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Technical notes & surgical techniques

Outcomes of intraoperative ultrasound for endoscopic endonasal transsphenoidal pituitary surgery in adenomas with parasellar extension

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ABSTRACT

Background: Pituitary adenomas with parasellar extension present a technical challenge for adequate visualization and gross total resection (GTR). The endoscope improves identification of parasellar extension, however, additional intraoperative imaging adjuncts can further augment visualization. Intraoperative ultrasound (iUS) may provide a viable and cost-effective solution for intraoperative imaging. We sought to assess the ability of intraoperative ultrasound to predict extent of resection on 3-month postoperative magnetic resonance imaging (MRI) in pituitary adenomas with parasellar extension.

Methods: Twenty consecutive patients undergoing endoscopic endonasal transsphenoidal surgery for pituitary adenomas with the assistance of intraoperative ultrasound were prospectively collected. Intraoperative ultrasound findings were recorded during each case. 3-month postoperative MRI studies were reviewed in a blinded fashion to assess for residual tumor and compared with the intraoperative ultrasound findings.

Results: Median preoperative Knosp grade was 2. Cavernous sinus invasion was encountered intraoperatively in 3 patients, all of whom were Knosp grade 3 preoperatively. Median operative time was 152 min. Based on iUS findings, 17 patients were expected to have a GTR while 3 patients underwent subtotal resection. 18 patients completed a 3-month postoperative MRI. The iUS and MRI findings were concordant in 16 cases (88.9%) with only two instances of discordance.

Conclusion: Intraoperative ultrasound can reliably predict tumor resection as assessed by 3-month postoperative MRI in pituitary adenomas with parasellar extension. Image capture and interpretation may vary based on operator experience. Ultrasound provides reliable immediate assessment of extent of resection, identification of normal pituitary gland and other important neurovascular structures.

1. Introduction

Pituitary adenomas with parasellar extension into the cavernous sinus present a technical challenge for adequate visualization and gross total resection (GTR). Endocrinological remission (ER) and GTR are significantly impacted by parasellar extension decreasing reported cure rates from 78 to 92% down to 20–52% [1]. The introduction of endoscopy for pituitary surgery has augmented the ability for intraoperative identification of parasellar extension with wider views and improved ability to inspect the medial wall of the cavernous sinus, achieving rates at least comparable to microscopic surgery [2]. Even with the use of endoscopic technique, assessing for residual tumor in those with parasellar extension can be difficult [1,2]. To improve patient outcomes for tumors with parasellar extension there has been interest in adjunctive techniques for enhanced detection of tumor which include intraoperative magnetic resonance imaging (iMRI) as well as Doppler and

Abbreviations: CSI, cavernous sinus invasion; ER, endocrinological remission; GTR, gross total resection; iMRI, intraoperative magnetic resonance imaging; iUS, intraoperative ultrasound; STR, subtotal resection; US, ultrasound.

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conventional ultrasound [3–8]. Intraoperative MRI has been shown in some studies to increase the likelihood of GTR by 15% to 40% with iMRI guiding further tumor removal in 15–83% of cases depending on the strength of magnet utilized [4,6,9]. However, this comes with a significant increase in operative time and implementation costs secondary to the required infrastructure and equipment [4]. Therefore, there remains interest in the development and validation of more time- and cost-effective intraoperative imaging techniques to aid in tumor resection.

Intraoperative ultrasound (iUS) may provide an effective and inexpensive solution [5,8,10]. The literature regarding iUS consists mostly of case series, which report GTR between 63.5 and 77.8% with a low complication rate [5]. A cohort study of patients with Cushing disease with negative or equivocal MRI findings specifically assessed ER without and with the use of iUS noting ER in 83.8% without versus 89.7% with ultrasound [11]. While the current literature suggests that iUS is safe and effective; studies validating iUS with surgeon observation intraoperatively and MRI postoperatively are lacking [5,8,10]. The aim of our study was to validate surgeon interpretation of iUS to 3-month postoperative MRI findings.

2. Methods

2.1. Study population

Consecutive patients undergoing endoscopic endonasal transsphenoidal surgery for pituitary macroadenoma with parasellar extension and planned use of iUS, between January 2017 and January 2019, were prospectively collected in a database. Patient demographics and characteristics were retrospectively collected via chart review once the patients had undergone surgery with intraoperative ultrasound findings recorded. This study was approved by our institutional review board (protocol #2019–1276). Patient consent was waived given the retrospective nature of imaging review and that the use of intraoperative ultrasound was within standard patient care.

2.2. Inclusion and exclusion criteria

Patients undergoing endoscopic endonasal transsphenoidal resection a pituitary tumor with parasellar extension were considered for the study. Parasellar extension was assessed on preoperative MRI, and those with Knosp grade 1, 2, or 3 were included [1]. Those with Knosp grade 4, defined by complete encasement of the internal carotid artery, were excluded from the study as complete resection would not be considered the goal of surgery. Patients aged less than 18 years of age were excluded from the study; all patients older than 18 years of age were eligible for inclusion.

2.3. Surgical intervention

All patients underwent endonasal transsphenoidal approaches to the sella with endoscopic assistance. The operative team included both an otolaryngology surgeon for approach and closure, as well as a neurosurgeon for adenoma resection. Straight and angled scopes were utilized as appropriate throughout the operations.

2.4. Imaging assessments

All patients underwent an MRI head with and without contrast utilizing a pituitary protocol preoperatively on a 3T MRI machine. Preoperative MRIs were reviewed independently by two individuals for assigning the extent of parasellar extension based on the modified Knosp grading scale with any disagreement resolved by the senior author [1]. Intraoperative US was utilized in each case at any time during resection and again at the completion of resection. As a standard practice our patients have their first postoperative MRI at 3-months postoperatively. These studies were independently reviewed by two neuroradiologists who were not involved in the original operation and were blinded to the iUS findings.

2.5. Intraoperative ultrasound

Ultrasound assessment was completed and interpreted by the operating surgeon at the initial completion of resection. If there was any tissue concerning for residual tumor, then an additional pass with suction and ring curette was made. Observations at completion of final resection were recorded assessing the lateral and superior borders of the sella. The location of any residual tumor or preserved normal pituitary gland was noted. The machine used was the Hitachi Arietta 70 (Hitachi Healthcare Americas, Twinsburg, OH) with a disposable probe designed for pituitary and neuro-endoscopic guidance. The probe is a side-fire linear array transducer producing a scan width of 10 mm in a trapezoidal shape. The diameter of the probe is 2.87 mm with frequency range 17 – 4 MHz. The relatively narrow diameter of the probe allows for work in small operative corridors.

2.6. Statistical analysis

Descriptive statistics of the study population were performed utilizing Microsoft Excel (Microsoft, Redmond, WA). Kappa agreement analysis was performed utilizing GraphPad Prism 8.1.2 (GraphPad Software, San Diego, CA).

3. Results

3.1. Intraoperative ultrasound observations

Twenty consecutive patients who underwent endoscopic endonasal transsphenoidal surgery for resection of pituitary adenoma with parasellar extension were included in the study. Patient demographics, clinical and imaging characteristics are included in Table 1 in a case by case format. The median age was 57 years (range 33–73) with 13 males (65%). Three patients had previous transsphenoidal surgery. Based on the preoperative MRI studies, the most frequent Knosp grade was 3 ($n = 9$; 45%), followed by grade 2 ($n = 8$; 40%). Cavernous sinus invasion was encountered in 3 patients, all of whom were Knosp grade 3 preoperatively. Intraoperative ultrasound findings were recorded for all 20 patients. Seventeen patients (85%) were expected to have GTR based on iUS interpretation, with residual tumor expected in 3 patients (15%). US was performed for confirmation at the end of resection and in 3 cases (15%) it revealed additional accessible tumor assisting in gaining GTR.

3.2. Postoperative MRI comparison

Eighteen patients completed a 3-month postoperative MRI study. Two patients were lost to follow-up for unknown reasons and did not complete any postoperative imaging. In those patients who completed postoperative imaging, the intraoperative ultrasound and MRI findings were concordant in 16 cases (88.9%) with only two instances of discordance (Table 1). There was strong agreement between iUS and MRI with a kappa value of 0.684 ($p < .001$). In the first discordant case GTR was expected based on iUS, however, on 3-month postoperative MRI there was a small amount of residual tumor was identified in the right sellar region. In the second discordant case GTR was again expected on iUS but only a small area of potential tumor versus soft-tissue thickening within the left cavernous sinus on 3-month postoperative MRI. This was followed closely on follow-up imaging and began to show subsequent growth consistent with recurrent tumor.

3.3. Operative characteristics

Intraoperative factors were not significantly impacted by the use of iUS. The average operative time was 158 min and average estimated

Table 1
Case descriptions with clinical and imaging variables.

	Patient Characteristics					Endocrinologic Function		Imaging Validation		
Case	Age	Sex	Knosp grade	Operative Time (min)	Prior resection	Preoperative Status	Postoperative Status	Expected EOR (iUS)	Residual tumor (MRI)	Concordance
1	58	F	3	123	N	Normal	Normal	GTR	No	Yes
2	61	M	2	137	N	Normal	Normal	GTR	No	Yes
3	42	F	3	140	Y	Cushing	Normal	GTR	No	Yes
4	33	M	2	183	Y	Panhypopituitarism	Panhypopituitarism	STR	Yes	Yes
5	54	M	3	161	N	Hyperprolactinemia	Normal	GTR	No	Yes
6	34	M	2	302	N	Panhypopituitarism	Panhypopituitarism	GTR	Yes	No
7	58	M	3	139	N	Hypothyroid	Hypothyroid	GTR	No	Yes
8	73	F	2	117	Y	Panhypopituitarism	Panhypopituitarism	STR	Yes	Yes
9	67	M	1	179	N	Normal	Normal	GTR	No	Yes
10	53	M	2	180	N	Normal	Normal	GTR	No	Yes
11	55	M	2	133	N	Normal	Normal	GTR	No	Yes
12	71	M	3	160	N	Normal	Panhypopituitarism	GTR	No	Yes
13	49	F	1	135	N	Hypothyroid	Hypothyroid	GTR	No	Yes
14	40	F	2	155	N	Cushing	Normal	GTR	n/a	n/a
15	49	M	3	164	N	Normal	Panhypopituitarism	GTR	n/a	n/a
16	58	F	3	154	N	Normal	Normal	STR	Yes	Yes
17	68	M	3	150	N	Normal	Normal	GTR	Yes	No
18	64	M	2	216	N	Normal	Normal	GTR	No	Yes
19	39	F	1	131	N	IGF1 excess	Normal	GTR	No	Yes
20	71	M	3	106	N	Normal	Normal	GTR	No	Yes

GTR = gross total resection, IGF1 = insulin-like growth factor 1, iUS = intraoperative ultrasound, STR = subtotal resection.

blood loss was 92 mL. There were no intraoperative complications observed, whether from the surgery itself or from use of the intraoperative ultrasound probe. Fig. 1 provides an example of a GTR with the expected findings on iUS and 3-month postoperative MRI. Fig. 2 provides an example of a STR with the expected appearance of residual tumor in contrast to normal gland, and its correlate on 3-month postoperative MRI. Intraoperative cerebrospinal fluid leak was encountered in 10 patients (50%) which was adequately treated with dural substitute in-lay covered by fibrin sealant. None of the patients in our series had a postoperative CSF leak.

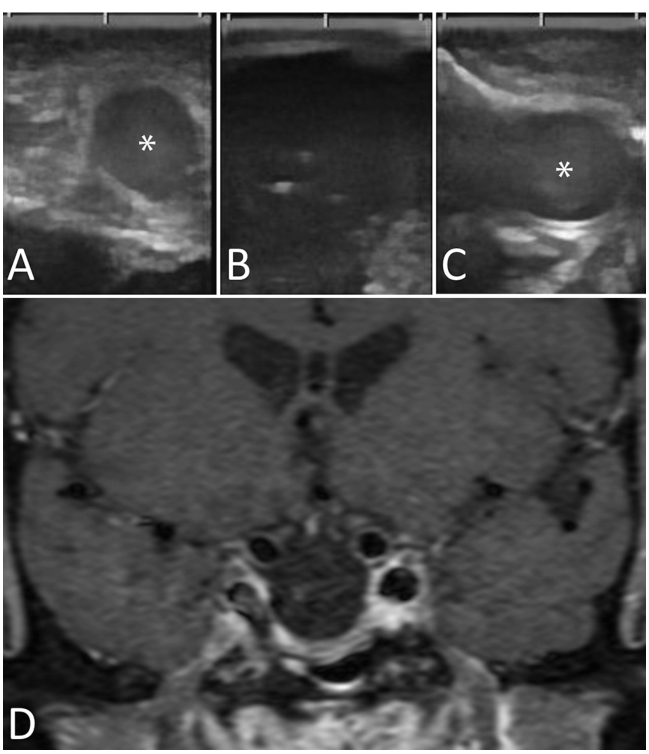

Fig. 1. Intraoperative ultrasound images from the superior sella **(B)**, and right **(A)** and left **(C)** walls of the sella showing the cavernous carotid arteries (*) and hyperechoic wall of the cavernous sinus with no residual tumor. Coronal T1-weighted, post-contrast image **(D)** showing gross total resection with no residual tumor.

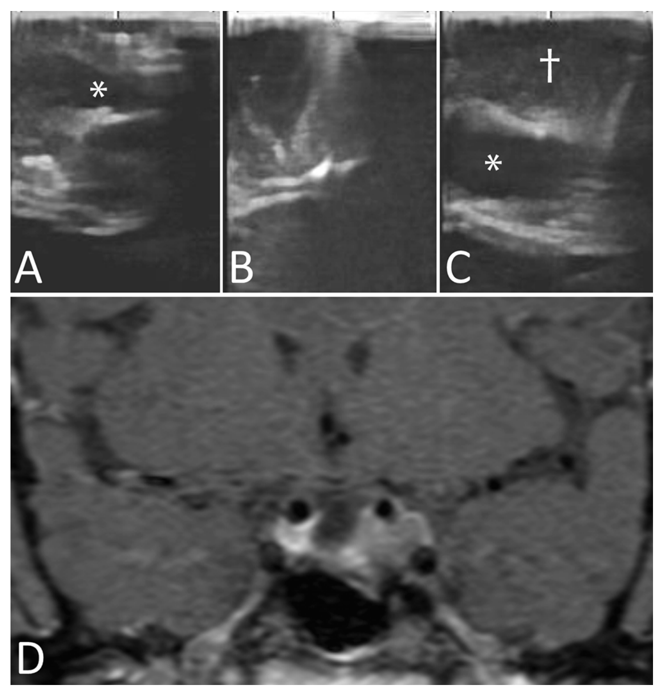

Fig. 2. Intraoperative ultrasound images from the superior sella **(B)**, right **(A)** wall, showing normal pituitary and cavernous carotid (*), and left **(C)** wall showing residual tumor (†) with cavernous carotid (*) deep to the tumor. Coronal T1-weighted, post-contrast image **(D)** showing subtotal resection with residual tumor in the left sella and normal pituitary gland in the right sella.

4. Discussion

4.1. Advances in intraoperative US

Intraoperative ultrasound in pituitary surgery has been in use since the 1990 s, describing use of iUS with sublabial microscopic surgery rather than endoscopic endonasal surgery, favoring the technique to maximize resection especially in functional adenomas given the endocrinological ramifications of residual tumor [11,12]. Adenomas were found most often to be hyperechoic, with a substantial amount mixed or isoechoic. In Ram *et al.*, adenomas were found to be iso- to hyperechoic compared to the normal pituitary gland, while the cavernous sinus wall was reported as hypoechoic, and a border between gland and tumor was easily identifiable using iUS [12]. In Watson *et al.*, surgical remission of endocrinological Cushing's disease was 95% with use of iUS compared to 87% without, which is notable as iUS identified lesions in some patients with negative or equivocal MRI's, where remission rates are reported to be as low as 50–70% without use of iUS [11]. This study also suggested adenomas were hyperechoic compared to normal gland. In our experience most adenomas were hyperechoic on ultrasound with cystic changes appearing hypoechoic. Since the aforementioned early studies there have been advances not only in MRI technology, with 3T scanners commonly in use now, but also in neuronavigation, ultrasound probes, and neuroendoscopy which itself increases resection rates in pituitary adenomas [13,14].

In our study population of complex, high Knosp grade tumors with parasellar extension, we were able to achieve a high rate of GTR while utilizing iUS. The high rate of concordance between iUS and postoperative MRI findings validate the usefulness of iUS as an intraoperative tool to aid in identification of residual tumor and vascular structures. Implementation of iUS in pituitary surgery carries a lower infrastructural burden than other intraoperative imaging techniques such as iMRI. In our experience the use of iUS does not add significant operative time for setup or image capture with the flow of the operation well preserved, though interpretation is limited by the lack of a comparison group. Advances in ultrasound probe technology have allowed for the production of low-profile probes which can be easily handled within a small working space such as the sella and sphenoid sinus via an endonasal approach. One of the major differences that can impact ease of image acquisition is the orientation of the image capture array. A traditional probe acquires images from the end of the tip in the same direction as the handle. A side-fire probe which obtains images along the last 10 mm of the probe orthogonal to the length of the probe. Based on our experience we suggest the use of a side-fire probe as this provides sufficient windows to assess the parasellar and suprasellar regions as opposed to an end-fire probe which requires significant manipulation for image acquisition.

More recent studies with use of iUS in endoscopic transsphenoidal surgery also cite the utility in decreasing residual, especially in cavernous and parasellar regions [5,8,10]. Solheim *et al.*, 2010, noted that use of iUS led to intraoperative decision to extend resection in 33.3% of their cases which ultimately ended up showing no residual on MRI, while 22.2% of their patients overall had residual on MRI despite iUS being interpreted as negative [8]. Solheim *et al.*, 2016, reported that use of iUS led to further resection in 16.7% of their cases where no further resection was deemed necessary based on endoscopic view [10]. A systematic review from Marcus *et al.* noted that studies reporting use of iUS in both microscopic or endoscopic had varying rates of resection from 63.5 to 100%, however, variability overall exists regarding which Knosp grades were included initially [5]. Ultimately, they concluded that surgeons overall prefer the iUS to help identify not only residual tumor, but also carotid artery, during continued resection [5].

4.2. Endoscopy versus microscopy

Multiple large meta-analyses have been completed over the past decade comparing endoscopic-assisted and traditional microscopic techniques with variable results [15–21]. Several demonstrate increased rates of GTR or complete resection with the use of endoscopy as opposed to microscopy, while others report no difference [15–21]. GTR rates vary from 53.5% to 71.8% using endoscopy versus 46.6% to 58% using traditional microscopy [18–20]. Complication profiles are generally similar in the literature but one study does report a higher incidence of vascular injury with endoscopy (1.58%) compared with microscopy (0.50%) [15]. Endoscopy has shown significantly reduced recurrence rate (7.8% endoscopy versus 29.6% microscopy) which is likely a product of increases in volumetric EOR (92.7% versus 88.4%) [20].

Parasellar extension and subsequent cavernous sinus invasion (CSI) have a significant impact on the ability to achieve GTR [1]. The best predictor of CSI remains the modified Knosp grading scale based on preoperative MRI with increasing grade predicting greater likelihood of invasion [22]. Knosp grade 3 and 4 are the best predictors of intraoperative CSI [16]. It has been reported that for each grade microscopy overestimates intraoperative CSI as compared to findings with endoscopy, though this is drawn from a *meta*-analysis and not direct case-level comparisons [16]. As endoscopy seems to result in improved visualization of CSI, surgeons may be more willing to attempt resection of parasellar tumor potentially explaining the reported carotid injury rate of 0.9–1.58% in endoscopic endonasal surgery compared to 0.50% with microscopy [15,16]. Intraoperative ultrasound allows for direct visualization of the carotid artery and may thereby lessen the risk of vascular injury.

4.3. Intraoperative MRI comparison

Multiple studies have previously shown that the use of iMRI in transsphenoidal pituitary surgery (microscopic or endoscopic) can increase immediate EOR [3,4,6,23,24]. The reported recurrence rate for iMRI combined with microscopy is 7%, which is similar to that of endoscopy alone (7.8%) [3,20]. The advantage of iMRI is most pronounced when using conventional microscopy as opposed to endoscopy [24]. The interpretation of these studies is tempered by a common design flaw in that resection is more likely to be stopped prematurely in iMRI cases as compared to control cases where intraoperative imaging is not available [7]. Additionally, iMRI is a newer technique and when assessing single institution, especially single surgeon data, temporal improvement in surgeon skill must be considered when comparing to historical controls from earlier in a surgeon's career. The surgical infrastructure required to routinely use iMRI for pituitary surgery is extensive and may not be present in centers that do not use iMRI often for other surgeries. There is also a time cost associated with iMRI which can add upwards of 100 min to mean operative time [23]. Therefore lower-cost imaging adjuncts for pituitary tumors with parasellar extension represent a desirable niche which iUS may be able to fill.

4.4. Limitations

Our data has the advantage of being collected in a prospective manner with blinded postoperative imaging review by neuroradiologists. However, interpretation of the data is limited by a lack of comparison group with intraoperative observations prior to our routine use of iUS in pituitary adenomas with parasellar extension. Using iUS requires a unique skill set and the surgeon must interpret the images in real-time, leading to the likely presence of an associated learning curve to maximize sensitivity and specificity. Additionally, we had only 3 patients in our series who had undergone prior resection limiting our ability to assess iUS utility in redo surgery where scar tissue may appear similar to remnant tumor. Further study is needed to directly assess the added value of iUS when combined with endoscopy and in which cases it may be of most benefit.

5. Conclusion

Intraoperative ultrasound can reliably predict tumor resection as assessed by 3-month postoperative MRI in pituitary adenomas with parasellar extension. Image capture and interpretation may vary based on operator experience with a learning curve likely present. However, once proficiency is gained, ultrasound provides immediate assessment of extent of resection and can assist in identification of tumor remnant, normal pituitary gland, and other important structures in the sellar and parasellar regions with limited additional cost or length of time to the case.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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CRediT authorship contribution statement

Joseph S. Domino: Methodology, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Domenico A. Gattozzi:** Formal analysis, Writing - original draft. **Megan Jack:** Data curation, Writing - original draft. **Melissa Carroll:** Formal analysis, Validation. **Nick Harn:** Formal analysis, Writing - review & editing. **D. David Beahm:** Conceptualization, Writing - review & editing. **Roukoz Chamoun:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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