Esthesioneuroblastoma

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KEYWORDS

• Esthesioneuroblastoma • Multimodality treatment • Endoscopic resection

KEY POINTS

- Esthesioneuroblastoma is a rare malignancy that arises in the midline of the anterior skull base.
- Accurate pathologic diagnosis relies on immunohistochemical evaluation in poorly differentiated cases, and discrimination from other neuroendocrine tumors is crucial for appropriate treatment and prognostication.
- Several staging systems exist, but none have been universally adopted.
- Lymph node metastatic disease increases the likelihood of recurrence and portends a poor prognosis.
- Multimodality treatment is commonly used. Complete surgical resection via anterior craniofacial resection with postoperative irradiation has been the most commonly advocated regimen for resectable disease. Endoscopic-assisted or complete endoscopic resection techniques are increasingly being used.

INTRODUCTION

Esthesioneuroblastoma (ENB) was first described by Berger and Richard in 1924.[1] It has been characterized as a rare malignant neoplasm of the sinonasal cavity that arises in the superior portion of the nasal vault. Since its first description, ENB has been referenced under several names, but the accepted terms at this time are "esthesioneuroblastoma" and "olfactory neuroblastoma." The exact origin of this tumor, both the location and cell type, is under debate. Proposed anatomic sites of origin include Jacobson organ, the sphenopalatine ganglion, the ectodermal olfactory placode, Loci's ganglion, sympathetic ganglia of the nasal mucosa, and the nasal mucosa itself.[2,3] However, the most likely site of origin, and the one most generally accepted, is the basal neural cells of the olfactory mucosa.[2–4] The olfactory epithelium is unique in the human nervous system in that it is capable of regeneration and the histologic organization of the olfactory organ reflects this ability. Several cell types are present: the mature olfactory neuroepithelial cells, a basal layer of stem cells that repopulate the differentiated epithelium, sustentacular supporting cells, and flat cells forming the ducts of Bowman in the olfactory lamina propria.[5] ENB seems to be of neuronal or neural crest origin, this idea is supported by the neural filaments present in tumor cells.[6] Also, molecular analysis suggests that ENB is derived from immature olfactory neurons.[4]

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Regardless of its origin, several factors have presented challenges to the characterization and treatment of ENB. First, the tumor is very rare, making it a difficult entity to study. Second, ENB can be difficult to differentiate from several other neoplasms. Third, ENB itself can demonstrate a wide spectrum of clinical behavior, ranging from relatively indolent to both locally aggressive and metastatic. Despite these challenges, the diagnosis and management of ENB has progressed significantly during the last 30 years.

EPIDEMIOLOGY

Malignancies of the sinonasal tract are rare, and ENB is uncommon even among neoplasms that fall within this category, accounting for roughly 3% of all tumors found in the nasal cavity.[2] No apparent causal factors have been identified for this disease. There is, perhaps, a very slight male predominance reported among large series, with an approximate 55% male to 45% female distribution[2,7–9] (Ow TJ, Hanna EY, Roberts DB, et al. Multimodality therapy optimizes long-term outcome in patients with esthesioneuroblastoma. Unpublished data, manuscript under review, 2012). ENB has been reported across several ethnicities, but published cases have been largely among the white population[9] (Ow TJ, Hanna EY, Roberts DB, et al. Multimodality therapy optimizes long-term outcome in patients with esthesioneuroblastoma. Unpublished data, manuscript under review, 2012). Although some investigators have suggested that the age at which ENB develops has a bimodal distribution,[10] this is not supported by recent large reviews, which more accurately suggest that the disease has been diagnosed across all decades, with a peak in the fifth or sixth decade.[2,7,9]

ANATOMY OF THE ANTERIOR SKULL BASE

The following is a brief description of the region of the anterior skull base. For more detail, the reader is referred to the work by Rhoton[11] and the article by Pinheiro-Neto and colleagues.[12] The anterior skull base can be divided into the medial and lateral compartments. The medial compartment is made up of the ethmoid, sphenoid, and frontal bones. The anterior-most aspect of the bony skull base is composed of the frontal bones, housing the pyramidal frontal sinuses. Inferiorly, the nasal cavity is found anteriorly and the sphenoid body housing the sphenoid sinus is found posteriorly. On the endocranial side, the crista galli is found at the midline. The gyri rectus, the anterior cerebral arteries, and the olfactory bulbs rest on the anteromedial base of the skull. Here, the roof of the ethmoid bone forms the cribriform plate anteriorly, where the olfactory rootlets pierce the bony skull base to enter the nasal cavity, and where an emissary vein traverses the foramen caecum. It is from this region the ENB is thought to arise. Posteriorly, the planum sphenoidale is found with the sella turcica housing the pituitary gland. Within the nasal cavity, the perpendicular plate of the ethmoid joins the vomer at the midline to make up the posterior nasal septum. The lateral plates of the ethmoid contribute to the medial orbital walls. The superior turbinates project from the roof of the ethmoid into the nasal cavity, lateral to the cribriform plate. The sphenoethmoid recesses and ostia to the sphenoid sinus can be found superior and posterior to the superior turbinates.

The lateral portion of the anterior skull base is the region of the orbit. Endocranially, the orbital gyri and middle cerebral arteries rest on the anterolateral skull base. The roof of the orbit is formed from the lesser wing of the sphenoid bone and the zygomatic bone. The inferior bony orbit is formed from the zygomatic, maxillary, and palatine bones. The medial wall of the orbit is formed from the maxilla, lacrimal bone, and ethmoid bones. There are several important foramina in the lateral portion of the anterior skull base. The anterior and posterior ethmoidal foramina are conduits for the branches of the ophthalmic artery bearing the same names, found traversing the superomedial orbital walls from the orbit to the superior nasal cavity. The supratrochlear foramen medially and the supraorbital foramen laterally house the neurovascular bundles superior to the orbits that supply the soft tissues of the forehead. In the posterior orbit, the optic canal is formed by the frontal bone and the lesser wing of the sphenoid, and the optic nerve and ophthalmic arteries are transmitted from intracranial to the orbit through this structure. The superior orbital fissure is found between the lesser wing and greater wing of the sphenoid. The oculomotor nerve (CN III), trochlear nerve (CN IV), lacrimal, frontal, nasociliary branches of the ophthalmic (CN V3) nerve, abducens nerve (CN VI), the ophthalmic vein, and sympathetic fibers from the cavernous sinus all pass through the superior orbital fissure. The inferior orbital fissure is found between the greater wing of the sphenoid and the anterior orbital floor formed by the maxillary and palatine bones. The maxillary nerve and its zygomatic branch, as well as the ascending branches from the pterygopalatine ganglion, can be found traversing the inferior orbital fissure. The adjacent infraorbital canal transmits the infraorbital artery and vein, which

exit the infraorbital foramen to the soft tissues of the cheek.

Access to the anterior cranial base can be achieved via a bifrontal craniotomy, a subfrontal-transglabellar approach, a transnasal approach, and a transmaxillary-transnasal route. A detailed understanding of the anatomy of the midface, nasal cavity, paranasal sinuses, orbit, and anterior cranial fossa are crucial to successful surgery for ENB.

CLINICAL PRESENTATION

ENB, like all sinonasal tumors, can grow insidiously, and the common symptoms are very nonspecific and commonly associated with benign processes. A usual delay of 6 to 12 months between the onset of symptoms and diagnosis of ENB has been reported.[13,14] Symptomatology is related to the anatomic structures affected by mass effect or local invasion. The most common presenting symptoms are nasal obstruction, followed by epistaxis.[2,3,8,10,13–15] Other nasal symptoms include headache, facial pain, "sinusitis," hyposmia or anosmia, or an asymptomatic nasal mass.[2,8,10,14] Visual symptoms occur when the orbit is invaded and include diplopia, vision loss, proptosis, and epiphora.[2,8,10,15] Intracranial invasion can rarely produce additional symptoms, including effects secondary to pituitary dysfunction, such as diabetes insipidus or hormonal disturbance, blindness secondary to effects on the optic nerves and chiasm, or neurologic symptoms secondary to mass effect or intracranial hypertension.[2,15] Because symptoms associated with ENB are nonspecific and mimic those of benign sinonasal processes, an increased index of suspicion is crucial to improve early detection of these tumors. It has been suggested that unilateral symptoms and recurrent epistaxis for more than 1 to 2 months warrant more thorough investigation for a possible malignant process.[3] It has been shown that patients with ENB present with unilateral symptoms more often than bilateral symptoms.[8] One study has also compared patients diagnosed preoperatively with bilateral polyposis to those with unilateral polyps and found that neoplastic and malignant processes were exclusively diagnosed in the group with unilateral findings.[16]

DIAGNOSTIC WORKUP

Any patient with a history that is suspicious for a sinonasal tumor deserves a thorough neurologic, ophthalmologic, and head and neck examination. Cranial nerve abnormalities, including deficits in olfaction, facial paresthesias, ophthalmoplegia, and visual field deficits are concerning and should be noted. Middle ear effusion may be identified if the eustachian tube is obstructed. Proptosis and conjunctival injection are, of course, significant findings for orbital involvement. Nasal endoscopy is a necessity. Flexible fiberoptic endoscopy has the advantages of greater patient comfort, more facile assessment of the entirety of the nasal cavity, and the ability to concurrently evaluate the pharynx and larynx, whereas rigid nasal endoscopy offers the advantage of improved resolution and the ability to manipulate with a second instrument such as a suction or forceps.

After a mass is identified, imaging is needed for qualitative evaluation and staging. High-resolution sinus CT scan with intravenous contrast should be performed[3,10] and the protocol should request thin (3 mm) sections through the skull base and paranasal sinuses. ENB metastasizes to the neck in 20% to 25% of cases, though only approximately 5% to 8% of patients present with cervical metastases.[17] Therefore, a CT scan of the neck should be included in the diagnostic workup, as well, to evaluate for regional metastasis. Views in three dimensions—axial, coronal, and sagittal—are optimal, and a protocol amenable to image-guidance is useful if there is a consideration for endoscopic management. MRI is complementary[3,10] and both imaging modalities are recommended. ENB is most typically hypointense compared with brain gray matter on T1-weighted MRI and should enhance with gadolinium. T2-weighted images show an isointense or hyperintense mass. Whereas CT scan is the optimal modality for evaluation of bony involvement (particularly the lamina papyracea, cribriform plate, and fovea ethmoidalis), MRI provides better discrimination between tumor and secretions and optimal evaluation of orbital and intracranial or brain parenchymal involvement.

After adequate examination on physical examination and imaging, biopsy is the next important step in securing a diagnosis. The authors generally recommend intraoperative biopsy under general anesthesia for any sinonasal mass, particularly lesions suspicious for malignancy, those deep in the nasal cavity, and those near the skull base or orbit. Biopsy is ideally performed after imaging has been reviewed to determine the vascularity of the mass. Bleeding from a vascular tumor is best managed in the operative setting. Because ENB can often be easily confused with several other sinonasal malignancies without careful immunohistologic characterization (see later discussion) it is best to reserve definitive management after thorough pathologic review on permanent section.

HISTOLOGIC FEATURES

When the tumor is well-differentiated, ENB forms submucosal, sharply-demarcated nests or sheets of cells, often separated by richly vascular or hyalinized fibrous stroma. The cells are often uniform, with sparse cytoplasm and round or ovoid nuclei with punctuate ("salt-and-pepper") chromatin and nucleoli that are either small or absent. The mitotic rate can be variable, but is usually low. ENB is characterized by fibrillary cytoplasm and interdigitating neuronal processes (neuropil). The cells can be arranged in glandular rings with a true lumen (called Flexner-Wintersteiner rosette) or pseudorosette (Homer-Wright pseudorosette). Examples of these characteristic features[3,18,19] are presented in **Figs. 1** and **2**.

ENB can be more difficult to diagnose when the tumor is less differentiated, with increasing pleomorphism, higher mitotic rate, and areas of necrosis (see later discussion of Hyams' grading), which can make this entity difficult to distinguish from other sinonasal tumors, particularly small blue cell tumors (see later discussion of sinonasal tumors considered in the differential diagnosis). In difficult cases, a panel of immunohistochemical markers is crucial to the establishment of a definitive diagnosis. ENB typically shows diffuse staining with neuron-specific enolase, synaptophysin, and chromogranin. Cytokeratins, glial fibrillary acid protein, neurofibrillary protein, β-tubulin, microtubule-associated protein, vimentin, epithelial membrane antigen, Leu-7 (CD57), and CD56 can all show variable reactivity. Desmin and myogenin, vimentin, and actin are negative, an important marker ruling out rhabdomyosarcoma. S-100 is variably positive, but positive cells are usually limited to the periphery of neoplastic nests, corresponding to sustentacular cells. This characteristic pattern differentiates ENB from sinonasal melanoma. FLI1 is negative, as is the EWS/FLI1 chimeric transcript, ruling out the rare diagnosis of peripheral neuroectodermal tumor or Ewing sarcoma. The typical immunohistochemistry panel and expected findings in ENB and other sinonasal tumors in the differential diagnosis are summarized in **Table 1**.[3,18,19] Typical staining patterns are exemplified in **Fig. 3**.

Electron microscopy, though less commonly used, can be helpful in the diagnosis of ENB. Typical findings are tumor cells with cytoplasmic dense-core neurosecretory granules, and neurite-like cell processes containing neurofilaments or neurotubules.[18,19]

GRADING SYSTEM

One grading system exists for ENB, which was described by Hyams in 1988.[20] This system scores mitotic activity, nuclear polymorphism, amount of fibrillary matrix, rosette formation, and amount of necrosis seen. Categories are scored, and characteristics are organized into four tiers (**Table 2**). When this system has been reviewed in the literature to compare grade to survival, grades I and II, and grades III and IV are often combined.[3] Data supporting the value of this system for prognostication have been mixed. A report by Zafereo and colleagues[14] did not find that Hyams' grade was associated with disease-specific or recurrence-free survival. In Dulguerov and colleagues[3] meta-analysis, only five studies were identified that evaluated Hyams' grading, and collectively grade III and IV tumors were associated with decreased survival. Some flaws of the Hyams' grading scale are that is subjective, leading to variable grading between pathologists, and there is sampling error when the entire tumor is not examined, as in

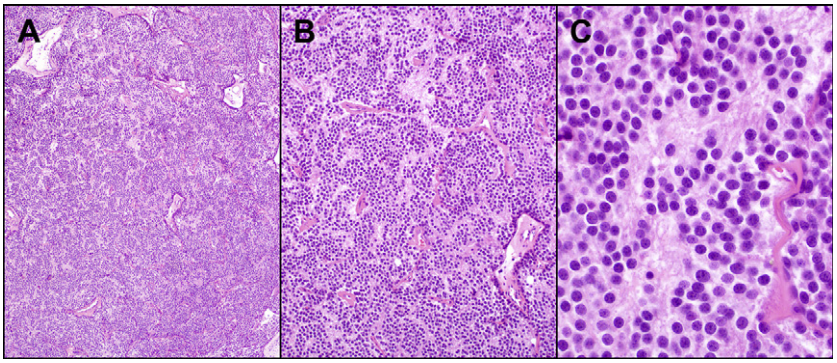

Fig. 1. Characteristic histologic features of lower grade ENB. (*A*, *B*) low-power (2×, 10×) magnification demonstrates monotonous cells growing in sharply demarcated nests and sheets. (*C*) High-power (40×) view demonstrates cells with round nuclei and punctuates "salt-and-pepper" chromatin embedded in a neurofibrillary stroma. See Hyams' grading system (see **Table 2**).

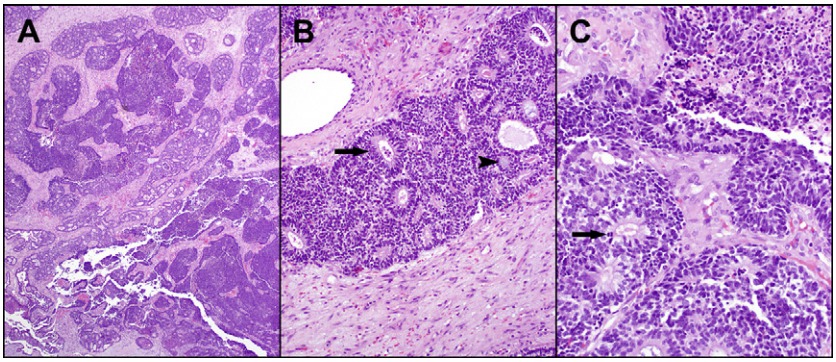

Fig. 2. Characteristic histologic features of higher grade ENB seen at (*A*) 2× magnification, (*B*) 10× magnification, and (*C*) 40× magnification with necrosis, increased mitotic activity and predominance of true-lumen, Flexner-Wintersteiner rosettes (*arrows*). Homer-Wright pseudorosettes (*arrowhead*) are more frequently seen in low-grade ENB. See Hyams' grading system (see **Table 2**).

Table 1
Immunohistochemical profile for ENB

Marker	Pattern	Diagnostic Significance
Neuron-Specific Enolase	Diffusely positive	Characteristic of ENB
Synaptophysin	Diffusely positive	Characteristic of ENB
Chromogranin	Often positive	Characteristic of ENB
Cytokeratin	Variable	Characteristically positive in SNUC, punctuate paranuclear positivity in SNNEC
Glial Fibrillary Acidic Protein	Variable	—
Neurofibrillary Protein	Variable	—
β-tubulin	Variable	—
Microtubule-Associated Protein	Variable	—
Epithelial Membrane Antigen	Variable	—
Leu-7 (CD57)	Variable	—
CD56	Variable	—
CD57	Variable	—
AE1/AE3	Variable	—
S-100	Variable, in peripheral Schwann-like cells	Sinonasal melanoma will be diffusely positive
HMB-45	Variable, and focal	Sinonasal melanoma will be diffusely positive
Common Leukocyte Antigen	Negative	Sinonasal lymphoma will be positive
Desmin	Negative	Rhabdomyosarcoma will be positive
Myogenin	Negative	Rhabdomyosarcoma will be positive
Vimentin	Negative	Rhabdomyosarcoma will be positive
Actin	Negative	Rhabdomyosarcoma will be positive
MIC2 (CD99)	Negative	PNET/EWS will be positive
FLI1	Negative	PNET/EWS will be positive
Pituitary Adenoma Hormones • GH, PRL, Corticotropin, TSH, FSH/LH • Glycoprotein hormone alpha subunit	Negative	Pituitary adenoma variably positive

Abbreviations: FSH/LH, follicle-stimulating hormone and luteinizing hormone; GH, growth hormone; PNET/EWS, peripheral neuroectodermal tumor and Ewing sarcoma; PRL, prolactin; SNNEC, sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; TSH, thyroid stimulating hormone.

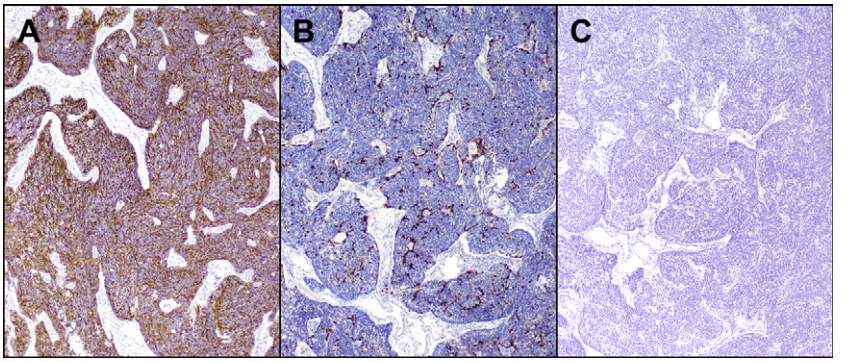

Fig. 3. Characteristic immunohistochemical staining of ENB. (*A*) Synaptophysin is diffusely positive. (*B*) S-100 highlights sustentacular cells. (*C*) Cytokeratin cocktail is negative.

a biopsy.[9] Additionally, poorly differentiated tumors can be difficult to distinguish from other, more aggressive, tumors that are associated with a worse outcome than ENB.[21]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for ENB is extremely broad. ENB must be considered whenever a sinonasal mass lesion is identified. In particular, ENB can be confused histologically with several other "round cell tumors" of the nasal cavity and paranasal sinuses.[18] **Box 1** presents several diagnoses that must be considered in the differential when an ENB is encountered. Tumors commonly confused with ENB include sinonasal undifferentiated carcinoma, sinonasal neuroendocrine carcinoma, small cell carcinoma, pituitary adenoma, melanoma, lymphoma, and rhabdomyosarcoma. Careful pathologic review and accurate immunohistochemical analysis are essential, and the typical differentiating characteristics are summarized above. The behavior of ENB compared with non-ENB neuroendocrine tumors differs greatly, with non-ENB tumors posing a greater risk of regional and distant failure.[21] Thus, the approach to treatment of these two entities also differs greatly. Optimal outcomes are achieved when systemic therapy is used for non-ENB neuroendocrine tumors, whereas ENB is often controlled with local therapy alone (most often, surgery with postoperative irradiation).[21] Thus, differentiating ENB from these other entities is essential. Characteristic histologic findings and immunohistochemical staining patterns in ENB are summarized in **Table 1**. Differentiating ENB from other neuroendocrine entities can be difficult. Histologically, sinonasal undifferentiated carcinoma (SNUC) and neuroendocrine carcinoma (NEC) tend to have a higher mitotic rate and show areas of necrosis. Immunohistochemistry will be positive for cytokeratin, whereas ENB is characteristically negative. S-100 stains sustentacular cells in ENB, but is characteristically absent in SNUC and NEC.[18,22,23]

STAGING SYSTEMS

As with any malignancy, once the diagnosis of ENB is established and the proper diagnostic workup has been obtained, it is necessary to stage

Table 2
Grading scale according to Hyams

Grade	1	2	3	4
Architecture	Lobular	Lobular	Variable	Variable
Mitotic activity	Absent	Present	Prominent	Marked
Nuclear pleomorphism	Absent	Moderate	Prominent	Marked
Fibrillary matrix	Prominent	Present	Minimal	Absent
Rosettes	HW	HW	FW	FW
Necrosis	Absent	Absent	+/− Present	Common

Abbreviations: FW, Flexner-Wintersteiner; HW, Homer-Wright.

Data from Hyams VJ. Olfactory neuroblastoma. In: Hyams VJ, BJ, Michaels L, editors. Tumors of the upper respiratory tract and ear. Washington, DC: Armed Forces Institute of Pathology; 1988. p. 240–8.

Box 1
Differential diagnosis for ENB

- Malignant neoplasms
  - Round cell tumors
    - ENB
    - Sinonasal undifferentiated carcinoma
    - Sinonasal neuroendocrine carcinoma
    - Sinonasal malignant melanoma
    - Small cell undifferentiated (neuroendocrine) carcinoma
    - Undifferentiated (lymphoepithelioma-like) carcinoma
    - Extraosseous Ewing sarcoma/PNET
    - Rhabdomyosarcoma
    - Mesenchymal chondrosarcoma
    - Small cell osteosarcoma
    - Synovial sarcoma
    - Natural killer/T-cell lymphoma
    - Extramedullary plasmacytoma
  - Other histologies
    - Sinonasal squamous cell carcinoma
    - Adenocarcinoma
    - Adenoid cystic carcinoma
    - Nasopharyngeal carcinoma
    - Osteosarcoma
    - Chondrosarcoma
- Benign neoplasms
  - Inverting papilloma
  - Pituitary adenoma
- Congenital lesion
  - Dermoid
  - Encephalocele
  - Glioma
- Infectious or inflammatory
  - Inflammatory polyps
  - Allergic fungal sinusitis
  - Sarcoidosis

the cancer to make treatment decisions and provide prognostic information. There have been several staging systems proposed for this disease and no single system has become universally accepted. The first staging system created, and the most commonly applied, was proposed by Kadish and colleagues[24] in 1976. This staging system classifies local disease only, and is simply divided into those that involve the nasal cavity alone (Kadish A), those extending to the paranasal sinuses (Kadish B), and those that extend outside of the paranasal sinuses (Kadish C)[24] (**Box 2**A). Noting that this system does not incorporate regional or distant metastasis, Morita and colleagues[25] modified the Kadish classification system in 1993, designating class D as those with metastases, which includes regional nodal disease and distant metastasis (see **Box 2**B). The classification system proposed by Dulguerov and colleagues[13] separates those patients with and without sphenoid sinus disease, as well as differentiates between those with intracranial and/or orbital extension from those with brain parenchymal invasion. This system also considers lymph node and distant metastasis separately (see **Box 2**C). A classification system proposed by Biller and colleagues[26] is perhaps the most detailed, differentiating between those tumors with extension to the brain that are amenable to surgery, and those that are not. It also segregates those with lymph node and distant metastases (see **Box 2**D). The TNM staging system for paranasal sinus tumors as described by the American Joint Committee on Cancer[27] can also be applied; however, the biologic behavior unique to ENB compared with other sinonasal tumors, makes the above-mentioned classification systems more applicable to this disease.

There remains debate as to which staging system is most appropriate and useful for the evaluation and treatment planning in ENB. Each of the factors emphasized by the different systems is important to consider when determining the surgical approach or options, the benefit of adjuvant treatments, and the overall prognosis of the patient. What seems clear is that there is a distinct difference in prognosis between those patients who present with metastatic disease and those who do not, and the authors recommend routine use of a system that considers nodal and distant metastasis. A review of the SEER database showed significant differences in outcome between the four groups when modified Kadish classification was applied. Also, there was a strong association between poor disease-specific survival and the presence of lymph node metastsis.[7] In their meta-analysis, Dulguerov and colleagues[3] also showed that lymph node metastasis was associated with a poor prognosis. The study by Zafereo and colleagues[14] found that the Dulguerov system or a TNM-based staging separated those patients with worse disease-free survival, whereas the Kadish system did not. Another large single-institution study noted that both the Kadish and Dulguerov system could

Box 2
Staging systems proposed for ENB

Systems proposed by (A) Kadish (B) Morita (C) Dulguerov and (D) Biller

A. Kadish stages
   A. Tumor confined to the nasal cavity
   B. Tumor involvement of the nasal cavity and paranasal sinuses
   C. Tumor extends beyond the nasal cavity and paranasal sinuses

B. Morita modification
   A. Tumor confined to the nasal cavity
   B. Tumor involvement of the nasal cavity and paranasal sinuses
   C. Tumor extends beyond the nasal cavity and paranasal sinuses
   D. Presence of metastases (regional or distant)

C. Dulguerov staging system
   T1. Tumor involves the nasal cavity and/or paranasal sinuses, but spares the sphenoid sinus and superior ethmoid cells
   T2. Tumor involves the sphenoid sinus and/or the cribriform plate
   T3. Tumor extends into the orbit or into the anterior cranial fossa, without invasion of the dura
   T4. Tumor involves the brain
   N0. No regional lymph node metastases
   N1. Lymph node metastases present
   M0. No distant metastases
   M1. Lymph node metastases present

D. Biller staging system
   T1. Tumor involves the nasal cavity/paranasal sinuses (excludes the sphenoid)
   T2. Extension into the orbit and/or cranial cavity
   T3. Brain involvement but deemed resectable
   T4. Extensive brain involvement, unresectable tumor
   N0. No regional lymph node metastases
   N1. Lymph node metastases present
   M0. No distant metastases
   M1. Lymph node metastases present

identify those patients at highest risk of local-regional recurrence[8] and supported the use of the latter system because it considers the presence of metastasis and the extent of local invasion, making it more informative.

The following sections describe the treatment and outcomes for patients with ENB. Outcomes are generally favorable, although ENB will recur in a significant number of patients, often after several years without evidence of disease. Optimal treatment regimens are still under investigation and there have been several recent advances that have potentially improved treatment and decreased morbidity, namely the applications of endoscopic surgery and intensity-modulated radiation therapy (IMRT). That there is not yet a universally accepted staging system is largely due to the evolution of the standard of care for ENB and the long follow-up necessary to compare outcomes among patients with this rare disease, making it difficult to assess which staging system is most useful.

TREATMENT

There are three modalities used to treat ENB: surgery, external beam radiation, and chemotherapy. Often, a combination of these modalities

is used, namely surgical resection with postoperative irradiation, for all but the smallest tumors. Chemotherapy has a role for more advanced cases, but the utility of chemotherapeutic agents is not well-defined. A detailed review of each modality follows.

Surgical Approaches

It has largely been established that the mainstay treatment of ENB is complete surgical resection. ENB arises in a region in close proximity to the structures of the orbit and anterior skull base. Preservation of these structures when they are not involved, and resection of these structures when there is clear invasion, adds to the complexity of the surgical approaches for these tumors. Also, the proximity of these structures makes it difficult to obtain wide resection with clear margins. Craniotomy can potentially be avoided if preoperative imaging clearly shows that the cribriform plate and superior ethmoid air cells are free of disease, but this is very rare. Otherwise, a craniofacial resection approach has been advocated as the standard of care.

The traditional and standard approach to resection of ENB is anterior craniofacial resection, involving a bifrontal craniotomy combined with a transfacial approach, through either a lateral rhinotomy incision or a Weber-Ferguson facial flap for increased exposure (**Fig. 4**). Craniotomy is usually performed via a bicoronal scalp incision with preservation of the pericranium pedicled anteriorly, which can be turned into the defect to eliminate the communication between the intracranial space and the nasal cavity after resection. Burr holes are created and the bifrontal craniotomy is performed with preservation of the underlying dura. The frontal lobes are allowed to relax back to expose the anterior skull base, olfactory region, and the ENB. The anterior craniofacial approach and resection are depicted in **Fig. 5**. All tumors which reach the skull base (Kadish B and C) require dural resection and resection of the olfactory tracts. It is typically not possible to successfully resect the tumor and preserve olfaction; even for unilateral disease. Intracerebral invasion is managed by focal cerebral resection. A margin of a millimeter or two is all that is necessary in the brain. Dural extension must be pursued to negative margins. Dural closure is performed under the operating microscope and should be watertight. Primary closure is usually not possible and dural grafting is typically required. Reconstruction of the floor of the anterior cranial fossa is achieved by rotating in a vascularized pericranial graft. The graft is sutured to the residual bone of the central skull base and/or the dura distal to the site of dural grafting.

With anterior craniofacial resection, the tumor is also inferiorly approached, and the traditional open techniques require a lateral rhinotomy or Weber-Ferguson incision. If the nasal component of the tumor is limited to the midline nasal cavity, a lateral rhinotomy incision with transnasal approach may be sufficient. A lip-split with a gingivobuccal incision can be added for increased exposure and access if necessary. As more lateral exposure is necessary, the Weber-Ferguson facial flap can be used. Another, less commonly used, approach is the facial degloving procedure, which avoids incisions on the face, but can distort the nasal anatomy because the lower lateral cartilages

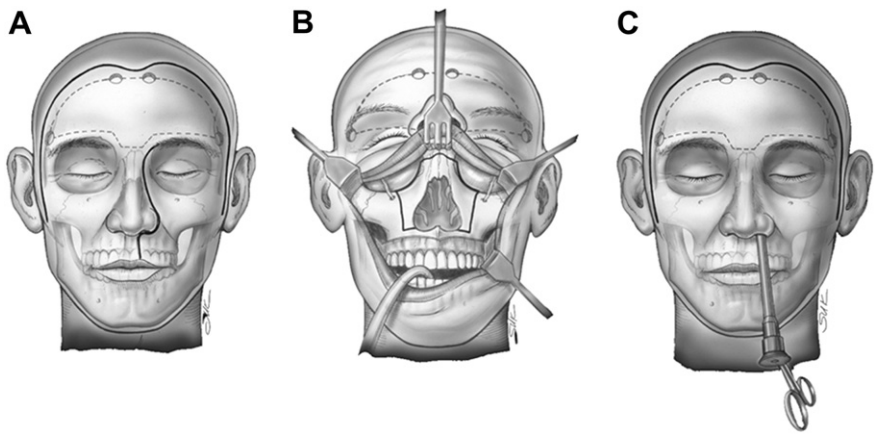

Fig. 4. Transfacial approaches for anterior craniofacial resection. (*A*) Lateral rhinotomy incision combined with lip-splitting incision to create the Weber-Ferguson flap. (*B*) Facial degloving approach. (*C*) Endoscopic approach can circumvent facial incisions in selected cases. (*From* Department of Head and Neck Surgery and Department of Neurosurgery, The University of Texas M.D. Anderson Cancer Center; with permission.)

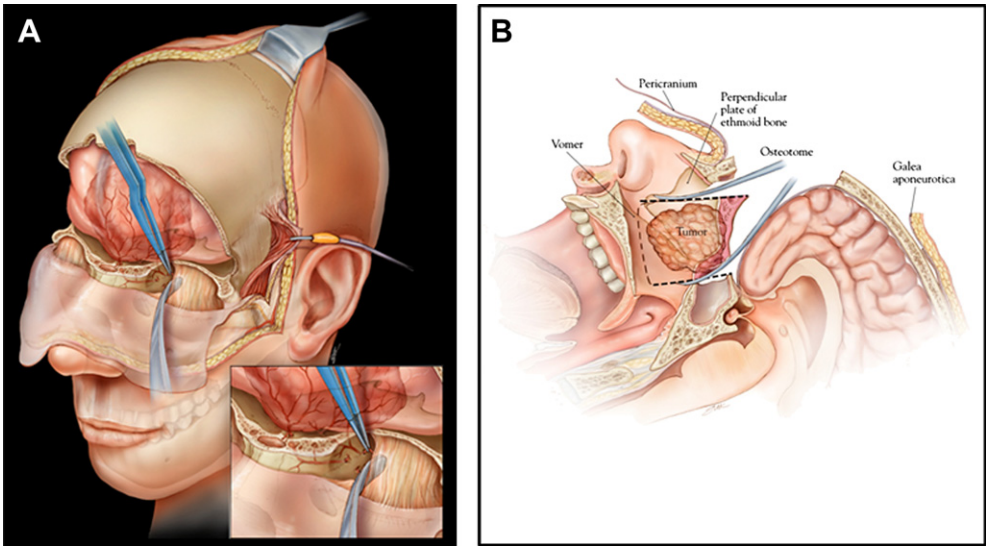

Fig. 5. Representations of the technical aspects of bifrontal craniotomy during anterior craniofacial resection. (*A*) A bicoronal incision is made, the pericranium is preserved and reflected anteriorly. Bifrontal craniotomy is performed and care is taken to preserve the dura. Inset shows reflection of the periorbita if necessary with control of the ethmoidal arterial system. (*B*) The frontal lobes are allowed to relax to expose the anterior skull base, and resection is performed with inferior exposure and tumor clearance via a transfacial or endoscopic approach. (*From* Department of Head and Neck Surgery and Department of Neurosurgery, The University of Texas M.D. Anderson Cancer Center; with permission.)

are disarticulated from the upper lateral cartilages and the nasal soft tissues are reflected superiorly. The exposure with this approach is also arguably more limited (see **Fig. 4**).

The lateral resection can range from medial maxillectomy, to subtotal, or even total, maxillectomy with or without orbital exenteration. The extent of resection necessary depends on the involvement of the tumor. Removal of portions of the bony maxilla, particularly the medial wall (eg, the lateral nasal wall, middle turbinate, and inferior turbinate), is often necessary to gain adequate exposure for complete resection of the midline tumor, even if these structures are not directly involved. The orbit can often be spared if the periorbita or orbital septum is not invaded. Once tumor has involved the orbital fat, extraocular muscles, or other intraorbital contents, the eye cannot be saved. Even if the globe can be spared, postoperative irradiation to the orbit often renders the eye nonfunctional with significant xerophthalmia after irradiation of the lacrimal system. Thus, exenteration provides better tumor control with a more satisfactory functional outcome in these cases. Tumor control rates and survival are often excellent with the anterior craniofacial approach; however, other approaches have been sought to limit both frontal lobe retraction and to eliminate facial scars.

The transglabellar-subcranial resection was first described by Raveh and colleagues[28] in 1988. This approach is executed via the bicoronal incision alone. The pericranial flap is preserved and the frontal craniotomy is performed. The transglabellar-subcranial modification places the inferior cuts of the craniotomy lower across the nasal bridge and superior orbital rims. The extent of superior orbital rim, frontal bone, and nasal bridge that is resected depends on tumor size, location, and exposure necessary for complete removal with negative margins. The distal 3 to 5 mm of nasal bone is preserved to maintain the internal nasal valve. To remove the bone flap, it must be fractured from the crista galli and nasal septum. Before removal of the flap, fixation plates are fashioned to replace the flap at the end of the procedure. This direct approach allows exposure and resection of the anterior skull base, with less retraction of the frontal lobes, but somewhat limited exposure inferiorly and posteriorly. The pericranial flap is turned inward to close the superior nasal cavity at the end of the procedure and the bony flap is replaced. Ward and colleagues[15] have recently reported a series of 15 patients with good outcomes using this technique.

Endoscopic surgery in the nasal cavity and paranasal sinuses has advanced significantly in the last two decades. Endoscopic-assisted craniofacial resection, as well as a purely transnasal endoscopic approach, has been advocated for carefully selected cases of ENB.[29–32] The endoscopic

approaches completely avoid facial incisions and alteration of the bony facial anatomy. Endoscopic resection can be performed via a purely transnasal approach or with the addition of a gingival-buccal, transmaxillary (Caldwell-Luc) approach for added exposure. To accomplish the endoscopic approach, the tumor is typically debulked in a systematic fashion to identify and preserve the root of the tumor (often the skull base at the superior nasal cavity for ENB). Then, uninvolved structures surrounding the tumor are resected or widely opened to provide exposure (eg, medial maxillectomy, sphenoid sinus, frontal sinuses). Vascular control of the feeding vessels to the tumor, for example from the anterior ethmoidal or sphenopalatine arteries, is obtained. The bony skull base surrounding the lesion is then exposed and, subsequently, opened. Tumor with surrounding bone, dura, or brain parenchyma can then be removed, either via the craniotomy approach or endoscopically. Steps from the purely endoscopic technique are shown in **Fig. 6**. Pinheiro-Neto and colleagues[12] provide an excellent detailed review of the technical aspects involved with the endoscopic approach to tumors of the anterior skull base. The authors have more often used endoscopic-assisted craniofacial resection for ENB, but have recently used the purely endoscopic approach for small tumors without extensive dural invasion. Early reports describing results of endoscopic resection have been favorable,[29,32] but large series with adequate long-term follow-up will be necessary to prove that these techniques are truly comparable to traditional resection for patients with ENB.

There is debate about appropriate management of the cervical lymph nodes for patients with ENB. Reports have varied greatly in the incidence of cervical lymph node metastases at the time of presentation to, as well as after, initial treatment. The incidence of cervical lymph node involvement at the time of presentation is likely 5% to 8%, but the incidence of the eventual development of neck disease is likely 20% to 25% (it should be noted that the cervical lymph nodes are often untreated previous to metastasis, in these cases).[17] Despite this relatively high rate, surgical management of the neck is generally reserved for patients who present with clinical or radiographic evidence of disease, or for those who develop lymph node metastases after treatment at the primary site. There are no reports indicating that elective or prophylactic neck dissection is beneficial, and an elective surgical approach has not generally been advocated. However, in current practice, the neck is often irradiated electively as part of the postoperative radiation plan. The extent of neck dissection when lymph node disease is present is tailored to the neck levels involved with disease, and a selective or functional approach is generally favored if this technique allows complete resection of known disease. Postoperative irradiation is advocated[33] and the role of concurrent chemotherapy is unclear.

Radiation Therapy

Radiation is an important treatment modality in the management of ENB, but the optimal use of this modality is not entirely clear. Radiation can be

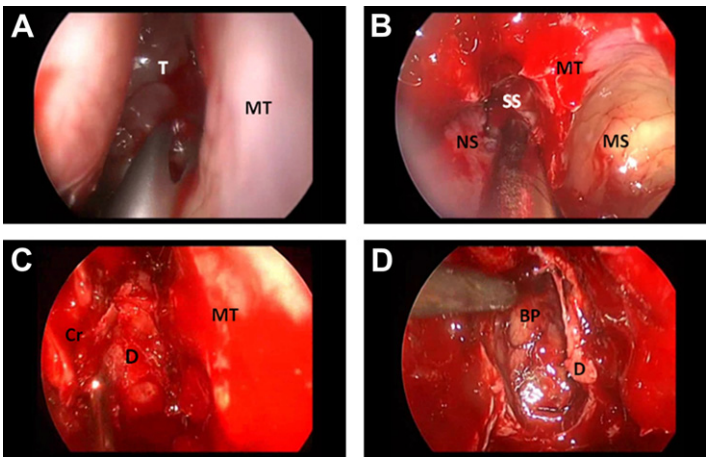

Fig. 6. Technical approach to endoscopic or endoscopic-assisted resection. (*A*) Tumor is debulked and origin identified (MT, middle turbinate; T, tumor). (*B*) Surrounding normal structures are resected or opened to provide exposure—the sphenoid and posterior ethmoid sinuses are opened to establish the level of the skull base and safely dissect from posterior to anterior (MS, opened maxillary sinus; SS, opened sphenoid sinus; MT, root of resected middle turbinate; NS, nasal septum). (*C*) The involved bony skull base is resected and the underlying dura is exposed (Cr, cribriform plate, containing olfactory rootlets near the superior attachment of the nasal septum; D, dura; MT, root of resected middle turbinate). (*D*) The underlying dura is resected with clear margins (BP, brain parenchyma; D, dura). (*From* Department of Head and Neck Surgery, The University of Texas M.D. Anderson Cancer Center; with permission.)

delivered as the primary modality of treatment, or in the preoperative or postoperative setting. The most common and most widely accepted method is postoperative radiotherapy delivered after definitive resection.

Irradiation as a primary mode of treatment has been used in the past, but several studies have demonstrated that surgery combined with irradiation is superior to irradiation used as definitive therapy.[3,7,32,34] Irradiation may be used alone or in combination with concurrent chemotherapy when surgical resection is not an option. This may be due to local or metastatic tumor involvement rendering complete resection impossible or if surgery is not an option due to medical contraindications. Radiation treatment at this time is typically delivered using IMRT, which provides optimal sparing of radiation dose to sensitive normal structures, such as the optic nerve or brain. Gross tumor is typically treated with 1.8 to 2 Gy fractions up to a total dose of 65 to 70 Gy.

The widely accepted role for radiation treatment is in the postoperative setting. Postoperative radiation therapy (PORT) is typically delivered in 2 Gy fractions up to a total dose of approximately 60 Gy, with the goal of treating microscopic residual disease and reduction of the rate of local-regional recurrence. The authors again advocate the use of IMRT to optimize off-target dosing. Reports limited to relatively small series and the lack of controlled, prospective analysis has made it difficult to demonstrate a clear advantage of surgery and irradiation over complete surgical resection alone. However, several large reviews show a trend toward improved survival with PORT[3,7] and several published series support this approach[15,35] (Ow TJ, Hanna EY, Roberts DB, et al. Multimodality therapy optimizes long-term outcome in patients with esthesioneuroblastoma. Unpublished data, manuscript under review, 2012).

Another potential strategy is to give radiation therapy in the preoperative setting. The theoretical advantages of this method are improved accuracy in delineating the target volume with improved sparing of adjacent critical structures, and less anticipated local hypoxia secondary to postsurgical changes. Preoperative radiation may potentially reduce tumor volume improving the respectability of large tumors.[36] However, the target lesion may also become less defined at the time of resection. A well-described protocol using preoperative irradiation or chemoradiation has been reported by the group at University of Virginia.[36,37] Bachar and colleagues[8] recently reported on a subset of patients treated with a preoperative irradiation approach and there were no clear differences in survival or recurrence identified when these patients were compared with those that received PORT in their series; however, these subgroups were small.

The data regarding elective irradiation of the neck parallel the paucity of data examining prophylactic neck dissection. Ozashin and colleagues[34] reported only a 7% rate of regional relapse when the neck was not irradiated, and Noh and colleagues[17] did not find that elective irradiation prevented regional failure. Other studies suggest that the development of regional disease is much higher over time, and there is some limited data providing support for elective irradiation of the cervical lymph nodes.[38] Currently, it remains unresolved if there is an advantage to elective irradiation of the neck, though this is commonly employed.

The recent utility of proton beam irradiation, particularly intensity-modulated proton beam radiation therapy (IMPBRT) deserves mention. This technique allows delivery of therapeutic-dose radiation to a target while minimizing the dose to the surrounding, uninvolved structures. There has been preliminary data using this technique in ENB,[39] and this modality may prove to be ideally suited for skull base malignancies.[40] Future studies are necessary to establish the role of IMPBRT in ENB, but this technique offers a promising option in the management of tumors of the skull base.

Chemotherapy

The data supporting chemotherapy for the treatment of ENB is limited. Chemotherapy as a single modality is reserved for palliation. Chemotherapeutic regimens are otherwise generally used in the induction setting prior to surgery, or concurrently with postoperative radiation. At our institution, neoadjuvant regimens often include cisplatin and etoposide, and are typically advocated for those patients with advanced disease, particularly those with significant intracranial or orbital invasion. We also advocate concurrent chemoradiation with platinum-based treatment after surgical resection for those patients at high risk of local-regional recurrence. This decision is not based on strong data in treating ENB, and is empirically extrapolated from the current practices in treating other head and neck malignancies.[41]

Data specifically examining the utility of chemotherapy for ENB is limited to case reports and small series. Interestingly, in a series published by Noh and colleagues,[42] elective neck irradiation did not reduce the incidence of regional treatment failure, whereas none of the patients who received systemic chemotherapy recurred in the cervical lymph nodes. Chao and colleagues[43] reported on

8 patients who received neoadjuvant chemotherapy (four received a cyclophosphamide/vincristine-based regimen, and 4 received cisplatin and etoposide), 6 of whom were NED at the time the study was completed. Two cases of preoperative chemoradiation with cisplatin and etoposide were detailed by Sohrabi and colleagues,[44] offering another potential treatment strategy employing chemotherapy for patients with advanced ENB. Neoadjuvant chemotherapy was also supported in a study of ifosfamide, cisplatin, and etoposide, in which nine of eleven patients achieved an objective response with this regimen.[45] Perhaps the most well-studied chemotherapy protocol has been the regimen developed at the University of Virginia, which advocates concurrent administration of cyclophosphamide and vincristine during preoperative irradiation.[37] A case of a durable response to sunitinib (a multi-kinase inhibitor that targets PDGFR, VEGFR, and KIT) in the palliative setting has also been published, offering another intriguing option for study in the era of targeted therapy.[46]

Summary of Treatment Strategies for ENB

Single-modality treatment of ENB is generally reserved for small tumors with no sign of regional or distant metastasis, and surgical resection is advocated. As disease becomes more locally advanced, more extensive surgery–typically an open or endoscopic-assisted craniofacial resection is advocated, along with post-operative radiation therapy. Preoperative radiation is an alternative strategy which may yield equivalent results, and induction chemotherapy, as well as concurrent post-operative chemoradiation may improve local, regional, and distant control. Treatment of the neck is reserved for those who present with or develop regional disease, and neck dissection with postoperative radiation or chemoradiation is advocated. Patients with distant disease can be treated palliatively. Systemic treatment is warranted, and surgery or irradiation for the primary site of disease may be considered. Chemoradiation is an approach for patients with unresectable local disease, which could subsequently improve the resectability for locally-advanced ENB.

PROGNOSIS AND FOLLOW-UP

Patients with ENB, even those with advanced local disease, often have an extended disease-free period, with a substantial number of patients demonstrating no evidence of disease after 10 to 15 years of follow-up. Recurrence can manifest late, often between 5–10 years after initial treatment[8,32,34,47,48] (Ow TJ, Hanna EY, Roberts DB, et al. Multimodality therapy optimizes long-term outcome in patients with esthesioneuroblastoma. Unpublished data, manuscript under review, 2012). Close, long-term follow-up is mandatory for patients with ENB, typically with clinical exam, nasal endoscopy, and anatomic imaging. The authors advocate examination every 3–6 months with CT scan and/or MRI for surveillance for a period of 2 years, which can be extended to 6–12 months afterward for a period of 10 years, or indefinitely. Surveillance for distant metastatic disease is warranted for those patients with advanced local disease, and certainly for those who present with or develop regional disease. We advocate yearly chest radiographs and liver function tests, and/or fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging for distant surveillance.

Several large series with long follow-up have reported a median time to recurrence or progression between 57–110 months,[8,34,47] and 10-year disease/recurrence-free survival rates in the range of roughly 50%–70%.[8,47] The meta-analysis by Dulguerov and colleagues[3] reviewed five studies that reported an average 10-year disease-free survival rate of 52%. It seems that, despite good long-term overall survival, recurrences are relatively high (approximately 50%) and can be most often expected to occur between 5 to 10 years after treatment. In a review of patients at the authors' institution, despite excellent survival outcomes (disease-specific survival of 11.6 years), 46% of patients eventually developed recurrent disease, with a median time to recurrence of 6.9 years (Ow TJ, Hanna EY, Roberts DB, et al. Multimodality therapy optimizes long-term outcome in patients with esthesioneuroblastoma. Unpublished data, manuscript under review, 2012).

From the existing literature, it seems that patients with ENB are at risk of local, regional, and distant recurrence during follow-up. In the large series by Bachar and colleagues,[8] local, regional, and distant failure rates were observed at 15%, 18%, and 8%, respectively. Ozsahin and colleagues[34] reported higher overall local, regional, and distant failure rates, reporting 31%, 26%, and 19%, respectively. In their meta-analysis, Dulguerov and colleagues[3] reported that local, regional, and distant failure was 29%, 16%, and 17%, respectively. Review of the authors' experience showed that the site of first recurrence was local in 18% patients, regional in 18% of patients, and at distant sites in 10%. Distant failure was intracranial, pericranial, or spinal in 10 of 12 sites recorded (Ow TJ, Hanna EY, Roberts DB, et al. Multimodality therapy optimizes long-term outcome in patients with esthesioneuroblastoma. Unpublished data, manuscript under review,

2012). It seems that patients are at relatively high risk for local-regional failure (perhaps 30%–40%) when followed for an extended period. However, distant failure also remains a concern, with an approximate long-term risk of 10%–20%.

There are no data to advocate an optimal approach to treat recurrent disease, but aggressive salvage treatment seems warranted when feasible. Local or regional recurrence should be treated with surgical salvage when disease is resectable. If local or regional sites have not been previously irradiated, radiation or chemoradiation can be used either postoperatively or as a primary salvage modality in unresectable patients. Due to the long disease-free intervals seen among patients with ENB, re-irradiation may be an option in the salvage setting, but this has not been studied.

CURRENT CONTROVERSIES AND FUTURE DIRECTIONS

The diagnosis and management of ENB has improved significantly in the last three decades, yet several important questions remain unanswered. Because the recurrence patterns of this disease are better described with long-term studies of large patient sets, it will become more clear which staging system is most accurate and useful for guiding treatment and for prognostication. Perhaps further molecular and genetic evaluation will be added to the diagnostic work-up to improve our ability to accurately discriminate ENBs that are poorly differentiated from other entities. IMRT and endoscopic surgery have decreased morbidity with treatment, but well-planned, multi-institutional prospective studies will be necessary to determine if new therapies are equivalent or better than current standards. Also, given the fairly high rate of early and late regional metastases that have been recently reported and the prognostic implications of regional disease, it seems that proper management of the neck during treatment and follow-up should be scrutinized. These studies will be crucial to the refinement of the multimodality approach to treating this rare disease. As the array of chemotherapeutics exponentially increases, molecular targets must be sought to further tailor strategies to treat ENB, especially in the cases of locoregionally advanced, recurrent, and distantly metastatic disease.

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