

Sinonasal Malignancies: Endoscopic Treatment Outcomes

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Sinonasal malignancies are rare and heterogeneous cancers located adjacent to critical neurovascular structures. Proximity to the orbit, brain, cranial nerves, and carotid arteries make surgical resection technically challenging and potentially morbid. The gold standard surgical procedure for these cancers has traditionally been the open craniofacial resection. Endoscopic endonasal approaches emerged in the last two decades as a viable alternative for carefully selected patients. The rarity and heterogeneity of the cancers precludes randomized controlled trials. Evidence for surgical approaches is based on case series and multi-analyses. Current evidence demonstrates that endoscopic approaches do not compromise survival and have lower complication rates. This article provides an update of the current literature examining outcomes for the endoscopic treatment of sinonasal malignancies.

INTRODUCTION

Sinonasal malignancies are a group of rare heterogeneous cancers that originate near critical neurovascular structures. The incidence is estimated to be 0.83 per 100,000 persons.¹ Proximity to the orbit, brain, cranial nerves, and carotid arteries make surgical resection inherently challenging and potentially morbid. Evidence for treatment strategy of these cancers is based on case series, meta-analyses, systematic reviews, and expert opinions. The rarity and heterogeneity of these cancers precludes randomized controlled trials. In the early to mid-20th century, surgical resection consisted of maxillectomy, nasal cavity exenteration, and curettage of the ethmoid and sphenoid sinuses with overall 5-year cure rates of 28%.² In 1963, Ketcham et al. described the transfacial and transcranial craniofacial resection (CFR) for sinonasal cancers.³ In contrast to curettage, the CFR described en bloc resection of the tumor and cribriform plate and patients from this series demonstrated improved survival outcomes. The open craniofacial resection became the gold standard for sinonasal malignancies. Overall 5-year survival rose to 51% in the 1990s for sinonasal malignancies, excluding esthesioneuroblastoma.⁴

Reports of endoscopic approaches to sinonasal malignancies were first published in the late 1990s. This development was a natural extension from endoscopic surgery for inflammatory sinus disease, benign sinonasal neoplasms,

and idiopathic and iatrogenic cerebrospinal fluid leaks. Early endoscopic approaches targeted early stage (T1/T2) sinonasal malignancies and combined a craniotomy for more advanced cancers—the cranioendoscopic approach (CEA). Indications for endonasal endoscopic approaches expanded as endoscopic experience with cancer resection and cerebrospinal fluid leak repair grew. The endonasal endoscopic approach (EEA) is now used to resect cancers invading the dura and brain. The philosophy of the endoscopic approach rests on the observation that sinonasal cancers frequently have a focal attachment point and that most tumor volume fills the air-filled sinonasal cavity.⁵ The endoscopic approach proceeds with piece-meal debulking with the goal of identifying and resecting the tumor pedicle en bloc. This approach is criticized for the theoretical inability to obtain negative margins.⁶ Conversely, proponents of the EEA cite improved visualization of the tumor margins with the endoscope as facilitating complete resection of the tumor origin resulting in negative margins.⁵ This article provides an update of the current literature evaluating the outcomes for the endoscopic approach to sinonasal malignancies.

The neurovascular structures adjacent to the sinonasal cavity makes surgical resection potentially morbid. Complications of open or endoscopic approaches include cerebrospinal fluid leaks and sequestrae, cranial nerve injuries, and hemorrhage. Open and CEA approaches have additional morbidity associated with performing a craniotomy.^{7,8} Additionally, the EEA avoids facial incisions and potential cosmetic issues that arise from lateral rhinotomy and coronal incisions.

MARGINS

The importance of obtaining negative margins for locoregional control and overall survival cannot be overstated. Multiple studies demonstrate that positive margins predict treatment failure and negatively impact survival.^{7,9,10} En bloc resection, in contrast to piecemeal resection, has been the traditional surgical method to obtain negative margins. Violation of the cancer via debulking was believed to spread cancer and reduce locoregional

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control and survival. However, this has not been supported in the literature. The outcomes of en bloc versus piecemeal resections for 30 open CFRs for sinonasal malignancies were studied to address this question.¹¹ En bloc resections were attempted for all patients except when intraoperatively or preoperatively it was determined that en bloc resection could not proceed safely. Three-year survival outcomes demonstrated that patients with negative margins had similar outcomes irrespective of the procedure being performed en bloc or in a piecemeal fashion. Though there were more positive margins in the piecemeal group this reflects that more locally advanced tumors were resected piecemeal. The authors concluded that obtaining negative margins optimizes survival independent of the surgery being performed piecemeal or en bloc.

SURVIVAL OUTCOMES OF OPEN CRANIOFACIAL RESECTION

Survival data for sinonasal malignancies is based on case reports, larger multi-institutional cohorts, and meta-analyses due to the relative rarity of these tumors. The largest open CFR cohort was a multi-institutional analysis of survival and complication data from 17 institutions performing open CFR for 334 primary paranasal sinus malignancies, excluding esthesioneuroblastoma.⁷ Esthesioneuroblastoma was excluded owing to its improved survival and delayed recurrence that may as many as 10 to 15 years out from initial treatment. Five-year disease-specific survival (DSS) for the entire cohort was 53.3%. This is similar to Dulguerov et al.'s findings in their cohort of 220 cases with 5-year DSS of 54.5% although this study excluded mucosal melanomas in addition to esthesioneuroblastomas.⁴ Tumor margins, histology, intracranial involvement, and orbital involvement were analyzed for their effect on disease-specific survival. Notably, 15.6% of margins were positive and 12.9% were close. Positive margins were predictive of treatment failure with a 5-year DSS of 25% for positive margins compared to 64% for negative margins (relative-risk (RR) 2.3, $P < .0001$). This highlights the importance of obtaining negative margins. Intracranial extension, orbital extension, and tumor histology were additionally found to be independent predictors of DSS. Mucosal melanoma had the worst prognosis followed by squamous cell carcinoma.

Similar survival figures were found in analysis of the 25-year experience with CFR at the Royal National Throat Nose and Ear Hospital in the United Kingdom.¹² Three hundred eight patients who underwent traditional craniofacial resection over up to a 25-year period were analyzed (259 malignant, 49 benign). The 5-year disease-free survival (DFS) for malignant tumors was 59% at 5 years. It should be noted that this analysis included esthesioneuroblastoma in contrast to the previous mentioned study. DFS fell to 40% at 10 years, and 33% at 15 years. Intracranial extension and orbital involvement were found on multivariate analysis to be the most prognostic factors influencing survival. Interestingly, the authors note an improvement in 5-year actuarial survival compared to their previous

report in 1998 that they attributed to earlier disease recognition, improvement in adjuvant therapy, and refinement of surgical technique. These survival figures from large cohort series and multi-institutional studies provide a benchmark to judge the EEA.

SURVIVAL OUTCOMES FOR ENDOSCOPIC TREATMENT FOR SINONASAL MALIGNANCIES

Survival data for the EEA for sinonasal malignancies is also based on cohort series, systematic reviews, and meta-analyses. In 2008, Nicolai et al. published their outcomes for 184 patients treated exclusively endoscopically or endoscopic-assisted between 1996 and 2006.¹³ Five-year DSS was found to be 94.4% for adenocarcinoma, 60.7% for squamous cell carcinoma, and 100% for adenoid cystic carcinoma. This is in contrast to the craniotomoscopic approach group that had similar survival figures to the aforementioned traditional cohorts with 5-year DSS's of 57.9%, 53.3%, and 100%, respectively. The overall cohort 5-year DSS was 81.9% with a 91.4% DSS for the endoscopic group and 58.8% for the craniotomoscopic group. Although these survival figures are promising, it is difficult to draw direct comparisons from this cohort to the traditional CFR cohorts due to the heterogeneity of histologies and staging. This cohort included 22 esthesioneuroblastomas (5-year DSS of 100%) and was comprised of 37% adenocarcinomas (5-year DSS 80.4%), and 13.6% SCC (5-year DSS of 60.7%). That is contrast to Ganly et al.'s cohort that contained 32% adenocarcinoma and 30.2% SCC and excluded esthesioneuroblastoma.⁷ The authors note that endoscopic approaches were initially limited to T1 and T2 and gradually extended indications to include tumors with skull base and dural involvement as their facility with dural repair grew.

A recent systematic review and meta-analysis by Rawal et al. investigated the survival outcomes for 952 patients treated with endoscopic or endoscopic-assisted surgery for malignant sinonasal tumors.¹⁴ In aggregate analysis of 759 patients, the overall 2-year survival was 87.5% and the 5-year survival was 72.3%. Direct-pooled analysis of the 193 patients with individual-level data demonstrated 2- and 5-year overall survival rates of 85.8% and 83.5%, respectively. Esthesioneuroblastoma was the most common pathology (32%) in the direct pooled analysis and 14.5% of patients had SCC. When comparing the survival figures from this study to those from open CFR it should be noted that most patients in the direct-pooled analysis (63%) had low-stage cancers (T1 or T2).

A retrospective review of endoscopic treatment of sinonasal SCC demonstrated acceptable survival outcomes.¹⁰ Thirty-four patients were included for analysis with 27 procedures performed for curative intent and seven performed for palliation or to reduce tumor bulk before chemoradiation. There were 10 patients with T4b, nine patients with T4a, and three patients with T3 disease among the 27 patients in the definitive resection group. The 5-year OS, DFS, and locoregional control rate for the definitive resection group was 78%, 62%, and 62%, respectively. Five patients from

the definitive resection group had positive margins (19%) and these patients had a 0% 5-year locoregional control rate, DFS, and OS. Patients in the definitive resection group with negative margins (22/29) had significantly better survival outcomes. The 5-year OS, DFS, and locoregional control rate was 93%, 74%, and 74%, respectively. These results compare favorably to previously reported outcomes.

COMPARISON OF ENDOSCOPIC VERSUS TRADITIONAL CFR

Several reviews and meta-analyses comparing outcomes between endoscopic and open CFRs have shown at least equivalent survival data. A systematic review and pooled-data analysis of 226 patients demonstrated that there was no difference in survival outcomes between endoscopic and traditional CFR for T1 and T2 sinonasal malignancies.⁸ Patients in this study were identified from 15 case studies reporting outcomes for esthesioneuroblastoma, adenocarcinoma, and sinonasal undifferentiated carcinoma. When stratifying for low-stage malignancies, the 5-year OS, DSS, and locoregional control were not statistically significant between the endoscopic and traditional CFR groups (87.4% vs. 76.8% OS, 94.7% vs. 87.7% DSS, 89.5% vs. 77.2%, endoscopic vs. open, respectively). The endoscopic group did have a greater number of low-staged malignancies (78.2 % T1/T2, Kadish A/B) compared to the traditional CFR group (22.3 % T1/T2, Kadish A/B) thereby making it difficult to draw conclusions on survival differences between the entire cohorts.

To compare outcomes for an EEA or traditional CFR for esthesioneuroblastoma, Harvey et al. performed a stage-matched analysis on 109 esthesioneuroblastomas treated at six cancer centers.⁹ Survival analysis demonstrated significant improvement in the EEA group for Kadish stage C (log-rank $P = .017$). Notably, the endoscopic group cohort had greater margin clearance for Kadish stage B (90% vs. 71.4%, $P = .001$) and Kadish stage C (84.2% vs. 53.1%, $P = .001$). Margin status was again found to be an important predictor of survival ($P = .004$). However, the authors note that Kadish stage C tumors treated via an open approach likely had greater intracranial extent, potentially biasing the results.

A recent systematic review and meta-analysis of esthesioneuroblastoma found similar survival results.¹⁵ Univariate analysis demonstrated that endoscopic surgery was associated with significantly better overall survival ($P = .001$) and DSS ($P = .004$). However, pooled individual data for the meta-analysis revealed that the endoscopically treated group had a lower proportion of Kadish stage C and D tumors compared to the open group. A subgroup analysis for Kadish stage C and D patients did demonstrate greater overall survival ($P = .04$) but the difference in DSS did not reach statistical significance ($P = .051$).

Similar results were found with respect to sinonasal adenocarcinoma. A recent pooled-analysis demonstrated improved survival outcomes for patients treated endoscopically.¹⁶ One thousand four hundred four cases were included from retrospective studies and crude survivals

were stratified based on T classification and surgical approach (endoscopic or open). The overall local recurrence rate was 17.8% in the endoscopic surgery group compared to 38.5% in the open group. However, smaller tumors were more likely to be treated endoscopically as in previous studies. DFS, local recurrence-free survival, and overall survival were statistically significantly higher in the endoscopic group for T2, T3, and T4 but not T1 cancers. However, cancers with more extensive intracranial and orbital involvement were more likely to be treated with an open approach among T4 tumors. The results of the systematic reviews and meta-analyses are summarized in Table I.

Mucosal melanoma, unlike adenocarcinoma, continues to have notoriously poor survival results. Although there has been a demonstrated improvement with squamous cell carcinoma and adenocarcinoma, there has not been an improvement in mucosal melanoma survival.⁴ Data for open CFR demonstrated a 3-year DSS of 29.7% for mucosal melanoma.¹⁷ Lund and Wei's endoscopic cohort published in 2015 found a 5-year DFS of 39% for 33 patients with mucosal melanoma.¹⁸ An additional consideration for mucosal melanoma is that wider margins are needed compared to other sinonasal malignancies due to high false-negative rates of intraoperative frozen margins.¹⁹

MORBIDITY RATES

Data from the international collaborative study on craniofacial resection demonstrated an overall postoperative mortality rate of 4.7% (56 of 1193).²⁰ Interestingly, neither prior radiation, dural invasion, or intraparenchymal invasion were predictive of mortality. Medical comorbidity was predictive of mortality on both univariate and multivariate analysis with a relative risk of 1.9. Age greater than 50 was predictive on univariate but not multivariate analysis of mortality. Postoperative complications occurred in 36.3% of patients with wound complication being most common (19.8%), followed by CNS complications (16.2%). Medical morbidity, prior radiation, dural invasion, and brain invasion were all predictive of postoperative complications. The cohort of 308 patients from the Royal National Throat Nose and Ear Hospital only had one immediate death and two deaths in the postoperative period.¹² CSF leaks occurred in eight patients in their cohort. The median hospital stay was 14 days.

In Nicolai et al.'s cohort of 184 patients, there were no mortalities in the endoscopic group (134 patients) and two mortalities in the CEA cohort (50 patients).¹³ Both of the mortalities were stage T4b. The overall complication rate was 8.7% with 6% in the EEA group and 16% in the CEA group. CSF leak was the most frequent complication with four occurring each in the EEA and CEA group. The length of stay (LOS) for the endoscopic group was 3.7 days compared to 15.4 for the cranioendoscopic group.

ADJUVANT THERAPY

Advances in radiation and chemotherapy have also contributed to improved outcomes and decreased morbidities

TABLE I.
Summary of Systematic Reviews and Meta-Analyses.

Source	N	Pathologies	Staging	Outcomes
Rawal (2016) ¹³	759 (aggregate) (90% purely endo)	SNAC (56%) Melanoma (13%) SCC (11%)	N/A	5-yr OS: 72.3%
	193 (pooled) (78% purely endo)	Esthesio (32%) Melanoma (13%) SCC (11%)	Low-stage: 63%	5-yr OS: 83.5%
Higgins (2011) ¹⁴	56 (endo)	Esthesio (51.8%) SNAC (17.9%) SCC (7.1%)	High-stage: 21.8%	5-yr OS: 88.4% 5-yr OS (low-stage): 87.4% 5-yr OS (high-stage): 90.9%
	101 (open)	Esthesio (43.6%) SNAC (21.8) SNUC (34.7%)	High-stage: 77.7%	5-yr OS: 55.2% 5-yr OS (low-stage): 76.8% 5-yr OS (high-stage): 47.9%
Harvey (2017) ⁸	67 (endo)	Esthesio (100%)	Kadish A: 13.4% Kadish B: 29.9% Kadish C: 56.7%	Entire cohort: 5-yr OS: 85%
	42(open)		Kadish A: 4.8% Kadish B: 16.7% Kadish C: 78.6%	
Fu (2016) ¹⁶	Aggregate: 486 (open) 123 (endo)	Esthesio (100%)		Locoreg recur: 45.0 % 17.4 %
	Individual Participant: 52 (endo) 177 (open)	Esthesio (100%)	High-stage: 40.4 % (endo) 48.6% (open)	5-yr OS: 100% (endo) 71.2 (open)
Meccariello (2014) ¹⁷	431 (endo)	SNAC (100%)	High-stage: 45.8 % (endo)	5 yr OS: T3: 79.5% (endo) T4: 66.4% (endo)
	1270 (open)		61.9 % (open)	T3: 66.5% (open) T4: 47.1% (open)

Endo = endoscopic; SNAC = sinonasal adenocarcinoma; SCC = squamous cell carcinoma; 5-yr OS = 5-year overall-survival, Esthesio = esthesioneuroblastoma; SNUC = sinonasal undifferentiated carcinoma; Low-stage = T1/T2 or Kadish A/B; High-stage = T3/T4 or Kadish C/D.

for sinonasal malignancies. Intensity-modulated radiation therapy (IMRT) was a major advance in radiotherapy allowing for improved targeting of the tumor while sparing the optic nerves, brainstem, and brain parenchyma. Postoperative IMRT has been found to significantly improve DFS and reduce the incidence of acute and delayed toxicities.^{21–23} Charged particle therapy with protons or carbon ions are an additional modality with the potential to further decrease toxicity to surrounding structures while maintaining delivery to the targeted areas.²⁴ Chemotherapy has been utilized in the neoadjuvant setting and concurrently with radiation either as definitive therapy or in the adjuvant setting. There are currently no randomized controlled trials evaluating whether incorporation of chemotherapy influences survival. Favorable response to induction chemotherapy for squamous cell carcinoma has been shown to be predictive of survival.²⁵ Multimodality therapy with induction chemotherapy,

surgical resection, and adjuvant chemoradiotherapy was shown in one series to have promising results with a 5-year DFS of 67%.²⁶ Further collaborative multi-institutional studies are needed to determine the optimal combination of surgery, radiation, and chemotherapy.

CONCLUSION

Sinonasal malignancies are a group of rare malignancies that remain challenging to treat. Much progress has been made in both treatment and our understanding of the disease process. The anterior craniofacial resection as described by Ketcham and refined by others was a major advancement in therapy. What is clear from the data is that resection to negative margins is the most important variable predictive of survival that surgeons may influence. The endoscopic approach is at least as

good as the open approach in obtaining negative margins. The endoscopic approach does carry less morbidity and a shorter hospital stay. The gold standard for surgery of sinonasal malignancies is therefore to select the approach that is most capable of obtaining negative margins while minimizing patient morbidity.

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