laryngol Otol*. 2008;122:1185-1189.
564. Eloy P, Watelet JB, Hatert AS, de Wispelaere J, Bertrand B. Endonasal endoscopic resection of juvenile nasopharyngeal angiofibroma. *Rhinology*. 2007;45:24-30.
565. Andrade NA, Pinto JA, Nobrega Mde O, Aguiar JE, Aguiar TF, Vinhaes ES. Exclusively endoscopic surgery for juvenile nasopharyngeal angiofibroma. *Otolaryngol Head Neck Surg*. 2007;137:492-496.
566. Tosun F, Ozer C, Gerek M, Yetiser S. Surgical approaches for nasopharyngeal angiofibroma: comparative analysis and current trends. *J Craniofac Surg*. 2006;17:15-20.
567. Sciarretta V, Pasquini E, Farneti G, Frank G, Mazzatenta D, Calbucci F. Endoscopic sinus surgery for the treatment of vascular tumors. *Am J Rhinol*. 2006;20:426-431.
568. Chen MK, Tsai YL, Lee KW, Chang CC. Strictly endoscopic and harmonic scalpel-assisted surgery of nasopharyngeal angiofibromas: eligible for advanced stage tumors. *Acta Otolaryngol*. 2006;126:1321-1325.
569. Hofmann T, Bernal-Sprekelsen M, Koele W, Reittner P, Klein E, Stammberger H. Endoscopic resection of juvenile angiofibromas—long term results. *Rhinology*. 2005;43:282-289.
570. Pryor SG, Moore EJ, Kasperbauer JL. Endoscopic versus traditional approaches for excision of juvenile nasopharyngeal angiofibroma. *Laryngoscope*. 2005;115:1201-1207.
571. Mann WJ, Jecker P, Amedee RG. Juvenile angiofibromas: changing surgical concept over the last 20 years. *Laryngoscope*. 2004;114:291-293.
572. Naraghi M, Kashfi A. Endoscopic resection of nasopharyngeal angiofibromas by combined transnasal and transoral routes. *Am J Otolaryngol*. 2003;24:149-154.
573. Wormald PJ, Van Hasselt A. Endoscopic removal of juvenile angiofibromas. *Otolaryngol Head Neck Surg*. 2003;129:684-691.
574. Onerci TM, Yucel OT, Ogretmenoglu O. Endoscopic surgery in treatment of juvenile nasopharyngeal angiofibroma. *Int J Pediatr Otorhinolaryngol*. 2003;67:1219-1225.
575. Roger G, Tran Ba Huy P, Froehlich P, et al. Exclusively endoscopic removal of juvenile nasopharyngeal angiofibroma: trends and limits. *Arch Otolaryngol Head Neck Surg*. 2002;128:928-935.
576. Hazarika P, Nayak DR, Balakrishnan R, Raj G, Pillai S. Endoscopic and KTP laser-assisted surgery for juvenile nasopharyngeal angiofibroma. *Am J Otolaryngol*. 2002;23:282-286.
577. Scholtz AW, Appenroth E, Kammen-Jolly K, Scholtz LU, Thumfart WF. Juvenile nasopharyngeal angiofibroma: management and therapy. *Laryngoscope*. 2001;111(4 Pt 1):681-687.
578. Jorissen M, Eloy P, Rombaux P, Bachert C, Daele J. Endoscopic sinus surgery for juvenile nasopharyngeal angiofibroma. *Acta Otorhinolaryngol Belg*. 2000;54:201-219.
579. Schick B, el Rahman el Tahan A, Brors D, Kahle G, Draf W. Experiences with endonasal surgery in angiofibroma. *Rhinology*. 1999;37:80-85.
580. Danesi G, Panciera DT, Harvey RJ, Agostinis C. Juvenile nasopharyngeal angiofibroma: evaluation and surgical management of advanced disease. *Otolaryngol Head Neck Surg*. 2008;138:581-586.
581. Kalani MY, Kalani MA, Kalb S, et al. Craniofacial approaches to large juvenile angiofibromas. *J Neurosurg Pediatr*. 2011;8:71-78.
582. Mair EA, Battiata A, Casler JD. Endoscopic laser-assisted excision of juvenile nasopharyngeal angiofibromas. *Arch Otolaryngol Head Neck Surg*. 2003;129:454-459.
583. Langdon C, Herman P, Verillaud B, et al. Expanded endoscopic endonasal surgery for advanced stage juvenile angiofibromas: a retrospective multi-center study. *Rhinology*. 2016;54:239-246.
584. Leong SC. A systematic review of surgical outcomes for advanced juvenile nasopharyngeal angiofibroma with intracranial involvement. *Laryngoscope*. 2013;123:1125-1131.
585. Liu JK, Husain Q, Kanumuri V, Khan MN, Mendelson ZS, Eloy JA. Endoscopic graduated multiangle, multicorridor resection of juvenile nasopharyngeal angiofibroma: an individualized, tailored, multicorridor skull base approach. *J Neurosurg*. 2016;124:1328-1338.
586. Godoy MD, Bezerra TF, Pinna Fde R, Voegels RL. Complications in the endoscopic and endoscopic-assisted treatment of juvenile nasopharyngeal angiofibroma with intracranial extension. *Braz J Otorhinolaryngol*. 2014;80:120-125.
587. Khalifa MA, Ragab SM. Endoscopic assisted antral window approach for type III nasopharyngeal angiofibroma with infratemporal fossa extension. *Int J Pediatr Otorhinolaryngol*. 2008;72:1855-1860.
588. Cummings BJ, Blend R, Keane T, et al. Primary radiation therapy for juvenile nasopharyngeal angiofibroma. *Laryngoscope*. 1984;94(12 Pt 1):1599-1605.
589. McAfee WJ, Morris CG, Amdur RJ, Werning JW, Mendenhall WM. Definitive radiotherapy for juvenile nasopharyngeal angiofibroma. *Am J Clin Oncol*. 2006;29:168-170.
590. Fields JN, Halverson KJ, Devineni VR, Simpson JR, Perez CA. Juvenile nasopharyngeal angiofibroma: efficacy of radiation therapy. *Radiology*. 1990;176:263-265.
591. Lee JT, Chen P, Safa A, Juillard G, Calcaterra TC. The role of radiation in the treatment of advanced juvenile angiofibroma. *Laryngoscope*. 2002;112(7 Pt 1):1213-1220.
592. Amdur RJ, Yeung AR, Fitzgerald BM, Mancuso AA, Werning JW, Mendenhall WM. Radiotherapy for juvenile nasopharyngeal angiofibroma. *Pract Radiat Oncol*. 2011;1:271-278.
593. Alvarez FL, Suarez V, Suarez C, Llorente JL. Multimodality approach for advanced-stage

juvenile nasopharyngeal angiofibromas. *Head Neck*. 2013;35:209-213.

594. Rowan NR, Stapleton AL, Heft-Neal ME, Gardner PA, Snyderman CH. The natural growth rate of residual juvenile angiofibroma. *J Neurol Surg B Skull Base*. 2018;79:257-261.
595. Goepfert H, Cangir A, Lee YY. Chemotherapy for aggressive juvenile nasopharyngeal angiofibroma. *Arch Otolaryngol*. 1985;111:285-289.
596. Schick B, Kahle G, Hassler R, Draf W. [Chemotherapy of juvenile angiofibroma—an alternative?]. *HNO*. 1996;44:148-152. German.
597. Thakar A, Gupta G, Bhalla AS, et al. Adjuvant therapy with flutamide for presurgical volume reduction in juvenile nasopharyngeal angiofibroma. *Head Neck*. 2011;33:1747-1753.
598. Labra A, Chavolla-Magana R, Lopez-Ugalde A, Alanis-Calderon J, Huerta-Delgado A. Flutamide as a preoperative treatment in juvenile angiofibroma (JA) with intracranial invasion: report of 7 cases. *Otolaryngol Head Neck Surg*. 2004;130:466-469.
599. Hota A, Sarkar C, Gupta SD, Kumar R, Bhalla AS, Thakar A. Expression of vascular endothelial growth factor in juvenile angiofibroma. *Int J Pediatr Otorhinolaryngol*. 2015;79:900-902.
600. Wendler O, Dlugaiczyk J, Birk S, Schick B. Antiproliferative effect of glucocorticoids on mesenchymal cells in juvenile angiofibromas. *Head Neck*. 2012;34:1615-1621.
601. Ooi EH, Glicksman JT, Vescan AD, Witterick IJ. An alternative management approach to paranasal sinus fibro-osseous lesions. *Int Forum Allergy Rhinol*. 2011;1:55-63.
602. Commins DJ, Tolley NS, Milford CA. Fibrous dysplasia and ossifying fibroma of the paranasal sinuses. *J Laryngol Otol*. 1998;112:964-968.
603. Earwaker J. Paranasal sinus osteomas: a review of 46 cases. *Skeletal Radiol*. 1993;22:417-423.
604. Ledderose GJ, Betz CS, Stelter K, Leunig A. Surgical management of osteomas of the frontal recess and sinus: extending the limits of the endoscopic approach. *Eur Arch Otorhinolaryngol*. 2011;268:525-532.
605. London SD, Schlosser RJ, Gross CW. Endoscopic management of benign sinonasal tumors: a decade of experience. *Am J Rhinol*. 2002;16:221-227.
606. Koivunen P, Lopponen H, Fors AP, Jokinen K. The growth rate of osteomas of the paranasal sinuses. *Clin Otolaryngol Allied Sci*. 1997;22:111-114.
607. Charlett SD, Mackay SG, Sacks R. Endoscopic treatment of fibrous dysplasia confined to the frontal sinus. *Otolaryngol Head Neck Surg*. 2007;136(4 Suppl):S59-S61.
608. Rao VM, Sharma D, Madan A. Imaging of frontal sinus disease: concepts, interpretation, and technology. *Otolaryngol Clin North Am*. 2001;34:23-39.
609. Efune G, Perez CL, Tong L, Rihani J, Batra PS. Paranasal sinus and skull base fibro-osseous lesions: when is biopsy indicated for diagnosis? *Int Forum Allergy Rhinol*. 2012;2:160-165.
610. Eller R, Sillers M. Common fibro-osseous lesions of the paranasal sinuses. *Otolaryngol Clin North Am*. 2006;39:585-600, x.
611. Rokade A, Sama A. Update on management of frontal sinus osteomas. *Curr Opin Otolaryngol Head Neck Surg*. 2012;20:40-44.
612. Strek P, Zagolski O, Skladzien J, Kurzynski M, Dyduch G. Osteomas of the paranasal sinuses: surgical treatment options. *Med Sci Monit*. 2007;13:CR244-CR250.
613. Mehta BS, Grewal GS. Osteoma of the paranasal sinuses along with a case report of an orbitoethmoidal osteoma. *J Laryngol Otol*. 1963;77:601-610.
614. Mohsenifar Z, Nouhi S, Abbas FM, Farhadi S, Abedin B. Ossifying fibroma of the ethmoid sinus: report of a rare case and review of literature. *J Res Med Sci*. 2011;16:841-847.
615. Post G, Kountakis SE. Endoscopic resection of large sinonasal ossifying fibroma. *Am J Otolaryngol*. 2005;26:54-56.
616. Riddle ND, Bui MM. Fibrous dysplasia. *Arch Pathol Lab Med*. 2013;137:134-138.
617. Rojas R, Palacios E, Kaplan J, Wong LK. Fibrous dysplasia of the frontal sinus. *Ear Nose Throat J*. 2004;83:14-15.
618. Mohammadi-Araghi H, Haery C. Fibro-osseous lesions of craniofacial bones. The role of imaging. *Radiol Clin North Am*. 1993;31:121-134.
619. Arslan HH, Tasli H, Cebeci S, Gerek M. The management of the paranasal sinus osteomas. *J Craniofac Surg*. 2017;28:741-745.
620. Senior BA, Lanza DC. Benign lesions of the frontal sinus. *Otolaryngol Clin North Am*. 2001;34:253-267.
621. Selleck AM, Desai D, Thorp BD, Ebert CS, Zanation AM. Management of frontal sinus tumors. *Otolaryngol Clin North Am*. 2016;49:1051-1065.
622. Turri-Zanoni M, Dallan I, Terranova P, et al. Frontoethmoidal and intraorbital osteomas: exploring the limits of the endoscopic approach. *Arch Otolaryngol Head Neck Surg*. 2012;138:498-504.
623. Schreiber A, Villaret AB, Maroldi R, Nicolai P. Fibrous dysplasia of the sinonasal tract and adjacent skull base. *Curr Opin Otolaryngol Head Neck Surg*. 2012;20:45-52.
624. Chiu AG, Schipor I, Cohen NA, Kennedy DW, Palmer JN. Surgical decisions in the management of frontal sinus osteomas. *Am J Rhinol*. 2005;19:191-197.
625. Sieskiewicz A, Lyson T, Piszczatowski B, Rogowski M. Endoscopic treatment of adversely located osteomas of the frontal sinus. *Ann Otol Rhinol Laryngol*. 2012;121:503-509.
626. Wang H, Sun X, Liu Q, Wang J, Wang D. Endoscopic resection of sinonasal ossifying fibroma: 31 cases report at an institution. *Eur Arch Otorhinolaryngol*. 2014;271:2975-2982.
627. Ledderose GJ, Stelter K, Becker S, Leunig A. Paranasal ossifying fibroma: endoscopic resection or wait and scan? *Eur Arch Otorhinolaryngol*. 2011;268:999-1004.
628. Bertrand B, Eloy P, Cornelis JP, Gosseye S, Clotuche J, Gilliard C. Juvenile aggressive cemento-ossifying fibroma: case report and review of the literature. *Laryngoscope*. 1993;103:1385-1390.
629. MacDonald-Jankowski DS. Fibro-osseous lesions of the face and jaws. *Clin Radiol*. 2004;59:11-25.
630. Chapurlat RD, Delmas PD, Liens D, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *J Bone Miner Res*. 1997;12:1746-1752.
631. DeKlotz TR, Stefko ST, Fernandez-Miranda JC, Gardner PA, Snyderman CH, Wang EW. Endoscopic endonasal optic nerve decompression for fibrous dysplasia. *J Neurol Surg B Skull Base*. 2017;78:24-29.
632. Amit M, Collins MT, FitzGibbon EJ, Butman JA, Fliss DM, Gil Z. Surgery versus watchful waiting in patients with craniofacial fibrous dysplasia—a meta-analysis. *PLoS One*. 2011;6:e25179.
633. Stevens-Simon C, Stewart J, Nakashima II, White M. Exacerbation of fibrous dysplasia associated with an adolescent pregnancy. *J Adolesc Health*. 1991;12:403-405.
634. Wenig BM, Vinh TN, Smirniotopoulos JG, Fowler CB, Houston GD, Heffner DK. Aggressive psammomatoid ossifying fibromas of the sinonasal region: a clinicopathologic study of a distinct group of fibro-osseous lesions. *Cancer*. 1995;76:1155-1165.
635. Macnaughtan IP. The chronic ear. The aetiology and treatment of cholesterol granuloma in the middle ear. *Proc R Soc Med*. 1964;57:767-769.
636. Durgam A, Batra PS. Paranasal sinus cholesterol granuloma: systematic review of diagnostic and management aspects. *Int Forum Allergy Rhinol*. 2013;3:242-247.
637. Shvili I, Hadar T, Shvero J, Feinmesser R, Koren R. Cholesterol granulomas in antrochoanal polyps: a clinicopathologic study. *Eur Arch Otorhinolaryngol*. 2005;262:821-825.
638. Le BH, Towfighi J, Kapadia SB, Lopes MB. Comparative immunohistochemical assessment of craniopharyngioma and related lesions. *Endocr Pathol*. 2007;18:23-30.
639. Rahmani R, Sukumaran M, Donaldson AM, Akselrod O, Lavi E, Schwartz TH. Parasellar xanthogranulomas. *J Neurosurg*. 2015;122:812-817.
640. Paulus W, Honegger J, Keyvani K, Fahlbusch R. Xanthogranuloma of the sellar region: a clinicopathological entity different from adamantinomatous craniopharyngioma. *Acta Neuropathol*. 1999;97:377-382.
641. Leonetti JP, Shownkeen H, Marzo SJ. Incidental petrous apex findings on magnetic resonance imaging. *Ear Nose Throat J*. 2001;80:200-202, 205-206.
642. Chapman PR, Shah R, Cure JK, Bag AK. Petrous apex lesions: pictorial review. *AJR Am J Roentgenol*. 2011;196(3 Suppl):WS26-WS37; Quiz S40-S23.
643. Chandra RK, Palmer JN. Epidermoids of the paranasal sinuses and beyond: endoscopic management. *Am J Rhinol*. 2006;20:441-444.
644. Brackmann DE, Toh EH. Surgical management of petrous apex cholesterol granulomas. *Otol Neurotol*. 2002;23:529-533.
645. Eytan DF, Kshettry VR, Sindwani R, Woodard TD, Recinos PF. Surgical outcomes after endoscopic management of cholesterol granulomas of the petrous apex: a systematic review. *Neurosurg Focus*. 2014;37:E14.
646. Griffith AJ, Terrell JE. Transsphenoid endoscopic management of petrous apex cholesterol granuloma. *Otolaryngol Head Neck Surg*. 1996;114:91-94.
647. Kingdom TT, Delgaudio JM. Endoscopic approach to lesions of the sphenoid sinus, orbital apex, and clivus. *Am J Otolaryngol*. 2003;24:317-322.
648. Georgalas C, Kania R, Guichard JP, Sauvaget E, Tran Ba Huy P, Herman P. Endoscopic transsphenoidal surgery for cholesterol granulomas involving the petrous apex. *Clin Otolaryngol*. 2008;33:38-42.
649. Jaberoo MC, Hassan A, Pulido MA, Saleh HA. Endoscopic endonasal approaches to management of cholesterol granuloma of the petrous apex. *Skull Base*. 2010;20:375-379.
650. Prabhu K, Kurien M, Chacko AG. Endoscopic transsphenoidal approach to petrous apex cholesterol granulomas. *Br J Neurosurg*. 2010;24:688-691.
651. Emanuelli E, Ciorba A, Bianchini C, Bossolesi P, Stomeo F, Pelucchi S. Transnasal endoscopic management of petrous apex and clivus selected lesions. *Eur Arch Otorhinolaryngol*. 2013;270:1747-1750.
652. Sade B, Batra PS, Scharpf J, Citardi MJ, Lee JH. Minimally invasive endoscopic endonasal management of skull base cholesterol granulomas. *World Neurosurg*. 2012;78:683-688.
653. Paluzzi A, Gardner P, Fernandez-Miranda JC, et al. Endoscopic endonasal approach to cholesterol granulomas of the petrous apex: a series of 17 patients: clinical article. *J Neurosurg*. 2012;116:792-798.
654. Karligkiotis A, Bignami M, Terranova P, et al. Use of the pedicled nasoseptal flap in the endoscopic management of cholesterol granulomas of the petrous apex. *Int Forum Allergy Rhinol*. 2015;5:747-753.
655. Shibao S, Toda M, Tomita T, et al. Petrous apex cholesterol granuloma: importance of pedicled nasoseptal flap in addition to silicone T-tube for prevention of occlusion of drainage route in transsphenoidal approach: a technical note. *Neurol Med Chir (Tokyo)*. 2015;55:351-355.
656. Bruchhage KL, Wollenberg B, Leichtle A. Transsphenoidal and infralabyrinthine approach of the petrous apex cholesterol granuloma. *Eur Arch Otorhinolaryngol*. 2017;274:2749-2756.
657. DiNardo LJ, Pippin GW, Sismanis A. Image-guided endoscopic transsphenoidal drainage of select petrous apex cholesterol granulomas. *Otol Neurotol*. 2003;24:939-941.
658. Oyama K, Ikezono T, Tahara S, Shindo S, Kitamura T, Teramoto A. Petrous apex cholesterol granuloma treated via the endoscopic transsphenoidal approach. *Acta Neurochir (Wien)*. 2007;149:299-302; discussion 302.
659. Presutti L, Villari D, Marchioni D. Petrous apex cholesterol granuloma: transsphenoid endoscopic approach. *J Laryngol Otol*. 2006;120:e20.
660. Dhanasekar G, Jones NS. Endoscopic transsphenoidal removal of cholesterol granuloma of the petrous apex: case report and literature review. *J Laryngol Otol*. 2011;125:169-172.
661. McLaughlin N, Kelly DF, Prevedello DM, Shahlaie K, Carrau RL, Kassam AB. Endoscopic endonasal management of recurrent petrous apex cholesterol granuloma. *J Neurol Surg B Skull Base*. 2012;73:190-196.
662. Park KC, Wong G, Stephens JC, Saleh HA. Endoscopic transsphenoidal drainage of an aggressive petrous apex cholesterol granuloma: unusual complications and lessons learnt. *J Laryngol Otol*. 2013;127:1230-1234.
663. Terranova P, Karligkiotis A, Gallo S, Meloni F, Bignami M, Castelnuovo P. A novel endoscopic technique for long-term patency of cholesterol

granulomas of the petrous apex. *Laryngoscope*. 2013;123:2639-2642.

664. Miyamura S, Yamaguchi S, Tominaga A, et al. A case of petrous apex cholesterol granuloma successfully treated with endoscopic endonasal surgery. *Hiroshima J Med Sci*. 2014;63:39-42.
665. Turan N, Baum GR, Holland CM, Ahmad FU, Henriquez OA, Pradilla G. Upper nasopharyngeal corridor for transnasal endoscopic drainage of petroclival cholesterol granulomas: alternative access in conchal sphenoid patients. *J Neurol Surg Rep*. 2016;77:e017-e022.
666. Sanna M, Dispenza F, Mathur N, De Stefano A, De Donato G. Otoneurological management of petrous apex cholesterol granuloma. *Am J Otolaryngol*. 2009;30:407-414.
667. Kusumi M, Fukushima T, Mehta AI, Cunningham CD 3rd, Friedman AH, Fujii K. Middle fossa approach for total resection of petrous apex cholesterol granulomas: use of vascularized galeofascial flap preventing recurrence. *Neurosurgery*. 2013;72(1 Suppl Operative):77-86; discussion 86.
668. Zanation AM, Snyderman CH, Carrau RL, Gardner PA, Prevedello DM, Kassam AB. Endoscopic endonasal surgery for petrous apex lesions. *Laryngoscope*. 2009;119:19-25.
669. Deep NL, Chaaban MR, Chaudhry AL, Woodworth BA. Frontal sinus cholesterol granuloma: case report. *Allergy Rhinol (Providence)*. 2014;5:36-38.
670. Jung CS, Schanzer A, Hattingen E, Plate KH, Seifert V. Xanthogranuloma of the sellar region. *Acta Neurochir (Wien)*. 2006;148:473-477.
671. Kamoshima Y, Sawamura Y, Motegi H, Kubota K, Houkin K. Xanthogranuloma of the sellar region of children: series of five cases and literature review. *Neurol Med Chir (Tokyo)*. 2011;51:689-693.
672. Kleinschmidt-DeMasters BK, Lillehei KO, Hankinson TC. Review of xanthomatous lesions of the sella. *Brain Pathol*. 2017;27:377-395.
673. Kurisaka M, Fukui N, Sakamoto T, Mori K, Okada T, Sogabe K. A case of Rathke's cleft cyst with apoplexy. *Childs Nerv Syst*. 1998;14:343-347.
674. Hama S, Arita K, Tominaga A, et al. Symptomatic Rathke's cleft cyst coexisting with central diabetes insipidus and hypophysitis: case report. *Endocr J*. 1999;46:187-192.
675. Nakasu Y, Nakasu S, Nakajima M, Itoh R, Matsuda M. Atypical Rathke's cleft cyst associated with ossification. *AJNR Am J Neuroradiol*. 1999;20:1287-1289.
676. Yonezawa K, Shirataki K, Sakagami Y, Kohmura E. Panhypopituitarism induced by cholesterol granuloma in the sellar region—case report. *Neurol Med Chir (Tokyo)*. 2003;43:259-262.
677. Liu ZH, Tzaan WC, Wu YY, Chen HC. Sellar xanthogranuloma manifesting as obstructive hydrocephalus. *J Clin Neurosci*. 2008;15:929-933.
678. Sugata S, Hirano H, Yatsushiro K, Yunoue S, Nakamura K, Arita K. Xanthogranuloma in the suprasellar region. *Neurol Med Chir (Tokyo)*. 2009;49:124-127.
679. Arai A, Nishihara M, Sasayama T, et al. Xanthogranuloma of the sellar region—case report. *Neurol Med Chir (Tokyo)*. 2010;50:488-491.
680. Miyajima Y, Oka H, Utsuki S, Fujii K. Rathke's cleft cyst with xanthogranulomatous change—case report. *Neurol Med Chir (Tokyo)*. 2011;51:740-742.
681. Agarwal A, Agarwal K, Lee HK. Xanthogranuloma of the sellar region. A case report. *Neuroradiol J*. 2012;25:181-184.
682. Nishiuchi T, Murao K, Imachi H, et al. Xanthogranuloma of the intrasellar region presenting in pituitary dysfunction: a case report. *J Med Case Rep*. 2012;6:119.
683. Gurcay AG, Gurcan O, Kazanci A, et al. Xanthogranuloma of the sellar region. *Neurol India*. 2016;64:1075-1079.
684. Dai CX, Guo XS, Liu XH, et al. Xanthogranuloma of the sellar region. *Chin Med J (Engl)*. 2017;130:249-250.
685. Butler S, Grossenbacher R. Cholesterol granuloma of the paranasal sinuses. *J Laryngol Otol*. 1989;103:776-779.
686. Hill CA, Moseley IF. Imaging of orbitofrontal cholesterol granuloma. *Clin Radiol*. 1992;46:237-242.
687. Arat YO, Chaudhry IA, Boniuk M. Orbitofrontal cholesterol granuloma: distinct diagnostic features and management. *Ophthalmic Plast Reconstr Surg*. 2003;19:382-387.
688. Hughes JD, Jacob JT, Garrity JA, Salomao DR, Link MJ. Orbitofrontal cholesterol granuloma: four case reports and a systematic review of the English literature. *World Neurosurg*. 2016;87:355-361.
689. Shrirao N, Mukherjee B, Krishnakumar S, Biswas J. Cholesterol granuloma: a case series & review of literature. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:185-188.
690. Armengot M, Barona R, Garin L, Sabater V, Basterra J. Ethmoid cholesterol granuloma. *Otolaryngol Head Neck Surg*. 1993;109:762-765.
691. Ochiai H, Yamakawa Y, Fukushima T, Nakano S, Wakisaka S. Large cholesterol granuloma arising from the frontal sinus—case report. *Neurol Med Chir (Tokyo)*. 2001;41:283-287.
692. Aferzon M, Millman B, O'Donnell TR, Gilroy PA. Cholesterol granuloma of the frontal bone. *Otolaryngol Head Neck Surg*. 2002;127:578-581.
693. Weiland DA, Aygun N. An unusual presentation of a cholesterol granuloma in a pneumatized pterygoid process of the sphenoid sinus. *Otolaryngol Head Neck Surg*. 2007;136:153-154.
694. Hwang DJ, Chung YS, Jun SY, Kim YJ, Lee JY, Park IW. A case of compressive optic neuropathy caused by sphenoid sinus cholesterol granuloma. *Jpn J Ophthalmol*. 2009;53:441-442.
695. Hammami B, Mnejja M, Chakroun A, et al. Cholesteatoma of the frontal sinus. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2010;127:213-216.
696. Korbmacher D, Lehmann M, Gehl HB, Ebmeyer J, Sudhoff H. Petrous apex cholesterol granuloma involving the sphenoid sinus. *Ear Nose Throat J*. 2011;90:E23-E25.
697. Marco M, Ida C, Francesco Luigi P, et al. Cholesterol granuloma of the frontal sinus: a case report. *Case Rep Otolaryngol*. 2012;2012:515986.
698. Imre A, Pinar E, Paker I, Imre SS, Duran R, Ozturkcan S. Osteoplastic flap approach versus orbitotomy in case of orbitofrontal cholesterol granuloma. *J Craniofac Surg*. 2015;26:e36-e37.
699. Catapano G, de Notaris M, Di Maria D, et al. The use of a three-dimensional endoscope for different skull base tumors: results of a preliminary extended endonasal surgical series. *Acta Neurochir (Wien)*. 2016;158:1605-1616.
700. Raza SM, Amine MA, Anand V, Schwartz TH. Endoscopic endonasal resection of trigeminal schwannomas. *Neurosurg Clin N Am*. 2015;26:473-479.
701. Jacquesson T, Berhouma M, Picart T, Jouanneau E. Total removal of a trigeminal schwannoma via the expanded endoscopic endonasal approach. Technical note. *Acta Neurochir (Wien)*. 2015;157:935-938; discussion 938.
702. Dallan I, Castelnuovo P, Locatelli D, et al. Multiportal combined transorbital transnasal endoscopic approach for the management of selected skull base lesions: preliminary experience. *World Neurosurg*. 2015;84:97-107.
703. Haidar H, Deveze A, Lavieille JP. Mini-invasive surgery of infratemporal fossa schwannomas. *J Laryngol Otol*. 2015;129:187-193.
704. Taylor RJ, Patel MR, Wheless SA, et al. Endoscopic endonasal approaches to infratemporal fossa tumors: a classification system and case series. *Laryngoscope*. 2014;124:2443-2450.
705. Raza SM, Donaldson AM, Mehta A, Tsiouris AJ, Anand VK, Schwartz TH. Surgical management of trigeminal schwannomas: defining the role for endoscopic endonasal approaches. *Neurosurg Focus*. 2014;37:E17.
706. Bresson D, McLaughlin N, Ditzel Filho LF, et al. Endoscopic endonasal approach for the treatment of schwannomas of the pterygopalatine fossa: case report and review of the literature. *Neurochirurgie*. 2014;60:174-179.
707. Komatsu F, Komatsu M, Di Ieva A, Tschabitscher M. Endoscopic approaches to the trigeminal nerve and clinical consideration for trigeminal schwannomas: a cadaveric study. *J Neurosurg*. 2012;117:690-696.
708. Zhang Q, Feng K, Ge C, Hongchuan G, Mingchu L. Endoscopic endonasal management of trigeminal schwannomas extending into the infratemporal fossa. *J Clin Neurosci*. 2012;19:862-865.
709. Samii M, Alimohamadi M, Gerganov V. Endoscope-assisted retrosigmoid intradural suprameatal approach for surgical treatment of trigeminal schwannomas. *Neurosurgery*. 2014;10(Suppl 4):565-575; discussion 575.
710. Konovalov AN, Kalinin PL, Shimanskii VN, et al. [Experience of surgical management of trigeminal schwannomas that simultaneously spread to the middle and posterior cranial fossae]. *Zh Vopr Neirokhir Im N N Burdenko*. 2014;78:23-32; discussion 32. English, Russian.
711. Shin SS, Gardner PA, Stefko ST, Madhok R, Fernandez-Miranda JC, Snyderman CH. Endoscopic endonasal approach for nonvestibular schwannomas. *Neurosurgery*. 2011;69:1046-1057; discussion 1057.
712. Rosique-Lopez L, Rosique-Arias M, Sanchez-Celemin FJ. [Pterygopalatine fossa schwannoma. Endoscopic approach]. *Neurocirugia (Astur)*. 2010;21:405-409; discussion 409-410. Spanish.
713. Liu J, Han J, Yang D, et al. [Surgical anatomy, technique and application of endoscopic endonasal transpterygoid approach in skull base surgery]. *Zhongbua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2015;50:909-914. Chinese.
714. Battaglia P, Turri-Zanoni M, Dallan I, et al. Endoscopic endonasal transpterygoid transmaxillary approach to the infratemporal and upper parapharyngeal tumors. *Otolaryngol Head Neck Surg*. 2014;150:696-702.
715. Martinez Ferreras A, Rodrigo Tapia JP, Llorente Pendas JL, Suarez Nieto C. Endoscopic nasal surgery for pterygopalatine fossa schwannoma. *Acta Otorrinolaringol Esp*. 2005;56:41-43.
716. Wallace SA, Michael Meyer R, Cirivello MJ, Cho RI. Lateral orbitotomy for a maxillary nerve schwannoma: case report. *J Neurosurg*. 2016;125:869-876.
717. Kassam AB, Prevedello DM, Carrau RL, et al. The front door to Meckel's cave: an anteromedial corridor via expanded endoscopic endonasal approach—technical considerations and clinical series. *Neurosurgery*. 2009;64(3 Suppl):ons71-ons82; discussion ons82-ons73.
718. Van Rompaey J, Suruliraj A, Carrau R, Panizza B, Solares CA. Meckel's cave access: anatomic study comparing the endoscopic transantral and endonasal approaches. *Eur Arch Otorhinolaryngol*. 2014;271:787-794.
719. Wanibuchi M, Fukushima T, Zomordi AR, Nonaka Y, Friedman AH. Trigeminal schwannomas: skull base approaches and operative results in 105 patients. *Neurosurgery*. 2012;70(1 Suppl Operative):132-143; discussion 143-134.
720. Hasegawa T, Kato T, Iizuka H, Kida Y. Long-term results for trigeminal schwannomas treated with gamma knife surgery. *Int J Radiat Oncol Biol Phys*. 2013;87:1115-1121.
721. Hofstetter CP, Singh A, Anand VK, Kacker A, Schwartz TH. The endoscopic, endonasal, transmaxillary transpterygoid approach to the pterygopalatine fossa, infratemporal fossa, petrous apex, and the Meckel cave. *J Neurosurg*. 2010;113:967-974.
722. Roth J, Singh A, Nyquist G, et al. Three-dimensional and 2-dimensional endoscopic exposure of midline cranial base targets using expanded endonasal and transcranial approaches. *Neurosurgery*. 2009;65:1116-1128; discussion 1128-1130.
723. Chen LF, Yang Y, Yu XG, et al. Operative management of trigeminal neuromas: an analysis of a surgical experience with 55 cases. *Acta Neurochir (Wien)*. 2014;156:1105-1114.
724. Siqueira MG, Fernandes AY, Vellutini EAS, Velasco OLP, Santos LRM, Moraes OJS, Marino R Jr. [Surgical treatment of trigeminal neurinomas]. *Arquivos Brasileiros de Neurocirurgia*. 1996;15:123-130. Portuguese.
725. Roh JL. Removal of infratemporal fossa schwannoma via a transmandibular transpterygoid approach. *Eur Arch Otorhinolaryngol*. 2005;262:428-431.
726. Youssef S, Kim EY, Aziz KM, Hemida S, Keller JT, van Loveren HR. The subtemporal interdural approach to dumbbell-shaped trigeminal schwannomas: cadaveric prosection. *Neurosurgery*. 2006;59(4 Suppl 2):ONS270-ONS277; discussion ONS277-ONS278.
727. Jouanneau E, Simon E, Jacquesson T, et al. The endoscopic endonasal approach to the Meckel's cave tumors: surgical technique and indications. *World Neurosurg*. 2014;82(6 Suppl):S155-S161.

728. Luxenberger W, Stammberger H, Jebeles JA, Walch C. Endoscopic optic nerve decompression: the Graz experience. *Laryngoscope*. 1998;108:873-882.

729. Cebula H, Lahlou A, De Battista JC, Debry C, Froelich S. [Endoscopic approaches to the orbit]. *Neurochirurgie*. 2010;56(2-3):230-235. French.

730. Chen C, Selva D, Floreani S, Wormald PJ. Endoscopic optic nerve decompression for traumatic optic neuropathy: an alternative. *Otolaryngol Head Neck Surg*. 2006;135:155-157.

731. De Ganseman A, Lasudry J, Choufani G, Daele J, Hassid S. Intranasal endoscopic surgery in traumatic optic neuropathy—the Belgian experience. *Acta Otorhinolaryngol Belg*. 2000;54:175-177.

732. Horiguchi K, Murai H, Hasegawa Y, Mine S, Yamakami I, Saeki N. Endoscopic endonasal transsphenoidal optic nerve decompression for traumatic optic neuropathy—technical note. *Neurol Med Chir (Tokyo)*. 2010;50:518-522.

733. Koc K, Anik I, Altintas O, Ceylan S. Endoscopic optic nerve decompression for idiopathic intracranial hypertension in two cases: case report. *Minim Invasive Neurosurg*. 2008;51:72-75.

734. Pletcher SD, Sindwani R, Metson R. Endoscopic orbital and optic nerve decompression. *Otolaryngol Clin North Am*. 2006;39:943-958, vi.

735. Stokken J, Gumber D, Antisdel J, Sindwani R. Endoscopic surgery of the orbital apex: outcomes and emerging techniques. *Laryngoscope*. 2016;126:20-24.

736. Anderson RL, Panje WR, Gross CE. Optic nerve blindness following blunt forehead trauma. *Ophthalmology*. 1982;89:445-455.

737. Hall ED. The neuroprotective pharmacology of methylprednisolone. *J Neurosurg*. 1992;76:13-22.

738. Levin LA, Beck RW, Joseph MP, Seiff S, Kraker R. The treatment of traumatic optic neuropathy: the International Optic Nerve Trauma Study. *Ophthalmology*. 1999;106:1268-1277.

739. Yu-Wai-Man P, Griffiths PG. Steroids for traumatic optic neuropathy. *Cochrane Database Syst Rev*. 2011;(1):CD006032.

740. Dhaliwal SS, Sowerby LJ, Rotenberg BW. Timing of endoscopic surgical decompression in traumatic optic neuropathy: a systematic review of the literature. *Int Forum Allergy Rhinol*. 2016;6:661-667.

741. Wang DH, Zheng CQ, Qian J, Barr JJ, Anderson AG Jr. Endoscopic optic nerve decompression for the treatment of traumatic optic nerve neuropathy. *ORL J Otorhinolaryngol Relat Spec*. 2008;70:130-133.

742. Rajiniganth MG, Gupta AK, Gupta A, Bapuraj JR. Traumatic optic neuropathy: visual outcome following combined therapy protocol. *Arch Otolaryngol Head Neck Surg*. 2003;129:1203-1206.

743. Jiang RS, Hsu CY, Shen BH. Endoscopic optic nerve decompression for the treatment of traumatic optic neuropathy. *Rhinology*. 2001;39:71-74.

744. Kountakis SE, Maillard AA, El-Harazi SM, Longhini L, Urso RG. Endoscopic optic nerve decompression for traumatic blindness. *Otolaryngol Head Neck Surg*. 2000;123(1 Pt 1):34-37.

745. Nayak SR, Kirtane MV, Ingle MV. Transethmoid decompression of the optic nerve in head injuries: an update. *J Laryngol Otol*. 1991;105:205-206.

746. Emanuelli E, Bignami M, Digilio E, Fusetti S, Volo T, Castelnuovo P. Post-traumatic optic neuropathy: our surgical and medical protocol. *Eur Arch Otorhinolaryngol*. 2015;272:3301-3309.

747. Hameed AS, Nampoothiri PM, Joseph B. A prospective study on outcome of endoscopic optic nerve decompression for visual loss after craniorbital trauma. *Journal of Evidence Based Medicine and Healthcare*. 2014;1:696-702.

748. Xu R, Chen F, Zuo K, et al. Endoscopic optic nerve decompression for patients with traumatic optic neuropathy: is nerve sheath incision necessary? *ORL J Otorhinolaryngol Relat Spec*. 2014;76:44-49.

749. Song Y, Li H, Ma Y, et al. Analysis of prognostic factors of endoscopic optic nerve decompression in traumatic blindness. *Acta Otolaryngol*. 2013;133:1196-1200.

750. Yang QT, Zhang GH, Liu X, Ye J, Li Y. The therapeutic efficacy of endoscopic optic nerve decompression and its effects on the prognoses of 96 cases of traumatic optic neuropathy. *J Trauma Acute Care Surg*. 2012;72:1350-1355.

751. Peng A, Li Y, Hu P, Wang Q. Endoscopic optic nerve decompression for traumatic optic neuropathy in children. *Int J Pediatr Otorhinolaryngol*. 2011;75:992-998.

752. Thaker A, Tandon DA, Mahapatra AK. Surgery for optic nerve injury: should nerve sheath incision supplement osseous decompression? *Skull Base*. 2009;19:263-271.

753. Li H, Zhou B, Shi J, Cheng L, Wen W, Xu G. Treatment of traumatic optic neuropathy: our experience of endoscopic optic nerve decompression. *J Laryngol Otol*. 2008;122:1325-1329.

754. Berhouma M, Jacquesson T, Abouaf L, Vighetto A, Jouanneau E. Endoscopic endonasal optic nerve and orbital apex decompression for nontraumatic optic neuropathy: surgical nuances and review of the literature. *Neurosurg Focus*. 2014;37:E19.

755. Sencer A, Akcakaya MO, Basaran B, et al. Unilateral endoscopic optic nerve decompression for idiopathic intracranial hypertension: a series of 10 patients. *World Neurosurg*. 2014;82:745-750.

756. Murchison AP, Rosen MR, Evans JJ, Bilyk JR. Endoscopic approach to the orbital apex and periorbital skull base. *Laryngoscope*. 2011;121:463-467.

757. Pletcher SD, Metson R. Endoscopic optic nerve decompression for nontraumatic optic neuropathy. *Arch Otolaryngol Head Neck Surg*. 2007;133:780-783.

758. Lund VJ, Rose GE. Endoscopic transnasal orbital decompression for visual failure due to sphenoid wing meningioma. *Eye (Lond)*. 2006;20:1213-1219.

759. Mabuchi F, Aihara M, Mackey MR, Lindsey JD, Weinreb RN. Optic nerve damage in experimental mouse ocular hypertension. *Invest Ophthalmol Vis Sci*. 2003;44:4321-4330.

760. Altay T, Patel BC, Couldwell WT. Lateral orbital wall approach to the cavernous sinus. *J Neurosurg*. 2012;116:755-763.

761. Bly RA, Ramakrishna R, Ferreira M, Moe KS. Lateral transorbital neuroendoscopic approach to the lateral cavernous sinus. *J Neurol Surg B Skull Base*. 2014;75:11-17.

762. Mariniello G, Maiuri F, de Divitiis E, et al. Lateral orbitotomy for removal of sphenoid wing meningiomas invading the orbit. *Neurosurgery*. 2010;66(6 Suppl Operative):287-292; discussion 292.

763. Chabot JD, Gardner PA, Stefko ST, Zwagerman NT, Fernandez-Miranda JC. Lateral orbitotomy approach for lesions involving the middle fossa: a retrospective review of thirteen patients. *Neurosurgery*. 2017;80:309-322.

764. Dollinger J. [Relieving pressure on the eyeholes by removing the upper orbital wall in high-grade exophthalmos (morbus basedowii) and consecutive corneal disease]. Die druckentlastung der augenhoehle durch entfernung der auBeren orbitalwand bei hochgradigem exophtalmus (morbus basedowii) und konsekutiver hornhauterkrankung. *Dtsch Med Wochenschr*. 1911;37:1888. German.

765. Walsh TE, Ogura JH. Transantral orbital decompression for malignant exophthalmos. *Laryngoscope*. 1957;67:544-568.

766. Kennedy DW, Goodstein ML, Miller NR, Zinreich SJ. Endoscopic transnasal orbital decompression. *Arch Otolaryngol Head Neck Surg*. 1990;116:275-282.

767. Sethi DS, Lau DP. Endoscopic management of orbital apex lesions. *Am J Rhinol*. 1997;11:449-455.

768. Karaki M, Kobayashi R, Mori N. Removal of an orbital apex hemangioma using an endoscopic transethmoidal approach: technical note. *Neurosurgery*. 2006;59(1 Suppl 1):ONSE159-ONSE160; discussion ONSE159-ONSE160.

769. Chhabra N, Wu AW, Fay A, Metson R. Endoscopic resection of orbital hemangiomas. *Int Forum Allergy Rhinol*. 2014;4:251-255.

770. Koopman JH, van der Heiden-van der Loo M, van Dijk MR, Bijlsma WR. Incidence of primary malignant orbital tumours in the Netherlands. *Eye (Lond)*. 2011;25:461-465.

771. Shields JA, Shields CL, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions: the 2002 Montgomery Lecture, part 1. *Ophthalmology*. 2004;111:997-1008.

772. Bleier BS, Castelnuovo P, Battaglia P, et al. Endoscopic endonasal orbital cavernous hemangioma resection: global experience in techniques and outcomes. *Int Forum Allergy Rhinol*. 2016;6:156-161.

773. Lenzi R, Bleier BS, Felisati G, Muscatello L. Purely endoscopic trans-nasal management of orbital intraconal cavernous haemangiomas: a systematic review of the literature. *Eur Arch Otorhinolaryngol*. 2016;273:2319-2322.

774. Yao WC, Bleier BS. Endoscopic management of orbital tumors. *Curr Opin Otolaryngol Head Neck Surg*. 2016;24:57-62.

775. Mueller SK, Freitag SK, Bleier BS. Morphometric analysis of the orbital process of the palatine bone and its relationship to endoscopic orbital apex surgery. *Ophthal Plast Reconstr Surg*. 2018;34:254-257.

776. Lin GC, Freitag SK, Kocharyan A, Yoon MK, Lefebvre DR, Bleier BS. Comparative techniques of medial rectus muscle retraction for endoscopic exposure of the medial intraconal space. *Am J Rhinol Allergy*. 2016;30:226-229.

777. Shafi F, Zaidi S, Mehta P, Ahluwalia HS, Ahmed SK. Endoscopic medial rectus sling: a window into the intraconal orbital apex. *Ophthal Plast Reconstr Surg*. 2016;32:233-236.

778. Bleier BS, Healy DY Jr, Chhabra N, Freitag S. Compartmental endoscopic surgical anatomy of the medial intraconal orbital space. *Int Forum Allergy Rhinol*. 2014;4:587-591.

779. Raza SM, Quinones-Hinojosa A, Lim M, Boahene KD. The transconjunctival transorbital approach: a keyhole approach to the midline anterior skull base. *World Neurosurg*. 2013;80:864-871.

780. Lew H, Rootman DB, Nassiri N, Goh A, Goldberg RA. Transorbital approach without craniotomy to orbital tumors with extradural intracranial extension. *Orbit*. 2014;33:343-351.

781. Margalit N, Ezer H, Fliss DM, Naftaliev E, Nossek E, Kesler A. Orbital tumors treated using transcranial approaches: surgical technique and neuroophthalmogical results in 41 patients. *Neurosurg Focus*. 2007;23:E11.

782. Kinnunen I, Aitasalo K. A review of 59 consecutive patients with lesions of the anterior cranial base operated on using the subcranial approach. *J Craniomaxillofac Surg*. 2006;34:405-411.

783. Chhabra N, Healy DY, Freitag SK, Bleier BS. The nasoseptal flap for reconstruction of the medial and inferior orbit. *Int Forum Allergy Rhinol*. 2014;4:763-766.

784. Healy DY Jr, Lee NG, Freitag SK, Bleier BS. Endoscopic bimanual approach to an intraconal cavernous hemangioma of the orbital apex with vascularized flap reconstruction. *Ophthal Plast Reconstr Surg*. 2014;30:e104-e106.

785. Wu W, Selva D, Jiang F, et al. Endoscopic transethmoidal approach with or without medial rectus detachment for orbital apical cavernous hemangiomas. *Am J Ophthalmol*. 2013;156:593-599.

786. Alimohamadi M, Hajiabadi M, Gerganov V, Fahlbusch R, Samii M. Combined endonasal and sublabial endoscopic transmaxillary approach to the pterygopalatine fossa and orbital apex. *Acta Neurochir (Wien)*. 2015;157:919-929; discussion 929.

787. Bleier BS, Lefebvre DR, Freitag SK. Endoscopic orbital floor decompression with preservation of the inferomedial strut. *Int Forum Allergy Rhinol*. 2014;4:82-84.

788. Jacquesson T, Abouaf L, Berhouma M, Jouanneau E. How I do it: the endoscopic endonasal optic nerve and orbital apex decompression. *Acta Neurochir (Wien)*. 2014;156:1891-1896.

789. Felippu A, Mora R, Guastini L, Peretti G. Transnasal approach to the orbital apex and cavernous sinus. *Ann Otol Rhinol Laryngol*. 2013;122:254-262.

790. Sia DI, Chan WO, Wormald PJ, Davis G, Selva D. Decompression of benign orbital apex lesion via medial endoscopic approach. *Orbit*. 2012;31:344-346.

791. Vohra ST, Escott EJ, Stevens D, Branstetter BF. Categorization and characterization of lesions of the orbital apex. *Neuroradiology*. 2011;53:89-107.

792. Lee JY, Ramakrishnan VR, Chiu AG, Palmer J, Gausas RE. Endoscopic endonasal surgical resection of tumors of the medial orbital apex and wall. *Clin Neurol Neurosurg*. 2012;114:93-98.

793. Chen L, White WL, Xu B, Tian X. Transnasal transsphenoid approach: a minimally invasive approach for removal of cavernous haemangiomas located at inferomedial part of orbital apex. *Clin Exp Ophthalmol*. 2010;38:439-443.

794. Almond MC, Cheng AG, Schiedler V, Sires BS, Most SP, Jian-Amadi A. Decompression of the orbital apex: an alternate approach to surgical

excision for radiographically benign orbital apex tumors. *Arch Otolaryngol Head Neck Surg*. 2009;135:1015-1018.

795. Murchison AP, Rosen MR, Evans JJ, Bilyk JR. Posterior nasal septectomy in endoscopic orbital apex surgery. *Ophthal Plast Reconstr Surg*. 2009;25:458-463.
796. Miller NR, Agrawal N, Sciubba JJ, Lane AP. Image-guided transnasal endoscopic resection of an orbital solitary fibrous tumor. *Ophthal Plast Reconstr Surg*. 2008;24:65-67.
797. Kloek CE, Bilyk JR, Pribitkin EA, Rubin PA. Orbital decompression as an alternative management strategy for patients with benign tumors located at the orbital apex. *Ophthalmology*. 2006;113:1214-1219.
798. Tsirbas A, Kazim M, Close L. Endoscopic approach to orbital apex lesions. *Ophthal Plast Reconstr Surg*. 2005;21:271-275.
799. Osawa S, Rhoton AL, Jr., Seker A, Shimizu S, Fujii K, Kassam AB. Microsurgical and endoscopic anatomy of the vidian canal. *Neurosurgery*. 2009;64(5 Suppl 2):385-411; discussion 411-382.
800. Marshak T, Yun WK, Hazout C, Sacks R, Harvey RJ. A systematic review of the evidence base for vidian neurectomy in managing rhinitis. *J Laryngol Otol*. 2016;130(Suppl 4):S7-S28.
801. Robinson SR, Wormald PJ. Endoscopic vidian neurectomy. *Am J Rhinol*. 2006;20:197-202.
802. Golding-Wood PH. Observations on petrosal and vidian neurectomy in chronic vasomotor rhinitis. *J Laryngol Otol*. 1961;75:232-247.
803. Konno A. Historical, pathophysiological, and therapeutic aspects of vidian neurectomy. *Curr Allergy Asthma Rep*. 2010;10:105-112.
804. el-Guindy A. Endoscopic transseptal vidian neurectomy. *Arch Otolaryngol Head Neck Surg*. 1994;120:1347-1351.
805. Halderman A, Sindwani R. Surgical management of vasomotor rhinitis: a systematic review. *Am J Rhinol Allergy*. 2015;29:128-134.
806. Hwang PH, Lin B, Weiss R, Atkins J, Johnson J. Cryosurgical posterior nasal tissue ablation for the treatment of rhinitis. *Int Forum Allergy Rhinol*. 2017;7:952-956.
807. Lai WS, Cheng SY, Lin YY, et al. Clinical assessment of diode laser-assisted endoscopic intrasphenoidal vidian neurectomy in the treatment of refractory rhinitis. *Lasers Med Sci*. 2017;32:2097-2104.
808. Zhang H, Micomonaco DC, Dziegielewski PT, Sowerby LJ, Weis E, Wright ED. Endoscopic vidian neurectomy: a prospective case series. *Int Forum Allergy Rhinol*. 2015;5:423-430.
809. Ma Y, Tan G, Zhao Z, Li W, Huang L, Liu G. Therapeutic effectiveness of endoscopic vidian neurectomy for the treatment of vasomotor rhinitis. *Acta Otolaryngol*. 2014;134:260-267.
810. Su WF, Liu SC, Hsu WC, Chen YC. Randomized, double-blind, controlled study to evaluate the effect of vidian nerve cauterization on lacrimation. *Am J Rhinol Allergy*. 2014;28:255-259.
811. Albu S, Trombitas V, Nagy A. Endoscopic microdebrider-assisted inferior turbinoplasty with and without posterior nasal neurectomy. *Auris Nasus Larynx*. 2014;41:273-277.
812. Hsu CY, Shen PH, Weitzel EK. Endoscopic vidian neurectomy assisted by power instrumentation and coblation. *J Chin Med Assoc*. 2013;76:517-520.
813. Tan G, Ma Y, Li H, Li W, Wang J. Long-term results of bilateral endoscopic vidian neurectomy in the management of moderate to severe persistent allergic rhinitis. *Arch Otolaryngol Head Neck Surg*. 2012;138:492-497.
814. Kobayashi T, Hyodo M, Nakamura K, Komobuchi H, Honda N. Resection of peripheral branches of the posterior nasal nerve compared to conventional posterior neurectomy in severe allergic rhinitis. *Auris Nasus Larynx*. 2012;39:593-596.
815. Cassano M, Marioni G, Russo L, Cassano P. Sphenopalatine artery ligation with nerve resection in patients with vasomotor rhinitis and polyposis: a prospective, randomized, double-blind investigation. *Acta Otolaryngol*. 2012;132:525-532.
816. Su WF, Liu SC, Chiu FS, Lee CH. Antegrade transsphenoidal vidian neurectomy: short-term surgical outcome analysis. *Am J Rhinol Allergy*. 2011;25:e217-e220.
817. Lee JC, Kao CH, Hsu CH, Lin YS. Endoscopic transsphenoidal vidian neurectomy. *Eur Arch Otorhinolaryngol*. 2011;268:851-856.
818. Jang TY, Kim YH, Shin SH. Long-term effectiveness and safety of endoscopic vidian neurectomy for the treatment of intractable rhinitis. *Clin Exp Otorhinolaryngol*. 2010;3:212-216.
819. Liu SC, Wang HW, Su WF. Endoscopic vidian neurectomy: the value of preoperative computed tomographic guidance. *Arch Otolaryngol Head Neck Surg*. 2010;136:595-602.
820. Ikeda K, Yokoi H, Saito T, Kawano K, Yao T, Furukawa M. Effect of resection of the posterior nasal nerve on functional and morphological changes in the inferior turbinate mucosa. *Acta Otolaryngol*. 2008;128:1337-1341.
821. Ogawa T, Takeno S, Ishino T, Hirakawa K. Submucous turbinectomy combined with posterior nasal neurectomy in the management of severe allergic rhinitis: clinical outcomes and local cytokine changes. *Auris Nasus Larynx*. 2007;34:319-326.
822. Ikeda K, Oshima T, Suzuki M, Suzuki H, Shimomura A. Functional inferior turbinosurgery (FITS) for the treatment of resistant chronic rhinitis. *Acta Otolaryngol*. 2006;126:739-745.
823. Lin PY, Cheng CY, Wu CC, et al. Bilateral neurotrophic keratopathy complicating Vidian neurectomy. *Am J Ophthalmol*. 2001;132:106-108.
824. Harvey RJ, Nalavenkata S, Sacks R, et al. Survival outcomes for stage-matched endoscopic and open resection of olfactory neuroblastoma. *Head Neck*. 2017;39:2425-2432.
825. Stamm AC, Vellutini E, Harvey RJ, Nogeira JF Jr, Herman DR. Endoscopic transnasal craniotomy and the resection of craniopharyngioma. *Laryngoscope*. 2008;118:1142-1148.
826. Abergel A, Cavel O, Margalit N, Fliss DM, Gil Z. Comparison of quality of life after transnasal endoscopic vs open skull base tumor resection. *Arch Otolaryngol Head Neck Surg*. 2012;138:142-147.
827. de Almeida JR, Witterick IJ, Vescan AD. Functional outcomes for endoscopic and open skull base surgery: an evidence-based review. *Otolaryngol Clin North Am*. 2011;44:1185-1200.
828. Eloy JA, Vivero RJ, Hoang K, et al. Comparison of transnasal endoscopic and open craniofacial resection for malignant tumors of the anterior skull base. *Laryngoscope*. 2009;119:834-840.
829. Bradley PJ, Jones NS, Robertson I. Diagnosis and management of esthesioneuroblastoma. *Curr Opin Otolaryngol Head Neck Surg*. 2003;11:112-118.
830. Rimmer J, Lund VJ, Beale T, Wei WI, Howard D. Olfactory neuroblastoma: a 35-year experience and suggested follow-up protocol. *Laryngoscope*. 2014;124:1542-1549.
831. Fu TS, Monteiro E, Muhanna N, Goldstein DP, de Almeida JR. Comparison of outcomes for open versus endoscopic approaches for olfactory neuroblastoma: a systematic review and individual participant data meta-analysis. *Head Neck*. 2016;38(Suppl 1):E2306-E2316.
832. Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH. Endoscopic endonasal compared with anterior craniofacial and combined cranionasal resection of esthesioneuroblastomas. *World Neurosurg*. 2013;80(1-2):148-159.
833. Higgins TS, Thorp B, Rawlings BA, Han JK. Outcome results of endoscopic vs craniofacial resection of sinonasal malignancies: a systematic review and pooled-data analysis. *Int Forum Allergy Rhinol*. 2011;1:255-261.
834. Konuthula N, Iloreta AM, Miles B, et al. Prognostic significance of Kadish staging in esthesioneuroblastoma: an analysis of the National Cancer Database. *Head Neck*. 2017;39:1962-1968.
835. Stokes WA, Camilon PR, Banglawala SM, et al. Is sex an independent prognostic factor in esthesioneuroblastoma? *Am J Rhinol Allergy*. 2015;29:369-372.
836. Tajudeen BA, Arshi A, Suh JD, St John M, Wang MB. Importance of tumor grade in esthesioneuroblastoma survival: a population-based analysis. *JAMA Otolaryngol Head Neck Surg*. 2014;140:1124-1129.
837. Xiong L, Zeng XL, Guo CK, Liu AW, Huang L. Optimal treatment and prognostic factors for esthesioneuroblastoma: retrospective analysis of 187 Chinese patients. *BMC Cancer*. 2017;17:254.
838. Schmidt C, Potter N, Porceddu S, Panizza B. Olfactory neuroblastoma: 14-year experience at an Australian tertiary centre and the role for longer-term surveillance. *J Laryngol Otol*. 2017;131(S2):S29-S34.
839. Nakagawa T, Kodama S, Kobayashi M, et al. Endoscopic endonasal management of esthesioneuroblastoma: a retrospective multicenter study. *Auris Nasus Larynx*. 2018;45:281-285.
840. Konig M, Osnes T, Jebsen P, Evensen JF, Meling TR. Olfactory neuroblastoma: a single-center experience. *Neurosurg Rev*. 2018;41:323-331.
841. Zhang L, Niu K, Zhu K, et al. Long-term prognostic analysis after endoscopic endonasal surgery for olfactory neuroblastoma: a retrospective study of 13 cases. *PLoS One*. 2016;11:e0166046.
842. Yin ZZ, Gao L, Luo JW, et al. Long-term outcomes of patients with esthesioneuroblastomas: a cohort from a single institution. *Oral Oncol*. 2016;53:48-53.
843. Tajudeen BA, Adappa ND, Kuan EC, et al. Smell preservation following endoscopic unilateral resection of esthesioneuroblastoma: a multi-institutional experience. *Int Forum Allergy Rhinol*. 2016;6:1047-1050.
844. Manthuruthil C, Lewis J, McLean C, Batra PS, Barnett SL. Endoscopic endonasal management of olfactory neuroblastoma: a retrospective analysis of 10 patients with quality-of-life measures. *World Neurosurg*. 2016;90:1-5.
845. Banuchi VE, Dooley L, Lee NY, et al. Patterns of regional and distant metastasis in esthesioneuroblastoma. *Laryngoscope*. 2016;126:1556-1561.
846. Tsang RK, Tsang AC, Lam JW, Ho WK, Leung GK. Long-term results of endoscopic-assisted cranionasal resection for olfactory neuroblastoma—single centre experience of fourteen patients. *Clin Otolaryngol*. 2015;40:274-277.
847. Tajudeen BA, Arshi A, Suh JD, et al. Esthesioneuroblastoma: an update on the UCLA experience, 2002-2013. *J Neurol Surg B Skull Base*. 2015;76:43-49.
848. Petruzzelli GJ, Howell JB, Pederson A, et al. Multidisciplinary treatment of olfactory neuroblastoma: patterns of failure and management of recurrence. *Am J Otolaryngol*. 2015;36:547-553.
849. Feng L, Fang J, Zhang L, et al. Endoscopic endonasal resection of esthesioneuroblastoma: a single center experience of 24 patients. *Clin Neurol Neurosurg*. 2015;138:94-98.
850. Bell D, Saade R, Roberts D, et al. Prognostic utility of Hyams histological grading and Kadish-Morita staging systems for esthesioneuroblastoma outcomes. *Head Neck Pathol*. 2015;9:51-59.
851. Ow TJ, Hanna EY, Roberts DB, et al. Optimization of long-term outcomes for patients with esthesioneuroblastoma. *Head Neck*. 2014;36:524-530.
852. Montava M, Verillaud B, Kania R, et al. Critical analysis of recurrences of esthesioneuroblastomas: can we prevent them? *Eur Arch Otorhinolaryngol*. 2014;271:3215-3222.
853. Gallagher KK, Spector ME, Pepper JP, McKean EL, Marentette LJ, McHugh JB. Esthesioneuroblastoma: updating histologic grading as it relates to prognosis. *Ann Otol Rhinol Laryngol*. 2014;123:353-358.
854. Modesto A, Blanchard P, Tao YG, et al. Multimodal treatment and long-term outcome of patients with esthesioneuroblastoma. *Oral Oncol*. 2013;49:830-834.
855. Malouf GG, Casiraghi O, Deutsch E, Guigay J, Temam S, Bourhis J. Low- and high-grade esthesioneuroblastomas display a distinct natural history and outcome. *Eur J Cancer*. 2013;49:1324-1334.
856. Kumar R, Ghoshal S, Khosla D, et al. Survival and failure outcomes in locally advanced esthesioneuroblastoma: a single centre experience of 15 patients. *Eur Arch Otorhinolaryngol*. 2013;270:1897-1901.
857. Back L, Oinas M, Pietarinen-Runtti P, et al. The developing management of esthesioneuroblastoma: a single institution experience. *Eur Arch Otorhinolaryngol*. 2012;269:213-221.
858. Patel MR, Taylor RJ, Hackman TG, et al. Beyond the nasoseptal flap: outcomes and pearls with secondary flaps in endoscopic endonasal skull base reconstruction. *Laryngoscope*. 2014;124:846-852.
859. Germani RM, Vivero R, Herzallah IR, Casiano RR. Endoscopic reconstruction of large anterior skull base defects using acellular dermal allograft. *Am J Rhinol*. 2007;21:615-618.
860. Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. Esthesioneuroblastoma: prognosis and management. *Neurosurgery*. 1993;32:706-714; discussion 714-705.

861. Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. *Lancet Oncol*. 2001;2:683-690.
862. Nalavenkata SB, Sacks R, Adappa ND, et al. Olfactory neuroblastoma: fate of the neck—a long-term multicenter retrospective study. *Otolaryngol Head Neck Surg*. 2016;154:383-389.
863. Demiroz C, Gutfeld O, Aboziada M, Brown D, Marentette LJ, Eisbruch A. Esthesioneuroblastoma: is there a need for elective neck treatment? *Int J Radiat Oncol Biol Phys*. 2011;81:e255-e261.
864. Loy AH, Reibel JF, Read PW, et al. Esthesioneuroblastoma: continued follow-up of a single institution's experience. *Arch Otolaryngol Head Neck Surg*. 2006;132:134-138.
865. Peacock JG, Harmsen WS, Link MJ, et al. Risk of delayed lymph node metastasis in clinically N0 esthesioneuroblastoma. *J Neurol Surg B Skull Base*. 2017;78:68-74.
866. Marinelli JP, Van Gompel JJ, Link MJ, et al. Volumetric analysis of olfactory neuroblastoma skull base laterality and implications on neck disease. *Laryngoscope*. 2018;128:864-870.
867. Naples JG, Spiro J, Tessema B, Kuwada C, Kuo CL, Brown SM. Neck recurrence and mortality in esthesioneuroblastoma: implications for management of the N0 neck. *Laryngoscope*. 2016;126:1373-1379.
868. Jiang W, Mohamed AS, Fuller CD, et al. The role of elective nodal irradiation for esthesioneuroblastoma patients with clinically negative neck. *Pract Radiat Oncol*. 2016;6:241-247.
869. Yin ZZ, Luo JW, Gao L, et al. Spread patterns of lymph nodes and the value of elective neck irradiation for esthesioneuroblastoma. *Radiother Oncol*. 2015;117:328-332.
870. Sanghvi S, Khan MN, Patel NR, Yeldandi S, Baredes S, Eloy JA. Epidemiology of sinonasal squamous cell carcinoma: a comprehensive analysis of 4994 patients. *Laryngoscope*. 2014;124:76-83.
871. Ansa B, Goodman M, Ward K, et al. Paranasal sinus squamous cell carcinoma incidence and survival based on Surveillance, Epidemiology, and End Results data, 1973 to 2009. *Cancer*. 2013;119:2602-2610.
872. de Almeida JR, Su SY, Koutourousiou M, et al. Endonasal endoscopic surgery for squamous cell carcinoma of the sinonasal cavities and skull base: oncologic outcomes based on treatment strategy and tumor etiology. *Head Neck*. 2015;37:1163-1169.
873. But-Hadzic J, Jenko K, Poljak M, Kocjan BJ, Gale N, Strojan P. Sinonasal inverted papilloma associated with squamous cell carcinoma. *Radiol Oncol*. 2011;45:267-272.
874. Karligkiotis A, Lepera D, Volpi L, et al. Survival outcomes after endoscopic resection for sinonasal squamous cell carcinoma arising on inverted papilloma. *Head Neck*. 2016;38:1604-1614.
875. Kilic S, Kilic SS, Baredes S, et al. Comparison of endoscopic and open resection of sinonasal squamous cell carcinoma: a propensity score-matched analysis of 652 patients. *Int Forum Allergy Rhinol*. 2018;8:421-434.
876. Luong A, Citardi MJ, Batra PS. Management of sinonasal malignant neoplasms: defining the role of endoscopy. *Am J Rhinol Allergy*. 2010;24:150-155.
877. Nicolai P, Battaglia P, Bignami M, et al. Endoscopic surgery for malignant tumors of the sinonasal tract and adjacent skull base: a 10-year experience. *Am J Rhinol*. 2008;22:308-316.
878. Shipchandler TZ, Batra PS, Citardi MJ, Bolger WE, Lanza DC. Outcomes for endoscopic resection of sinonasal squamous cell carcinoma. *Laryngoscope*. 2005;115:1983-1987.
879. Yan CH, Newman JG, Kennedy DW, Palmer JN, Adappa ND. Clinical outcomes of sinonasal squamous cell carcinomas based on tumor etiology. *Int Forum Allergy Rhinol*. 2017;7:508-513.
880. Rosenthal DI, Barker JL Jr, El-Naggar AK, et al. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. *Cancer*. 2004;101:2567-2573.
881. Silva EG, Butler JJ, Mackay B, Goepfert H. Neuroblastomas and neuroendocrine carcinomas of the nasal cavity: a proposed new classification. *Cancer*. 1982;50:2388-2405.
882. Frierson HF Jr, Mills SE, Fechner RE, Taxy JB, Levine PA. Sinonasal undifferentiated carcinoma: an aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. *Am J Surg Pathol*. 1986;10:771-779.
883. Ejaz A, Wenig BM. Sinonasal undifferentiated carcinoma: clinical and pathologic features and a discussion on classification, cellular differentiation, and differential diagnosis. *Adv Anat Pathol*. 2005;12:134-143.
884. Franchi A, Moroni M, Massi D, Paglierani M, Santucci M. Sinonasal undifferentiated carcinoma, nasopharyngeal-type undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinoma express different cytokeratin patterns. *Am J Surg Pathol*. 2002;26:1597-1604.
885. Singh L, Ranjan R, Arava S, Singh MK. Role of p40 and cytokeratin 5/6 in the differential diagnosis of sinonasal undifferentiated carcinoma. *Ann Diagn Pathol*. 2014;18:261-265.
886. Gelbard A, Hale KS, Takahashi Y, et al. Molecular profiling of sinonasal undifferentiated carcinoma. *Head Neck*. 2014;36:15-21.
887. Alos L, Hakim S, Larque AB, et al. p16 overexpression in high-grade neuroendocrine carcinomas of the head and neck: potential diagnostic pitfall with HPV-related carcinomas. *Virchows Arch*. 2016;469:277-284.
888. Thompson ED, Stelow EB, Mills SE, Westra WH, Bishop JA. Large cell neuroendocrine carcinoma of the head and neck: a clinicopathologic series of 10 cases with an emphasis on HPV status. *Am J Surg Pathol*. 2016;40:471-478.
889. Jeng YM, Sung MT, Fang CL, et al. Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma: two clinically, biologically, and histopathologically distinct entities. *Am J Surg Pathol*. 2002;26:371-376.
890. Wadsworth B, Bumpous JM, Martin AW, Nowacki MR, Jenson AB, Farghaly H. Expression of p16 in sinonasal undifferentiated carcinoma (SNUC) without associated human papillomavirus (HPV). *Head Neck Pathol*. 2011;5:349-354.
891. Gray ST, Herr MW, Sethi RK, et al. Treatment outcomes and prognostic factors, including human papillomavirus, for sinonasal undifferentiated carcinoma: a retrospective review. *Head Neck*. 2015;37:366-374.
892. Agaimy A, Hartmann A, Antonescu CR, et al. SMARCB1 (INI-1)-deficient sinonasal carcinoma: a series of 39 cases expanding the morphologic and clinicopathologic spectrum of a recently described entity. *Am J Surg Pathol*. 2017;41:458-471.
893. Taggart MW, Hanna EY, Gidley P, Weber RS, Bell D. Achaete-scute homolog 1 expression closely correlates with endocrine phenotype and degree of differentiation in sinonasal neuroendocrine tumors. *Ann Diagn Pathol*. 2015;19:154-156.
894. Felix-Ravelo M, Bey A, Arous F, Paris-Grandpierre S, Jankowski R, Nguyen DT. Relationship between (18)FDG-PET and different types of sinonasal malignancies. *Acta Otolaryngol*. 2017;137:191-195.
895. van der Laan TP, Iepsma R, Witjes MJ, van der Laan BF, Plaat BE, Halmos GB. Meta-analysis of 701 published cases of sinonasal neuroendocrine carcinoma: the importance of differentiation grade in determining treatment strategy. *Oral Oncol*. 2016;63:1-9.
896. Musy PY, Reibel JF, Levine PA. Sinonasal undifferentiated carcinoma: the search for a better outcome. *Laryngoscope*. 2002;112(8 Pt 1):1450-1455.
897. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. *Cancer*. 1976;37:1571-1576.
898. Kuan EC, Arshi A, Mallen-St Clair J, Tajudeen BA, Abemayor E, St John MA. Significance of tumor stage in sinonasal undifferentiated carcinoma survival: a population-based analysis. *Otolaryngol Head Neck Surg*. 2016;154:667-673.
899. Miyamoto RC, Gleich LL, Biddinger PW, Gluckman JL. Esthesioneuroblastoma and sinonasal undifferentiated carcinoma: impact of histological grading and clinical staging on survival and prognosis. *Laryngoscope*. 2000;110:1262-1265.
900. O'Reilly AG, Wismayer DJ, Moore EJ. Prognostic factors for patients with sinonasal undifferentiated carcinoma. *Laryngoscope*. 2010;120(Suppl 4):S173.
901. Patel TD, Vazquez A, Dubal PM, Baredes S, Liu JK, Eloy JA. Sinonasal neuroendocrine carcinoma: a population-based analysis of incidence and survival. *Int Forum Allergy Rhinol*. 2015;5:448-453.
902. Rawal RB, Farzal Z, Federspiel JJ, Sreenath SB, Thorp BD, Zanation AM. Endoscopic resection of sinonasal malignancy: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2016;155:376-386.
903. Bhasker S, Mallick S, Benson R, Bhanuprasad V, Sharma A, Thakar A. A multimodality approach to sinonasal undifferentiated carcinoma: a single institute experience. *J Laryngol Otol*. 2017;131:19-25.
904. Kuo P, Manes RP, Schwam ZG, Judson BL. Survival outcomes for combined modality therapy for sinonasal undifferentiated carcinoma. *Otolaryngol Head Neck Surg*. 2017;156:132-136.
905. Hosokawa S, Takahashi G, Baba S, Mineta H. Small cell neuroendocrine carcinomas arising in the head and neck region. *J Oral Maxillofac Surg*. 2016;74:1091-1095.
906. Lund VJ, Wei WI. Endoscopic surgery for malignant sinonasal tumours: an eighteen year experience. *Rhinology*. 2015;53:204-211.
907. Lopez F, Suarez V, Vivanco B, Suarez C, Llorente JL. Current management of sinonasal undifferentiated carcinoma. *Rhinology*. 2015;53:212-220.
908. Christopherson K, Werning JW, Malyapa RS, Morris CG, Mendenhall WM. Radiotherapy for sinonasal undifferentiated carcinoma. *Am J Otolaryngol*. 2014;35:141-146.
909. Mourad WF, Hauerstock D, Shourbaji RA, et al. Trimodality management of sinonasal undifferentiated carcinoma and review of the literature. *Am J Clin Oncol*. 2013;36:584-588.
910. Yoshida E, Aouad R, Fragoso R, et al. Improved clinical outcomes with multi-modality therapy for sinonasal undifferentiated carcinoma of the head and neck. *Am J Otolaryngol*. 2013;34:658-663.
911. van der Laan TP, Bij HP, van Hemel BM, et al. The importance of multimodality therapy in the treatment of sinonasal neuroendocrine carcinoma. *Eur Arch Otorhinolaryngol*. 2013;270:2565-2568.
912. Gorner M, Brasch F, Hirnle P, et al. Multimodality treatment for poorly differentiated neuroendocrine head and neck carcinomas—a single institution experience. *Eur J Cancer Care (Engl)*. 2013;22:648-652.
913. Xu CC, Dziegielewski PT, McGaw WT, Seikaly H. Sinonasal undifferentiated carcinoma (SNUC): the Alberta experience and literature review. *J Otolaryngol Head Neck Surg*. 2013;42:2.
914. Al-Mamgani A, van Rooij P, Mehilal R, Tans L, Levendag PC. Combined-modality treatment improved outcome in sinonasal undifferentiated carcinoma: single-institutional experience of 21 patients and review of the literature. *Eur Arch Otorhinolaryngol*. 2013;270:293-299.
915. Fried D, Zanation AM, Huang B, et al. Management of nonesthesioneuroblastoma sinonasal malignancies with neuroendocrine differentiation. *Laryngoscope*. 2012;122:2210-2215.
916. Mitchell EH, Diaz A, Yilmaz T, et al. Multimodality treatment for sinonasal neuroendocrine carcinoma. *Head Neck*. 2012;34:1372-1376.
917. Reiersen DA, Pahilan ME, Devaiah AK. Meta-analysis of treatment outcomes for sinonasal undifferentiated carcinoma. *Otolaryngol Head Neck Surg*. 2012;147:7-14.
918. Likhacheva A, Rosenthal DI, Hanna E, Kupferman M, Demonte F, El-Naggar AK. Sinonasal neuroendocrine carcinoma: impact of differentiation status on response and outcome. *Head Neck Oncol*. 2011;3:32.
919. Lin EM, Sparano A, Spalding A, et al. Sinonasal undifferentiated carcinoma: a 13-year experience at a single institution. *Skull Base*. 2010;20:61-67.
920. Tanzler ED, Morris CG, Orlando CA, Werning JW, Mendenhall WM. Management of sinonasal undifferentiated carcinoma. *Head Neck*. 2008;30:595-599.
921. Chen AM, Daly ME, El-Sayed I, et al. Patterns of failure after combined-modality approaches incorporating radiotherapy for sinonasal undifferentiated carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. 2008;70:338-343.
922. Babin E, Rouleau V, Vedrine PO, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. *J Laryngol Otol*. 2006;120:289-297.
923. Kim BS, Vongtama R, Juillard G. Sinonasal undifferentiated carcinoma: case series and literature review. *Am J Otolaryngol*. 2004;25:162-166.
924. Rischin D, Porceddu S, Peters L, Martin J, Corry J, Weih L. Promising results with chemoradiation in patients with sinonasal undifferentiated carcinoma. *Head Neck*. 2004;26:435-441.

925. Smith SR, Som P, Fahmy A, Lawson W, Sacks S, Brandwein M. A clinicopathological study of sinonasal neuroendocrine carcinoma and sinonasal undifferentiated carcinoma. *Laryngoscope*. 2000;110(10 Pt 1):1617-1622.
926. Gorelick J, Ross D, Marentette L, Blaivas M. Sinonasal undifferentiated carcinoma: case series and review of the literature. *Neurosurgery*. 2000;47:750-754; discussion 754-755.
927. Righi PD, Francis F, Aron BS, Weitzner S, Wilson KM, Gluckman J. Sinonasal undifferentiated carcinoma: a 10-year experience. *Am J Otolaryngol*. 1996;17:167-171.
928. Patil VM, Joshi A, Noronha V, et al. Neoadjuvant chemotherapy in locally advanced and borderline resectable nonsquamous sinonasal tumors (esthesioneuroblastoma and sinonasal tumor with neuroendocrine differentiation). *Int J Surg Oncol*. 2016;2016:6923730.
929. Ansari M, Guo S, Fakhri S, et al. Sinonasal undifferentiated carcinoma (SNUC): morphoproteomic-guided treatment paradigm with clinical efficacy. *Ann Clin Lab Sci*. 2013;43:45-53.
930. Fitzek MM, Thornton AF, Varvares M, et al. Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy. *Cancer*. 2002;94:2623-2634.
931. Buchmann L, Larsen C, Pollack A, Tawfik O, Sykes K, Hoover LA. Endoscopic techniques in resection of anterior skull base/paranasal sinus malignancies. *Laryngoscope*. 2006;116:1749-1754.
932. Revenaugh PC, Seth R, Pavlovich JB, Knott PD, Batra PS. Minimally invasive endoscopic resection of sinonasal undifferentiated carcinoma. *Am J Otolaryngol*. 2011;32:464-469.
933. Ellington CL, Goodman M, Kono SA, et al. Adenoid cystic carcinoma of the head and neck: incidence and survival trends based on 1973-2007 Surveillance, Epidemiology, and End Results data. *Cancer*. 2012;118:4444-4451.
934. Haerle SK, Gullane PJ, Witterick IJ, Zweifel C, Gentili F. Sinonasal carcinomas: epidemiology, pathology, and management. *Neurosurg Clin N Am*. 2013;24:39-49.
935. Barnes L, Tse LL, Hunt J, et al. Tumors of the nasal cavity. WHO and TNM classification. In: Barnes L, Eveson J, Reichart P, Sidansky D, eds. *World Health Organization. Classification of Tumors, Pathology and Genetics of Head and Neck Tumors*. Lyon, France: IARC Press; 2005:24.
936. Boukheris H, Curtis RE, Land CE, Dores GM. Incidence of carcinoma of the major salivary glands according to the WHO classification, 1992 to 2006: a population-based study in the United States. *Cancer Epidemiol Biomarkers Prev*. 2009;18:2899-2906.
937. Turner JH, Reh DD. Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data. *Head Neck*. 2012;34:877-885.
938. Thompson LD, Penner C, Ho NJ, et al. Sinonasal tract and nasopharyngeal adenoid cystic carcinoma: a clinicopathologic and immunophenotypic study of 86 cases. *Head Neck Pathol*. 2014;8:88-109.
939. Bishop JA, Ma XJ, Wang H, et al. Detection of transcriptionally active high-risk HPV in patients with head and neck squamous cell carcinoma as visualized by a novel E6/E7 mRNA in situ hybridization method. *Am J Surg Pathol*. 2012;36:1874-1882.
940. Howard DJ, Lund VJ, Wei WI. Craniofacial resection for tumors of the nasal cavity and paranasal sinuses: a 25-year experience. *Head Neck*. 2006;28:867-873.
941. Amit M, Binenbaum Y, Sharma K, et al. Analysis of failure in patients with adenoid cystic carcinoma of the head and neck. An international collaborative study. *Head Neck*. 2014;36:998-1004.
942. Gil Z, Carlson DL, Gupta A, et al. Patterns and incidence of neural invasion in patients with cancers of the paranasal sinuses. *Arch Otolaryngol Head Neck Surg*. 2009;135:173-179.
943. Amit M, Binenbaum Y, Sharma K, et al. Adenoid cystic carcinoma of the nasal cavity and paranasal sinuses: a meta-analysis. *J Neurol Surg B Skull Base*. 2013;74:118-125.
944. Unsal AA, Chung SY, Zhou AH, Baredes S, Eloy JA. Sinonasal adenoid cystic carcinoma: a population-based analysis of 694 cases. *Int Forum Allergy Rhinol*. 2017;7:312-320.
945. Thompson CF, Suh JD, Liu Y, Bergsneider M, Wang MB. Modifications to the endoscopic approach for anterior skull base lesions improve postoperative sinonasal symptoms. *J Neurol Surg B Skull Base*. 2014;75:65-72.
946. Lupinetti AD, Roberts DB, Williams MD, et al. Sinonasal adenoid cystic carcinoma: the M. D. Anderson Cancer Center experience. *Cancer*. 2007;110:2726-2731.
947. Askoxylakis V, Hegenbarth P, Timke C, et al. Intensity modulated radiation therapy (IMRT) for sinonasal tumors: a single center long-term clinical analysis. *Radiat Oncol*. 2016;11:17.
948. Wiseman SM, Popat SR, Rigual NR, et al. Adenoid cystic carcinoma of the paranasal sinuses or nasal cavity: a 40-year review of 35 cases. *Ear Nose Throat J*. 2002;81:510-514, 516-517.
949. Liu WS, Xu ZG, Gao L, Tang PZ, Xu GZ, Zhang GF. [Adenoid cystic carcinoma of maxillary sinus: diagnosis, treatment and prognostic factors]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2011;46:402-407. Chinese.
950. Husain Q, Kanumuri VV, Svider PF, et al. Sinonasal adenoid cystic carcinoma: systematic review of survival and treatment strategies. *Otolaryngol Head Neck Surg*. 2013;148:29-39.
951. Michel G, Joubert M, Delemazure AS, Espitalier F, Durand N, Malard O. Adenoid cystic carcinoma of the paranasal sinuses: retrospective series and review of the literature. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2013;130:257-262.
952. Seong SY, Hyun DW, Kim YS, et al. Treatment outcomes of sinonasal adenoid cystic carcinoma: 30 cases from a single institution. *J Craniomaxillofac Surg*. 2014;42:e171-e175.
953. Rhee CS, Won TB, Lee CH, et al. Adenoid cystic carcinoma of the sinonasal tract: treatment results. *Laryngoscope*. 2006;116:982-986.
954. Zhang Q, Yang L, Yang AK, Guo ZM. [Clinical study on 88 cases of adenoid cystic carcinoma in nasal cavity and paranasal sinuses]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2009;44:311-314. Chinese.
955. Wei M, Tang, P., Xu, Z., Qi, Y., Yin, Y. [Clinical analysis of 40 cases with sinonasal adenoid cystic carcinoma]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2009;44:381-384. Chinese.
956. Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Hinerman RW, Villaret DB. Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. *Head Neck*. 2004;26:154-162.
957. Silverman DA, Carlson TP, Khuntia D, Bergstrom RT, Saxton J, Esclamado RM. Role for postoperative radiation therapy in adenoid cystic carcinoma of the head and neck. *Laryngoscope*. 2004;114:1194-1199.
958. Vikram B, Strong EW, Shah JP, Spiro RH. Radiation therapy in adenoid-cystic carcinoma. *Int J Radiat Oncol Biol Phys*. 1984;10:221-223.
959. Spiers AS, Esseltine DL, Ruckdeschel JC, Davies JN, Horton J. Metastatic adenoid cystic carcinoma of salivary glands: case reports and review of the literature. *Cancer Control*. 1996;3:336-342.
960. Radiation Therapy Oncology Group. Radiation therapy with or without chemotherapy in treating patients with high-risk malignant salivary gland tumors that have been removed by surgery. (Official title: A randomized phase II/phase III study of adjuvant concurrent radiation and chemotherapy versus radiation alone in resected high-risk malignant salivary gland tumors). https://clinicaltrials.gov/ct2/show/NCT01220583. Accessed March 28, 2019.
961. Issing PR, Hemmanouil I, Stover T, et al. Adenoid cystic carcinoma of the skull base. *Skull Base Surg*. 1999;9:271-275.
962. Lund V, Howard DJ, Wei WI. Endoscopic resection of malignant tumors of the nose and sinuses. *Am J Rhinol*. 2007;21:89-94.
963. Hanna E, Vural E, Prokopakis E, Carrau R, Snyderman C, Weissman J. The sensitivity and specificity of high-resolution imaging in evaluating perineural spread of adenoid cystic carcinoma to the skull base. *Arch Otolaryngol Head Neck Surg*. 2007;133:541-545.
964. Panizza B, Warren TA, Solares CA, Boyle GM, Lambie D, Brown I. Histopathological features of clinical perineural invasion of cutaneous squamous cell carcinoma of the head and neck and the potential implications for treatment. *Head Neck*. 2014;36:1611-1618.
965. Al-Sheibani S, Zanation AM, Carrau RL, et al. Endoscopic endonasal transpterygoid nasopharyngectomy. *Laryngoscope*. 2011;121:2081-2089.
966. Lai YS, Chen MK. Exclusively endoscopic resection of nasopharyngeal adenocarcinoma. *Clin Exp Otorhinolaryngol*. 2013;6:263-265.
967. Wei WI, Lam KH, Sham JS. New approach to the nasopharynx: the maxillary swing approach. *Head Neck*. 1991;13:200-207.
968. Tu GY, Hu YH, Xu GZ, Ye M. Salvage surgery for nasopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg*. 1988;114:328-329.
969. Morton RP, Liavaag PG, McLean M, Freeman JL. Transcervico-mandibulo-palatal approach for surgical salvage of recurrent nasopharyngeal cancer. *Head Neck*. 1996;18:352-358.
970. Chan JY, Tsang RK, Wei WI. Morbidities after maxillary swing nasopharyngectomy for recurrent nasopharyngeal carcinoma. *Head Neck*. 2015;37:487-492.
971. Yoshizaki T, Wakisaka N, Murono S, Shimizu Y, Furukawa M. Endoscopic nasopharyngectomy for patients with recurrent nasopharyngeal carcinoma at the primary site. *Laryngoscope*. 2005;115:1517-1519.
972. Chen MK, Lai JC, Chang CC, Liu MT. Minimally invasive endoscopic nasopharyngectomy in the treatment of recurrent T1-2a nasopharyngeal carcinoma. *Laryngoscope*. 2007;117:894-896.
973. Ko JY, Wang CP, Ting LL, Yang TL, Tan CT. Endoscopic nasopharyngectomy with potassium-titanyl-phosphate (KTP) laser for early locally recurrent nasopharyngeal carcinoma. *Head Neck*. 2009;31:1309-1315.
974. Chen MY, Wang SL, Zhu YL, et al. Use of a posterior pedicle nasal septum and floor mucoperiosteum flap to resurface the nasopharynx after endoscopic nasopharyngectomy for recurrent nasopharyngeal carcinoma. *Head Neck*. 2012;34:1383-1388.
975. Ho AS, Kaplan MJ, Fee WE Jr, Yao M, Sunwoo JB, Hwang PH. Targeted endoscopic salvage nasopharyngectomy for recurrent nasopharyngeal carcinoma. *Int Forum Allergy Rhinol*. 2012;2:166-173.
976. Montiero E, Witterick I. Endoscopic nasopharyngectomy: patient selection and surgical execution. *Oper Tech Otolayngol Head Neck Surg*. 2014;25:284-288.
977. Becker AM, Hwang PH. Endoscopic endonasal anatomy of the nasopharynx in a cadaver model. *Int Forum Allergy Rhinol*. 2013;3:319-324.
978. Wen YH, Wen WP, Chen HX, Li J, Zeng YH, Xu G. Endoscopic nasopharyngectomy for salvage in nasopharyngeal carcinoma: a novel anatomic orientation. *Laryngoscope*. 2010;120:1298-1302.
979. Mattavelli D, Bolzoni Villaret A, Ferrari M, et al. Different perspectives of internal carotid artery in transnasal endoscopic surgery. *World Neurosurg*. 2016;95:222-228.
980. Hsu NI, Shen PH, Chao SS, Ong YK, Li CS. En bloc resection concept for endoscopic endonasal nasopharyngectomy: surgical anatomy and outcome. *Chin Med J (Engl)*. 2014;127:2934-2939.
981. Liu CL, Hsu NI, Shen PH. Endoscopic endonasal nasopharyngectomy: tensor veli palatine muscle as a landmark for the parapharyngeal internal carotid artery. *Int Forum Allergy Rhinol*. 2017;7:624-628.
982. Chen MY, Wen WP, Guo X, et al. Endoscopic nasopharyngectomy for locally recurrent nasopharyngeal carcinoma. *Laryngoscope*. 2009;119:516-522.
983. Veyrat M, Verillaud B, Herman P, Bresson D. How I do it. The pedicled temporoparietal fascia flap for skull base reconstruction after endonasal endoscopic approaches. *Acta Neurochir (Wien)*. 2016;158:2291-2294.
984. Markey J, Benet A, El-Sayed IH. The endonasal endoscopic harvest and anatomy of the buccal fat pad flap for closure of skull base defects. *Laryngoscope*. 2015;125:2247-2252.
985. Vlantis AC, Lee DL, Wong EW, Chow SM, Ng SK, Chan JY. Endoscopic nasopharyngectomy in recurrent nasopharyngeal carcinoma: a case series, literature review, and pooled analysis. *Int Forum Allergy Rhinol*. 2017;7:425-432.
986. Rohaizam J, Subramaniam SK, Vikneswaran T, Tan VE, Tan TY. Endoscopic nasopharyngectomy: the Sarawak experience. *Med J Malaysia*. 2009;64:213-215.
987. Castelnuovo P, Dallan I, Bignami M, et al. Nasopharyngeal endoscopic resection in the

management of selected malignancies: ten-year experience. *Rhinology*. 2010;48:84-89.

988. Tay HN, Leong JL, Sethi DS. Long-term results of endoscopic resection of nasopharyngeal tumours. *Med J Malaysia*. 2009;64:159-162.
989. Castelnuovo P, Nicolai P, Turri-Zanoni M, et al. Endoscopic endonasal nasopharyngectomy in selected cancers. *Otolaryngol Head Neck Surg*. 2013;149:424-430.
990. Wong EHC, Liew YT, Abu Bakar MZ, Lim EYL, Prepageran N. A preliminary report on the role of endoscopic endonasal nasopharyngectomy in recurrent rT3 and rT4 nasopharyngeal carcinoma. *Eur Arch Otorhinolaryngol*. 2017;274:275-281.
991. Na'ara S, Amit M, Billan S, Cohen JT, Gil Z. Outcome of patients undergoing salvage surgery for recurrent nasopharyngeal carcinoma: a meta-analysis. *Ann Surg Oncol*. 2014;21:3056-3062.
992. Zou X, Han F, Ma WJ, et al. Salvage endoscopic nasopharyngectomy and intensity-modulated radiotherapy versus conventional radiotherapy in treating locally recurrent nasopharyngeal carcinoma. *Head Neck*. 2015;37:1108-1115.
993. You R, Zou X, Hua YJ, et al. Salvage endoscopic nasopharyngectomy is superior to intensity-modulated radiation therapy for local recurrence of selected T1-T3 nasopharyngeal carcinoma: a case-matched comparison. *Radiother Oncol*. 2015;115:399-406.
994. Stamm AC, Pignatari SS, Vellutini E. Transnasal endoscopic surgical approaches to the clivus. *Otolaryngol Clin North Am*. 2006;39:639-656, xi.
995. Mangussi-Gomes J, Beer-Furlan A, Balsalobre L, Vellutini EA, Stamm AC. Endoscopic endonasal management of skull base chordomas: surgical technique, nuances, and pitfalls. *Otolaryngol Clin North Am*. 2016;49:167-182.
996. Folbe AJ, Svider PF, Liu JK, Eloy JA. Endoscopic resection of clival malignancies. *Otolaryngol Clin North Am*. 2017;50:315-329.
997. Erdem E, Angtuaco EC, Van Hemert R, Park JS, Al-Mefty O. Comprehensive review of intracranial chordoma. *Radiographics*. 2003;23:995-1009.
998. Firooznia H, Pinto RS, Lin JP, Baruch HH, Zausner J. Chordoma: radiologic evaluation of 20 cases. *AJR Am J Roentgenol*. 1976;127:797-805.
999. Meyers SP, Hirsch WL Jr, Curtin HD, Barnes L, Sekhar LN, Sen C. Chordomas of the skull base: MR features. *AJNR Am J Neuroradiol*. 1992;13:1627-1636.
1000. Oot RF, Melville GE, New PF, et al. The role of MR and CT in evaluating clival chordomas and chondrosarcomas. *AJR Am J Roentgenol*. 1988;151:567-575.
1001. Weber AL, Liebsch NJ, Sanchez R, Sweriduk ST Jr. Chordomas of the skull base. Radiologic and clinical evaluation. *Neuroimaging Clin N Am*. 1994;4:515-527.
1002. Vescan AD, Snyderman CH, Carrau RL, et al. Vidian canal: analysis and relationship to the internal carotid artery. *Laryngoscope*. 2007;117:1338-1342.
1003. Arbolay OL, Gonzalez JG, Gonzalez RH, Galvez YH. Extended endoscopic endonasal approach to the skull base. *Minim Invasive Neurosurg*. 2009;52:114-118.
1004. Frank G, Sciarretta V, Calbucci F, Farneti G, Mazzatenta D, Pasquini E. The endoscopic transnasal transsphenoidal approach for the treatment of cranial base chordomas and chondrosarcomas. *Neurosurgery*. 2006;59(1 Suppl 1):ONS50-ONS57; discussion ONS50-ONS57.
1005. Chibbaro S, Cornelius JF, Froelich S, et al. Endoscopic endonasal approach in the management of skull base chordomas—clinical experience on a large series, technique, outcome, and pitfalls. *Neurosurg Rev*. 2014;37:217-224; discussion 224-215.
1006. Fraser JF, Nyquist GG, Moore N, Anand VK, Schwartz TH. Endoscopic endonasal transclival resection of chordomas: operative technique, clinical outcome, and review of the literature. *J Neurosurg*. 2010;112:1061-1069.
1007. Garzaro M, Zenga F, Raimondo L, et al. Three-dimensional endoscopy in transnasal transsphenoidal approach to clival chordomas. *Head Neck*. 2016;38(Suppl 1):E1814-E1819.
1008. Holzmann D, Reisch R, Krayenbuhl N, Hug E, Bernays RL. The transnasal transclival approach for clivus chordoma. *Minim Invasive Neurosurg*. 2010;53(5-6):211-217.
1009. Hwang PY, Ho CL. Neuronavigation using an image-guided endoscopic transnasal-sphenoethmoidal approach to clival chordomas. *Neurosurgery*. 2007;61(5 Suppl 2):212-217; discussion 217-218.
1010. Koutourousiou M, Gardner PA, Tormenti MJ, et al. Endoscopic endonasal approach for resection of cranial base chordomas: outcomes and learning curve. *Neurosurgery*. 2012;71:614-624; discussion 624-615.
1011. Messerer M, Cossu G, Pasche P, et al. Extended endoscopic endonasal approach to clival and paraclival tumors: indications and limits. *Neurochirurgie*. 2016;62:136-145.
1012. Ramm-Pettersen J, Fric R, Berg-Johnsen J. Long-term follow-up after endoscopic trans-sphenoidal surgery or initial observation in clivus chordomas. *Acta Neurochir (Wien)*. 2017;159:1849-1855.
1013. Shidoh S, Toda M, Kawase T, et al. Transoral vs. endoscopic endonasal approach for clival/upper cervical chordoma. *Neurol Med Chir (Tokyo)*. 2014;54:991-998.
1014. Solares CA, Grindler D, Luong A, et al. Endoscopic management of sphenoclival neoplasms: anatomical correlates and patient outcomes. *Otolaryngol Head Neck Surg*. 2010;142:315-321.
1015. Tan NC, Naidoo Y, Oue S, et al. Endoscopic surgery of skull base chordomas. *J Neurol Surg B Skull Base*. 2012;73:379-386.
1016. Taniguchi M, Kohmura E. Endoscopic endonasal removal of laterally extended clival chordoma using side-viewing scopes. *Acta Neurochir (Wien)*. 2012;154:627-632.
1017. Vellutini Ede A, Balsalobre L, Hermann DR, Stamm AC. The endoscopic endonasal approach for extradural and intradural clivus lesions. *World Neurosurg*. 2014;82(6 Suppl):S106-S115.
1018. Zhang Q, Kong F, Yan B, Ni Z, Liu H. Endoscopic endonasal surgery for clival chordoma and chondrosarcoma. *ORL J Otorhinolaryngol Relat Spec*. 2008;70:124-129.
1019. Hong Jiang W, Ping Zhao S, Hai Xie Z, Zhang H, Zhang J, Yun Xiao J. Endoscopic resection of chordomas in different clival regions. *Acta Otolaryngol*. 2009;129:71-83.
1020. Zoli M, Milanese L, Bonfatti R, et al. Clival chordomas: considerations after 16 years of endoscopic endonasal surgery. *J Neurosurg*. 2018;128:329-338.
1021. Dehdashti AR, Karabatsou K, Ganna A, Witterick I, Gentili F. Expanded endoscopic endonasal approach for treatment of clival chordomas: early results in 12 patients. *Neurosurgery*. 2008;63:299-307; discussion 307-299.
1022. Fraser JF, Nyquist GG, Moore N, Anand VK, Schwartz TH. Endoscopic endonasal minimal access approach to the clivus: case series and technical nuances. *Neurosurgery*. 2010;67(3 Suppl Operative):ons150-ons158; discussion ons158.
1023. Saito K, Toda M, Tomita T, Ogawa K, Yoshida K. Surgical results of an endoscopic endonasal approach for clival chordomas. *Acta Neurochir (Wien)*. 2012;154:879-886.
1024. Solares CA, Fakhri S, Batra PS, Lee J, Lanza DC. Transnasal endoscopic resection of lesions of the clivus: a preliminary report. *Laryngoscope*. 2005;115:1917-1922.
1025. Kim YH, Jeon C, Se YB, et al. Clinical outcomes of an endoscopic transclival and transpetrosal approach for primary skull base malignancies involving the clivus. *J Neurosurg*. 2018;128:1454-1462.
1026. Fernandes Cabral DT, Zenonos GA, Fernandez-Miranda JC, Wang EW, Gardner PA. Iatrogenic seeding of skull base chordoma following endoscopic endonasal surgery. *J Neurosurg*. 2017:129:947-953.
1027. Labidi M, Watanabe K, Bouazza S, et al. Clivus chordomas: a systematic review and meta-analysis of contemporary surgical management. *J Neurosurg Sci*. 2016;60:476-484.
1028. Stippler M, Gardner PA, Snyderman CH, Carrau RL, Prevedello DM, Kassam AB. Endoscopic endonasal approach for clival chordomas. *Neurosurgery*. 2009;64:268-277; discussion 277-268.
1029. Jones PS, Aghi MK, Muzikansky A, Shih HA, Barker FG 2nd, Curry WT Jr. Outcomes and patterns of care in adult skull base chordomas from the Surveillance, Epidemiology, and End Results (SEER) database. *J Clin Neurosci*. 2014;21:1490-1496.
1030. Bohman LE, Koch M, Bailey RL, Alonso-Basanta M, Lee JY. Skull base chordoma and chondrosarcoma: influence of clinical and demographic factors on prognosis: a SEER analysis. *World Neurosurg*. 2014;82:806-814.
1031. Wang AC, Darlin S, Lai W, et al. Pituitary and skull-base lesions and the litigious patient. *Int Forum Allergy Rhinol*. 2017;7:1022-1028.
1032. Kooshkabadi A, Choi PA, Koutourousiou M, et al. Atlanto-occipital instability following endoscopic endonasal approach for lower clival lesions: experience with 212 cases. *Neurosurgery*. 2015;77:888-897; discussion 897.
1033. Arnautovic KI, Al-Mefty O. Surgical seeding of chordomas. *Neurosurg Focus*. 2001;10:E7.
1034. Asano S, Kawahara N, Kirino T. Intradural spinal seeding of a clival chordoma. *Acta Neurochir (Wien)*. 2003;145:599-603; discussion 603.
1035. Fischbein NJ, Kaplan MJ, Holliday RA, Dillon WP. Recurrence of clival chordoma along the surgical pathway. *AJNR Am J Neuroradiol*. 2000;21:578-583.
1036. Hines JP, Ashmead MG, Stringer SP. Clival chordoma of the nasal septum secondary to surgical pathway seeding. *Am J Otolaryngol*. 2014;35:431-434.
1037. Iloreta AM, Nyquist GG, Friedel M, Farrell C, Rosen MR, Evans JJ. Surgical pathway seeding of clivo-cervical chordomas. *J Neurol Surg Rep*. 2014;75:e246-e250.
1038. Krengli M, Poletti A, Ferrara E, Fossati P. Tumour seeding in the surgical pathway after resection of skull base chordoma. *Rep Pract Oncol Radiother*. 2016;21:407-411.
1039. van Lierop AC, Fagan JJ, Taylor KL. Recurrent chordoma of the palate occurring in the surgical pathway: a case report. *Auris Nasus Larynx*. 2008;35:447-450.
1040. Koutourousiou M, Filho FV, Costacou T, et al. Pontine encephalocele and abnormalities of the posterior fossa following transclival endoscopic endonasal surgery. *J Neurosurg*. 2014;121:359-366.
1041. Gay E, Sekhar LN, Rubinstein E, et al. Chordomas and chondrosarcomas of the cranial base: results and follow-up of 60 patients. *Neurosurgery*. 1995;36:887-896; discussion 896-887.
1042. Colli BO, Al-Mefty O. Chordomas of the skull base: follow-up review and prognostic factors. *Neurosurg Focus*. 2001;10:E1.
1043. Crockard HA, Steel T, Plowman N, et al. A multidisciplinary team approach to skull base chordomas. *J Neurosurg*. 2001;95:175-183.
1044. Tzortzidis F, Elahi F, Wright D, Natarajan SK, Sekhar LN. Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chordomas. *Neurosurgery*. 2006;59:230-237; discussion 230-237.
1045. Amichetti M, Cianchetti M, Amelio D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. *Neurosurg Rev*. 2009;32:403-416.
1046. Bloch C Jr, Richardson M. A new family of small (5 kDa) protein inhibitors of insect alpha-amylases from seeds or sorghum (Sorghum bicolar (L) Moench) have sequence homologies with wheat gamma-purothionins. *FEBS Lett*. 1991;279:101-104.
1047. Matloob SA, Nasir HA, Choi D. Proton beam therapy in the management of skull base chordomas: systematic review of indications, outcomes, and implications for neurosurgeons. *Br J Neurosurg*. 2016;30:382-387.
1048. Krishnan S, Foote RL, Brown PD, Pollock BE, Link MJ, Garces YI. Radiosurgery for cranial base chordomas and chondrosarcomas. *Neurosurgery*. 2005;56:777-784; discussion 777-784.
1049. Rosenberg AE, Nielsen GP, Keel SB, et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. *Am J Surg Pathol*. 1999;23:1370-1378.
1050. Bloch O, Parsa AT. Skull base chondrosarcoma: evidence-based treatment paradigms. *Neurosurg Clin N Am*. 2013;24:89-96.
1051. Castelnuovo P, Pagella F, Semino L, De Bernardi F, Delu G. Endoscopic treatment of the isolated sphenoid sinus lesions. *Eur Arch Otorhinolaryngol*. 2005;262:142-147.
1052. Tami TA. Surgical management of lesions of the sphenoid lateral recess. *Am J Rhinol*. 2006;20:412-416.

1053. Cho YH, Kim JH, Khang SK, Lee JK, Kim CJ. Chordomas and chondrosarcomas of the skull base: comparative analysis of clinical results in 30 patients. *Neurosurg Rev*. 2008;31:35-43; discussion 43.

1054. Mesquita Filho PM, Ditzel Filho LF, Prevedello DM, et al. Endoscopic endonasal surgical management of chondrosarcomas with cerebellopontine angle extension. *Neurosurg Focus*. 2014;37:E13.

1055. Moussazadeh N, Kulwin C, Anand VK, et al. Endoscopic endonasal resection of skull base chondrosarcomas: technique and early results. *J Neurosurg*. 2015;122:735-742.

1056. Carlson ML, O'Connell BP, Breen JT, et al. Petroclival chondrosarcoma: a multicenter review of 55 cases and new staging system. *Otol Neurotol*. 2016;37:940-950.

1057. Patrona A, Patel KS, Bander ED, et al. Endoscopic endonasal surgery for nonadenomatous, nonmeningeal pathology involving the cavernous sinus. *J Neurosurg*. 2017;126:880-888.

1058. Raza SM, Gidley PW, Meis JM, Grosshans DR, Bell D, DeMonte F. Multimodality treatment of skull base chondrosarcomas: the role of histology specific treatment protocols. *Neurosurgery*. 2017;81:520-530.

1059. Vaz-Guimaraes F, Fernandez-Miranda JC, Koutourousiou M, et al. Endoscopic endonasal surgery for cranial base chondrosarcomas. *Oper Neurosurg (Hagerstown)*. 2017;13:421-434.

1060. Hasegawa H, Shin M, Kondo K, et al. Role of endoscopic transnasal surgery for skull base chondrosarcoma: a retrospective analysis of 19 cases at a single institution. *J Neurosurg*. 2018;128:1438-1447.

1061. Beer-Furlan A, Balsalobre L, Vellutini EA, Stamm AC. Endoscopic endonasal approach in skull base chondrosarcoma associated with Maffucci syndrome: case series and literature review. *World Neurosurg*. 2016;85:365.e7-365.e15.

1062. Kuge A, Sato S, Sakurada K, et al. Technical notes on endoscopic transnasal transsphenoidal approach for clival chondrosarcoma. *Sarcoma*. 2011;2011:953047.

1063. Fernandez-Miranda JC, Morera VA, Snyderman CH, Gardner P. Endoscopic endonasal transclival approach to the jugular tubercle. *Neurosurgery*. 2012;71(1 Suppl Operative):146-158; discussion 158-149.

1064. Frassanito P, Massimi L, Rigante M, et al. Recurrent and self-remitting sixth cranial nerve palsy: pathophysiological insight from skull base chondrosarcoma. *J Neurosurg Pediatr*. 2013;12:633-636.

1065. Maurer AJ, Bonney PA, Iser CR, Ali R, Sanclement JA, Sughrue ME. Endoscopic endonasal infrapetrous transpterygoid approach to the petroclival junction for petrous apex chondrosarcoma: technical report. *J Neurol Surg Rep*. 2015;76:e113-e116.

1066. Sarafoleanu C, Manea C. Chondrosarcoma of the sphenoid sinuses and skull base. *Romanian Journal of Rhinology*. 2011;1:34-36.

1067. Spear S, Iskandar J, Seaquist D, Sorensen D. Nasoseptal chondrosarcoma resection requiring anterior fossa floor repair: a case report. *Ear Nose Throat J*. 2008;87:696-699.

1068. Taniguchi M, Akutsu N, Mizukawa K, Kohta M, Kimura H, Kohmura E. Endoscopic endonasal translacerum approach to the inferior petrous apex. *J Neurosurg*. 2016;124:1032-1038.

1069. Awad M, Gogos AJ, Kaye AH. Skull base chondrosarcoma. *J Clin Neurosci*. 2016;24:1-5.

1070. Li MC, Guo HC, Chen G, Kong F, Zhang QH. Meningitis caused by *Enterococcus casseliflavus* with refractory cerebrospinal fluid leakage following endoscopic endonasal removal of skull base chondrosarcoma. *Chin Med J (Engl)*. 2011;124:3440.

1071. Snyderman CH, Pant H, Carrau RL, Prevedello D, Gardner P, Kassam AB. What are the limits of endoscopic sinus surgery?: the expanded endonasal approach to the skull base. *Keio J Med*. 2009;58:152-160.

1072. McCoul ED, Anand VK, Singh A, Nyquist GG, Schaberg MR, Schwartz TH. Long-term effectiveness of a reconstructive protocol using the nasoseptal flap after endoscopic skull base surgery. *World Neurosurg*. 2014;81:136-143.

1073. Thorp BD, Sreenath SB, Ebert CS, Zanation AM. Endoscopic skull base reconstruction: a review and clinical case series of 152 vascularized flaps used for surgical skull base defects in the setting of intraoperative cerebrospinal fluid leak. *Neurosurg Focus*. 2014;37:E4.

1074. Gruss CL, Al Komser M, Aghi MK, et al. Risk factors for cerebrospinal leak after endoscopic skull base reconstruction with nasoseptal flap. *Otolaryngol Head Neck Surg*. 2014;151:516-521.

1075. Hirsch O. Successful closure of cere brospinal fluid rhinorrhea by endonasal surgery. *AMA Arch Otolaryngol*. 1952;56:1-12.

1076. Montgomery WW. Surgery for cerebrospinal fluid rhinorrhea and otorrhea. *Arch Otolaryngol*. 1966;84:538-550.

1077. Horiguchi K, Murai H, Hasegawa Y, Hanazawa T, Yamakami I, Saeki N. Endoscopic endonasal skull base reconstruction using a nasal septal flap: surgical results and comparison with previous reconstructions. *Neurosurg Rev*. 2010;33:235-241; discussion 241.

1078. Nyquist GG, Anand VK, Singh A, Schwartz TH. Janus flap: bilateral nasoseptal flaps for anterior skull base reconstruction. *Otolaryngol Head Neck Surg*. 2010;142:327-331.

1079. Gil Z, Margalit N. Anteriorly based inferior turbinate flap for endoscopic skull base reconstruction. *Otolaryngol Head Neck Surg*. 2012;146:842-847.

1080. Harvey RJ, Sheahan PO, Schlosser RJ. Inferior turbinate pedicle flap for endoscopic skull base defect repair. *Am J Rhinol Allergy*. 2009;23:522-526.

1081. Prevedello DM, Barges-Coll J, Fernandez-Miranda JC, et al. Middle turbinate flap for skull base reconstruction: cadaveric feasibility study. *Laryngoscope*. 2009;119:2094-2098.

1082. Amin SM, Fawzy TO, Hegazy AA. Composite vascular pedicled middle turbinate flap for reconstruction of sellar defects. *Ann Otol Rhinol Laryngol*. 2016;125:770-774.

1083. Bleier BS, Curry WT, Wang EW, Schlosser RJ. The bipedicled anterior septal flap: a radioanatomic and cadaveric study. *Laryngoscope*. 2011;121:1367-1371.

1084. Hadad G, Rivera-Serrano CM, Bassagaisteguy LH, et al. Anterior pedicle lateral nasal wall flap: a novel technique for the reconstruction of anterior skull base defects. *Laryngoscope*. 2011;121:1606-1610.

1085. Rivera-Serrano CM, Bassagaisteguy LH, Hadad G, et al. Posterior pedicle lateral nasal wall flap: new reconstructive technique for large defects of the skull base. *Am J Rhinol Allergy*. 2011;25:e212-e216.

1086. Schreiber A, Mattavelli D, Ferrari M, et al. The turbinal flap: an additional option for anterior skull base reconstruction. Cadaveric feasibility study and case report. *Int Forum Allergy Rhinol*. 2017;7:199-204.

1087. Battaglia P, Turri-Zanoni M, De Bernardi F, et al. Septal flip flap for anterior skull base reconstruction after endoscopic resection of sinonasal cancers: preliminary outcomes. *Acta Otorhinolaryngol Ital*. 2016;36:194-198.

1088. Daraei P, Oyesiku NM, Patel ZM. The nasal floor pedicled flap: a novel technique for use in skull base reconstruction. *Int Forum Allergy Rhinol*. 2014;4:937-943.

1089. Patel MR, Shah RN, Snyderman CH, et al. Pericranial flap for endoscopic anterior skull-base reconstruction: clinical outcomes and radioanatomic analysis of preoperative planning. *Neurosurgery*. 2010;66:506-512; discussion 512.

1090. Bolzoni Villaret A, Nicolai P, Schreiber A, Bizzoni A, Farina D, Tschabitscher M. The temporoparietal fascial flap in extended transnasal endoscopic procedures: cadaver dissection and personal clinical experience. *Eur Arch Otorhinolaryngol*. 2013;270:1473-1479.

1091. Oliver CL, Hackman TG, Carrau RL, et al. Palatal flap modifications allow pedicled reconstruction of the skull base. *Laryngoscope*. 2008;118:2102-2106.

1092. Rivera-Serrano CM, Oliver C, Prevedello D, et al. Pedicled facial buccinator (FAB) flap: a new flap for reconstruction of skull base defects. *Laryngoscope*. 2010;120(Suppl 4):S234.

1093. Xie L, Lavigne F, Rahal A, Moubayed SP, Ayad T. Facial artery musculomucosal flap for reconstruction of skull base defects: a cadaveric study. *Laryngoscope*. 2013;123:1854-1861.

1094. Rivera-Serrano CM, Snyderman CH, Carrau RL, Durmaz A, Gardner PA. Transparapharyngeal and transpterygoid transposition of a pedicled occipital galeopericranial flap: a new flap for skull base reconstruction. *Laryngoscope*. 2011;121:914-922.

1095. Reyes C, Solares CA, Fritz MA, Groves M, Bentley H. Fascia lata free flap anastomosed to the superior trochlear system for reconstruction of the anterior skull base. *J Neurol Surg B Skull Base*. 2017;78:393-398.

1096. Costantino PD, Shamouelian D, Tham T, Andrews R, Dec W. The laparoscopically harvested omental free flap: a compelling option for craniofacial and cranial base reconstruction. *J Neurol Surg B Skull Base*. 2017;78:191-196.

1097. Hackman TG. Endoscopic adipofascial radial forearm flap reconstruction of a clival defect. *Plast Reconstr Surg Glob Open*. 2016;4:e1109.

1098. Heredero S, Solivera J, Garcia B, Dean A. Osteomyocutaneous peroneal artery perforator flap for reconstruction of the skull base. *Br J Oral Maxillofac Surg*. 2016;54:99-101.

1099. Smith JE, Ducic Y. The versatile extended pericranial flap for closure of skull base defects. *Otolaryngol Head Neck Surg*. 2004;130:704-711.

1100. Karnezis TT, Baker AB, Soler ZM, et al. Factors impacting cerebrospinal fluid leak rates in endoscopic sellar surgery. *Int Forum Allergy Rhinol*. 2016;6:1117-1125.

1101. Greig SR, Cooper TJ, Sommer DD, Nair S, Wright ED. Objective sinonasal functional outcomes in endoscopic anterior skull-base surgery: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2016;6:1040-1046.

1102. Tam S, Duggal N, Rotenberg BW. Olfactory outcomes following endoscopic pituitary surgery with or without septal flap reconstruction: a randomized controlled trial. *Int Forum Allergy Rhinol*. 2013;3:62-65.

1103. Kim SW, Park KB, Khalmuratova R, Lee HK, Jeon SY, Kim DW. Clinical and histologic studies of olfactory outcomes after nasoseptal flap harvesting. *Laryngoscope*. 2013;123:1602-1606.

1104. Patel MR, Stadler ME, Snyderman CH, et al. How to choose? Endoscopic skull base reconstructive options and limitations. *Skull Base*. 2010;20:397-404.

1105. MacArthur FJD, McGarry GW. The radioanatomy of endonasal flap coverage of skull base defects: a tool for preoperative planning. *Laryngoscope*. 2018;128:1287-1293.

1106. Eloy JA, Marchiano E, Vazquez A, et al. Management of skull base defects after surgical resection of sinonasal and ventral skull base malignancies. *Otolaryngol Clin North Am*. 2017;50:397-417.

1107. Zanation AM, Thorp BD, Parmar P, Harvey RJ. Reconstructive options for endoscopic skull base surgery. *Otolaryngol Clin North Am*. 2011;44:1201-1222.

1108. Shahangian A, Soler ZM, Baker A, et al. Successful repair of intraoperative cerebrospinal fluid leaks improves outcomes in endoscopic skull base surgery. *Int Forum Allergy Rhinol*. 2017;7:80-86.

1109. Rawal RB, Sreenath SB, Ebert CS Jr, et al. Endoscopic sinonasal meningoencephalocele repair: a 13-year experience with stratification by defect and reconstruction type. *Otolaryngol Head Neck Surg*. 2015;152:361-368.

1110. Wheless SA, McKinney KA, Carrau RL, et al. Nasoseptal flap closure of traumatic cerebrospinal fluid leaks. *Skull Base*. 2011;21:93-98.

1111. Safavi-Abbasi S, Komune N, Archer JB, et al. Surgical anatomy and utility of pedicled vascularized tissue flaps for multilayered repair of skull base defects. *J Neurosurg*. 2016;125:419-430.

1112. Shah RN, Surowitz JB, Patel MR, et al. Endoscopic pedicled nasoseptal flap reconstruction for pediatric skull base defects. *Laryngoscope*. 2009;119:1067-1075.

1113. Giannoni CM, Whitehead WE. Use of endoscopic vascularized nasoseptal flap in children. *Otolaryngol Head Neck Surg*. 2013;148:344-346.

1114. Ghosh A, Hatten K, Learned KO, et al. Pediatric nasoseptal flap reconstruction for suprasellar approaches. *Laryngoscope*. 2015;125:2451-2456.

1115. Stapleton AL, Tyler-Kabara EC, Gardner PA, Snyderman CH, Wang EW. Risk factors for cerebrospinal fluid leak in pediatric patients undergoing endoscopic endonasal skull base surgery. *Int J Pediatr Otorhinolaryngol*. 2017;93:163-166.

1116. Soudry E, Psaltis AJ, Lee KH, Vaezafshar R, Nayak JV, Hwang PH. Complications associated with the pedicled nasoseptal flap for skull base reconstruction. *Laryngoscope*. 2015;125:80-85.

1117. Rowan NR, Wang EW, Gardner PA, Fernandez-Miranda JC, Snyderman CH. Nasal deformities following nasoseptal flap reconstruction of skull base defects. *J Neurol Surg B Skull Base*. 2016;77:14-18.

1118. Park W, Hong SD, Nam DH, et al. Nasoseptal flap elevation in patients with history of septal surgery: does it increase flap failure or cerebrospinal fluid leakage? *World Neurosurg*. 2016;93:164-167.

1119. Zanation AM, Carrau RL, Snyderman CH, et al. Nasoseptal flap takedown and reuse in revision endoscopic skull base reconstruction. *Laryngoscope*. 2011;121:42-46.

1120. Huntley C, Iloreta AM, Nyquist GG, et al. Perforation of a nasoseptal flap does not increase the rate of postoperative cerebrospinal fluid leak. *Int Forum Allergy Rhinol*. 2015;5:353-355.

1121. Choby GW, Mattos JL, Hughes MA, et al. Delayed nasoseptal flaps for endoscopic skull base reconstruction: proof of concept and evaluation of outcomes. *Otolaryngol Head Neck Surg*. 2015;152:255-259.

1122. Alves MV, Roberts D, Levine NB, DeMonte F, Hanna EY, Kupferman ME. Impact of chemoradiotherapy on CSF leak repair after skull base surgery. *J Neurol Surg B Skull Base*. 2014;75:354-357.

1123. Zanation AM, Carrau RL, Snyderman CH, et al. Nasoseptal flap reconstruction of high flow intraoperative cerebral spinal fluid leaks during endoscopic skull base surgery. *Am J Rhinol Allergy*. 2009;23:518-521.

1124. El-Sayed IH, Roediger FC, Goldberg AN, Parsa AT, McDermott MW. Endoscopic reconstruction of skull base defects with the nasal septal flap. *Skull Base*. 2008;18:385-394.

1125. Vaezeafshar R, Hwang PH, Harsh G, Turner JH. Mucocele formation under pedicled nasoseptal flap. *Am J Otolaryngol*. 2012;33:634-636.

1126. Husain Q, Sanghvi S, Kovalerchik O, et al. Assessment of mucocele formation after endoscopic nasoseptal flap reconstruction of skull base defects. *Allergy Rhinol (Providence)*. 2013;4:e27-e31.

1127. Walsh E, Illing E, Riley KO, et al. Inaccurate assessments of anterior cranial base malignancy following nasoseptal flap reconstruction. *J Neurol Surg B Skull Base*. 2015;76:385-389.

1128. Learned KO, Adappa ND, Lee JY, Newman JG, Palmer JN, Loevner LA. MR imaging evolution of endoscopic cranial defect reconstructions using nasoseptal flaps and their distinction from neoplasm. *AJNR Am J Neuroradiol*. 2014;35:1182-1189.

1129. de Almeida JR, Snyderman CH, Gardner PA, Carrau RL, Vescan AD. Nasal morbidity following endoscopic skull base surgery: a prospective cohort study. *Head Neck*. 2011;33:547-551.

1130. Kimple AJ, Leight WD, Wheless SA, Zanation AM. Reducing nasal morbidity after skull base reconstruction with the nasoseptal flap: free middle turbinate mucosal grafts. *Laryngoscope*. 2012;122:1920-1924.

1131. Caicedo-Granados E, Carrau R, Snyderman CH, et al. Reverse rotation flap for reconstruction of donor site after vascular pedicled nasoseptal flap in skull base surgery. *Laryngoscope*. 2010;120:1550-1552.

1132. Kasemsiri P, Carrau RL, Otto BA, et al. Reconstruction of the pedicled nasoseptal flap donor site with a contralateral reverse rotation flap: technical modifications and outcomes. *Laryngoscope*. 2013;123:2601-2604.

1133. Rotenberg BW, Saunders S, Duggal N. Olfactory outcomes after endoscopic transsphenoidal pituitary surgery. *Laryngoscope*. 2011;121:1611-1613.

1134. Chaaban MR, Chaudhry AL, Riley KO, Woodworth BA. Objective assessment of olfaction after transsphenoidal pituitary surgery. *Am J Rhinol Allergy*. 2015;29:365-368.

1135. Mascarenhas L, Moshel YA, Bayad F, et al. The transplanum transtuberculum approaches for suprasellar and sellar-suprasellar lesions: avoidance of cerebrospinal fluid leak and lessons learned. *World Neurosurg*. 2014;82(1-2):186-195.

1136. Harvey RJ, Smith JE, Wise SK, Patel SJ, Frankel BM, Schlosser RJ. Intracranial complications before and after endoscopic skull base reconstruction. *Am J Rhinol*. 2008;22:516-521.

1137. Wigand ME. Transnasal ethmoidectomy under endoscopical control. *Rhinology*. 1981;19:7-15.

1138. Lorenz RR, Dean RL, Hurley DB, Chuang J, Citardi MJ. Endoscopic reconstruction of anterior and middle cranial fossa defects using acellular dermal allograft. *Laryngoscope*. 2003;113:496-501.

1139. Reyes C, Mason E, Solares CA. Panorama of reconstruction of skull base defects: from traditional open to endonasal endoscopic approaches, from free grafts to microvascular flaps. *Int Arch Otorhinolaryngol*. 2014;18(Suppl 2):S179-S186.

1140. Zuniga MG, Turner JH, Chandra RK. Updates in anterior skull base reconstruction. *Curr Opin Otolaryngol Head Neck Surg*. 2016;24:75-82.

1141. Clavenna MJ, Turner JH, Chandra RK. Pedicled flaps in endoscopic skull base reconstruction: review of current techniques. *Curr Opin Otolaryngol Head Neck Surg*. 2015;23:71-77.

1142. Kim GG, Hang AX, Mitchell CA, Zanation AM. Pedicled extranasal flaps in skull base reconstruction. *Adv Otorhinolaryngol*. 2013;74:71-80.

1143. Gagliardi F, Boari N, Mortini P. Reconstruction techniques in skull base surgery. *J Craniofac Surg*. 2011;22:1015-1020.

1144. Hosemann W, Goede U, Sauer M. Wound healing of mucosal autografts for frontal cerebrospinal fluid leaks—clinical and experimental investigations. *Rhinology*. 1999;37:108-112.

1145. Pinheiro-Neto CD, Snyderman CH. Nasoseptal flap. *Adv Otorhinolaryngol*. 2013;74:42-55.

1146. Briggs RJ, Wormald PJ. Endoscopic transnasal intradural repair of anterior skull base cerebrospinal fluid fistulae. *J Clin Neurosci*. 2004;11:597-599.

1147. Cavallo LM, Messina A, Cappabianca P, et al. Endoscopic endonasal surgery of the midline skull base: anatomical study and clinical considerations. *Neurosurg Focus*. 2005;19:E2.

1148. Dlouhy BJ, Madhavan K, Clinger JD, et al. Elevated body mass index and risk of postoperative CSF leak following transsphenoidal surgery. *J Neurosurg*. 2012;116:1311-1317.

1149. Wood JW, Eloy JA, Vivero RJ, et al. Efficacy of transnasal endoscopic resection for malignant anterior skull-base tumors. *Int Forum Allergy Rhinol*. 2012;2:487-495.

1150. Kassam A, Carrau RL, Snyderman CH, Gardner P, Mintz A. Evolution of reconstructive techniques following endoscopic expanded endonasal approaches. *Neurosurg Focus*. 2005;19:E8.

1151. Roxbury CR, Saavedra T, Ramanathan M Jr, et al. Layered sellar reconstruction with avascular free grafts: acceptable alternative to the nasoseptal flap for repair of low-volume intraoperative cerebrospinal fluid leak. *Am J Rhinol Allergy*. 2016;30:367-371.

1152. Fishpool SJ, Amato-Watkins A, Hayhurst C. Free middle turbinate mucosal graft reconstruction after primary endoscopic endonasal pituitary surgery. *Eur Arch Otorhinolaryngol*. 2017;274:837-844.

1153. Fraser S, Gardner PA, Koutourousiou M, et al. Risk factors associated with postoperative cerebrospinal fluid leak after endoscopic endonasal skull base surgery. *J Neurosurg*. 2018;128:1066-1071.

1154. Leong JL, Citardi MJ, Batra PS. Reconstruction of skull base defects after minimally invasive endoscopic resection of anterior skull base neoplasms. *Am J Rhinol*. 2006;20:476-482.

1155. Zhan R, Chen S, Xu S, Liu JK, Li X. Postoperative low-flow cerebrospinal fluid leak of endoscopic endonasal transsphenoidal surgery for pituitary adenoma—wait and see, or lumbar drain? *J Craniofac Surg*. 2015;26:1261-1264.

1156. Cohen S, Jones SH, Dhandapani S, Negm HM, Anand VK, Schwartz TH. Lumbar drains decrease the risk of postoperative cerebrospinal fluid leak following endonasal endoscopic surgery for suprasellar meningiomas in patients with high body mass index. *Oper Neurosurg (Hagerstown)*. 2018;14:66-71.

1157. Martinez-Capoccioni G, Serramito-Garcia R, Huertas-Pardo B, Garcia-Allut A, Martin-Martin C. Spontaneous cerebrospinal fluid leaks in the anterior skull base: a surgical challenge. *J Laryngol Otol*. 2015;129:358-364.

1158. Hu F, Gu Y, Zhang X, et al. Combined use of a gasket seal closure and a vascularized pedicle nasoseptal flap multilayered reconstruction technique for high-flow cerebrospinal fluid leaks after endonasal endoscopic skull base surgery. *World Neurosurg*. 2015;83:181-187.

1159. Yang T, Bayad F, Schaberg MR, et al. Endoscopic endonasal transsphenoidal treatment of pituitary apoplexy: outcomes in a series of 20 patients. *Cureus*. 2015;7:e357.

1160. Negm HM, Al-Mahfoudh R, Pai M, et al. Reoperative endoscopic endonasal surgery for residual or recurrent pituitary adenomas. *J Neurosurg*. 2017;127:397-408.

1161. Wilson PJ, Omay SB, Kacker A, Anand VK, Schwartz TH. Endonasal endoscopic pituitary surgery in the elderly. *J Neurosurg*. 2018;128:429-436.

1162. Gardner P. Lumbar drain after endoscopic surgery of the skull base. 2017; https://clinicaltrials.gov/ct2/show/NCT03163134. Accessed May 30, 2018.

1163. Liang B, Shetty SR, Omay SB, et al. Predictors and incidence of orthostatic headache associated with lumbar drain placement following endoscopic endonasal skull base surgery. *Acta Neurochir (Wien)*. 2017;159:1379-1385.

1164. Lai LT, Trooboff S, Morgan MK, Harvey RJ. The risk of meningitis following expanded endoscopic endonasal skull base surgery: a systematic review. *J Neurol Surg B Skull Base*. 2014;75:18-26.

1165. Shriver MF, Kshettry VR, Sindwani R, Woodard T, Benzel EC, Recinos PF. Transoral and transnasal odontoidectomy complications: a systematic review and meta-analysis. *Clin Neurol Neurosurg*. 2016;148:121-129.

1166. Przybylowski CJ, Dallapiazza RF, Williams BJ, et al. Primary versus revision transsphenoidal resection for nonfunctioning pituitary macroadenomas: matched cohort study. *J Neurosurg*. 2017;126:889-896.

1167. Jeon C, Hong SD, Seol HJ, et al. Reconstructive outcome of intraoperative cerebrospinal fluid leak after endoscopic endonasal surgery for tumors involving skull base. *J Clin Neurosci*. 2017;45:227-231.

1168. Chibbaro S, Cebula H, Aldea S, et al. Endonasal endoscopic odontoidectomy in ventral diseases of the craniocervical junction: results of a multicenter experience. *World Neurosurg*. 2017;106:382-393.

1169. Zwagerman NT, Tormenti MJ, Tempel ZJ, et al. Endoscopic endonasal resection of the odontoid process: clinical outcomes in 34 adults. *J Neurosurg*. 2018;128:923-931.

1170. Thawani JP, Ramayya AG, Pisapia JM, Abdullah KG, Lee JY, Grady MS. Operative strategies to minimize complications following resection of pituitary macroadenomas. *J Neurol Surg B Skull Base*. 2017;78:184-190.

1171. Shikary T, Andaluz N, Meinzen-Derr J, Edwards C, Theodosopoulos P, Zimmer LA. Operative learning curve after transition to endoscopic transsphenoidal pituitary surgery. *World Neurosurg*. 2017;102:608-612.

1172. Kshettry VR, Do H, Elshazly K, et al. The learning curve in endoscopic endonasal resection of craniopharyngiomas. *Neurosurg Focus*. 2016;41:E9.

1173. Fomichev D, Kalinin P, Kutin M, Sharipov O. Extended transsphenoidal endoscopic endonasal surgery of suprasellar craniopharyngiomas. *World Neurosurg*. 2016;94:181-187.

1174. Boling CC, Karnezis TT, Baker AB, et al. Multiinstitutional study of risk factors for perioperative morbidity following transnasal endoscopic pituitary adenoma surgery. *Int Forum Allergy Rhinol*. 2016;6:101-107.

1175. Song Y, Li H, Liu H, et al. Endoscopic endonasal transsphenoidal approach for sellar tumors beyond the sellar turcica. *Acta Otolaryngol*. 2014;134:326-330.

1176. Eloy JA, Choudhry OJ, Shukla PA, Kuperan AB, Friedel ME, Liu JK. Nasoseptal flap repair after endoscopic transsellar versus expanded endonasal approaches: is there an increased risk of postoperative cerebrospinal fluid leak? *Laryngoscope*. 2012;122:1219-1225.

1177. Mortuaire G, Vandeville S, Assaker R, Chevalier D. Endoscopic repair of anterior or middle skull base cerebrospinal fluid leaks after tumour resection. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2012;129:77-81.

1178. Cavallo LM, Solari D, Tasiou A, et al. Endoscopic endonasal transsphenoidal removal of recurrent and regrowing pituitary adenomas: experience on a 59-patient series. *World Neurosurg*. 2013;80(3-4):342-350.

1179. Cutler AR, Mundi JS, Solomon N, Suh JD, Wang MB, Bergsneider M. Critical appraisal of extent of resection of clival lesions using the expanded endoscopic endonasal approach. *J Neurol Surg B Skull Base*. 2013;74:217-224.

1180. Fleischman GM, Ambrose EC, Rawal RB, et al. Obstructive sleep apnea in patients undergoing

endoscopic surgical repair of cerebrospinal fluid rhinorrhea. *Laryngoscope*. 2014;124:2645-2650.

1181. Little RE, Taylor RJ, Miller JD, et al. Endoscopic endonasal transclival approaches: case series and outcomes for different clival regions. *J Neurol Surg B Skull Base*. 2014;75:247-254.
1182. Murad A, Ghostine S, Colohan AR. Role of controlled lumbar CSF drainage for ICP control in aneurysmal SAH. *Acta Neurochir Suppl*. 2011;110(Pt 2):183-187.
1183. Kongstad L, Grande PO. Effects on intracranial pressure of dural puncture in supine and head-elevated positions. A study on the cat. *Acta Anaesthesiol Scand*. 2005;49:614-618.
1184. Ransom ER, Palmer JN, Kennedy DW, Chiu AG. Assessing risk/benefit of lumbar drain use for endoscopic skull-base surgery. *Int Forum Allergy Rhinol*. 2011;1:173-177.
1185. AlQahtani A, Castelnuovo P, Nicolai P, Prevedello DM, Locatelli D, Carrau RL. Injury of the internal carotid artery during endoscopic skull base surgery: prevention and management protocol. *Otolaryngol Clin North Am*. 2016;49:237-252.
1186. Valentine R, Wormald PJ. Controlling the surgical field during a large endoscopic vascular injury. *Laryngoscope*. 2011;121:562-566.
1187. Cavallo LM, Briganti F, Cappabianca P, et al. Hemorrhagic vascular complications of endoscopic transsphenoidal surgery. *Minim Invasive Neurosurg*. 2004;47:145-150.
1188. Gardner PA, Tormenti MJ, Pant H, Fernandez-Miranda JC, Snyderman CH, Horowitz MB. Carotid artery injury during endoscopic endonasal skull base surgery: incidence and outcomes. *Neurosurgery*. 2013;73(2 Suppl Operative):ons261-ons269; discussion ons269-ons270.
1189. Gondim JA, Almeida JP, Albuquerque LA, et al. Endoscopic endonasal approach for pituitary adenoma: surgical complications in 301 patients. *Pituitary*. 2011;14:174-183.
1190. Kalinin PL, Sharipov OI, Shkarubo AN, et al. [Damage to the cavernous segment of internal carotid artery in transsphenoidal endoscopic removal of pituitary adenomas (report of 4 cases)]. *Zh Vopr Neirokhir Im N N Burdenko*. 2013;77:28-37; discussion 38. Russian.
1191. Zhang HK, Ma N, Sun XC, Wang DH. Endoscopic repair of the injured internal carotid artery utilizing oxidized regenerated cellulose and a free fascia lata graft. *J Craniofac Surg*. 2016;27:1021-1024.
1192. Chin OY, Ghosh R, Fang CH, Baredes S, Liu JK, Eloy JA. Internal carotid artery injury in endoscopic endonasal surgery: a systematic review. *Laryngoscope*. 2016;126:582-590.
1193. Inamasu J, Guiot BH. Iatrogenic carotid artery injury in neurosurgery. *Neurosurg Rev*. 2005;28:239-247; discussion 248.
1194. Gardner PA, Snyderman CH, Fernandez-Miranda JC, Jankowitz BT. Management of major vascular injury during endoscopic endonasal skull base surgery. *Otolaryngol Clin North Am*. 2016;49:819-828.
1195. Solares CA, Ong YK, Carrau RL, et al. Prevention and management of vascular injuries in endoscopic surgery of the sinonasal tract and skull base. *Otolaryngol Clin North Am*. 2010;43:817-825.
1196. Rangel-Castilla L, McDougall CG, Spetzler RF, Nakaji P. Urgent cerebral revascularization bypass surgery for iatrogenic skull base internal carotid artery injury. *Neurosurgery*. 2014;10(Suppl 4):640-647; discussion 647-648.
1197. Iacoangeli M, Di Rienzo A, Re M, et al. Endoscopic endonasal approach for the treatment of a large clival giant cell tumor complicated by an intraoperative internal carotid artery rupture. *Cancer Manag Res*. 2013;5:21-24.
1198. Padhye V, Valentine R, Wormald PJ. Management of carotid artery injury in endonasal surgery. *Int Arch Otorhinolaryngol*. 2014;18(Suppl 2):S173-S178.
1199. Romero A, Lal Gangadharan J, Bander ED, Gobin YP, Anand VK, Schwartz TH. Managing arterial injury in endoscopic skull base surgery: case series and review of the literature. *Oper Neurosurg (Hagerstown)*. 2017;13:138-149.
1200. Biswas D, Daudia A, Jones NS, McConachie NS. Profuse epistaxis following sphenoid surgery: a ruptured carotid artery pseudoaneurysm and its management. *J Laryngol Otol*. 2009;123:692-694.
1201. Golinelli G, Toso A, Taranto F, Aluffi P, Pia F. Delayed carotid pseudoaneurysm: a life-threatening complication after endoscopic sinus surgery. *J Craniofac Surg*. 2012;23:1822-1824.
1202. Weidenbecher M, Huk WJ, Iro H. Internal carotid artery injury during functional endoscopic sinus surgery and its management. *Eur Arch Otorhinolaryngol*. 2005;262:640-645.
1203. Padhye V, Valentine R, Sacks R, et al. Coping with catastrophe: the value of endoscopic vascular injury training. *Int Forum Allergy Rhinol*. 2015;5:247-252.
1204. Valentine R, Wormald PJ. A vascular catastrophe during endonasal surgery: an endoscopic sheep model. *Skull Base*. 2011;21:109-114.
1205. Valentine R, Boase S, Jervis-Bardy J, Dones Cabral JD, Robinson S, Wormald PJ. The efficacy of hemostatic techniques in the sheep model of carotid artery injury. *Int Forum Allergy Rhinol*. 2011;1:118-122.
1206. Padhye V, Valentine R, Paramasivan S, et al. Early and late complications of endoscopic hemostatic techniques following different carotid artery injury characteristics. *Int Forum Allergy Rhinol*. 2014;4:651-657.
1207. Padhye V, Murphy J, Bassiouni A, Valentine R, Wormald PJ. Endoscopic direct vessel closure in carotid artery injury. *Int Forum Allergy Rhinol*. 2015;5:253-257.
1208. Raymond J, Hardy J, Czepko R, Roy D. Arterial injuries in transsphenoidal surgery for pituitary adenoma; the role of angiography and endovascular treatment. *AJNR Am J Neuroradiol*. 1997;18:655-665.
1209. Sylvester PT, Moran CJ, Derdeyn CP, et al. Endovascular management of internal carotid artery injuries secondary to endonasal surgery: case series and review of the literature. *J Neurosurg*. 2016;125:1256-1276.
1210. Mathis JM, Barr JD, Jungreis CA, et al. Temporary balloon test occlusion of the internal carotid artery: experience in 500 cases. *AJNR Am J Neuroradiol*. 1995;16:749-754.
1211. Buerke B, Tombach B, Stoll W, Heindel W, Niederstadt T. Magnetic resonance angiography follow-up examinations to detect iatrogenic pseudoaneurysms following otorhinolaryngological surgery. *J Laryngol Otol*. 2007;121:698-701.
1212. Mortimer AM, Klimczak K, Nelson RJ, Renowden SA. Endovascular management of cavernous internal carotid artery pseudoaneurysms following transsphenoidal surgery: a report of two cases and review of the literature. *Clin Neuroradiol*. 2015;25:295-300.
1213. Fujii K, Chambers SM, Rhoton AL Jr. Neurovascular relationships of the sphenoid sinus. A microsurgical study. *J Neurosurg*. 1979;50:31-39.
1214. Labib MA, Prevedello DM, Carrau R, et al. A road map to the internal carotid artery in expanded endoscopic endonasal approaches to the ventral cranial base. *Neurosurgery*. 2014;10(Suppl 3):448-471; discussion 471.
1215. Fernandez-Miranda JC, Prevedello DM, Madhok R, et al. Sphenoid septations and their relationship with internal carotid arteries: anatomical and radiological study. *Laryngoscope*. 2009;119:1893-1896.
1216. Zada G, Cavallo LM, Esposito F, et al. Transsphenoidal surgery in patients with acromegaly: operative strategies for overcoming technically challenging anatomical variations. *Neurosurg Focus*. 2010;29:E8.
1217. Dolati P, Eichberg D, Golby A, Zamani A, Laws E. Multimodal navigation in endoscopic transsphenoidal resection of pituitary tumors using image-based vascular and cranial nerve segmentation: a prospective validation study. *World Neurosurg*. 2016;95:406-413.
1218. Liu HS, Di X. Endoscopic endonasal surgery for biopsy of cavernous sinus lesions. *Minim Invasive Neurosurg*. 2009;52:69-73.
1219. Dusick JR, Esposito F, Malkasian D, Kelly DF. Avoidance of carotid artery injuries in transsphenoidal surgery with the Doppler probe and microhook blades. *Neurosurgery*. 2007;60(4 Suppl 2):322-328; discussion 328-329.
1220. Hudgins PA, Browning DG, Gallups J, et al. Endoscopic paranasal sinus surgery: radiographic evaluation of severe complications. *AJNR Am J Neuroradiol*. 1992;13:1161-1167.
1221. Cobb MI, Nimjee S, Gonzalez LF, Jang DW, Zomorodi A. Direct repair of iatrogenic internal carotid artery injury during endoscopic endonasal approach surgery with temporary endovascular balloon-assisted occlusion: technical case report. *Neurosurgery*. 2015;11(Suppl 3):E483-E486; discussion E486-E487.
1222. Nerva JD, Morton RP, Levitt MR, et al. Pipeline embolization device as primary treatment for blister aneurysms and iatrogenic pseudoaneurysms of the internal carotid artery. *J Neurointerv Surg*. 2015;7:210-216.
1223. Smith TR, Hulou MM, Huang KT, et al. Complications after transsphenoidal surgery for patients with Cushing's disease and silent corticotroph adenomas. *Neurosurg Focus*. 2015;38:E12.
1224. Dedmon M, Meier J, Chambers K, et al. Delayed endovascular coil extrusion following internal carotid artery embolization. *J Neurol Surg Rep*. 2014;75:e255-e258.
1225. Shakir HJ, Garson AD, Sorkin GC, et al. Combined use of covered stent and flow diversion to seal iatrogenic carotid injury with vessel preservation during transsphenoidal endoscopic resection of clival tumor. *Surg Neurol Int*. 2014;5:81.
1226. Pawar SS, Loehrl TA, Michel MA, Fitzsimmons BF. Cavernous carotid pseudoaneurysm after endoscopic sphenoid mucocele marsupialization. *Arch Otolaryngol Head Neck Surg*. 2010;136:407-410.
1227. Cathelinaud O, Bizeau A, Rimbot A, Arteaga C, Verdalle P. Endoscopic endonasal surgery complication: new methods of intracavernous internal carotid artery injury treatment. *Rev Laryngol Otol Rhinol (Bord)*. 2008;129(4-5):305-308.
1228. Pepper JP, Wadhwa AK, Tsai F, Shibuya T, Wong BJ. Cavernous carotid injury during functional endoscopic sinus surgery: case presentations and guidelines for optimal management. *Am J Rhinol*. 2007;21:105-109.
1229. Koitschev A, Simon C, Lowenheim H, Naegele T, Ernemann U. Management and outcome after internal carotid artery laceration during surgery of the paranasal sinuses. *Acta Otolaryngol*. 2006;126:730-738.
1230. Cappabianca P, Briganti F, Cavallo LM, de Divitiis E. Pseudoaneurysm of the intracavernous carotid artery following endoscopic endonasal transsphenoidal surgery, treated by endovascular approach. *Acta Neurochir (Wien)*. 2001;143:95-96.
1231. Park AH, Stankiewicz JA, Chow J, Azar-Kia B. A protocol for management of a catastrophic complication of functional endoscopic sinus surgery: internal carotid artery injury. *Am J Rhinol*. 1998;12:153-158.
1232. Isenberg SF, Scott JA. Management of massive hemorrhage during endoscopic sinus surgery. *Otolaryngol Head Neck Surg*. 1994;111:134-136.
1233. Ciporen JN, Lucke-Wold B, Mendez G, Cameron WE, McCartney S. Endoscopic management of cavernous carotid surgical complications: evaluation of a simulated perfusion model. *World Neurosurg*. 2017;98:388-396.
1234. Muto J, Carrau RL, Oyama K, Otto BA, Prevedello DM. Training model for control of an internal carotid artery injury during transsphenoidal surgery. *Laryngoscope*. 2017;127:38-43.
1235. Pham M, Kale A, Marquez Y, et al. A perfusion-based human cadaveric model for management of carotid artery injury during endoscopic endonasal skull base surgery. *J Neurol Surg B Skull Base*. 2014;75:309-313.
1236. Pacca P, Jhawar SS, Seclen DV, et al. "Live cadaver" model for internal carotid artery injury simulation in endoscopic endonasal skull base surgery. *Oper Neurosurg (Hagerstown)*. 2017;13:732-738.
1237. Speelman JP, Cahalane AK, Van Hasselt CA. Evaluation of a porcine vascular model to assess the efficacy of various hemostatic techniques. *J Invest Surg*. 2013;26:253-260.
1238. Awad AJ, Mohyeldin A, El-Sayed IH, Aghi MK. Sinonasal morbidity following endoscopic endonasal skull base surgery. *Clin Neurol Neurosurg*. 2015;130:162-167.
1239. Kim BY, Kang SG, Kim SW, et al. Olfactory changes after endoscopic endonasal transsphenoidal approach for skull base tumors. *Laryngoscope*. 2014;124:2470-2475.
1240. Alobid I, Ensenat J, Marino-Sanchez F, et al. Impairment of olfaction and mucociliary clearance after expanded endonasal approach using vascularized septal flap reconstruction for skull base tumors. *Neurosurgery*. 2013;72:540-546.
1241. Kahilogullari G, Beton S, Al-Beyati ES, et al. Olfactory functions after transsphenoidal pituitary

surgery: endoscopic versus microscopic approach. *Laryngoscope*. 2013;123:2112-2119.

1242. Hong SD, Nam DH, Park J, Kim HY, Chung SK, Dhong HJ. Olfactory outcomes after endoscopic pituitary surgery with nasoseptal "rescue" flaps: electrocautery versus cold knife. *Am J Rhinol Allergy*. 2014;28:517-519.
1243. Harvey RJ, Winder M, Davidson A, et al. The olfactory strip and its preservation in endoscopic pituitary surgery maintains smell and sinonasal function. *J Neurol Surg B Skull Base*. 2015;76:464-470.
1244. Hong SD, Nam DH, Seol HJ, et al. Endoscopic binostril versus transnasal transseptal microscopic pituitary surgery: sinonasal quality of life and olfactory function. *Am J Rhinol Allergy*. 2015;29:221-225.
1245. Hong SD, Nam DH, Kong DS, Kim HY, Chung SK, Dhong HJ. Endoscopic modified transseptal transsphenoidal approach for maximal preservation of sinonasal quality of life and olfaction. *World Neurosurg*. 2016;87:162-169.
1246. Upadhyay S, Buohliqah L, Dolci RLL, Otto BA, Prevedello DM, Carrau RL. Periodic olfactory assessment in patients undergoing skull base surgery with preservation of the olfactory strip. *Laryngoscope*. 2017;127:1970-1975.
1247. Kim BY, Son HL, Kang SG, et al. Postoperative nasal symptoms associated with an endoscopic endonasal transsphenoidal approach. *Eur Arch Otorhinolaryngol*. 2013;270:1355-1359.
1248. Bedrosian JC, McCoul ED, Raithatha R, Akselrod OA, Anand VK, Schwartz TH. A prospective study of postoperative symptoms in sinonasal quality-of-life following endoscopic skull-base surgery: dissociations based on specific symptoms. *Int Forum Allergy Rhinol*. 2013;3:664-669.
1249. Sowerby LJ, Gross M, Broad R, Wright ED. Olfactory and sinonasal outcomes in endoscopic transsphenoidal skull-base surgery. *Int Forum Allergy Rhinol*. 2013;3:217-220.
1250. Wessell A, Singh A, Litvack Z. Preservation of olfaction after unilateral endoscopic approach for resection of esthesioneuroblastoma. *J Neurol Surg Rep*. 2014;75:e149-e153.
1251. Say P, Leopold D, Cochran G, Smith L, Greiner T. Resection of the inferior superior turbinate: does it affect olfactory ability or contain olfactory neuronal tissue? *Am J Rhinol*. 2004;18:157-160.
1252. DelGaudio JM. The superior turbinate straddling sphenoidotomy. *Int Forum Allergy Rhinol*. 2015;5:445-447.
1253. Zimmer LA, Shah O, Theodosopoulos PV. Short-term quality-of-life changes after endoscopic pituitary surgery rated with SNOT-22. *J Neurol Surg B Skull Base*. 2014;75:288-292.
1254. Balaker AE, Bergsneider M, Martin NA, Wang MB. Evolution of sinonasal symptoms following endoscopic anterior skull base surgery. *Skull Base*. 2010;20:245-251.
1255. Davies BM, Tirr E, Wang YY, Gnanalingham KK. Transient exacerbation of nasal symptoms following endoscopic transsphenoidal surgery for pituitary tumors: a prospective study. *J Neurol Surg B Skull Base*. 2017;78:266-272.
1256. Gallagher MJ, Durnford AJ, Wahab SS, Nair S, Rokade A, Mathad N. Patient-reported nasal morbidity following endoscopic endonasal skull base surgery. *Br J Neurosurg*. 2014;28:622-625.
1257. de Almeida JR, Witterick IJ, Gullane PJ, et al. Physical morbidity by surgical approach and tumor location in skull base surgery. *Head Neck*. 2013;35:493-499.
1258. Jalessi M, Jahanbakhshi A, Amini E, Kamrava SK, Farhadi M. Impact of nasoseptal flap elevation on sinonasal quality of life in endoscopic endonasal approach to pituitary adenomas. *Eur Arch Otorhinolaryngol*. 2016;273:1199-1205.
1259. Alobid I, Ensenat J, Marino-Sanchez F, et al. Expanded endonasal approach using vascularized septal flap reconstruction for skull base tumors has a negative impact on sinonasal symptoms and quality of life. *Am J Rhinol Allergy*. 2013;27:426-431.
1260. Harvey RJ, Malek J, Winder M, et al. Sinonasal morbidity following tumour resection with and without nasoseptal flap reconstruction. *Rhinology*. 2015;53:122-128.
1261. Hanson M, Patel PM, Betz C, Olson S, Panizza B, Wallwork B. Sinonasal outcomes following endoscopic anterior skull base surgery with nasoseptal flap reconstruction: a prospective study. *J Laryngol Otol*. 2015;129(Suppl 3):S41-S46.
1262. Pant H, Bhatki AM, Snyderman CH, et al. Quality of life following endonasal skull base surgery. *Skull Base*. 2010;20:35-40.
1263. Little AS, Kelly D, Milligan J, et al. Predictors of sinonasal quality of life and nasal morbidity after fully endoscopic transsphenoidal surgery. *J Neurosurg*. 2015;122:1458-1465.
1264. McCoul ED, Patel AS, Bedrosian JC, Anand VK, Schwartz TH. Intranasal cross-sectional area and quality of life changes following endoscopic transsphenoidal skull base surgery. *Int Forum Allergy Rhinol*. 2015;5:1124-1128.
1265. Wang YY, Srirathan V, Tirr E, Kearney T, Gnanalingham KK. Nasal symptoms following endoscopic transsphenoidal pituitary surgery: assessment using the General Nasal Patient Inventory. *Neurosurg Focus*. 2011;30:E12.
1266. Georgalas C, Badloe R, van Furth W, Reinartz S, Fokkens WJ. Quality of life in extended endonasal approaches for skull base tumours. *Rhinology*. 2012;50:255-261.
1267. McCoul ED, Anand VK, Bedrosian JC, Schwartz TH. Endoscopic skull base surgery and its impact on sinonasal-related quality of life. *Int Forum Allergy Rhinol*. 2012;2:174-181.
1268. McCoul ED, Anand VK, Schwartz TH. Improvements in site-specific quality of life 6 months after endoscopic anterior skull base surgery: a prospective study. *J Neurosurg*. 2012;117:498-506.
1269. Rawal RB, Kimple AJ, Dugar DR, Zanation AM. Minimizing morbidity in endoscopic pituitary surgery: outcomes of the novel nasoseptal rescue flap technique. *Otolaryngol Head Neck Surg*. 2012;147:434-437.
1270. McCoul ED, Bedrosian JC, Akselrod O, Anand VK, Schwartz TH. Preservation of multidimensional quality of life after endoscopic pituitary adenoma resection. *J Neurosurg*. 2015;123:813-820.
1271. Rivera-Serrano CM, Snyderman CH, Gardner P, et al. Nasoseptal "rescue" flap: a novel modification of the nasoseptal flap technique for pituitary surgery. *Laryngoscope*. 2011;121:990-993.
1272. Yoo F, Kuan EC, Bergsneider M, Wang MB. Free mucosal graft reconstruction of the septum after nasoseptal flap harvest: a novel technique using a posterior septal free mucosal graft. *J Neurol Surg B Skull Base*. 2017;78:201-206.
1273. Koren I, Hadar T, Rappaport ZH, Yaniv E. Endoscopic transnasal transsphenoidal microsurgery versus the sublabial approach for the treatment of pituitary tumors: endonasal complications. *Laryngoscope*. 1999;109:1838-1840.
1274. Cheng Y, Xue F, Wang TY, et al. Analyses and treatments of postoperative nasal complications after endonasal transsphenoidal resection of pituitary neoplasms. *Medicine (Baltimore)*. 2017;96:e6614.
1275. Dolci RLL, Miyake MM, Tateno DA, et al. Postoperative otorhinolaryngologic complications in transnasal endoscopic surgery to access the skull base. *Braz J Otorhinolaryngol*. 2017;83:349-355.
1276. Heo KW, Park SK. Rhinologic outcomes of concurrent operation for pituitary adenoma and chronic rhinosinusitis: an early experience. *Am J Rhinol*. 2008;22:533-536.
1277. Deconde AS, Vira D, Thompson CF, Wang MB, Bergsneider M, Suh JD. Radiologic assessment of the paranasal sinuses after endoscopic skull base surgery. *J Neurol Surg B Skull Base*. 2013;74:351-357.
1278. Langdon C, Ensenat J, Rioja E, et al. Long-term radiological findings after endonasal endoscopic approach to the skull base. *Am J Otolaryngol*. 2016;37:103-107.
1279. Cappabianca P, Esposito F, Esposito I, Cavallo LM, Leone CA. Use of a thrombin-gelatin haemostatic matrix in endoscopic endonasal extended approaches: technical note. *Acta Neurochir (Wien)*. 2009;151:69-77; discussion 77.
1280. Reeves A, Muhonen M, Loudon W. FloSeal hemostatic matrix use for intraventricular hemorrhage during a neuroendoscopic procedure. *Minim Invasive Neurosurg*. 2011;54:132-134.
1281. Alobaid A, Dehdashti AR. Hemostasis in skull base surgery. *Otolaryngol Clin North Am*. 2016;49:677-690.
1282. Vaz-Guimaraes F, Su SY, Fernandez-Miranda JC, Wang EW, Snyderman CH, Gardner PA. Hemostasis in endoscopic endonasal skull base surgery. *J Neurol Surg B Skull Base*. 2015;76:296-302.
1283. Kassam A, Snyderman CH, Carrau RL, Gardner P, Mintz A. Endoneurosurgical hemostasis techniques: lessons learned from 400 cases. *Neurosurg Focus*. 2005;19:E7.
1284. Kim EH, Ahn JY, Chang JH, Kim SH. Management strategies of intercavernous sinus bleeding during transsphenoidal surgery. *Acta Neurochir (Wien)*. 2009;151:803-808.
1285. Sekhar LN, Natarajan SK, Manning T, Bhagawati D. The use of fibrin glue to stop venous bleeding in the epidural space, vertebral venous plexus, and anterior cavernous sinus: technical note. *Neurosurgery*. 2007;61(3 Suppl):E51; discussion E51.
1286. Tavanaiepour D, Jernigan S, Abolfotoh M, Al-Mefty O. Fibrin glue injection for cavernous sinus hemostasis associated with cranial nerve deficit: a case report. *J Neurol Surg Rep*. 2015;76:e72-e74.
1287. Ellegala DB, Maartens NF, Laws ER Jr. Use of FloSeal hemostatic sealant in transsphenoidal pituitary surgery: technical note. *Neurosurgery*. 2002;51:513-515; discussion 515-516.
1288. Bedi AD, Toms SA, Dehdashti AR. Use of hemostatic matrix for hemostasis of the cavernous sinus during endoscopic endonasal pituitary and suprasellar tumor surgery. *Skull Base*. 2011;21:189-192.
1289. Fiss I, Danne M, Stendel R. Use of gelatin-thrombin matrix hemostatic sealant in cranial neurosurgery. *Neurol Med Chir (Tokyo)*. 2007;47:462-467.
1290. Gazzeri R, Galarza M, Conti C, De Bonis C. Incidence of thromboembolic events after use of gelatin-thrombin-based hemostatic matrix during intracranial tumor surgery. *Neurosurg Rev*. 2018;41:303-310.
1291. Stangerup SE, Dommerby H, Lau T. Hot-water irrigation as a treatment of posterior epistaxis. *Rhinology*. 1996;34:18-20.
1292. Amelot A. Letter: Washing and irrigation: faithful allies of the neurosurgeon for endoscopy hemostasis. *Neurosurgery*. 2017;81:E48-E49.
1293. Fujita Y, Doi K, Harada D, Kamikawa S. Modulation of physiological hemostasis by irrigation solution: comparison of various irrigation solutions using a mouse brain surface bleeding model. *J Neurosurg*. 2010;112:824-828.
1294. Gazzeri R, Galarza M, Neroni M, Alfieri A, Giordano M. Hemostatic matrix sealant in neurosurgery: a clinical and imaging study. *Acta Neurochir (Wien)*. 2011;153:148-154; discussion 155.
1295. Ramakrishnan VR, Feazel LM, Gitomer SA, Ir D, Robertson CE, Frank DN. The microbiome of the middle meatus in healthy adults. *PLoS One*. 2013;8:e85507.
1296. Kraus DH, Gonen M, Mener D, Brown AE, Bilsky MH, Shah JP. A standardized regimen of antibiotics prevents infectious complications in skull base surgery. *Laryngoscope*. 2005;115:1347-1357.
1297. Little AS, White WL. Short-duration, single-agent antibiotic prophylaxis for meningitis in transsphenoidal surgery. *Pituitary*. 2011;14:335-339.
1298. Orlando R, Cappabianca P, Tosone G, Esposito F, Piazza M, de Divitiis E. Retrospective analysis of a new antibiotic chemoprophylaxis regimen in 170 patients undergoing endoscopic endonasal transsphenoidal surgery. *Surg Neurol*. 2007;68:145-148; discussion 148.
1299. Brown SM, Anand VK, Tabaee A, Schwartz TH. Role of perioperative antibiotics in endoscopic skull base surgery. *Laryngoscope*. 2007;117:1528-1532.
1300. Somma T, Maraolo AE, Esposito F, et al. Efficacy of ultra-short single agent regimen antibiotic chemo-prophylaxis in reducing the risk of meningitis in patients undergoing endoscopic endonasal transsphenoidal surgery. *Clin Neurol Neurosurg*. 2015;139:206-209.
1301. Milanese L, Zoli M, Sollini G, et al. Antibiotic prophylaxis in endoscopic endonasal pituitary and skull base surgery. *World Neurosurg*. 2017;106:912-918.
1302. Rosen SA, Getz AE, Kingdom T, Youssef AS, Ramakrishnan VR. Systematic review of the effectiveness of perioperative prophylactic antibiotics for skull base surgeries. *Am J Rhinol Allergy*. 2016;30:e10-e16.
1303. Oshino S, Saitoh Y, Yoshimine T. Withstand pressure of a simple fibrin glue sealant: experimental study of mimicked sellar reconstruction in extended transsphenoidal surgery. *World Neurosurg*. 2010;73:701-704.
1304. Saitoh Y, Oshino S. Enhancement of withstanding pressure of fibrin sealant by modified mixing ratio of fibrin sealant components for skull base

reconstruction: technical note. *Neurol Med Chir (Tokyo)*. 2013;53:65-68.

1305. de Almeida JR, Morris A, Whyne CM, James AL, Witterick IJ. Testing biomechanical strength of in vitro cerebrospinal fluid leak repairs. *J Otolaryngol Head Neck Surg*. 2009;38:106-111.
1306. de Almeida JR, Ghotme K, Leong I, Drake J, James AL, Witterick IJ. A new porcine skull base model: fibrin glue improves strength of cerebrospinal fluid leak repairs. *Otolaryngol Head Neck Surg*. 2009;141:184-189.
1307. Chauvet D, Tran V, Mutlu G, George B, Allain JM. Study of dural suture watertightness: an in vitro comparison of different sealants. *Acta Neurochir (Wien)*. 2011;153:2465-2472.
1308. Fandino M, Macdonald K, Singh D, Whyne C, Witterick I. Determining the best graft-sealant combination for skull base repair using a soft tissue in vitro porcine model. *Int Forum Allergy Rhinol*. 2013;3:212-216.
1309. Van Velthoven V, Clarici G, Auer LM. Fibrin tissue adhesive sealant for the prevention of CSF leakage following transsphenoidal microsurgery. *Acta Neurochir (Wien)*. 1991;109(1-2):26-29.
1310. Seda L, Camara RB, Cukiert A, Burattini JA, Mariani PP. Sellar floor reconstruction after transsphenoidal surgery using fibrin glue without grafting or implants: technical note. *Surg Neurol*. 2006;66:46-49; discussion 49.
1311. Black PM, Zervas NT, Candia G. Management of large pituitary adenomas by transsphenoidal surgery. *Surg Neurol*. 1988;29:443-447.
1312. Ciric I, Mikhael M, Stafford T, Lawson L, Garces R. Transsphenoidal microsurgery of pituitary macroadenomas with long-term follow-up results. *J Neurosurg*. 1983;59:395-401.
1313. Derome PJ, Visot A, Delalande O, Guiot G. Mechanical complications after the transsphenoidal removal of pituitary adenomas. In: Derome PJ, ed. *Pituitary Adenomas*. Paris: Ascelpios; 1980:233-235.
1314. Faria MA Jr, Tindall GT. Transsphenoidal microsurgery for prolactin-secreting pituitary adenomas. *J Neurosurg*. 1982;56:33-43.
1315. Hardy J, Mohr G. [Prolactinoma: surgical aspects]. *Neurochirurgie*. 1981;27(Suppl 1):41-60. French.
1316. Kennedy DW, Cohn ES, Papel ID, Holliday MJ. Transsphenoidal approach to the sella: the Johns Hopkins experience. *Laryngoscope*. 1984;94:1066-1074.
1317. Kern EB, Pearson BW, McDonald TJ, Laws ER Jr. The transseptal approach to lesions of the pituitary and parasellar regions. *Laryngoscope*. 1979;89(5 Pt 2 Suppl 15):1-34.
1318. Laws ER Jr, Kern EB. Complications of transsphenoidal surgery. *Clin Neurosurg*. 1976;23:401-416.
1319. Pasztor E, Kemeny AA, Piffko P. Trans-sphenoidal surgery for suprasellar pituitary adenomas. *Acta Neurochir (Wien)*. 1983;67(1-2):11-17.
1320. Spaziante R, de Divitiis E, Cappabianca P. Reconstruction of the pituitary fossa in transsphenoidal surgery: an experience of 140 cases. *Neurosurgery*. 1985;17:453-458.
1321. Waldbauer H, Fahlbusch R. The use of fibrin sealant in the neurosurgical treatment of lesions of the base of the skull. In: Schlag G, Redl H, ed. *Fibrin Sealant in Operative Medicine*. Vol 2. Berlin: Springer; 1986:176-180.
1322. Wilson CB, Dempsey LC. Transsphenoidal microsurgical removal of 250 pituitary adenomas. *J Neurosurg*. 1978;48:13-22.
1323. Wilson CB. A decade of pituitary microsurgery. The Herbert Olivecrona lecture. *J Neurosurg*. 1984;61:814-833.
1324. Cappabianca P, Cavallo LM, Valente V, et al. Sellar repair with fibrin sealant and collagen fleece after endoscopic endonasal transsphenoidal surgery. *Surg Neurol*. 2004;62:227-233; discussion 233.
1325. Yano S, Tsuiki H, Kudo M, et al. Sellar repair with resorbable polyglactin acid sheet and fibrin glue in endoscopic endonasal transsphenoidal surgery. *Surg Neurol*. 2007;67:59-64; discussion 64.
1326. Cavallo LM, Solari D, Somma T, Savic D, Cappabianca P. The awake endoscope-guided sealant technique with fibrin glue in the treatment of postoperative cerebrospinal fluid leak after extended transsphenoidal surgery: technical note. *World Neurosurg*. 2014;82(3-4):e479-e485.
1327. Kumar A, Maartens NF, Kaye AH. Reconstruction of the sellar floor using Bioglue following transsphenoidal procedures. *J Clin Neurosci*. 2003;10:92-95.
1328. Dusick JR, Mattozo CA, Esposito F, Kelly DF. BioGlue for prevention of postoperative cerebrospinal fluid leaks in transsphenoidal surgery: a case series. *Surg Neurol*. 2006;66:371-376; discussion 376.
1329. Chin CJ, Kus L, Rotenberg BW. Use of duraseal in repair of cerebrospinal fluid leaks. *J Otolaryngol Head Neck Surg*. 2010;39:594-599.
1330. Tomazic PV, Edlinger S, Gellner V, et al. Vivostat(R): an autologous fibrin sealant as useful adjunct in endoscopic transnasal CSF-leak repair. *Eur Arch Otorhinolaryngol*. 2015;272:1423-1427.
1331. Yildirim AE, Dursun E, Ozdol C, et al. Using an autologous fibrin sealant in the preventing of cerebrospinal fluid leak with large skull base defect following endoscopic endonasal transsphenoidal surgery. *Turk Neurosurg*. 2013;23:736-741.
1332. Kus LH, Rotenberg BW, Duggal N. Use of tissue glues in endoscopic pituitary surgery: a cost comparison. *Can J Neurol Sci*. 2010;37:650-655.
1333. Eloy JA, Choudhry OJ, Friedel ME, Kuperan AB, Liu JK. Endoscopic nasoseptal flap repair of skull base defects: is addition of a dural sealant necessary? *Otolaryngol Head Neck Surg*. 2012;147:161-166.
1334. Glicksman JT, Parasher AK, Brooks SG, et al. Sinonasal quality of life after endoscopic resection of malignant sinonasal and skull base tumors. *Laryngoscope*. 2018;128:789-793.
1335. Suh JD, Ramakrishnan VR, Chi JJ, Palmer JN, Chiu AG. Outcomes and complications of endoscopic approaches for malignancies of the paranasal sinuses and anterior skull base. *Ann Otol Rhinol Laryngol*. 2013;122:54-59.
1336. Solari D, Morace R, Cavallo LM, et al. The endoscopic endonasal approach for the management of craniopharyngiomas. *J Neurosurg Sci*. 2016;60:454-462.
1337. Cappabianca P, Cavallo LM, Solari D, Stagno V, Esposito F, de Angelis M. Endoscopic endonasal surgery for pituitary adenomas. *World Neurosurg*. 2014;82(6 Suppl):S3-S11.
1338. Hardy J, Wigser SM. Trans-sphenoidal surgery of pituitary fossa tumors with televised radiofluoroscopic control. *J Neurosurg*. 1965;23:612-619.
1339. Lasio G, Ferroli P, Felisati G, Broggi G. Image-guided endoscopic transnasal removal of recurrent pituitary adenomas. *Neurosurgery*. 2002;51:132-136; discussion 136-137.
1340. Chung TK, Riley KO, Woodworth BA. The use of image-guidance during transsphenoidal pituitary surgery in the United States. *Am J Rhinol Allergy*. 2015;29:215-220.
1341. Patel SN, Youssef AS, Vale FL, Padhya TA. Re-evaluation of the role of image guidance in minimally invasive pituitary surgery: benefits and outcomes. *Comput Aided Surg*. 2011;16:47-53.
1342. Jagannathan J, Prevedello DM, Ayer VS, Dumont AS, Jane JA Jr, Laws ER. Computer-assisted frameless stereotaxy in transsphenoidal surgery at a single institution: review of 176 cases. *Neurosurg Focus*. 2006;20:E9.
1343. Eboli P, Shafa B, Mayberg M. Intraoperative computed tomography registration and electromagnetic neuronavigation for transsphenoidal pituitary surgery: accuracy and time effectiveness. *J Neurosurg*. 2011;114:329-335.
1344. Tosaka M, Nagaki T, Honda F, Takahashi K, Yoshimoto Y. Multi-slice computed tomography-assisted endoscopic transsphenoidal surgery for pituitary macroadenoma: a comparison with conventional microscopic transsphenoidal surgery. *Neurol Res*. 2015;37:951-958.
1345. Mori R, Joki T, Matsuwaki Y, Karagiozov K, Murayama Y, Abe T. Initial experience of real-time intraoperative C-arm computed-tomography-guided navigation surgery for pituitary tumors. *World Neurosurg*. 2013;79:319-326.
1346. Coburger J, Konig R, Seitz K, Bazner U, Wirtz CR, Hlavac M. Determining the utility of intraoperative magnetic resonance imaging for transsphenoidal surgery: a retrospective study. *J Neurosurg*. 2014;120:346-356.
1347. Berkmann S, Schlaffer S, Nimsky C, Fahlbusch R, Buchfelder M. Follow-up and long-term outcome of nonfunctioning pituitary adenoma operated by transsphenoidal surgery with intraoperative high-field magnetic resonance imaging. *Acta Neurochir (Wien)*. 2014;156:2233-2243; discussion 2243.
1348. Hlavica M, Bellut D, Lemm D, Schmid C, Bernays RL. Impact of ultra-low-field intraoperative magnetic resonance imaging on extent of resection and frequency of tumor recurrence in 104 surgically treated nonfunctioning pituitary adenomas. *World Neurosurg*. 2013;79:99-109.
1349. Nimsky C, Keller BV, Ganslandt O, Fahlbusch R. Intraoperative high-field magnetic resonance imaging in transsphenoidal surgery of hormonally inactive pituitary macroadenomas. *Neurosurgery*. 2006;59:105-114.
1350. Berkmann S, Fandino J, Zosso S, Killer HE, Remonda L, Landolt H. Intraoperative magnetic resonance imaging and early prognosis for vision after transsphenoidal surgery for sellar lesions. *J Neurosurg*. 2011;115:518-527.
1351. Wu JS, Shou XF, Yao CJ, et al. Transsphenoidal pituitary macroadenomas resection guided by PoleStar N20 low-field intraoperative magnetic resonance imaging: comparison with early postoperative high-field magnetic resonance imaging. *Neurosurgery*. 2009;65:63-70; discussion 70-61.
1352. Kim EH, Oh MC, Kim SH. Application of low-field intraoperative magnetic resonance imaging in transsphenoidal surgery for pituitary adenomas: technical points to improve the visibility of the tumor resection margin. *Acta Neurochir (Wien)*. 2013;155:485-493.
1353. Gerlach R, du Mesnil de Rochemont R, Gasser T, et al. Feasibility of Polestar N20, an ultra-low-field intraoperative magnetic resonance imaging system in resection control of pituitary macroadenomas: lessons learned from the first 40 cases. *Neurosurgery*. 2008;63:272-284; discussion 284-275.
1354. Kuo JS, Barkhoudarian G, Farrell CJ, et al. Congress of Neurological Surgeons systematic review and evidence-based guideline on surgical techniques and technologies for the management of patients with nonfunctioning pituitary adenomas. *Neurosurgery*. 2016;79:E536-E538.
1355. Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol*. 2006;7:392-401.
1356. Eljamel MS, Leese G, Moseley H. Intraoperative optical identification of pituitary adenomas. *J Neurooncol*. 2009;92:417-421.
1357. Marbacher S, Klinger E, Schwyzer L, et al. Use of fluorescence to guide resection or biopsy of primary brain tumors and brain metastases. *Neurosurg Focus*. 2014;36:E10.
1358. Hide T, Yano S, Shinojima N, Kuratsu J. Usefulness of the indocyanine green fluorescence endoscope in endonasal transsphenoidal surgery. *J Neurosurg*. 2015;122:1185-1192.
1359. Verstegen MJT, Tummers Q, Schutte PJ, et al. Intraoperative identification of a normal pituitary gland and an adenoma using near-infrared fluorescence imaging and low-dose indocyanine green. *Oper Neurosurg (Hagerstown)*. 2016;12:260-268.
1360. Litvack ZN, Zada G, Laws ER Jr. Indocyanine green fluorescence endoscopy for visual differentiation of pituitary tumor from surrounding structures. *J Neurosurg*. 2012;116:935-941.
1361. Lee JYK, Cho SS, Zeh R, et al. Folate receptor overexpression can be visualized in real time during pituitary adenoma endoscopic transsphenoidal surgery with near-infrared imaging. *J Neurosurg*. 2018;129:390-403.
1362. Tabaee A, Anand VK, Barron Y, et al. Endoscopic pituitary surgery: a systematic review and meta-analysis. *J Neurosurg*. 2009;111:545-554.
1363. Borg A, Kirkman MA, Choi D. Endoscopic endonasal anterior skull base surgery: a systematic review of complications during the past 65 years. *World Neurosurg*. 2016;95:383-391.
1364. Lloyd KM, DelGaudio JM, Hudgins PA. Imaging of skull base cerebrospinal fluid leaks in adults. *Radiology*. 2008;248:725-736.
1365. Adappa ND, Learned KO, Palmer JN, Newman JG, Lee JY. Radiographic enhancement of the nasoseptal flap does not predict postoperative cerebrospinal fluid leaks in endoscopic skull base reconstruction. *Laryngoscope*. 2012;122:1226-1234.
1366. Learned KO, Adappa ND, Loevner LA, Palmer JN, Newman JG, Lee JY. MR imaging evaluation of endoscopic cranial base reconstruction with pedicled

nasoseptal flap following endoscopic endonasal skull base surgery. *Eur J Radiol*. 2013;82:544-551.

1367. Snyderman CH, Kassam AB, Carrau R, Mintz A. Endoscopic reconstruction of cranial base defects following endonasal skull base surgery. *Skull Base*. 2007;17:73-78.
1368. Thirumala PD, Kassasm AB, Habeych M, et al. Somatosensory evoked potential monitoring during endoscopic endonasal approach to skull base surgery: analysis of observed changes. *Neurosurgery*. 2011;69(1 Suppl Operative):ons64-ons76; discussion ons76.
1369. Balzer JR, Rose RD, Welch WC, Sclabassi RJ. Simultaneous somatosensory evoked potential and electromyographic recordings during lumbosacral decompression and instrumentation. *Neurosurgery*. 1998;42:1318-1324; discussion 1324-1315.
1370. Chen ZY, Wong HK, Chan YH. Variability of somatosensory evoked potential monitoring during scoliosis surgery. *J Spinal Disord Tech*. 2004;17:470-476.
1371. Singh H, Vogel RW, Lober RM, et al. Intraoperative neurophysiological monitoring for endoscopic endonasal approaches to the skull base: a technical guide. *Scientifica (Cairo)*. 2016;2016:1751245.
1372. Nuwer MR, Daube J, Fischer C, Schramm J, Yingling CD. Neuromonitoring during surgery. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol*. 1993;87:263-276.
1373. Astrup J, Symon L, Branston NM, Lassen NA. Cortical evoked potential and extracellular K+ and H+ at critical levels of brain ischemia. *Stroke*. 1977;8:51-57.
1374. Branston NM, Symon L, Crockard HA, Pasztor E. Relationship between the cortical evoked potential and local cortical blood flow following acute middle cerebral artery occlusion in the baboon. *Exp Neurol*. 1974;45:195-208.
1375. Thirumala PD, Kodavatiganti HS, Habeych M, et al. Value of multimodality monitoring using brainstem auditory evoked potentials and somatosensory evoked potentials in endoscopic endonasal surgery. *Neurol Res*. 2013;35:622-630.
1376. Elangovan C, Singh SP, Gardner P, et al. Intraoperative neurophysiological monitoring during endoscopic endonasal surgery for pediatric skull base tumors. *J Neurosurg Pediatr*. 2016;17:147-155.
1377. Slotty PJ, Abdulazim A, Kodama K, et al. Intraoperative neurophysiological monitoring during resection of infratentorial lesions: the surgeon's view. *J Neurosurg*. 2017;126:281-288.
1378. Sebel PS, Erwin CW, Neville WK. Effects of halothane and enflurane on far and near field somatosensory evoked potentials. *Br J Anaesth*. 1987;59:1492-1496.
1379. Sloan TB. Anesthetic effects on electrophysiologic recordings. *J Clin Neurophysiol*. 1998;15:217-226.
1380. Romstock J, Strauss C, Fahlbusch R. Continuous electromyography monitoring of motor cranial nerves during cerebellopontine angle surgery. *J Neurosurg*. 2000;93:586-593.
1381. Prass RL, Kinney SE, Hardy RW, Jr., Hahn JF, Luders H. Acoustic (loudspeaker) facial EMG monitoring: II. Use of evoked EMG activity during acoustic neuroma resection. *Otolaryngol Head Neck Surg*. 1987;97:541-551.
1382. Prass RL, Luders H. Acoustic (loudspeaker) facial electromyographic monitoring: Part 1. Evoked electromyographic activity during acoustic neuroma resection. *Neurosurgery*. 1986;19:392-400.
1383. Harper CM, Daube JR. Facial nerve electromyography and other cranial nerve monitoring. *J Clin Neurophysiol*. 1998;15:206-216.
1384. Thirumala P, Lai D, Engh J, Habeych M, Crammond D, Balzer J. Predictive value of somatosensory evoked potential monitoring during resection of intraparenchymal and intraventricular tumors using an endoscopic port. *J Clin Neurol*. 2013;9:244-251.
1385. Thirumala PD, Mohanraj SK, Habeych M, et al. Value of free-run electromyographic monitoring of lower cranial nerves in endoscopic endonasal approach to skull base surgeries. *J Neurol Surg B Skull Base*. 2012;73:236-244.
1386. Schlake HP, Goldbrunner R, Siebert M, Behr R, Roosen K. Intra-operative electromyographic monitoring of extra-ocular motor nerves (Nn. III, VI) in skull base surgery. *Acta Neurochir (Wien)*. 2001;143:251-261.
1387. Nelson KR, Vasconez HC. Nerve transection without neurotonic discharges during intraoperative electromyographic monitoring. *Muscle Nerve*. 1995;18:236-238.
1388. Isaacson B, Kileny PR, El-Kashlan HK. Prediction of long-term facial nerve outcomes with intraoperative nerve monitoring. *Otol Neurotol*. 2005;26:270-273.
1389. Zhou Q, Zhang M, Jiang Y. Intraoperative oculomotor nerve monitoring predicts outcome following clipping of posterior communicating artery aneurysms. *J Clin Neurosci*. 2012;19:706-711.
1390. Kawaguchi M, Ohnishi H, Sakamoto T, et al. Intraoperative electrophysiologic monitoring of cranial motor nerves in skull base surgery. *Surg Neurol*. 1995;43:177-181.
1391. Acioly MA, Liebsch M, de Aguiar PH, Tatagiba M. Facial nerve monitoring during cerebellopontine angle and skull base tumor surgery: a systematic review from description to current success on function prediction. *World Neurosurg*. 2013;80:e271-e300.
1392. San-juan D, Barges-Coll J, Gomez Amador JL, et al. Intraoperative monitoring of the abducens nerve in extended endonasal endoscopic approach: a pilot study technical report. *J Electromyogr Kinesiol*. 2014;24:558-564.
1393. Stechison MT. Neurophysiologic monitoring during cranial base surgery. *J Neurooncol*. 1994;20:313-325.
1394. Neuloh G, Pechstein U, Cedzich C, Schramm J. Motor evoked potential monitoring with supratentorial surgery. *Neurosurgery*. 2004;54:1061-1070; discussion 1070-1062.
1395. Neuloh G, Pechstein U, Schramm J. Motor tract monitoring during insular glioma surgery. *J Neurosurg*. 2007;106:582-592.
1396. Kang DZ, Wu ZY, Lan Q, et al. Combined monitoring of evoked potentials during microsurgery for lesions adjacent to the brainstem and intracranial aneurysms. *Chin Med J (Engl)*. 2007;120:1567-1573.
1397. Kodama K, Javadi M, Seifert V, Szelenyi A. Conjunct SEP and MEP monitoring in resection of infratentorial lesions: lessons learned in a cohort of 210 patients. *J Neurosurg*. 2014;121:1453-1461.
1398. Thirumala PD, Crammond DJ, Loke YK, Cheng HL, Huang J, Balzer JR. Diagnostic accuracy of motor evoked potentials to detect neurological deficit during idiopathic scoliosis correction: a systematic review. *J Neurosurg Spine*. 2017;26:374-383.
1399. Fukuda M, Takao T, Hiraishi T, Yajima N, Saito A, Fujii Y. Pharyngeal motor evoked potential monitoring during skull base surgery predicts postoperative recovery from swallowing dysfunction. *World Neurosurg*. 2015;84:555-560.
1400. Kullmann M, Tatagiba M, Liebsch M, Feigl GC. Evaluation of the predictive value of intraoperative changes in motor-evoked potentials of caudal cranial nerves for the postoperative functional outcome. *World Neurosurg*. 2016;95:329-334.
1401. Ito E, Ichikawa M, Itakura T, et al. Motor evoked potential monitoring of the vagus nerve with transcranial electrical stimulation during skull base surgeries. *J Neurosurg*. 2013;118:195-201.
1402. Akagami R, Dong CC, Westerberg BD. Localized transcranial electrical motor evoked potentials for monitoring cranial nerves in cranial base surgery. *Neurosurgery*. 2005;57(1 Suppl):78-85; discussion 78-85.
1403. Acioly MA, Liebsch M, Carvalho CH, Gharabaghi A, Tatagiba M. Transcranial electrocortical stimulation to monitor the facial nerve motor function during cerebellopontine angle surgery. *Neurosurgery*. 2010;66(6 Suppl Operative):354-361; discussion 362.
1404. Bejjani GK, Nora PC, Vera PL, Broemling L, Sekhar LN. The predictive value of intraoperative somatosensory evoked potential monitoring: review of 244 procedures. *Neurosurgery*. 1998;43:491-498; discussion 498-500.
1405. Jho HD, Carrau RL. Endoscopy assisted transsphenoidal surgery for pituitary adenoma. Technical note. *Acta Neurochir (Wien)*. 1996;138:1416-1425.
1406. Li A, Liu W, Cao P, Zheng Y, Bu Z, Zhou T. Endoscopic versus microscopic transsphenoidal surgery in the treatment of pituitary adenoma: a systematic review and meta-Analysis. *World Neurosurg*. 2017;101:236-246.
1407. Goudakos JK, Markou KD, Georgalas C. Endoscopic versus microscopic trans-sphenoidal pituitary surgery: a systematic review and meta-analysis. *Clin Otolaryngol*. 2011;36:212-220.
1408. Rudmik L, Starreveld YP, Vandergrift WA, Banglawala SM, Soler ZM. Cost-effectiveness of the endoscopic versus microscopic approach for pituitary adenoma resection. *Laryngoscope*. 2015;125:16-24.
1409. Little AS, Chapple K. Predictors of resource utilization in transsphenoidal surgery for Cushing disease. *J Neurosurg*. 2013;119:504-511.
1410. Dong H, Coyle D, Buxton M. Value of information analysis for a new technology: computer-assisted total knee replacement. *Int J Technol Assess Health Care*. 2007;23:337-342.
1411. Oosmanally N, Paul JE, Zanation AM, Ewend MG, Senior BA, Ebert CS Jr. Comparative analysis of cost of endoscopic endonasal minimally invasive and sublabial-transseptal approaches to the pituitary. *Int Forum Allergy Rhinol*. 2011;1:242-249.
1412. Technology assessment: a tool for technology managment and improved patient outcomes. Conference sponsored by the U.S. Department of Veterans Affairs Health Services Research & Development Service, its Management Decision and Research Center, and the Association for Health Services Research. January 23-25, 1995. Washington, DC. https://www.nlm.nih.gov/nichsr/ta101/ta101.pdf.
1413. Jethwa PR, Patel TD, Hajart AF, Eloy JA, Couldwell WT, Liu JK. Cost-effectiveness analysis of microscopic and endoscopic transsphenoidal surgery versus medical therapy in the management of microprolactinoma in the United States. *World Neurosurg*. 2016;87:65-76.
1414. Azad TD, Lee YJ, Vail D, et al. Endoscopic vs. microscopic resection of sellar lesions—a matched analysis of clinical and socioeconomic outcomes. *Front Surg*. 2017;4:33.
1415. McLaughlin N, Martin NA, Upadhyaya P, et al. Assessing the cost of contemporary pituitary care. *Neurosurg Focus*. 2014;37:E7.
1416. Eseonu CI, ReFaey K, Garcia O, Salvatori R, Quinones-Hinojosa A. Comparative cost analysis of endoscopic versus microscopic endonasal transsphenoidal surgery for pituitary adenomas. *J Neurol Surg B Skull Base*. 2018;79:131-138.
1417. Fu TS, Monteiro E, Witterick I, et al. Costs and perioperative outcomes associated with open versus endoscopic resection of sinonasal malignancies with skull base involvement. *J Neurol Surg B Skull Base*. 2017;78:430-440.
1418. Gandhoke GS, Pease M, Smith KJ, Sekula RF, Jr. Supraorbital versus endoscopic endonasal approaches for olfactory groove meningiomas: a cost-minimization study. *World Neurosurg*. 2017;105:126-136.
1419. Morita A, Shin M, Sekhar LN, Kirino T. Endoscopic microneurosurgery: usefulness and cost-effectiveness in the consecutive experience of 210 patients. *Neurosurgery*. 2006;58:315-321; discussion 315-321.
1420. Stapleton AL, Tyler-Kabara EC, Gardner PA, Snyderman CH. The costs of skull base surgery in the pediatric population. *J Neurol Surg B Skull Base*. 2015;76:39-42.
1421. Gardner PA, Snyderman CH, Fernandez-Miranda JC, Wang EW. Apples and oranges: proper comparison of costs—endonasal vs. transnasal. *World Neurosurg*. 2017;106:984-985.

XVII. Appendix: Author Disclosures

Author	Conflict of interest	Company	Relationship
Nithin D. Adappa, MD	None		
Catherine Banks, MbChB	None		
Martin Bettag, MD, PhD	Yes	Karl Storz	Consultant
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Paolo Cappabianca, MD	Yes	Karl Storz	Royalties
Ricardo L. Carrau, MD	None		
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Alberto Di Somma, MD	None		
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Juan C. Fernandez-Miranda, MD	None		
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Sebastien Froelich, MD, PhD	None		
Hermes G. Garcia, MD	None		
Paul A. Gardner, MD	Yes	Peter Lazic US, Inc. SPIWay, LLC	Royalties Consultant/Ownership Interest
Fred Gentili, MD, MSc	Yes	Stryker Canada	Consultant
Praveen Hariharan, MBBS	None		
Richard J. Harvey, MD	Yes	AstraZeneca Meda Medtronic NeilMed Olympus Seqirus	Speakers' Bureau Speakers' Bureau Consultant Consultant Consultant Speakers' Bureau
Reid Hoshide, MD, MPH	None		
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Devyani Lal, MD	None		
Philippe Lavigne, MD	None		
John Y.K. Lee, MD	Yes	VisionSense	Stockholder
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Camilo A. Reyes, MD	None		
Nicholas R. Rowan, MD	None		
Christopher R. Roxbury, MD	None		
Nivedita Sahu, MD	None		
Rodney J. Schlosser, MD	Yes	Arrinex AstraZeneca Entellus GlaxoSmithKline Olympus Optinose Roche Sanofi	Consultant Grant Support Grant Support Grant Support Consultant Consultant + Grant Support Grant Support Consultant + Grant Support

(*Continued*)

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Kyle Van Koevering, MD	None		
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Eric W. Wang, MD	None		
Ian Witterick, MD	Yes	Proteocyte Diagnostics Inc.	Stockholder/Advisory Board
Bradford A. Woodworth, MD	Yes	Cook Medical Olympus	Consultant/Grant Support Consultant
Peter-John Wormald, MD	Yes	Chitogel Integra Medtronic ENT NeilMed Scopis	Shareholder Royalties Royalties Consultant Royalties
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