Systematic Review/Meta-analysis

Endoscopic Resection of Sinonasal Malignancy: A Systematic Review and Meta-analysis

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Abstract

Objectives. The use of endoscopic approaches for sinonasal malignancy resection has increased, but survival data are limited secondary to disease rarity and new surgical technique. Here we present a systematic review and meta-analysis of endoscopic endonasal resection of sinonasal malignancy.

Data Sources. MEDLINE, PubMed Central, NCBI Bookshelf, Cochrane Library, clinicaltrials.gov, National Guideline Clearinghouse.

Review Methods. PRISMA/MOOSE guidelines were followed. MeSH terms were "endoscopic" AND ("esthesioneuroblastoma" OR "sinonasal adenocarcinoma" OR "squamous cell carcinoma" OR "sinonasal undifferentiated carcinoma"). For studies in which individual-level data were available, results were obtained by direct pooling. For studies in which only summary Kaplan-Meier curves were available, numerical data were extracted, traced, and aggregated by fitting a Weibull model.

Results. Of 320 studies identified, 35 case series were included (n = 952 patients), with 15 studies analyzed via aggregate modeling and 20 studies analyzed via direct pooling. Two- and 5-year survival rates for patients in aggregate modeling were 87.5% and 72.3%, respectively (mean follow-up: 32.9 months). Two- and 5-year survival for patients in direct pooling were 85.8% and 83.5%, respectively (mean follow-up: 43.0 ± 19.5 months). Significant overall survival difference was found between low- and high-grade cancers (*P* = .015) but not between low- and high-stage cancers (*P* = .79).

Conclusion. Overall 2- and 5-year survival rates are comparable and sometimes greater than those from open craniofacial resection. Survival rates significantly differ by cancer grade but not stage. Journals and investigators should be encouraged to publish retrospective and prospective case series with staged survival updates based on established guidelines.

Keywords

sinonasal malignancy, endoscopic, meta-analysis, systematic review

The expanded endonasal approach has allowed for extirpation of benign sinonasal tumors via minimally invasive techniques since the first series published by Jho and Carrau in 1996.[1] While expanded endonasal approach indications continue to broaden for benign disease processes, open craniofacial resection continues to be the gold standard for extirpation of malignant sinonasal tumors. The preference of open technique is often driven by the desire for an en bloc resection of tumor with negative margins rather than a progressive resection with negative margins. Additional concerns include ensuring adequate hemostasis while minimizing vascular, soft tissue, and dural injury, along with operator familiarity with endoscopic technology.[2-4] However, nearly 2 decades have passed since the introduction of endoscopic technology, and with continued advancement in endoscopic hemostatic techniques, reconstructive options, and standardized safety precautions, its use in malignant disease resection continues to rise.[5-9]

Malignant sinonasal cancer comprises a variety of rare heterogeneous disease processes, with reported incidences <1.5 per 100,000 in men and <1 per 100,000 in women.[10] The rarity and high degree of heterogeneity in these cancers result in a paucity of evidence-based management. Published data are relegated to case series with various sample populations, staging, follow-up periods, surgical

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techniques, and adjuvant therapies. To study the effect of endoscopic endonasal management of patients with these rare malignancies in a quantifiable generalizable method, we conducted a meta-analysis and systematic review of the current literature.

Methods

Search Methodology

A meta-analysis and systematic review of the literature was conducted in accordance with PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses).[11,12] As many studies were found to be observational, MOOSE guidelines (Meta-analysis of Observational Studies in Epidemiology) were also used.[13]

MEDLINE, PubMed Central, NCBI Bookshelf, Cochrane Library, clinicaltrials.gov, and the National Guideline Clearinghouse databases were searched for the following MeSH terms: "endoscopic" AND ("esthesioneuroblastoma" OR "sinonasal adenocarcinoma" OR "squamous cell carcinoma" OR "sinonasal undifferentiated carcinoma"). In addition, references of retrieved studies were searched to identify all relevant articles. Studies with the following criteria were included for analysis: English-language studies with overall survival outcome data for patients having undergone endoscopic or endoscopic-assisted resection of sinonasal malignancy with a mean follow-up of at least 24 months. Studies with the following criteria were excluded from analysis: previously reported patient data with significant overlap, pooled data with patients who had open craniofacial resection that could not be extracted, patients operated on with only palliative intent, patients presenting with recurrent cancer, and case series with <3 patients, as authors of such series may have insufficient experience with surgical management. If studies also included results of patients who had open approaches for resection of sinonasal malignancy, only those patients who had endoscopic resection were included. A schematic flow diagram detailing the systematic search is included (**Figure 1**).

Statistical Analysis

Data were aggregated according to the nature of the available source data. For studies in which individual-level data were provided, results were obtained by direct pooling of observations. For studies in which individual data were not available and only summary Kaplan-Meier curves were provided, 2 authors extracted numerical data from the provided graphical data (R.B.R. and S.B.S.) by tracing via DigitizeIt 2.0 software (DigitizeIt, Braunschweig, Germany), as previously described.[14] These curves were then aggregated by fitting a Weibull model to the resultant data points. A random effects framework allowed for interstudy heterogeneity in outcomes.[15] If a study provided both Kaplan-Meier curves and individual data, the latter were preferentially collected over numeric data extraction and model creation. For all studies, accompanying demographic data were collected for individual or pooled samples of patients.

Given the greater detail of the pooled individual data subset, additional data points were extracted from these

studies, including cancer staging. Cancer staging was then separated into "low stage," defined as American Joint Committee on Cancer (AJCC) stages T1/T2 or Kadish stages A/B, and "high stage," defined as AJCC stages T3/T4 or Kadish stages C/D.[16] Overall mortality was compared on the basis of stage via a log-rank test. Histopathologic grading was also studied. "High grade" malignancies included the following: squamous cell carcinoma (including that originating from inverted papilloma), melanoma, sinonasal undifferentiated carcinoma, meibomian gland carcinoma, sarcoma, and spindle cell carcinoma. Overall mortality was compared according to histopathologic grading via a log-rank test. Differences in histopathology between aggregate model and pooled analyses were tested with a 2-tailed Fisher's exact test. Differences between patients in surgery and surgery and radiotherapy groups in regard to staging and grading were tested with a 2-tailed Fisher's exact test. All data analyses were performed in Stata 13.1 (StataCorp, College Station, Texas).

Results

Of 320 initial search results, 61 full-text articles were assessed for eligibility, and 35 studies were ultimately included for systematic review and meta-analysis.[17-52] A total of 952 patients were included. Fifteen studies (n = 759, 79.7%) provided only summary Kaplan-Meier curves, allowing only for aggregate model analysis, summarized in **Table 1** and illustrated in an aggregated Kaplan-Meier curve in **Figure 2**. Twenty studies (n = 193 patients, 20.2%) provided individual-level data, allowing for direct pooling of observations, summarized in **Table 2** and illustrated in a pooled Kaplan-Meier curve in **Figure 3** (for complete individual-level data, see Table S1 at www.oto-journal.org/supplemental). Individual-level data were then further classified into low- and high-stage disease and stratified by histopathology (**Table 3**).

Overall 2- and 5-year survival rates for patients in the aggregate model analysis were 87.5% and 72.3%, respectively. Mean follow-up for studies in the aggregate model analysis was 33.9 months. Of 759 patients, 684 patients had purely endoscopic surgical management of disease (90%), while 75 patients had endoscopic-assisted surgical management (9.9%). The majority of patients were male (64%), and the mean age was 61.4. The most prevalent histopathologies were sinonasal adenocarcinoma (56%), sinonasal melanoma (13%), and squamous cell carcinoma (11%).

Overall 2- and 5-year survival rates for patients in the direct pooled analysis were 85.8% and 83.5%, respectively. Follow-up (mean ± SD) for studies in the pooled analysis was 43.0 ± 19.5 months. Of 193 patients, 157 patients had purely endoscopic surgical management of disease (78%), while 36 had endoscopic-assisted surgical management (19%). The majority of patients were male (64%), and the mean age was 56.6 ± 8.1 years. The most prevalent histopathologies were esthesioneuroblastoma (32%), sinonasal adenocarcinoma (28%), and sinonasal melanoma (18%).

Given the greater detail of the pooled individual data subset, additional analysis was done on this group of patients.
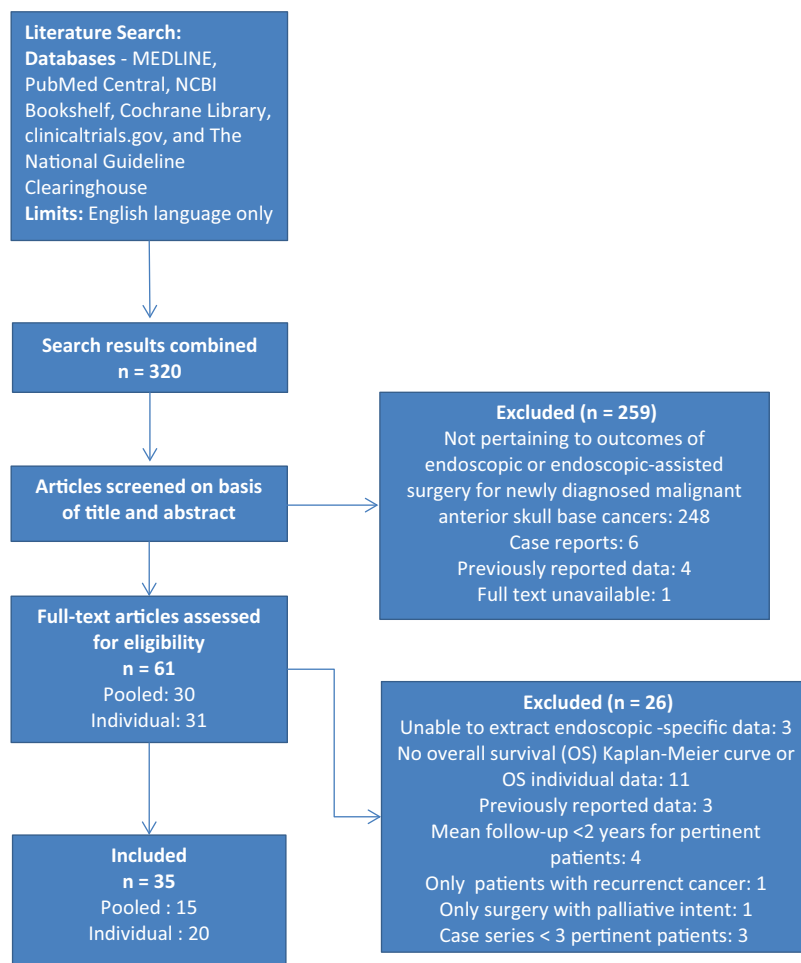
Figure 1. Flow diagram detailing systematic search.

The majority of patients in the pooled analyses had low-stage cancer (63%), although staging data were not available for 22% of the malignancies (**Table 3**). The majority of esthesioneuroblastomas (61%), sinonasal adenocarcinomas (73%), and squamous cell carcinomas ± inverted papilloma (74%) were low-stage malignancies. Sinonasal undifferentiated cancers represented the only disease process with a majority of high-stage malignancies (67%). For the majority of melanomas and more uncommon malignancies included, staging data were unavailable. No significant difference in overall survival between low- and high-stage cancers was found ($P = .79$; **Figure 4**). Histopathologic grading was also studied. Among the high-grade malignancies, the most common were squamous cell carcinoma (51.9%), melanoma (22.6%), and sarcoma (7.7%), while among the low-grade malignancies, the most common were sinonasal adenocarcinoma (61.0%) and esthesioneuroblastoma (12.7%; **Table 4**). A significant survival difference between high- and low-grade cancer was found ($P = .015$; **Figure 5**).

Last, survival analysis was performed on patients who received radiotherapy in addition to surgery. No statistically significant difference in overall survival was found between those patients who only underwent surgery and those patients who underwent surgery and radiotherapy ($P = .85$;

Figure 6). These 2 groups (surgery only versus surgery + radiotherapy) were compared to assess whether an unequal distribution of patients was confounding survival rates based on tumor stage and grade. The 2 groups were significantly different according to stage: in the surgery-only cohort, 11.6% of tumors were high stage, and 88.4% of tumors were low stage, while in the surgery + radiotherapy cohort, 46.7% of tumors were high stage, and 53.3% of tumors were low stage ($P < .001$). The 2 groups were not significantly different in respect to grading: in the surgery-only cohort, 33.3% of tumors were high grade, and 66.7% of tumors were low grade, while in the surgery + radiotherapy cohort, 28.3% of tumors were high grade, and 71.7% of tumors were low grade ($P = .602$).

Histopathology differed greatly between analyses. The aggregate model analyses had a significantly greater prevalence of SNAC (sinonasal adenocarcinoma; 56% vs 28%, $P < .0001$). The reason for this skew was the large prevalence of SNAC described in a single multicenter study from France (n = 159, 49%).[17] Because of this high prevalence of a single pathology, we sought to reanalyze our data after exclusion of SNAC. An attempt at data analysis excluding SNAC was made for studies in the aggregate model, but this was not feasible, as many studies included

Table 1. Studies Included for Aggregate Model Analysis.[a]

Source	Location	Years	Patients	EO	EA	Malignancies	Mean Age, y	Sex Male	Sex Female	Mean Follow-up, mo
Antognoni (2015)[20]	Varese, Italy	2003-2010	30	3	27	SNAC (30)	68.3	28	2	48
Batra (2010)[32]	Cleveland, USA	2000-2008	25	25	0	SCC (6), esthesio (5), mel (5), SNUC (4), SNAC (1), leiomyosarcoma (1), other CAs (3)	57.5	10	15	31.7
Batra (2005)[45]	Cleveland, USA	1995-2003	9	9	0	SCC (2), SNAC (2), mel (2), sarcoma (1), SNUC (1), adenosquamous CA (1)	55	6	3	24
de Almeida (2015)[21]	Pittsburgh, USA	2000-2012	34	25	9	SCC (34)	57	20	14	33
Eloy (2009)[36]	Miami, USA	1997-2006	18	18	0	Esthesio (10), adenoid cystic CA (3), SNUC (1), hemangiopericytoma (3), small cell CA (1)	61.2	10	8	31.7
Goffart (2000)[52]	Liege and Leuven, Belgium	1992-1999	78	66	12	SNAC (40), SCC (13), mel (7), esthesio (5), others (13)	62.4	64	14	25.9
Hanna (2009)[34]	Houston, USA	1992-2007	120	93	27	—[b]	52.6	65	55	37
Lund (2012)[26]	London, UK	1963-2010	31	31	0	Mel (31)	65.9[b]	—[b]	—[b]	37.5[b]
Lund (2007)[41]	London, UK	Unknown	49	49	0	SNAC (15), mel (11), esthesio (11), SCC (3), chondrosarcoma (3), hemangiopericytoma (2), malignant schwannoma (1), transitional cell CA (1), adenoid cystic CA (1), SNUC (1)	60	26	23	21
Luong (2010)[29]	Cleveland, USA	1998-2007	52	52	0	—[b]	59[b]	—[b]	—[b]	38.5
Suh (2013)[24]	Philadelphia, USA	2002-2010	36	36	0	SCC (4), SNAC (8), sarcoma (6), mel (4), esthesio (5), adenoid cystic CA (3), SNUC (1), others (5)	56.7	19	17	39
Swegal (2014)[19]	Cleveland, USA	1998-2012	12	12	0	Mel (12)	65.5	6	6	32
Van Gerven (2011)[31]	Leuven, Belgium	1992-2004	44	44	0	SNAC (44)	62	43	1	61
Vergez (2014)[17]	France (multicenter)	1998-2010	159	159	0	SNAC (159)	68.9	148	11	32.5
Villaret (2010)[30]	Brescia/Pavia and Varese, Italy	1996-2008	62	62	0	SNAC (36), esthesio (13), mel (3), adenoid cystic CA (2), hemangiopericytoma (2), SCC (2), others (4)	61.7	44	18	20.5
All		1963-2012[c]	759	684	75	587	61.4	489	187	33.9

Abbreviations: CA, carcinoma; EA, endoscopically assisted; EO, endoscopic only; esthesio, esthesioneuroblastoma; IP, inverted papilloma; mel, melanoma; SCC, squamous cell carcinoma; SNAC, sinonasal adenocarcinoma

[a]Values presented as n or mean. Number of patients reviewed includes only those who met inclusion criteria. The listed studies reviewed more patients than the number included in our analysis.

[b]Demographic data for endoscopic population unable to be extracted from overall patient population.

[c]Studies may predate advent of endoscopic techniques (1991) because patients with open resection were included.
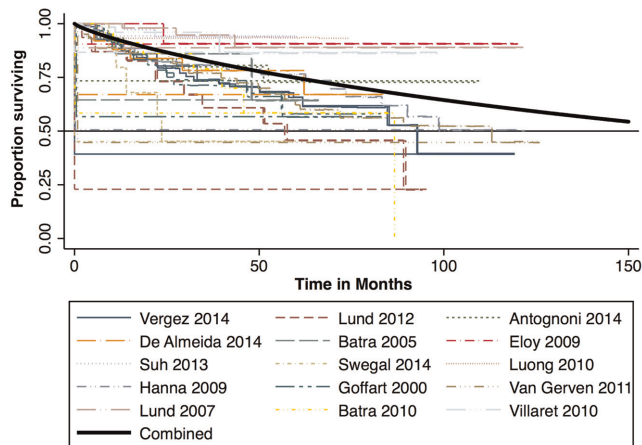
Figure 2. Kaplan-Meier overall survival curve of patients in aggregate model analysis (n = 15 studies, n = 759 patients).

SNAC among other histopathologies, making non-SNAC data inextricable. This was easily extracted in the pooled group, however. In the pooled group, no significant difference in overall survival between low- and high-stage cancers was found even once SNAC was excluded ($P = .67$; **Figure 7**). In the pooled group, there was still a statistically significant difference in survival between high- and low-grade malignancies even once SNAC was excluded ($P = .010$; **Figure 8**).

Interextractor reliability in data extraction was excellent. Estimated 2-year survival was 87.0% with data only from extractor 1 versus 87.5% for data from extractor 2, while estimated 5-year survival was 74.7% with extractor 1's data versus 72.3% with extractor 2's data.

Discussion

The Kaplan-Meier overall survival curves and percentages at 2 and 5 years in patients in the pooled analysis and the aggregate model analysis provide strong evidence for continued use and further adoption of endoscopic endonasal resection of sinonasal malignancy. While open craniofacial resection remains the gold standard surgical technique for extirpation of sinonasal malignancy,[53] endoscopic resection may allow for decreased cosmetic deformity, associated hospital stay, and complication rates. The endoscopic surgeon must be able and willing to sacrifice these advantages and convert to an open approach when necessary to adhere to oncologic principles, especially that of margin-negative en bloc resection. Our data support the use of endoscopic techniques only with adherence to this caveat. Our analysis does not compare endoscopic resection with open resection, as no randomized controlled trials exist comparing the 2 surgical modalities. We therefore sought only to quantify the existing data to determine overall survival rates and explore possible predictors for increased survival.

Comparing endoscopic management with open craniofacial management is difficult. In the preendoscopic era, a previous systematic review by Dulguerov et al in 2001 outlined overall survival rates of sinonasal malignancy throughout the

decades, showing survival rates of 28% ± 13% in the 1960s, 36% ± 13% in the 1970s, 43% ± 15% in the 1980s, and 51% ± 14% in the 1990s.[54] Patients treated prior to the 1990s could not have been treated endoscopically; as such, our data show excellent continuation of this upward trend of overall survival rates. Comparisons with such historical data may be misleading, however, as multiple confounding factors undoubtedly played a role, such as increased training standards, differences in staging, standardized measures (preoperative, operative, and postoperative), adjunctive therapies, and better diagnostic modalities. A more recent systematic review by Higgins et al in 2011 shows overall 5-year survival rates of open craniofacial resection at 55.2% (n = 101).[16] Our 5-year survival rates of 72.3% and 83.5% are therefore encouraging.

Our aggregate and pooled model overall survival outcomes were similar for the 2-year benchmark (87.5% vs 85.8%) but somewhat different for the 5-year benchmark (72.3% vs 83.5%). As noted earlier, the aggregate analysis had a significantly increased proportion of SNAC as compared with the pooled analysis largely due to one French multicenter study (56% vs 28%, $P < .0001$). In this study, the overall 5-year survival rate was 62% and likely skewed the overall survival rate of the aggregate model.[17] SNAC has historically been further classified into intestinal-type adenocarcinomas and nonintestinal-type adenocarcinomas, with varying survival outcomes for each histologic type, but the authors did not explicitly stratify their results by these groupings, possibly also confounding survival outcomes.[53,55] To determine whether SNAC prevalence confounded the results for our pooled analysis, we repeated survival analysis by stage (**Figures 4**, **7**) and grade (**Figures 5**, **8**) excluding patients with SNAC, but our results were comparable for these secondary subanalyses.

Based on the smaller, pooled analysis of patients, stage had a nonsignificant effect on overall survival outcomes when based on endoscopic surgical techniques. Upon closer inspection, however, this may be misleading for 2 reasons: sinonasal undifferentiated carcinoma was the only histopathology type with a majority of high-stage cancers (67%), and staging for sinonasal melanoma, a particularly fatal disease, was unavailable for 18 of the 20 patients and therefore could not be included in this analysis.[56] Indeed, mucosal melanoma by definition is high stage, as staging begins at T3 according to the latest AJCC guidelines.[57]

According to our data, histopathologic grade does have a significant effect on overall survival outcomes. As noted earlier, skull base malignancies encompass a variety of histopathology, and classifying these malignancies into low- and high-grade subtypes may allow for better counseling for patients in regard to survival outcomes.[10,53]

Other variables were also initially considered for study in the pooled data analysis, including disease-specific survival, recurrence-free survival, previous therapy, metastasis/nodal status, and extent/location of disease process. However, published data were too variable in reporting of these outcomes; therefore, we were confined in our ability to draw

Table 2. Studies Included for Pooled Model Analysis.[a]

Source	Location	Years	Patients	EO	EA	Malignancies	Age, y	Sex		Follow-up, mo
								Male	Female	
Castelnuovo (2010)[28]	Varese/Pisa/Brescia, Italy	1997-2008	4	4	0	Adenoid cystic CA (2), papillary ACC (1), SNUC (1)	49.75 ± 12.09	4	0	34.25 ± 34.23
Chen (2006)[42]	Changhua, Taiwan	2000-2004	7	7	0	ACC (4), SCC (1), SNUC (1), sarcoma (1)	57 ± 16.57	5	2	30.7 ± 16.84
Constantinidis (2004)[46]	Erlangen/Nuremberg, Germany	1975-2000	11	6	5	Esthesio (12)	51 ± 13.53	—[b]	—[b]	102.55 ± 78.39
Devaiah (2003)[49]	Boston/Kansas City, USA	1991-2002	7	0	7	Esthesio (7)	47.71 ± 7.87	4	3	62.29 ± 34.49
Gallia (2013)[23]	Baltimore, USA	2005-2012	9	9	0	Esthesio (9)	51.22 ± 10.21	6	3	30.44 ± 16.45
Huber (2011)[50]	Zurich, Switzerland	1992-2007	12	11	1	ACC (12)	61.5 ± 19.26	9	3	16.08 ± 8.33
Jardeleza (2009)[35]	Adelaide, Australia	1999-2008	12	12	0	ACC (12)	65.83 ± 10.18	9	3	42 ± 32.12
Kim (2008)[39]	Seoul, South Korea	1989-2006	8	0	8	Esthesio (8)	46.13 ± 14.40	5	3	18.25 ± 11.78
Mohindra (2014)[18]	Chandigarh, India	2005-2009	8	6	2	Esthesio (8)	43 ± 9.62	6	2	35.5 ± 11.11
Nicolai (2007)[51]	Brescia/Varese, Italy	1999-2003	16	16	0	ACC (12), SCC (4)	62.19 ± 17.71	9	7	47.25 ± 12.97
Orvidas (2005)[47]	Rochester, USA	1980-2001	3	3	0	ACC (3)	71.33 ± 11.02	1	2	36.33 ± 32.52
Podboj (2007)[40]	Ljubljana, Slovenia	1991-2006	16	16	0	ACC (3), SNUC (6), Leiomyosarcoma (1), papillary adenocarcinoma (2), mel (2), esthesio (1), chondrosarcoma (1)	56.69 ± 21.76	8	8	66.25 ± 40.71
Poetkar (2005)[43]	Milwaukee, USA	1993-2003	16	14	2	Esthesio (5), SCC (5), ACC (2), adenoid cystic CA (1), mel (1), chondrosarcoma (1), hemangiopericytoma (1)	57 ± 1.45	—[b]	—[b]	51.5 ± 38.11
Revenaugh (2011)[27]	Cleveland, USA	2002-2009	7	6	1	SNUC (7)	42.86 ± 17.24	—[b]	—[b]	32.29 ± 19.65
Roh (2004)[48]	Cleveland / Philadelphia, USA	1996-2003	19	19	0	SCC (1), SCC + IP (5), ACC (3), mel (4), esthesio (1), leiomyosarcoma (1), Others (4)	56.95 ± 17.24	10	9	26.42 ± 21.85
Roth (2010)[33]	Zurich, Switzerland	1992-2007	13	13	0	Mel (13)	65.23 ± 12.81	—[b]	—[b]	46.46 ± 42.11
Shipchandler (2005)[37]	Cleveland, USA	1996-2004	9	6	3	SCC (5), SCC + IP (4)	62.78 ± 10.99	7	2	26.56 ± 25.64
Tojima (2012)[25]	Otsu, Japan	2000-2009	6	6	0	SCC (1), SCC + IP (1), esthesio (1), others (3)	65 ± 14.67	4	2	43.33 ± 39.94
Yuen (2005)[44]	Hong Kong, Hong Kong	1996-2003	6	0	6	Esthesio (6)	51 ± 17.79	4	2	32.83 ± 22.42
Zafereo (2008)[38]	Cleveland, USA	1980-2004	4	3	1	Esthesio (4)	60.25 ± 11.44	2	2	54 ± 62.55
All		1975-2014[c]	193	157	36	193	56.64 ± 8.12	93	53	42.97 ± 19.52

Abbreviations: ACC, adenocarcinoma; CA, carcinoma; EA, endoscopically assisted; EO, endoscopic only; esthesio, esthesioneuroblastoma; IP, inverted papilloma; mel, melanoma; SCC, squamous cell carcinoma.

[a]Values presented as n or mean ± SD. Number of patients reviewed includes only those who met inclusion criteria. The listed studies reviewed more patients than the number included in our analysis.

[b]Demographic data for endoscopic population unable to be extracted from overall patient population.

[c]Studies may predate advent of endoscopic techniques (191) because patients with open resection were included in study.
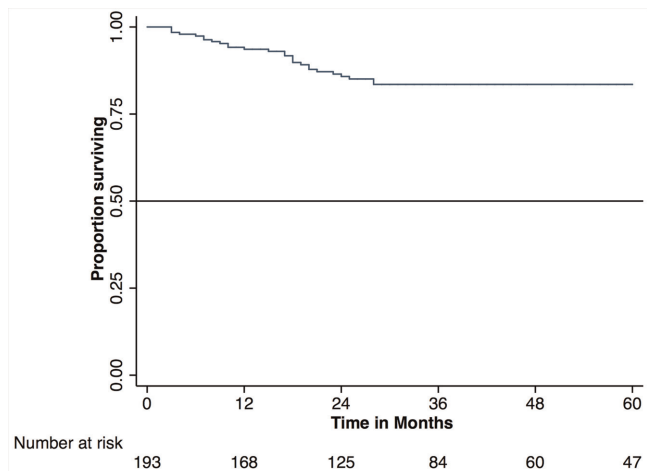
Figure 3. Kaplan-Meier overall survival curve of patients in pooled individual data analysis (n = 193 patients).
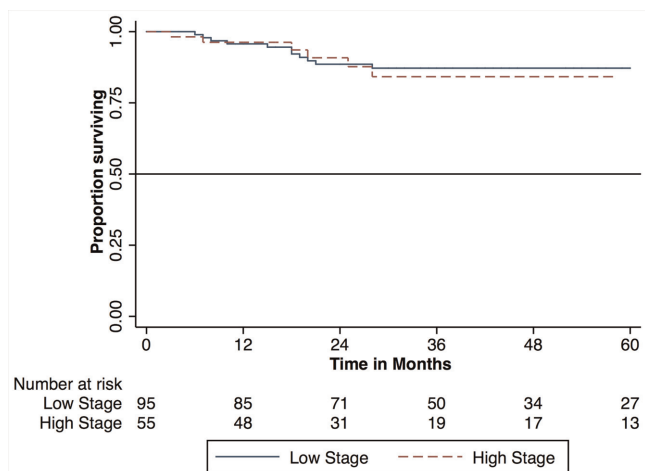

Figure 4. Kaplan-Meier overall survival curve of patients in pooled individual data analysis stratified by cancer stage (n = 193 patients).

Table 3. Histopathology of Tumors in Pooled Model Analysis Stratified by Stage.

	Low Stage	High Stage	N/A	Total
Esthesioneuroblastoma	36	23	2	61
SNAC	37	14	3	54
SCC	12	3	2	17
SCC + IP	2	2	6	10
Melanoma	2	0	18	20
SNUC	5	10	0	15
Adenoid cystic carcinoma	1	2	0	3
Other[a]	0	1	12	13
Total	95	55	43	193

Abbreviations: IP, inverted papilloma; N/A, not applicable; SCC, squamous cell carcinoma; SNAC, sinonasal adenocarcinoma; SNUC, sinonasal undifferentiated carcinoma.

[a]Other malignancy types include chondrosarcoma (3), chordoma (1), hemangiopericytoma (2), leiomyosarcoma (2), malignant peripheral nerve sheath tumor (1), Meibomian gland carcinoma (1), plasmocytoma (1), sarcoma (1), and spindle cell carcinoma (1).

Table 4. Histopathology of Tumors in Pooled Model Analysis Stratified by Grade.[a]

	Studies, n (%)	
Grade	Aggregate (n = 693)	Pooled (n = 186)
Low		
Esthesioblastoma	74	61
SNAC	355	54
Adenoid cystic carcinoma	18	3
Hemangiopericytoma	7	2
Chondrosarcoma	5	3
Total	459 (66.2)	123 (66.1)
High		
Squamous cell carcinoma	127	27
Melanoma	67	20
SNUC	12	15
Sarcoma	23	1
Neuroendocrine	5	0
Total	234 (33.8)	63 (33.9)

Abbreviations: SNAC, sinonasal adenocarcinoma; SNUC, sinonasal undifferentiated carcinoma.

[a]More uncommon malignancies that were present but excluded from analysis of tumor grade included the following: leiomyosarcoma, clear cell carcinoma, basal cell carcinoma, angiomyxoid neoplasm, angiosarcoma, osteosarcoma, spindle cell carcinoma, nonspecified carcinoma, carcinoma ex pleomorphic adenoma, poorly differentiated carcinoma, teratocarcinoma, plasmacytoma, teratocarcinoma, fibrosarcoma, extrapleural solitary fibrous tumor, small cell carcinoma, malignant schwannoma, and transitional cell carcinoma.

conclusions solely based on overall survival and cancer stage.

It is important to note that 112 patients included in the study (10.9%) had "endoscopic assisted" surgery. The definition of endoscopic-assisted surgery was also variable, sometimes including orbital incision, frontal/subfrontal craniotomy, or anterior craniotomy.[34,49,52] It is theoretically possible that these endoscopic-assisted techniques allowed for greater access and visualization of the sinonasal malignancy, artificially increasing overall survival rates for some studies. It is difficult to generalize conclusions for this subset of the population.

The effect of radiation therapy with or without chemotherapy after surgery cannot be underestimated. Although indications for adjuvant therapy differ from institution to institution, it is generally reserved for patients with high-grade tumors, advanced tumor stage, bone invasion, perineural spread, intracranial

extension, dural or brain involvement, and/or positive margins.[34] In addition, controversy exists for elective neck dissection or elective radiotherapy.[58]

At first glance, our data seem to indicate that adjuvant radiation therapy did not result in a statistically significant survival benefit, but there were significantly higher numbers of patients with high-stage tumors in the surgery + radiotherapy
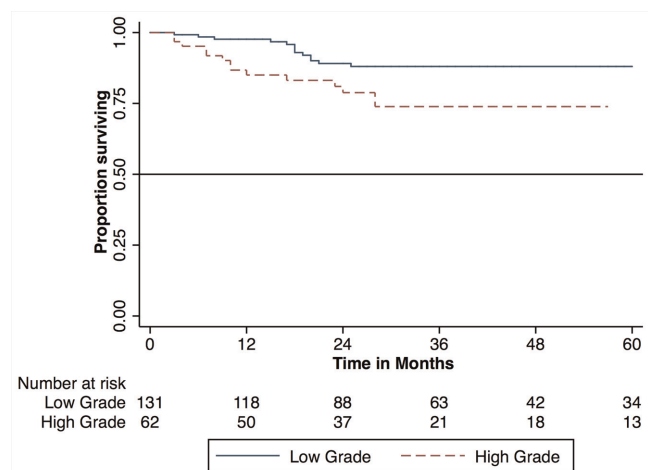
Figure 5. Kaplan-Meier overall survival curve of patients in pooled individual data analysis stratified by cancer grade (n = 193 patients).
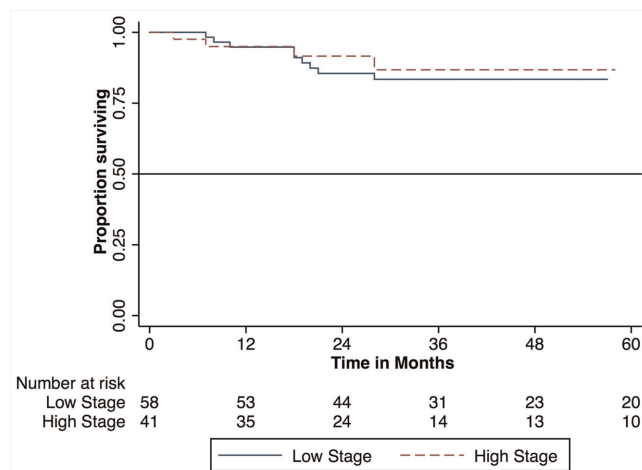

Figure 7. Kaplan-Meier overall survival curve of patients in pooled individual data analysis stratified by cancer stage excluding sinonasal adenocarcinoma (n = 193 patients).
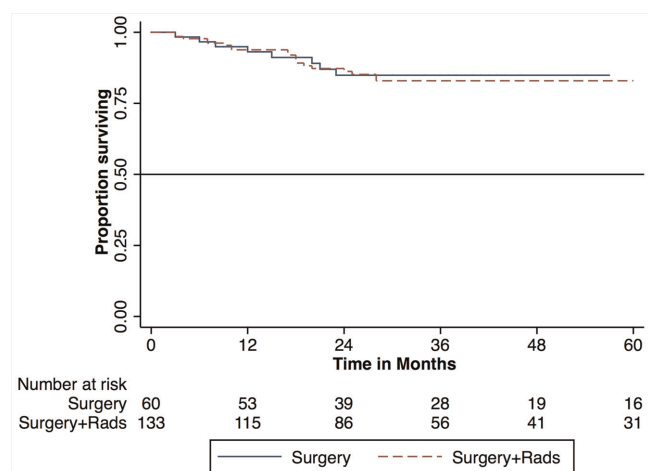

Figure 6. Kaplan-Meier overall survival curve of patients in pooled individual data analysis stratified by type of intervention (n = 193 patients).
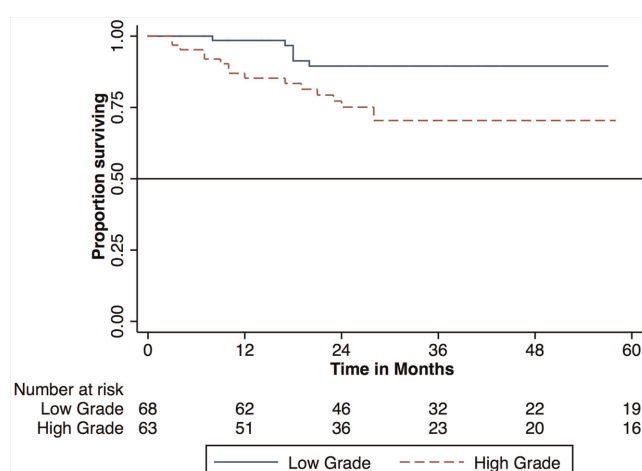

Figure 8. Kaplan-Meier overall survival curve of patients in pooled individual data analysis stratified by cancer grade excluding sinonasal adenocarcinoma (n = 193 patients).

cohort as compared with the surgery-only cohort. Our results therefore continue to support the use of multimodality therapy for low- and high-stage tumors. There were no differences in patient distribution in regard to tumor grade. Further prospective trials are therefore needed to evaluate whether patients with low-grade tumors would benefit from multimodality therapy. For now, the most important factor for multimodality therapy remains the presence of a multidisciplinary skull base team to decide on therapeutic options for patients with these rare malignancies in a case-by-case scenario.

Conclusions based on systematic reviews and meta-analyses are limited by several factors. Publication bias may have allowed for investigators with the largest case series to be published. rather than those with smaller case series and less experience, as has been noted.[59] If so, our data set may have an artificially inflated survival rate due to high-volume experience with resection of sinonasal malignancy. When compounded with the inherent referral bias of tertiary and

quaternary skull base centers, our published survival rates may not be generalizable to smaller skull base practices. In addition, during data collection, all attempts were made to not include studies that had a significant amount of previously reported data, but it is possible that results of several patients may have been repeated, especially as authors may have changed institutions and/or reported results twice, as some included studies were multi-institutional.

Sinonasal malignancy is heterogeneous, and our data support epidemiologic studies describing variations in prevalence and presentation throughout the world.[55] Pooled analyses offer an advantage in allowing increased sample sizes for data analysis and a disadvantage in that conclusions may not always be applicable to populations with a high degree of heterogeneity in cancer subtypes.[13] This pooled analysis attempts to mitigate the retrospective limitations of nonrandomized treatment selection by offering a global perspective.[54]

Although retrospective comparisons between open and endoscopic surgical methods have been attempted, an ideal comparison would include a multicenter prospective randomized controlled trial for open versus endoscopic techniques with stratification by histopathology and staging. This is unlikely to happen due to worldwide rarity of disease, surgeon preference and comfort with surgical technique, and variation in presentation and anatomic location of disease. Instead, we urge investigators to publish further prospective and retrospective case series with staged survival updates concerning patient cohorts. As journals have done by requiring investigators to adhere to the CONSORT guideline for reporting randomized controlled trials, they should require investigators to report observational studies in a standardized fashion using PRISMA or MOOSE guidelines.[12,13,60] In this way, information may not be missed, such as adjuvant therapy, location, staging, margin status, and recurrence. Journals may require investigators to summarize their results for the body of the journal article, but they should encourage investigators to explicitly submit individual data in appendices and supplements. Only in this way will we be able to continue to draw evidence-based conclusions regarding endoscopic surgical management of sinonasal malignancy.

Conclusion

Overall 2- and 5-year survival rates of endoscopic endonasal resection of sinonasal malignancy are comparable and sometimes greater than the published literature for open craniofacial resection of sinonasal malignancy. Survival rates of endoscopic endonasal resection appear to significantly correlate with cancer grading but not with cancer staging. Journals and investigators should be encouraged to publish retrospective and prospective case series with staged survival updates based on established guidelines to provide outcomes that may be used in future systematic reviews and meta-analysis.

Author Contributions

Rounak B. Rawal, conception of work, acquisition/analysis/interpretation of data, drafting/critical revision, final approval, agreement to be accountable for all aspects of the work; **Zainab Farzal**, conception of work, acquisition/analysis/interpretation of data, drafting/critical revision, final approval, agreement to be accountable for all aspects of the work; **Jerome J. Federspiel**, conception of work, analysis/interpretation of data, drafting/critical revision, final approval, agreement to be accountable for all aspects of the work; **Satyan B. Sreenath**, conception of work, acquisition/analysis of data, critical revision, final approval, agreement to be accountable for all aspects of the work; **Brian D. Thorp**, conception of work, analysis/interpretation of data, critical revision, final approval, agreement to be accountable for all aspects of the work; **Adam M. Zanation**, conception of work, analysis/interpretation of data, critical revision, final approval, agreement to be accountable for all aspects of the work.

Disclosures

Competing interests: Brian Thorp, Medtronic Energy—consultant; Adam Zanation Acclarent, Stryker, Medtronic—consultant.

Supplemental Material

Additional supporting information may be found at http://otojournal.org/supplemental.

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