Neurosurg Rev (2011) 34:465–475
DOI 10.1007/s10143-011-0329-2

ORIGINAL ARTICLE

Endonasal endoscopic resection of esthesioneuroblastoma: the Johns Hopkins Hospital experience and review of the literature

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Received: 12 October 2010 / Revised: 27 February 2011 / Accepted: 4 April 2011 / Published online: 8 June 2011

Abstract Esthesioneuroblastoma is an uncommon malignant tumor originating in the upper nasal cavity. The surgical treatment for this tumor has traditionally been via an open craniofacial resection. Over the past decade, there has been tremendous development in endoscopic techniques. In this report, we performed a retrospective analysis of patients with esthesioneuroblastomas treated with a purely endonasal endoscopic approach and resection at the Johns Hopkins Hospital between January 2005 and April 2010. A total of eight patients with esthesioneuroblastoma, five men and three women, were identified. Six patients were treated for primary disease, and two were treated for tumor recurrence. The modified Kadish staging was A in one patient (12.5%), B in two patients (25%), C in four patients (50%), and D in one patient (12.5%). All patients had a complete resection with negative intraoperative margins. One patient had intraoperative hypertension; there were no perioperative complications. With a mean follow-up of over 27 months, all patients are without evidence of disease. In addition, we reviewed the literature and identified several overlapping case series of patients with esthesioneuroblastoma treated via a purely endoscopic technique. Our series adds to the growing experience of expanded endonasal endoscopic surgery in the treatment of skull base tumors including esthesioneuroblastoma. Longer follow-up on a larger number of patients is required to further demonstrate the utility of endoscopic approaches in the management of this malignancy.

Keywords Esthesioneuroblastoma · Olfactory neuroblastoma · Expanded endonasal approach · Endoscopy · Endoscopic · Skull base

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Introduction

Esthesioneuroblastoma is an uncommon tumor of the nasal cavity originating from the olfactory epithelium. Since its original description in 1924 by Berger et al. [2], more than 1,000 cases have been reported in the literature. These malignant tumors, also referred to as olfactory neuroblastoma, are locally aggressive invading into the nasal cavity, paranasal sinuses, cribriform plate, intracranial cavity, brain parenchyma, and/or orbit. They also have a propensity to metastasize to the neck, thorax, and skeleton.

Due to the rarity of this malignancy and its heterogeneous clinical biology, there is some variability in the treatment strategies for patients with this tumor. Several large studies and meta-analyses have demonstrated that the combination of surgery and radiation therapy yield the best survival rates [11, 16, 20]. Consequently, many authors and institutions consider multimodality therapy the standard of care.

Surgical approaches in the treatment of this disease have evolved. Early surgical approaches for this tumor involved extracranial approaches [24]. In 1954, Smith et al. described a combined transcranial and transfacial approach for resection of a paranasal sinus carcinoma [25], and in the early 1970s, the initial craniofacial resections were performed on patients with esthesioneuroblastoma [10, 23].

For the past several decades, this approach has been the gold standard in the surgical treatment of sinonasal malignancies. In the past decade, the application of endoscopic techniques has increased in the treatment of skull base pathologies including esthesioneuroblastoma. In this report, we describe our experience with purely endoscopic resections of esthesioneuroblastomas and perform a review of the literature.

Materials and methods

Patients' characteristics

We completed a retrospective analysis of patients with esthesioneuroblastomas treated at Johns Hopkins Hospital between January 2005 and April 2010. We included patients treated solely with an endonasal endoscopic approach and resection. Patient records were reviewed for demographic data, presenting symptoms, clinical staging, postoperative therapy, follow-up, disease status, and complications. A total of eight patients were identified. This study was approved by the Johns Hopkins Hospital Institutional Review Board.

Literature review

PubMed and Medline databases were searched with combinations of the search terms "esthesioneuroblastoma," "olfactory neuroblastoma," "endoscopic", and "endoscopy." References contained within these papers were reviewed, and additional articles related to our search terms, but not identified in our original search results, were included. Overall, 81 studies were identified, and these were analyzed in detail. Case reports, articles reporting endoscopic-assisted surgical resections, and non-English papers were excluded from our analysis. Additionally, studies which included patients with esthesioneuroblastomas treated endoscopically were excluded if these patients were grouped together with patients with other sinonasal tumors and no distinction between these groups was possible. This resulted in a total of 17 papers which were included in our analysis [1, 4–8, 12, 18, 19, 21, 22, 27–32].

Operative technique

Patients typically presented following an endoscopic biopsy/resection confirming the diagnosis of an esthesioneuroblastoma. Patients are evaluated with a LandmarX head CT scan and high-resolution skull base MRI protocol (Figs. 1 and 2a, b). This MRI scan consists of high-resolution imaging of the skull base with submillimeter isotropic sequences. These images are reviewed, and the cases in which a negative margin resection is thought to be achievable are considered candidates for an expanded endonasal endoscopic approach. Patients with tumor

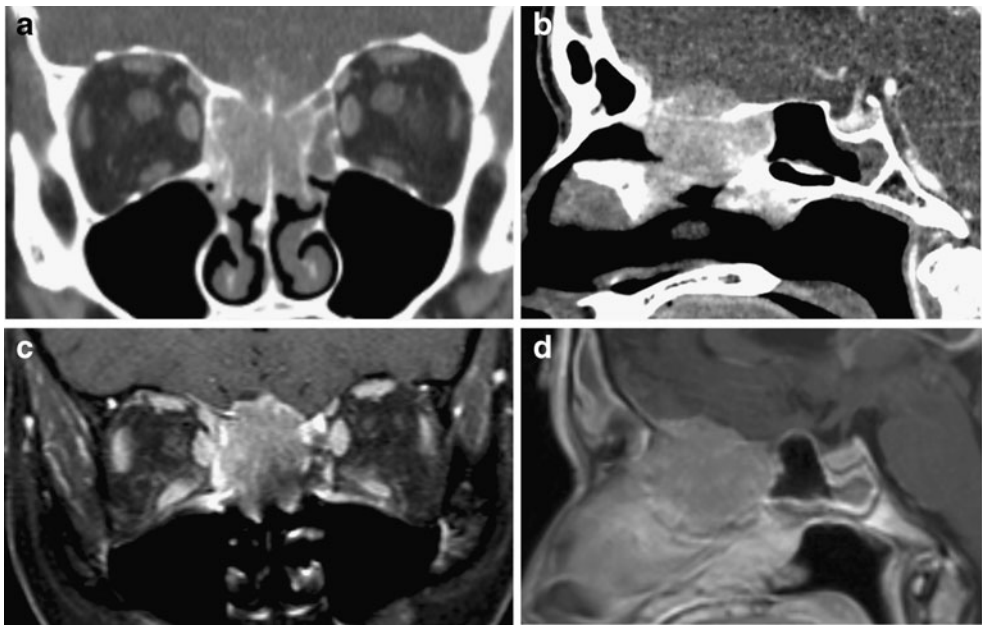

Fig. 1 Preoperative high-resolution imaging studies of case #3. Coronal (**a**) and sagittal (**b**) preoperative postcontrast CT images demonstrating a soft tissue mass centered in the ethmoid sinuses with intracranial extension through the cribriform plate. Coronal (**c**) and sagittal (**d**) preoperative postcontrast MRI images demonstrating a soft tissue mass in the ethmoid sinuses extending intracranially through the cribriform plate. There is no extension of the intracranial component laterally over the orbital roofs and there is no obvious invasion of the brain parenchyma. The anterior component of the mass begins at the crista galli. The mass abuts the right lamina papyracea with a minimal amount of soft tissue seen in the right orbit. In this case, the right lamina was removed and the underlying periorbita sent as a frozen specimen. No gross tumor was seen under the lamina and no tumor identified in the periorbita

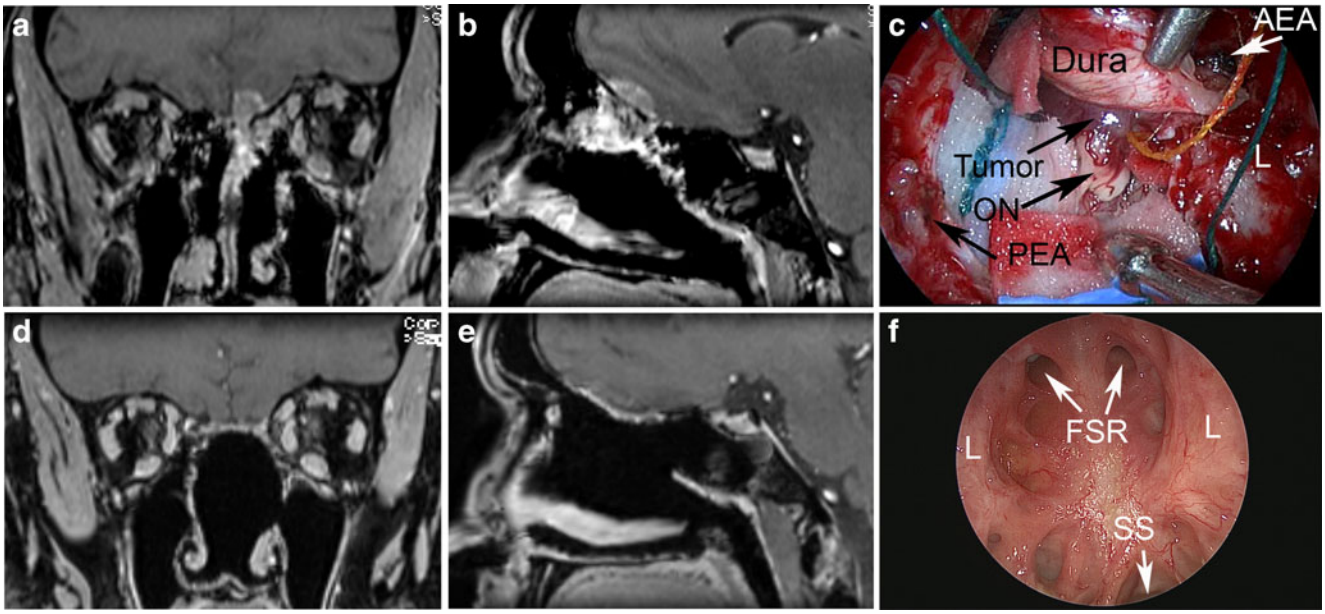

Fig. 2 Coronal (**a**) and sagittal (**b**) preoperative high-resolution MRI scan from case #6 demonstrating a soft tissue mass involving the ethmoids and skull base, more eccentric to the left. There is intracranial extension through the cribriform on the left. There is no obvious intraparenchymal nor orbital invasion. The anterior aspect of the mass extends to the anterior ethmoids. Previous sinus surgery from the patient's original tumor debulking are evident. Intraoperative endoscopic view (**c**) using a 30° endoscope following circumferential dural incisions encompassing the tumor and sectioning of the olfactory nerves. Tumor is seen extending intracranially and involving the left olfactory nerve (ON). The proximal left olfactory nerve was sent for frozen histopathological analysis; no tumor was identified. The right posterior ethmoidal artery (PEA) and left anterior ethmoidal artery (AEA) have been coagulated and cut. The left lamina (L) is also seen. The underlying brain is protected with cotton patties. Coronal (**d**) and sagittal (**e**) postcontrast MRI images obtained 20 months after the initial diagnosis. There is no evidence of recurrent tumor. (**f**) Postoperative endoscopic photograph 20 months after surgery. The skull base reconstruction is well mucosalized without any evidence of tumor. The frontal sinus recesses (FSR) are patent. *SS* sphenoid sinus

extending laterally above the orbit, with significant periorbital or intracranial/intraparenchymal involvement, and with involvement of facial soft tissues were excluded from this approach and underwent a traditional craniofacial resection. Patients also have a PET/CT scan performed preoperatively for evaluation of systemic disease.

Cases involving resection of the skull base are performed together with an otolaryngologist and neurosurgeon allowing for the use of three and four handed techniques. A lumbar drain is placed for removal of CSF during reconstruction of the skull base. Patients are positioned supine on the operating room table. The head is fixed in the Mayfield 3-point head fixator and the neck is extended, slightly rotated to the right and tilted to the left. The neuronavigation system is registered to the patient using both the high-resolution CT and MRI scans. The nasal cavity is irrigated with clindamycin irrigation, and ceftriaxone is administered intravenously as the perioperative antibiotic.

Tumor resection begins by debulking the nasal component to achieve circumferential access to the margins. This is performed sharply or with powered instrumentation. Care is taken to preserve the peripheral mucosal integrity to permit adequate assessment of the tumor boundaries. After debulking, maxillary antrostomies, total ethmoidectomies, sphenoidotomies, and frontal sinusotomies are performed. If necessary, the middle turbinates can be removed during this portion of the dissection. Anterior, inferior, and posterior septal transfixion incisions are performed. The locations of the incisions are adjusted to fully incorporate the tumor in the excised specimen. The rostrum, face of the sphenoid sinus, and intersinus septae are removed using a coarse diamond drill to provide sufficient access to the planum sphenoidale. Next, a Draf III sinusotomy is completed widely opening the frontal sinuses. Circumferential tumor margins are taken; we take margins several millimeters in width. Care is taken to maintain the orientation of the specimens. A sufficient number of specimens are taken to ensure the tumor is fully circumscribed by the margins. All bone involved with tumor or adjacent to mucosa involved with tumor is removed when possible. For example, the lamina papyracea may be removed as a lateral margin. This can be done either alone or in continuity with the medial maxillary wall. Regions that cannot be removed (e.g., portions of the sphenoid bone) are aggressively burred with the drill.

At this point, the entire ventral skull base is exposed from the frontal sinus to the planum sphenoidale or sella turcica and from lamina to lamina. Depending on the extent of the tumor and in similar fashion to the nasal resection,

circumferential margins are taken at the ventral aspect of the skull base for frozen analysis. For tumors involving the midline, mucosa from the anterior and posterior ethmoidal air cells is taken bilaterally for frozen histopathological analysis. Additional margins typically include the anterior septum, the mucosa from the inferior aspect of the posterior table of the frontal sinus, as well as posterior margins. Additional specimens are taken until tumor-free tissue is confirmed.

For tumors abutting or involving the skull base, the cribriform, dura, olfactory nerves, and tumor are resected in one specimen. The anterior and posterior ethmoidal arteries are identified. Often, there is bone over these canals which must be removed with the drill or curette. Once these arteries are exposed, they are coagulated and cut sharply as medially as possible to prevent retraction and hemorrhage into the orbit. At this point, anterior skull base osteotomies are performed. Lateral osteotomies are performed initially. The bone of the skull base is drilled with a curved drill and following dissection of the dura away from the skull base, the bone just medial to the orbit is removed with reverse Kerrison punches. Horizontal osteotomies are then performed, one just posterior to the posterior table of the frontal sinus and one at the level of the planum sphenoidale. The lateral and horizontal osteotomies are then connected. The crista galli is then removed. It is first dissected from the dura and then drilled internally at the attachment to the posterior table of the frontal sinus. Once thin enough, it is fractured and removed. This is essential for the subsequent dural resection and skull base reconstruction. At this time, the cribriform plate is separate from the skull base.

Dural incisions are made next. These are planned based on the preoperative imaging studies and are lateral, anterior, and posterior to the dura involved with tumor (Fig. 2c). The lateral cuts are made initially, followed by the anterior and posterior dural incisions. The olfactory nerves are cut sharply, and the distal margins of the nerve are sent for frozen histopathological analysis. The falx is then incised in an anterior to posterior direction as the specimen is reflected posteriorly. Arachnoid adhesions are cut sharply and the specimen is then removed from the operative field. Numerous dural margins are sent for frozen histopathological analysis from this specimen including the right and left lateral, bilateral anterior and posterior margins, as well as falcine specimens. Should any margins return positive, additional resection is performed until negative margins are obtained.

For the skull base reconstruction, we prefer to use a nasal septal flap to reconstruct the skull base if possible as described by Hadad et al. [15]. The flap is elevated on the opposite side of the septum as the tumor with the superior mucosal incision below the level of septal involvement on the contralateral side. Superior mucosal margins are sent for frozen analysis to ensure no tumor involvement of the flap. Occasionally, the flap is not of sufficient length to reach the posterior aspect of the frontal sinus, or the tumor's extent prevents the use of this flap. In these cases, we use a variety of materials including a subdural inlay graft (Duragen), a graft placed between the bone of the skull base and the dural edges (DuraMatrix) and an acellular dermal onlay graft. The onlay graft and septal flap are supported in position with Gelfoam wrapped in Surgicell. Merocel sponges and/or a 14 Fr Foley catheter are used as a buttress.

Patients are routinely imaged the night of surgery with a spiral head CT scan to evaluate for postoperative hemorrhage, the degree of pneumocephalus, and the placement of the nasal Foley and packing (Fig. 3a, b). Patients typically spend one night in the intensive care unit and are transferred to the general neurosurgical floor the following day. A high-resolution MRI is performed within 48 h of surgery. Lumbar drainage was initially performed for 72 h; recently, we have decreased this to 36–48 h. Ceftriaxone is continued during the hospital stay and patients are discharged on a fluoroquinolone antibiotic until packs are removed, typically 7–14 days after surgery.

Patients are initially seen every 2 weeks postoperatively to evaluate the skull base and for conservative nasal debridement. Crusts and packing along the skull base are not disturbed until the packing separates from the skull base and the integrity of the skull base can be confirmed endoscopically. At this time, nasal irrigations can be safely used to debride the nasal cavity. Patients are referred for radiotherapy and typically start approximately 6–8 weeks after surgery. Patients with systemic disease or extensive mucosal spread are referred for chemotherapy. Patients are reimaged every 3–4 months during the first year, every 6 months during the second and annually thereafter (Figs. 2d, e and 3c, d). Nasal endoscopy is performed routinely at postoperative visits (Fig. 2f). A 1-year PET/CT scan is now routine in our practice.

Results

Case series

Eight patients underwent a purely endoscopic endonasal resection of an esthesioneuroblastoma between January 2005 and April 2010 (Tables 1 and 2). The mean age was 56.9 years with a range from 44 to 72 years, and the male to female ratio was 1.7:1. Six patients presented with newly diagnosed (primary) esthesioneuroblastomas; while two patients had recurrent disease (patients 7 and 8). All patients underwent an endonasal endoscopic biopsy and/or partial resection of the nasal mass, either at outside facilities or at Johns Hopkins; one patient developed a cerebrospinal

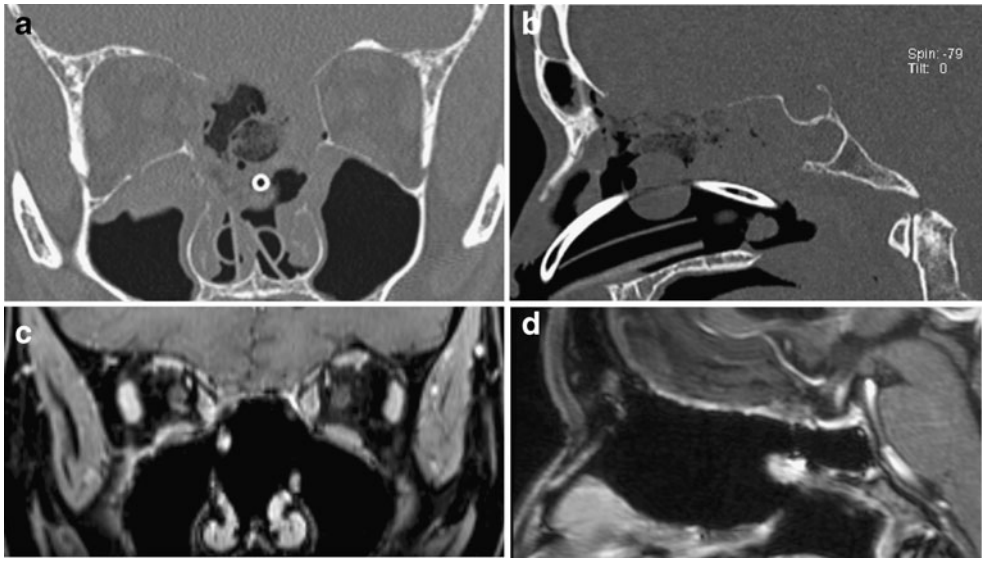

Fig. 3 Postoperative high-resolution imaging studies of case #3. Coronal (**a**) and sagittal (**b**) postoperative CT images obtained the night of surgery. The extent of the bony skull base resection is seen extending from the posterior table of the frontal sinus to the planum sphenoidale and from the right orbit to the left lamina. Part of the right lamina was removed, as seen in panel **a**. For the skull base reconstruction, a Duragen inlay was placed followed by Alloderm and a pedicled nasoseptal flap which augmented the posterior aspect of the reconstruction. Gelfoam wrapped in surgical was placed over the entire reconstruction. In this case, a Foley catheter was used as a buttress. Coronal (**c**) and sagittal (**d**) postcontrast MRI images obtained 31 months after initial diagnosis. There is no evidence of recurrent tumor

fluid leak (CSF) leak following debulking. All specimens were formally interpreted at Johns Hopkins as esthesioneuroblastoma. The Kadish staging at presentation is noted in Table 1. The most common stage at presentation was C (50%), and then Kadish stage B (25%) followed by stages D and A (12.5% each). The patient with stage D (patient 5) had a positive PET/CT scan which demonstrated an FDG-avid 0.8×0.6 cm lymph node in the left parapharyngeal space.

All patients underwent a purely endonasal endoscopic approach for definitive tumor resection. Two cases (patients 5 and 6) were performed in a staged fashion. During the first stage, patient 5 also underwent an extended selective modified neck dissection including resection of the parapharyngeal node; this was positive for esthesioneuroblastoma on histopathology, and 21 other level II and III lymph nodes were negative for tumor. In all eight cases, intraoperative negative margins were obtained on frozen pathological analysis. Seven patients (87.5%) underwent skull base reconstruction following tumor resection; one patient did not require resection nor reconstruction of her skull base (patient 1). One patient (case 5) developed intraoperative hypertension at the conclusion of the first stage of a planned 2 staged procedure (Table 2). There were

Table 1 Clinical information, including stage, previous intervention, and intra-operative and postoperative details of patients included in this study

Pt	Age/sex	Presenting symptoms	Stage	Previous surgical intervention	Negative margins	Skull base reconstruction	Postop CSF leak
1	72/F	Obstruction, hyposmia, facial pain	A	PR (endoscopic)	Yes	None	No
2	46/M	Obstruction, epistaxis	B	PR (endoscopic)	Yes	Duragen, Alloderm	No
3	57/F	Dysosmia, hyposmia	C	Bx (endoscopic)	Yes	Duragen, Alloderm, NSF	No
4	44/M	Sinusitis, facial pain	B	PR (endoscopic)	Yes	Duragen, NSF	No
5	56/M	Congestion	D	PR (endoscopic)	Yes	Duragen, Alloderm	No
6	55/M	Epistaxis	C	PR (endoscopic)	Yes	Duragen, Alloderm, NSF	No
7	58/M	Obstruction	C[a]	Res (endoscopic)	Yes	Duragen, DuraMatrix, Alloderm	No
8	67/F	Recurrent sinusitis	C[a]	Res (endoscopic)	Yes	Duragen, DuraMatrix, Alloderm, NSF	No

Bx biopsy, *CSF* cerebrospinal fluid, *NSF* nasal septal flap, *PR* partial resection, *Res* resection

[a] Stage at recurrence

Table 2 Clinical information, including postoperative treatment, local and distant recurrence, complications and follow-up of patients included in this study

Pt	Postop treatment	Local recurrence	Mets	Complications	Last F/U (months)[a]	Post treatment PET/CT	Status at last F/U
1	XRT	None	None	None	57	None	NED
2	XRT	None	None	Frontal sinusitis, punctal stenosis	36	13 mo/neg.	NED
3	XRT	None	None	Worsening dysosmia	31	13 mo/neg.	NED
4	XRT/Chemo	None	None	None	31	14 mo/neg.	NED
5	XRT/Chemo	None	None	Intraoperative hypertension	25	12 mo/neg.	NED
6	XRT	None	None	None	20	12 mo/neg.	NED
7	XRT	None	None	None	9	Planned	NED
8	XRT	None	None	None	9	Planned	NED

Chemo chemotherapy, *F/U* follow-up, *Mets* metastases, *XRT* radiation therapy, *NED* no evidence of disease

[a] For recurrent cases (#7 and 8), the listed follow-up is since tumor recurrence

no perioperative complications encountered. There were no postoperative CSF leaks following resection and reconstruction of the skull base and no episodes of meningitis.

Postoperative radiotherapy was administered to all patients. Two patients (patients 4 and 5) also received systemic chemotherapy. Patient 4 had significant submucosal spread in the contralateral sphenoid sinus and patient 5 had a positive cervical lymph node. Follow-up visits included both nasal endoscopy and skull base imaging. The mean follow-up was 27.2 months with a range from 9 to 57 months. All patients had no evidence of disease at their last follow-up visit.

Late complications were encountered in two patients (Table 2). Patient 2 developed symptomatic frontal sinusitis and nasolacrimal duct dysfunction following radiotherapy requiring an endoscopic frontal sinusotomy and bilateral lacrimal duct dilation, respectively. Patient 3 developed worsening dysosmia following radiotherapy requiring treatment with depakote, neurontin, and alpha lipoic acid.

Literature review

Over 80 reports were generated from our systematic literature search. Seventeen of these met our inclusion criteria for further analysis and are summarized in Table 3. There is significant overlap between many of these studies, and to reduce the risk of redundancy, our review below focuses on the most recent publication from the group/institution with the most detailed patient information.

Unger et al. [30] updated the experience from the University Hospital in Graz, Austria with endoscopic surgery for esthesioneuroblastoma in 2005. This group has a long interest in endonasal endoscopic surgery for esthesioneuroblastoma and has previously reported their experience [1, 27, 29, 31]. In their latest report, this group described 14 patients treated between May 1993 and December 2003 with esthesioneuroblastoma who underwent an endoscopic procedure. Two of these patients also underwent a simultaneous bifrontal craniotomy due to excessive tumor invasion into the anterior cranial fossa. Twelve of these patients were newly diagnosed and two had previously undergone surgery. All patients underwent postoperative radiosurgery. One patient developed a CSF leak requiring endoscopic repair, and another patient developed chronic bilateral frontal sinusitis which was treated endoscopically and subsequently via a craniotomy. Median follow-up was 58 months. Five patients progressed (36%) at a mean of 36.6 months after combined endoscopic/radiosurgical treatment. These originated from sites beyond the initial radiosurgery volumes with two extending into the previously treated areas. Four underwent repeat radiosurgery, and one patient, who was not applicable to further radiosurgery, underwent a craniotomy. In the reported follow-up, all patients were alive and at least 13 had no evidence of disease at last follow-up.

Poetker et al. [21] reported on a total of 40 patients with sinonasal tumors treated with primary endoscopic management between January 1993 and November 2003, five of these were esthesioneuroblastoma. Four of these patients underwent a purely endonasal endoscopic procedure and the fifth underwent an endoscopic-assisted resection. Of these four patients, one patient developed two recurrences. At last follow-up (mean of 68 months), all patients with esthesioneuroblastoma were free of disease.

Castelnuovo et al. [5, 6] reported on a series of ten patients treated purely endoscopically between 1999 and 2004. All patients underwent a negative margin resection. Nine out of the ten patients received adjuvant radiotherapy, and one received adjuvant chemotherapy. None of the patients recurred locally; however, one patient developed a neck metastasis 21 months after surgery and underwent a modified neck dissection plus radiotherapy. With a median of 37 months, all patients were alive and disease free (5). In

Table 3 Literature review of patients with esthesioneuroblastoma treated purely endoscopically

Series [ref. no.]	No. of ENB pts	Stage of tumor (Kadish)	Extent of Resection (# cases)	Postop therapy (# cases)	Recurrence (months)	Metastases (months)	Follow-up range (mean), months	Status at last follow-up (# cases)	Comments
Anderhuber et al.[a] [1]	6	B, 5; C, 1	NR	GKS (6)	1 (26)	NR	DFS 29.2	NED (5)	Total of 33 pts in series
Stamberger et al.[a] [27]	8	B, 7; C, 1	NR	GKS (8)	1 (26)	NR	DFS 37.2	NED (7)	Total of 43 pts in series Recurrent case initial procedure combined with NUS
Walch et al.[a] [31]	3	B, 2; C, 1	No obvious tumor left	GKS (3)	None	None	39–71 (53.3)	NED (3)	
Unger et al.[a] [29]	6	B, 3; C, 3	NR	GKS (6)	None	NR	9–79 (43.5)	NED (6)	1 pt underwent simultaneous bifrontal craniotomy
Casiano et al.[b] [4]	5	A, 1; B, 2	NR	XRT (3 primary cases)	None	2 (8, 36)	6–63 (30.8)	NED (4), AWD (1)	3 primary cases, 2 recurrent cases after CFR Case 1 likely a SNUC (7)
Unger et al.[a] [30]	14	B, 5; C, 9	NR	GKS (14)	3 (79, 18, 34)	2 (46, 6)	13–128 (59.8) (median, 58)	All pts alive, NED (likely 13)	12 primary cases, 2 recurrent cases after CFR 2 pts underwent simultaneous bifrontal craniotomy
Poetker et al. [21]	5	A, 1; B, 2; C, 1	NR	XRT (3), chemotherapy (1)	1 pt (3, 30)	None	38–95 (68)	NED (4)	Total of 40 pts in series 1 pt underwent endoscopic-assisted resection
Castelnuovo et al.[c] [6]	10	A, 3; B, 5; C, 2	Negative margin (10)	XRT (9), chemotherapy (1)	None	None	11–74 (38.1)	NED (10)	
Castelnuovo et al.[c] [5]	10	A, 3; B, 4; C, 3	Negative margin (10)	XRT (9), chemotherapy (1)	None	1 (21)	15–79 (median, 37)	NED (10)	
Dave et al.[b] [7]	10	A, 5; B, 2; C, 2	Negative margin (10)	XRT (9)	None	1	3–105 (40.5)	NED (9)	Total of 19 pts in series; 9 primary cases, 1 recurrent 1 case from previous report [4] is SNUC
Suriano et al. [28]	9	A, 3; B, 6	Gross inspection (9)	XRT (9)	None	None	26–60 (42.8)	NED (9)	
Lund et al. [18]	11	NR	NR	NR	NR	NR	NR	5 year survival : 89% 5 year DFS: 56%	Total of 49 pts in series 1 case converted to a craniofacial resection
Zafereo et al. [32]	3	A, 2; B, 1	Negative margin (2)	XRT (1)	1 pt (38, 70)	None	21–147 (67.3)	NED (3)	Total of 18 pts with ENB in series
Schwartz et al. [22]	3	NR	Radiographic GTR (3), positive margin (2)	XRT (2)	NR	NR	NR	NR	Total of 150 pts in series
Nicolai et	19	A, 3; B, 11;	NR	NR	1	None	NR	5 year survival:	Total of 184 pts in series

Table 3 (continued)

Series [ref. no.]	No. of ENB pts	Stage of tumor (Kadish)	Extent of Resection (# cases)	Postop therapy (# cases)	Recurrence (months)	Metastases (months)	Follow-up range (mean), months	Status at last follow-up (# cases)	Comments
al.[c] [19]		C, 5						100%	
Dehdashti et al. [8]	4	NR	Total (4)	NR	None noted in 1 case	NR	20 months (1 case)	NED (1)	Total of 22 pts in series 1 case described in detail
Folbe et al.[b] [12]	23	A, 2; B, 11; C, 5; D, 1	Negative margin (17/19 primary cases)	XRT (16)	NR	NR	11–152 (45.2)	NED (22)	19 primary cases, 4 recurrent cases 1 pt required an additional craniotomy
current study	8	A, 1; B, 2; C, 4; D, 1	Negative margin (8)	XRT (8), chemotherapy (2)	None	None	9–57 (27.2)	NED (8)	6 primary cases, 2 recurrent cases

AWD alive with disease, *DFS* disease-free survival, *GKS* gamma knife radiosurgery, *GTR* gross total resection, *NR* not reported, *NED* no evidence of disease, *pts* patients, *SNUC* sinonasal undifferentiated carcinoma, *XRT* radiation therapy

[a] There is overlap between these series

[b] There is overlap between these series

[c] There is overlap between these series

2008, Nicolai et al. [19] reported on the 10-year experience with endoscopic surgery for patients with malignant tumors of the sinonasal tract and skull base; this report also included some cases from the earlier studies from Castelnuovo et al. [5, 6]. In this recent publication, 19 patients with esthesioneuroblastoma were treated with a purely endoscopic approach [19]. Although these patients were analyzed together with other tumor types, and individual data is not readily available for the esthesioneuroblastoma subtype, only one recurrence was reported among the 19 esthesioneuroblastoma patients treated purely endoscopically, and the 5-year survival for this group was 100%.

Suriano et al. [28] reported their experience with nine esthesioneuroblastoma patients treated endoscopically. All patients received adjuvant radiotherapy. With a mean follow-up of 42.8 months, all patients were alive without evidence of recurrent or metastatic disease. Zafereo et al. [32] reported outcomes in 18 patients with esthesioneuroblastoma, three of whom were treated endoscopically. One patient developed 2 recurrences and, at a mean follow-up of 67.3 months, all patients were free of disease. In the series of 49 patients with sinonasal malignancies by Lund et al. [18], 11 cases of esthesioneuroblastoma were reported, including one of which was converted to a craniofacial resection. In the esthesioneuroblastoma subgroup, the 5-year overall survival was reported at 89%, and the 5-year disease-free survival was 56%. There are other endoscopic series which include esthesioneuroblastoma patients [8, 22]. These studies, however, report limited individual patient details.

The largest series of esthesioneuroblastomas resected endoscopically is a combined study between the groups at the University of Pittsburgh and the University of Miami [12] which builds on previous reports from these authors [3, 4, 7]. In this latest study, 23 patients were retrospectively reviewed, 19 of whom had primary tumors and 4 of whom underwent revision surgeries for recurrent tumors. The modified Kadish staging at presentation for the primary 19 patients was stage B (58.9%), stage C (26.3%), stage A (10.5%), and stage D (5.3%). Complete resection and negative intraoperative margins were achieved endoscopically in 17 of the 19 primarily treated patients. The mean follow-up for the primary treated cases was 45.2 months, and all patients except one with recurrent disease at presentation had no evidence of disease at their last follow-up.

Discussion

Esthesioneuroblastoma is a rare, malignant neoplasm of the nasal cavity. Open craniofacial resection has been the gold standard surgical treatment of this and other tumors

involving the anterior skull base. In the 2001 meta-analysis by Dulguerov et al. [11], the 5-year overall and disease-free survival rates were 45% and 41% and the combination of surgery and radiotherapy was associated with the best average survival rates of 65%. In a population-based analysis of patients in the Surveillance, Epidemiology, and End Results tumor registry, the 5- and 10-year overall survival rates were 62.1% and 45.6%, respectively [16].

Over the past decade, there have been significant advances in endoscopic skull base surgery including treatment of malignant sinonasal tumors such as esthesioneuroblastomas. There are now numerous studies, including our own, reporting a purely endoscopic approach for the treatment of esthesioneuroblastomas and such approaches are currently being critically analyzed in the treatment of this malignancy. To the best of our knowledge, the earliest purely endoscopic resection of an esthesioneuroblastoma, we are aware of occurred in 1993 [31]. Since then, there have been numerous case reports and case series (Table 3). Of note, there are a small number of patients, significant overlap between several of the studies and limited detailed data in many of the patient series. As such, this data is somewhat difficult to interpret. A recent meta-analysis by Devaiah and Andreoli of outcomes related to open and endoscopic treatment of esthesioneuroblastoma, however, suggests that endoscopic surgery is a valid treatment with better survival rates as compared to open surgery [9]. This study, however, has numerous limitations including the limited number of patients and the length of follow-up in the endoscopic treatment group. Additional bias in this analysis comes from the fact that most of the tumors treated with an open surgical approach were Kadish stages C and D, whereas most tumors resected endoscopically were Kadish stages A and B. Additional studies are required to definitively address the utility of endoscopic surgery for patients with esthesioneuroblastoma.

Although there are numerous series reporting endoscopic resections of sinonasal malignancies, this approach to the management of these patients remains controversial. One of the main issues at the center of this debate is the ability to perform an oncologically sound resection endoscopically. Although the goal in the surgical management of sinonasal malignancies is en bloc resection, there is little data comparing outcomes for a negative margin resection of sinonasal tumors resected piecemeal vs. en bloc. Additionally, even with traditional open surgical procedures, an en bloc resection is sometimes unachievable. Our intraoperative approach is based on oncologic principles. The intranasal portion of the tumor is debulked at its free hanging polypoid aspect from below to enable visualization of the tumor margins. Circumferential contiguous intraoperative margins are then taken and analyzed to define the extent of the disease. Once intraoperative negative sinonasal margins are obtained, attention is then focused on the skull base. The involved skull base is then removed in an en bloc fashion and numerous contiguous dural and falcine margins are also analyzed. If any frozen margins return positive, additional tissue is resected until tissue negative for tumor is obtained. We have been able to achieve negative margins in all eight of our cases.

Our approach is to individualize the surgical treatment plan for each patient. High-resolution CT and MR imaging is performed and the ability to obtain a negative margin resection is evaluated. Should a negative margin resection be considered feasible via an endoscopic approach, both endoscopic and open procedures are discussed with the patient. Should a negative margin resection only be attainable via a traditional craniofacial resection, an open or endoscopic-assisted approach is recommended. There are also cases in which neither approach will be able to achieve a negative margin resection.

Another major concern regarding endonasal skull base surgical procedures lies in the ability to effectively reconstruct the skull base following resection. Indeed, early studies reported CSF leak rates between 20–30% [13, 26]. As more experience is gained, this leak rate is decreasing. There are numerous series now reporting CSF leak rates less than 10% [14, 15, 17].

Conclusions

This patient series adds to the growing experience of expanded endonasal endoscopic surgery in the treatment of skull base tumors including esthesioneuroblastoma. We feel this approach is oncologically sound and requires careful preoperative evaluation and surgical experience. As additional studies are reported, the utility of this approach will continue to be defined.

Acknowledgements We thank Christine Hann, MD, PhD for critical review of the manuscript.

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Comments

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Gallia et al. have performed a retrospective analysis of eight patients with esthesioneuroblastomas who were treated with a purely endonasal endoscopic approach. Six patients were treated for primary disease and the other two were treated for tumor recurrence. The modified Kadish staging applied in this series was A in one patient, B in two patients, C in four patients, and D in one patient. All the eight patients had a complete resection, and a mean follow-up of 27 months showed all of them without evidence of disease. Despite the fact that there are many research papers describing endoscopic resection of esthesioneuroblastomas, this paper is both quite clear and concise and contributes to our understanding of the gold standard treatment of esthesioneuroblastoma nowadays. Furthermore, the description of the surgical technique, given step by step, will certainly help many surgeons around the world who are actually interested in using this approach. As the authors suggested, further research with longer follow-up as well as with a larger number of patients should be carried out in order to demonstrate the efficacious of purely endonasal endoscopic approaches in the management of esthesioneuroblastomas. Moreover, further research should clarify in which cases is better performing a traditional craniofacial resection rather than endoscopic surgery.

Domenico Solari, Paolo Cappabianca, Naples, Italy

In this manuscript, the authors have demonstrated the experience gained with the endoscopic endonasal approach to deal with pathologies involving the anterior area of the skull base either the extracranial but also of intracranial and intradural compartments. This technique, in last decades, has tremendously boosted the development of endo- and parasinonasal surgery affording its extension among neurosurgeons on one hand and ENT and head and neck surgeons as well.

Even though not original in regard to the multidisciplinary treatment of esthesioneuroblastoma, the article is well conducted giving an overall comprehensive evaluation of the correct management of such a disease. A quite good case series and literature review are reported with detailed information on the technique, results, advantages, and limitations of the approach for such condition. Their strategy resulted to be winning and this has to be much more highlighted, considering the high rate of morbidity that burdens surgery of this area; indeed, they demonstrated skillfulness in complication prevention as well in their treatment. Finally, we would like to remark, once again, the relevant role played by image-guidance systems in providing surgeon with correct orientation.

Leo F. S. Ditzel Filho, Bradley A. Otto, Ricardo L. Carrau, Daniel M. Prevedello, Columbus, OH, USA

In this interesting and well-written article, Gallia et al. report their experience on the purely endonasal endoscopic approach and resection of esthesioneuroblastomas (ENB), as well as a thorough review of the related literature. Their group of eight patients included six primary lesions and two recurrences, half of which were Kadish stage C at presentation. In all cases, negative margins were successfully achieved with no cerebrospinal fluid leaks, meningitis, or other major complication. At a mean follow-up of 27 months, they encountered no evidence of local recurrences or distant metastases.

This report adds to the existing and increasingly growing literature on the efficacy and limitations of endoscopic surgery for resection of skull base malignancies. We agree with their treatment philosophy and use a similar surgical technique and rationale when dealing with these lesions. However, we should make a couple of observations. We do not advocate the routine use of lumbar spinal drains on these cases or the routine use of antibiotic solution irrigations of the nasal cavity. Our patients receive antibiotics only while the nasal packing is in place, which is usually 5 days after surgery.

In addition, we would like to emphasize the ENB propensity for perineural spread, and; therefore, the need for resection of the overlying dura and olfactory bulb for all ENBs (except for rare tumors that arise from the inferior aspect of the middle turbinate). In our experience, a negative MRI is unreliable predicting the presence of intracranial perineural spread. However, we perform a unilateral resection in select patients with unilateral disease (confirmed histologically). The authors did not make clear why patient number 1 did not undergo a skull base resection, even deviating from their own protocol (as described in Methods).

This study reflects the experience of a seasoned and skillful skull base team, which, like ours, includes neurosurgeons and otolaryngologist—head and neck surgeons. It also confirms our belief and philosophy that properly selected tumors can be safely and efficiently addressed endonasally achieving oncologic outcomes that are comparable, if not superior, to traditional approaches. This is evident on their reported experience as well as on their literature review. To this effect, one must observe that the majority of the authors' patients were Kadish stage C at presentation. Despite this advanced disease status, the authors were capable of yielding excellent resection rates with little to no morbidity.

There are, nonetheless, two shortcomings to this report that must be acknowledged: small number of patients and short period of follow-up. Longer follow-up periods are needed to confirm and validate the efficacy of the endoscopic technique in the management of these challenging lesions. We congratulate the authors on their article and on their results.