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REVIEW ARTICLE

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Exclusively endoscopic surgical resection of esthesioneuroblastoma: A systematic review

Daniel B. Spielman[1] | Andi Liebowitz[1] | Maeher Grewal[1] | Chetan Safi[1] | Jonathan B. Overdevest[1] | Alfred M. Iloreta[2] | Brett E. Youngerman[3] | David A. Gudis[1]

[1]Department of Otolaryngology-Head and Neck Surgery, New York-Presbyterian Hospital—Columbia University Irving Medical Center, New York, New York, USA

[2]Department of Otolaryngology-Head and Neck Surgery, The Mount Sinai Hospital/Icahn School of Medicine at Mount Sinai, New York, New York, USA

[3]Department of Neurological Surgery, New York-Presbyterian Hospital—Columbia University Irving Medical Center, New York, New York, USA

Correspondence

Daniel B. Spielman, Department of Otolaryngology-Head and Neck Surgery, New York-Presbyterian Hospital—Columbia University Irving Medical Center, 180 Ft Washington Ave, New York, NY 10032, USA.
Email: DBSpielman@gmail.com

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Abstract

Background: Historically sinonasal malignancies were always addressed via open craniofacial surgery for an oncologic resection. Increasingly esthesioneuroblastomas are excised using an exclusively endoscopic approach, however, the rarity of this disease limits the availability of long-term and large scale outcomes data.

Objective: The primary objective is to evaluate the treatment modalities used and the overall survival of patients with esthesioneuroblastoma managed with exclusively endoscopic surgery.

Methods: In accordance with PRISMA guidelines, PubMed was queried to identify studies describing outcomes associated with endoscopic management of esthesioneuroblastomas.

Results: Forty-four out of 2462 articles met inclusion criteria, totaling 399 patients with esthesioneuroblastoma treated with an exclusively endoscopic approach. Seventy-two patients (18.0%) received adjuvant chemotherapy and 331 patients (83.0%) received postoperative radiation therapy. The average age was 50.6 years old (range 6–83). Of the 399 patients, 57 (16.6%) were Kadish stage A, 121 (35.2%) were Kadish stage B, 145 (42.2%) were Kadish stage C, and 21 (6.1%) were Kadish stage D. Pooled analysis demonstrated that 66.0% of patients had Hyams histologic Grade I or II, while 34.0% of patients had Grade III or IV disease. Negative surgical margins were achieved in 86.9% of patients, and recurrence was identified in 10.3% of patients. Of those with 5-year follow-up, reported overall survival was 91.1%.

Conclusion: Exclusively endoscopic surgery for esthesioneuroblastoma is performed for a wide range of disease stages and grades, and the majority of these patients are also treated with adjuvant chemotherapy or radiation therapy. Reported overall recurrence rate is 10.3% and 5-year survival is 91.1%.

KEYWORDS

anterior skull base, endoscopic skull base surgery, esthesioneuroblastoma, olfactory neuroblastoma, skull base

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INTRODUCTION

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a rare small round blue cell tumor of the olfactory neuroepithelium that usually arises in the superior aspects of the nasal cavity along the skull base. Historically, sinonasal malignancies such as esthesioneuroblastomas were treated via open craniofacial or transfacial surgery to achieve an oncologic resection.[1,2] As endoscopic technology and surgical technique advanced, combined endonasal endoscopic and open surgical approaches for esthesioneuroblastomas became common.[3,4] Presently, many skull base surgery centers manage esthesioneuroblastomas with an exclusively endonasal endoscopic approach. However, the rarity of this disease limits evaluation of large-scale outcomes. By evaluating all reported cases of this disease, this systematic review aims to strengthen our understanding and ability to treat patients with esthesioneuroblastoma, while recognizing the limitations of retrospectively analyzing heterogeneously pooled data. The purpose of this study is to review the characteristics and outcomes of patients who undergo exclusively endoscopic surgery for esthesioneuroblastoma.

METHODS

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study was exempt from institutional review board approval, as no human subjects were affected. The PubMed database was queried using the search terms "esthesioneuroblastoma" and "olfactory neuroblastoma" to identify studies publishing outcomes associated with the endoscopic management of esthesioneuroblastoma. Articles published up until April 10th, 2020, were included. Initial screening was performed by one reviewer according to the title and abstract. Studies not available in English were excluded. Covidence (http://www.covidence.org/) software was utilized to facilitate article screening. Following the preliminary round of screening, articles were then screened using full text to determine relevance. Only articles describing exclusively endoscopic resection were included. Many studies report series of patients including some who underwent endoscopic surgery and others who underwent open resection. From these studies, only patients whose surgeries were performed exclusively endoscopically were included in the analysis. Likewise, patients who underwent a combined endoscopic and open transcranial approach were excluded. In the event of studies with overlapping subjects, the largest study was included and all smaller studies were excluded. Additionally, studies without relevant information regarding adjuvant treatment modalities or patient characteristics were excluded. Summary statistics were calculated using Microsoft Excel (Version 16.30).

RESULTS

Forty-four out of 2462 articles met inclusion criteria (Figure 1), yielding 399 patients with esthesioneuroblastoma treated with an exclusively endoscopic surgical approach. Characteristics of each of the included studies are reported in Table 1. The average age was 50.8 years old (range 6–83). Eight of the 49 studies included at least one pediatric patient; 11 of the 410 (2.7%) patients were <18 years of age. Pooled analysis demonstrated that 57 (16.6%) were Kadish stage A, 145 (35.2%) were Kadish stage B, 145 (42.2%) were Kadish stage C, and 21 (6.1%) were Kadish stage D. Regarding disease grade, 66.0% of patients had Hyams histologic grade I or II while 34.0% of patients had Grade III or IV

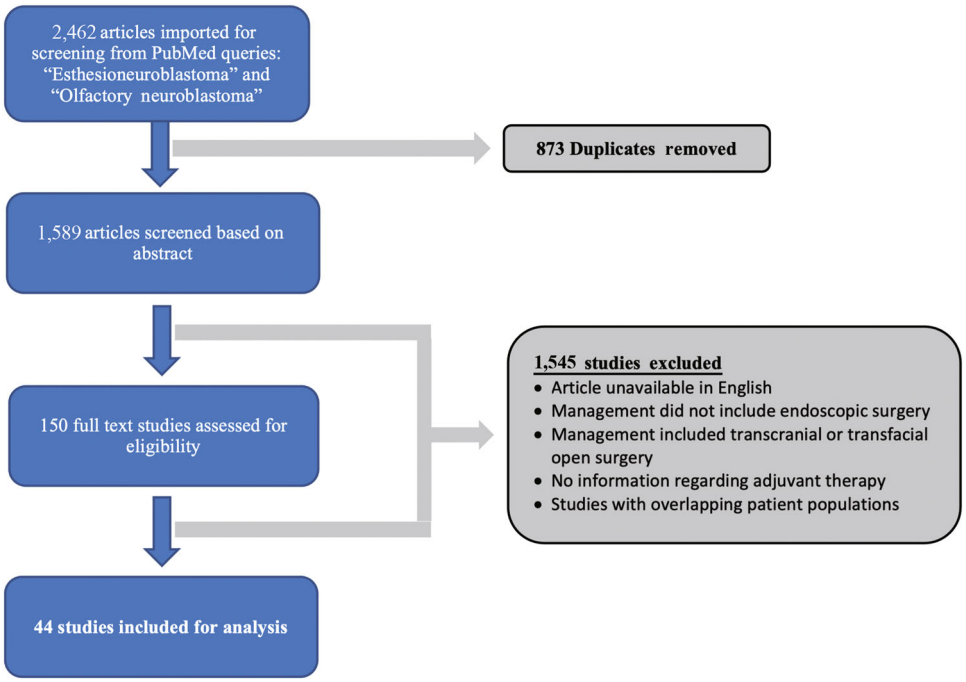

FIGURE 1 Flow chart of study selection

TABLE 1 Baseline characteristics and outcomes from included studies

First author	Year	Patients (*n*)	Mean age (range)	Kadish stage	Hyams grade	CTX	RT	Follow-up (months)	5 yr survival (#/total)
Dumont[5]	2020	4	12 (8–14)	A1, B1, C2	II - 1	3 (etoposide-carboplatin; cyclophosphamide-adriamycin-vincristine)	3	61.25 (41–86)	2/4
Martinez-Perez R[6]	2019	2	43 (31–55)	B2	n/a	1 (cisplatin)	2	103 (86–120)	2/2
DeGabory[7]	2018	53	54.3 ± 19[a]	A9, B12, C25, D7	I - 6, II - 23, III - 10, IV - 6	10 (cisplatin ± etoposide)	48	45.4	47/53
Gallia[8]	2018	20	51.1 (34–73)	A2, B3, C11, D2	I - 3, II - 11, III - 6	5	19	70.3 (16–141)	12/12
Klironomos[9]	2018	10	47.5 (24–70)	A2, B2, C4, D2	II - 5, III - 2, IV - 3		9	74.8 (6–120)	6/6
Maggiore[10]	2018	1	13	B1	n/a		0	24	
Nakagawa[11]	2018	22	49 (27–83)	A4, B5, C13	I - 2, II - 18, III - 2		20	44 (11–104)	
Rasool[12]	2018	1	28	n/a	I - 1	0	1		
Saito[13]	2018	1	66	A1	n/a		1	192	1/1
Woods[14]	2018	6	n/a	B4, C2	n/a				6/6
Yu[15]	2018	1	55	n/a	II - 1		1	12	
Bartel[16]	2017	4	n/a	A1, B2, C1	II - 3, IV - 1		2	66.5 (41–107)	4/4
Harvey[17]	2017	67	51.5	A9, B20, C38	I - 8, II - 35, III - 21, IV - 3		52	58.5	
Hwang[18]	2017	10	52.1 (33–71)	A1, B7, C2	n/a	3	8	63.9 (13–165)	8/10
Wertz[19]	2017	6	n/a	B4, C2	n/a		1	21.6 (3.6–48)	5/5
Battaglia[20]	2016	1	16	C1	II - 1	1 (vincristine, adriamycin, cyclophosphamide)	1	18	
Manthuruthil[21]	2016	10	49.1 ± 14[a]	B3, C5, D2	n/a	7 (cisplatin)	10		
Nakano[22]	2016	1	27	n/a	n/a	1 (cisplatin)	1	14	
Soldatova[23]	2016	13	52.4 (24–77)	A2, B4, C5, D2	I - 1, II - 7, III - 5	1	10	31.8 (4.5–58)	
Zhang[24]	2016	13	43 (15–69)	A1, B3, C6, D3	I - 1, II - 5, III - 7	3 (etoposide, cisplatin)	12	65 (23–116)	6/13
Chang[25]	2015	5	48	n/a	n/a	1	3	(18–115)	5/5
Feng[26]	2015	24	46.5 (13–76)	A3, B6, C15	n/a	7	20	44 (8–130)	
Lund[27]	2015	36	n/a	n/a	n/a	25 (cisplatin)	33	77.6 (6–162)	35/36

TABLE 1 (Continued)

First author	Year	Patients (*n*)	Mean age (range)	Kadish stage	Hyams grade	CTX	RT	Follow-up (months)	5 yr survival (#/total)
Matsunaga[28]	2015	1	46	B1	n/a		1	16	
Petruzzelli[29]	2015	9	50 (27–72)	A4, B5	n/a	0	7	67 (43–88)	6/6
Uslu[30]	2015	1	69	n/a	II - 1		1	36	
Yokoi[31]	2015	2	54.5 (42–67)	A/B 1	(I/II) - 1, II - 1	0	1		
ElKababri[32]	2014	1	10	B1	n/a		1	120	1/1
Wessell[33]	2014	1	28	C1	n/a			18	
Song[34]	2012	5	42 (19–67)	A2, B2, C1	n/a			88	5/5
Carta[35]	2011	5	59.5	n/a	III - 2, IV - 3		5	21	4/5
Monteiro[36]	2011	4	33 (22–46)	B2, C1, D1	n/a		4	14 (7–17)	
Zhang[37]	2010	3	39 (27–56)	A1, B2	n/a		3	18.3 (18–20)	
Kim[38]	2008	1	47	D1	n/a	1 (etoposide, cisplatin, ifosfomide)	1	16	
Nicolai[39]	2008	19	n/a	A3, B11, C5	n/a				
Zafereo[40]	2008	3	57 (45–68)	A2, B1	I - 1, II - 2		1	67.3 (21–147)	
Dave[41]	2007	10	57.2 (39–81)	A5, B2, C2, D1	n/a		9	40.4 (3–105)	
PodBoj[42]	2007	1	67	n/a	n/a		0	88	1/1
Suriano[43]	2007	9	51.5 (38–65)	A3, B6	n/a		9	42.8 (26–60)	
Poetker[44]	2005	5	54.8 (40–69)	A1, B2, C2	n/a	2	4	74.8 (38–102)	4/4
Constandtinidis[45]	2004	5	56.2 (35–80)	B4, C1	I - 2		3	125.8 (20–242)	3/5
Morris[46]	2004	1	63	n/a	n/a			15	
Pasquini[47]	2003	1	72	B1	n/a			53	
Cakmak[48]	2002	1	12	B1	n/a		1	24	
Sharma[49]	2002	1	40	n/a	n/a	1 (cisplatin, etoposide, cyclophosphamide, vincristine)	1		
Totals		399	50.8 yrs	A57, B121, C 145, D21	I - 24, II - 114, III - 55, IV - 16	72	331	53.5 months	154/169 (91.1%)

Note: mean ± SD.

Abbreviations: CTX, chemotherapy; RT, radiation therapy.

TABLE 2 Complications

Intraoperative complications	Patients (*n*)
Moderate hemorrhage	1
Unexpected CSF leak	1
Orbital hematoma	1
Postoperative Complications	
Altered mental status	1
Atrial fibrillation	1
Brain abscess	1
Clostridium Difficile infection	1
CSF leak	4
Dacrocystitis	1
Dural graft extrusion	1
Epistaxis	4
Intranasal synechiae	2
Infraorbital anesthesia	3
Meningitis	7
Meningoencephalocele	1
Mucocele	1
Nasal infection/Sinusitis	3
Nasal vestibular stenosis	1
Olfactory loss	Not quantified
Pneumocephalus	4
Pulmonary embolism	1
Subdural hemorrhage	1
Symptomatic anemia	2

disease. Negative surgical margins were achieved in 86.9% of patients. Of the 399 patients, 72 (18.0%) received adjuvant chemotherapy and 331 patients (83.0%) received postoperative radiation therapy. Complications data unique to patients who underwent endoscopic surgery were reported by 30 of 44 papers. Complications are summarized in Table 2 with a total of 23 complication types in 42 patients although some patients experienced multiple complications. Disease recurrence was identified in 41 (10.3%) patients. The mean time to recurrence was 56.6 months, with a range of 7–192 months. Of those patients with 5-year follow-up, overall survival was 91.1%.

DISCUSSION

In 2019, the International Consensus Statement on Endoscopic Skull-Base Surgery suggested that Kadish stage A or B tumors should be resected endoscopically, while tumors with significant intracranial, orbital, and facial soft tissue involvement may require open or combined approaches to achieve negative margins.

This systematic review demonstrates the utility of an exclusively endoscopic approach in resecting esthesioneuroblastoma tumors. The rarity of this disease has limited the evaluation of outcomes on a large scale, as the majority of publications report results from single centers. To date, the largest primary studies on surgical management of esthesioneuroblastomas report on the outcomes of 53 and 67 patients respectively who underwent exclusively endoscopic resection. The results of the present study demonstrate the utility of exclusively endoscopic approaches, even for certain cases of advanced disease.

In 2017, Harvey et al.[17] reported the results from six institutions across the United States and Australia, demonstrating improved overall survival for 67 endoscopically treated patients as compared to 42 stage-matched open craniofacial resections. It is essential to recognize that the nonrandomized nature of this trial confers inherent selection bias towards performing open procedures for those in whom it appeared more challenging to obtain negative margins endoscopically. Importantly, there was a high rate of achieving negative margins (88.1%), despite the fact that 53.5% of the patients within Kadish C stage underwent endoscopic resection in their cohort.

In 2015, Fu et al.[50] published a systematic review comparing the open versus endoscopic surgical approaches to esthesioneuroblastoma, concluding an improvement in overall survival in patients treated endoscopically. The 5-year overall survival for patients undergoing endoscopic resection was 100%, based on the available data for 49 patients. This high rate of overall survival suggests the possibility of reporting bias in the literature preceding that publication. Notably, only 123 cases of endoscopic resections of esthesioneuroblastoma had been reported in the literature and included in that study. We presently report on 410 patients.

The results of this systematic review demonstrate the success of an endoscopic approach even for advanced stage tumors, as 48.3% of patients were Kadish C or D stage. The outcomes analyzed in this systematic review of exclusively endoscopic management of esthesioneuroblastoma are encouraging, with a low recurrence rate of 10.3% in patients for whom data is available. The mean time to recurrence was 56.6 months, with a range of 7–192 months. Previously published recurrence rates and time to recurrence vary widely. In a systematic review, Komotar et al. reported a recurrence rate of 22% in 285 patients who underwent craniofacial resection and a mean time to recurrence of 42.2 months (range 12.6–70.8).[51] Their reported 5-year overall survival rate for this group was 81.5%, compared to 91.1% found in our systematic review for patients who underwent exclusively endoscopic resection. These findings lend greater support to the endoscopic management of esthesioneuroblastoma, as it has previously been demonstrated that the endoscopic approach results in shorter hospitalization times and faster recovery.[52]

The most common complications in the 399 patients included in this study were meningitis (7/399, 1.8%), CSF leak (4/399, 1.0%), epistaxis (4/399, 1.0%), and pneumocephalus (4/399, 1.0%). In comparison, Komotar et al. reported higher complication rates of 4.5% for meningitis, 6.0% for CSF leak in patients treated with

open craniofacial resection.[51] Although CSF leak remains a concern for the endoscopic approach, Palejwala et al. similarly reported a lower rate of CSF leak with exclusively endoscopic approach compared to open or combined approaches, which they attribute to advancements in endonasal skull base reconstruction techniques.[53]

Although esthesioneuroblastoma is the most common malignancy of the naval cavity in the pediatric patient population, it is nevertheless extremely rare, with fewer than 100 cases reported in the literature to date.[5] Because of its rarity, there is no consensus on treatment guidelines in this population. Seven studies in this systematic review included pediatric patients, for a total of 10 patients <18 years of age treated with exclusively endoscopic endonasal resection. Intraoperative complications in this group included moderate hemorrhage in one patient.[48] Only one study reported any postoperative complications in pediatric patients.[5] However, this study included patients treated with an open craniofacial resection as well and did not separate complications by surgical approach. Multiple studies did report reduced postoperative morbidity and/or complication rates with endoscopic approach with similar oncologic outcomes.[5,10,26,48]

This systematic review carries several inherent limitations secondary to the heterogenous nature of the included studies. The pooled data reported from individual publications precludes the performance of a multivariable regression analysis to assess the relationship between presenting characteristics and patient outcomes. Similarly, we are unable to report the rates of combined chemoradiation adjuvant therapy because many of the studies within the literature do not specify whether patients received dual-modality adjuvant therapy. This systematic review likely underreports the true complication rate of exclusively endoscopic surgery because many of the studies analyzed pooled data with open craniofacial resection, which was not included in this analysis. Additional research is warranted to determine the extent to which advanced Kadish stage or Hyams grade impacts the ability to endoscopically achieve negative margins, as well as the risk of recurrence, need for adjuvant therapy, and overall survival.

CONCLUSION

Exclusively endonasal endoscopic surgery for esthesioneuroblastoma is performed for a wide range of disease stages and grades, and the majority of patients are also treated with adjuvant radiation therapy. In patients for whom published data is available, there is an overall recurrence rate of 10.3% and a 5-year overall survival of 91.1%.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

All listed authors made substantial contributions to this work in accordance with the standards set forth by The International Committee of Medical Journal Editors (ICMJE).

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