Esthesioneuroblastoma
A Contemporary Review of Diagnosis and Management

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KEYWORDS

- Esthesioneuroblastoma
- Olfactory neuroblastoma
- Craniofacial resection

KEY POINTS

- For selected presentations, endoscopy-assisted craniofacial resections and “endoscopic-only” resections have demonstrated success with long-term results comparable to those of conventional open craniofacial resection techniques.
- Most series advocate combined modality therapy (surgery and radiation therapy with or without chemotherapy) in the management of esthesioneuroblastoma (ENB).
- Neoadjuvant chemotherapy has been advocated for locally invasive and advanced staged ENBs and has demonstrated the capacity to significantly decrease gross tumor volume before definitive surgery and/or radiation.
- Elective management of the neck in patients with ENB remains a controversial topic. Early surgical salvage of patients with regional recurrence is possible in a portion of patients.
- ENB requires long-term follow-up (>10 years) given the extended time to local and regional recurrence.

INTRODUCTION

Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is an uncommon malignancy of the head and neck, representing only 3% to 6% of nasal cavity and sinonasal neoplasms.\textsuperscript{1} First described by Berger, Luc, and Richard in 1924,\textsuperscript{2} ENB is a tumor of neural crest origin that is considered to arise from the olfactory neuroepithelium of the olfactory cleft in the superior nasal cavity at the anterior skull base.\textsuperscript{3} Local spread of tumor can extend throughout the paranasal sinuses and skull base with invasion of the orbit, cavernous sinus, and brain.

Several treatment approaches for ENB have been described in the literature, but rigorous, prospective treatment studies are absent given the tumor’s rarity and pattern of recurrence that requires an extended posttreatment observation period. The
behavior of the tumor varies from an indolent slow-growing neoplasm to that of a highly aggressive and locally invasive malignancy with a capacity for regional and distant metastases. Unfortunately, ENB is typically diagnosed after extensive local spread. However, the advances in surgical and radiation techniques and the use of novel chemotherapeutic approaches have lead to the development of an evolving array of encouraging treatment options reported on this diagnosis.

Traditionally, surgery using a craniofacial resection (with a transfacial approach and craniotomy) and adjuvant radiation therapy have been the mainstay of treatment of patients with resectable disease. Endoscopic resection has gained popularity for selected lesions and can spare some patients the morbidity of facial incisions and even craniotomy while remaining an oncologically sound operation. Neoadjuvant, concurrent, and adjuvant chemotherapy (single agent and combination) has been used in combination with surgery and radiation therapy to exploit ENBs' biologically similarity to other tumors of neural crest cell origin that are also chemosensitive.

This article will review the typical presentation, diagnostic assessment, and various treatment options that have been advocated for ENB, while illustrating the limitations of staging and the impact of long-term recurrence on advocated treatment strategies.

**EPIDEMIOLOGY**

ENBs represent only 0.3% of all upper aerodigestive tract malignancies and 3% to 6% of all sinonasal malignacies. A bimodal age distribution has classically been described for ENB, but recent Surveillance Epidemiology and End Results (SEER) data and meta-analyses support a unimodal age distribution with a reported mean age of presentation ranging from 45 to 56 years of age.\(^1,4\)–\(^7\)

Of note, approximately 7% to 20% of patients present at between 10 and 24 years of age.\(^1,5\) Of the impact of age on prognosis is unclear, with one study showing no impact,\(^8\) whereas univariate analyses in other studies suggest an impact on survival in patients diagnosed older than 65.\(^9\) One study suggests that pediatric patients with ENB present with more aggressive local disease that typically requires combined modality care.\(^10\) There is no defined cause and no sex or race predilection. There is no specific laterality that is more common in presentation.\(^5\)

**PATIENT EVALUATION**

*Clinical Presentation*

Patients with ENB present with symptoms related to the local extension of their tumor. Initial symptoms are typically unilateral nasal obstruction (53%–100%), epistaxis (10%–52%), headache (10%–20%), and hyposmia/anosmia (6%–35%).\(^8,11\)–\(^16\) With extension of disease outside the nasal cavity and paranasal sinuses, symptoms of orbital and cranial involvement can manifest. Up to 20% of patients will present with orbital symptoms, including visual loss, diplopia, epiphora with nasolacrimal obstruction, and proptosis.\(^14\) Headaches, nausea, and vomiting can be indicative of dural or intracranial involvement.\(^8\) Rarely, patients will present with frontal lobe symptoms, seizures, or symptoms of syndrome of inappropriate antidiuretic hormone secretion.\(^12\)

Advanced stage presentation is common because of the subtlety of the initial presenting symptoms, which may be initially mistaken as inflammatory or infectious sinonasal disease. The average reported delay between the appearance of first symptoms and diagnosis is 6 months\(^17\); however, the median time to diagnosis by radiographic imaging after onset of first symptoms was as long as 23.1 months in one study.\(^8\)

A listing of differential diagnoses (clinical and histopathologic) for ENB is given in Box 1.
Diagnosis

Clinical examination

Rigid nasal endoscopy often reveals a reddish gray pedunculated mass with a smooth surface that readily bleeds with manipulation (Fig. 1). Given the enhanced vascularity of ENBs, biopsy is typically performed in the operating room to control potential hemorrhage. Additionally, the tumor’s close proximity to the orbit and anterior cranial fossa warrant obtaining imaging before endoscopic biopsy.

Most series report that less than 15% of individuals present with regional nodal metastasis at the time of initial evaluation.\textsuperscript{5,11,17} Zafereo and colleagues\textsuperscript{16} noted that 22% their patients were stage N+ at diagnosis. Office-based fine needle aspiration may assist in appropriate staging and establishing the need for treatment of the neck in these patients.

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**Box 1**

Differential diagnosis for sinonasal pathologic conditions with a similar presentation (clinical and histopathologic) as ENB

- Sinonasal undifferentiated carcinoma (SNUC)
- Sinonasal squamous cell carcinoma
- Neuroendocrine carcinoma (NEC)
- Merkel cell carcinoma
- Ewing's sarcoma
- Metastatic pulmonary small cell NEC
- Small cell lymphoma
- Atypical extracranial menigioma
- Rhabdomyosarcoma
- Pituitary adenoma
- Melanoma

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**Fig. 1.** Endoscopic view of ENB appearing as a vascular polypoid mass with irregular surface in the left nasal cavity between septum (left) and inferior turbinate (right).
**Imaging**

Initially, imaging is obtained to distinguish between inflammatory and neoplastic causes given a patient’s symptoms and clinical examination findings. This is usually accomplished with a fine-cut computed tomography (CT) scan of the paranasal sinuses. If a neoplastic process is suspected, CT can be used to identify bony erosion of the cribriform plate and lamina papyracea, but magnetic resonance (MR) imaging is also needed for a thorough evaluation. On CT, ENB can display isodensity or slight hyperdensity with scattered necroses and marginal cysts.\(^\text{18}\)

MR imaging is superior to CT scanning at delineating the extent of the tumor and distinguishing it from inspissated sinonasal secretions, which can have a significant impact on the surgical approach or treatment planning for radiation. Fine-cut cross-sectional imaging for coronal and sagittal reconstructions aid in identifying intracranial, orbital, and pterygopalatine fossa involvement. MR imaging is also superior at showing dural enhancement, perineural spread, and submucosal extension.\(^\text{19}\) ENB is best evaluated with fat-suppressed, contrast-enhanced T1-weighted images and will be hypointense on T1-weighted images and have a heterogeneous hyperintensity on T2-weighted images with variable enhancement.\(^\text{18}\)

**Figs. 2–5** feature various levels of Kadish staging of ENB imaged with CT and MR imaging.

Intracalvarial invasion is generally considered poor prognostic finding.\(^\text{8}\) Using pretreatment CT and MR imaging, Yu and colleagues\(^\text{18}\) classified direct intracranial extension in Kadish stage C ENB into 3 different categories based on extent of invasion. These patterns of invasion were cranio-orbital-nasal-communicating ENB, cranio-nasal-communicating ENB (most common), and orbital-nasal-communicating ENB. Response to therapy was not correlated to pattern of invasion in this series.

Clinical staging should be completed with a metastatic assessment for cases with advanced local disease or regional metastasis on presentation. In one meta-analysis, 1.5% of patients presented with distant metastases at initial diagnosis.\(^\text{5}\) Wu and colleagues\(^\text{20}\) showed ENB was positron-emission tomography (PET) positive in 7 of 9 patients (77.7%) with a maximal standard uptake value (SUV\(_{\text{max}}\)) of 6.37 ± 4.22 in primary tumors. Tracer uptake did not correlate with tumor size. PET/CT detected regional metastases in 2 (cervical and parapharyngeal) patients and distant metastases in 4 (lung, liver, and bone). PET/CT altered the clinical staging in 3 of the 9 patients. The use of pretreatment PET/CT has also been advocated by other authors.\(^\text{21}\)

![Fig. 2. CT axial (A) and coronal (B) cuts illustrating a Kadish A ENB.](image-url)
**Pathologic Conditions**

Olfactory epithelium contains 3 types of cells: basal, olfactory neurosensory, and sustentacular. ENB is thought to arise from the mitotically active basal cells that give rise to neuronal and sustentacular cells. Molecular studies have suggested ENB may be a member of the Ewing sarcoma/primitive neuroectodermal tumor group of tumors.

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**Fig. 3.** MR imaging coronal cut illustrating the findings of a Kadish B ENB.

**Fig. 4.** CT axial cut of a Kadish C ENB presenting in a pediatric patient with regional metastatic lymphadenopathy with orbital extension of tumor.
ENB is categorized as a “small, round, blue cell tumor” on light microscopy. The cells can have indistinct cytoplasmic borders, hyperchromatic nuclei, infrequent mitoses, and rare nucleoli. Additionally, ENB demonstrates a highly vascularized stroma that is infiltrated with nests of cells. Two types of rosettes are seen. Homer-Wright (HW) rosettes, also known as pseudorosettes, are present in approximately 30%–50% of cases. They are characterized by neurofibrillary and edematous stroma in the center of a cuffing arrangement of cells. Flexner-Wintersteiner rosettes, also known as true rosettes, are seen in up to 5% of cases and distinguished by a tight annular arrangement with glandlike spaces.

The extent of differentiation is classified by the Hyams grading system based on histologic features including architecture, mitotic activity, nuclear pleomorphism, rosettes and necrosis (Box 2, Figs. 6 and 7).

The literature typically refers to ENB as low grade, consistent with Hyams grade 1 or 2, or high grade (grades 3 or 4). The diagnosis of a high-grade ENB has been shown to have a significant impact on survival. In a retrospective review by Dias and

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**Box 2**

**Hyams’ histopathologic grading**

- Grade 1 – Well differentiated with lobular preservation, prominent fibrillary matrix, no nuclear pleomorphism, Homer-Wright (HW) rosettes
- Grade 2 – Low mitotic index, moderate nuclear polymorphism, fibrillary matrix present, HW rosettes
- Grade 3 – Moderate mitotic index, prominent nuclear polymorphism, low fibrillary matrix, HW rosettes, rare necrosis
- Grade 4 – High mitotic index, anaplasia, marked nuclear pleomorphism, absence of fibrillary matrix and HW rosettes, frequent necrosis

colleagues, the 5-year disease-specific survival (DSS) for patients with low-grade tumors was 64%, whereas for patients with high-grade tumors it was 43%.

The importance of a patient’s tumor histopathologic findings, as they relate to prognosis, vary among reports. Levine and colleagues found no valuable pathologic or molecular indicators to predict aggressive clinical behavior in their series of patients. Morita and colleagues examined the pathologic findings of 49 patients with ENB and noted the pathologic grade correlated with prognosis. Patients with low-grade lesions were able to undergo surgery alone if negative margins were obtained with resection. The authors advocated that patients with high-grade lesions be treated with surgery and postoperative radiation with a consideration for the inclusion of chemotherapy.

Care must be taken when interpreting older studies in which the histopathologic differentiation of similar yet distinctly unique sinonasal tumors, such as SNUC or neuroendocrine carcinoma (NEC), may have been combined under the diagnosis of ENB. Some authors have even suggested the seemingly dichotomous behavior of the tumor may be an indication of this problem. ENBs are typically considered low-grade tumors that respond well to treatment. However, when an ENB is considered a high-grade or anaplastic variant and actively progresses despite standard combined modality therapy, the potential for initial misdiagnosis should be considered.

Fig. 6. Pathologic examination of a low-grade ENB. (A) Biopsy specimen with nasal mucosa noted on superior aspect, demonstrating lobular growth pattern with small hyperchromatic nuclei (hematoxylin and eosin, original magnification ×2). (B) Lobules featuring fibrillary matrix and lacking nuclear pleomorphism with focal cytoplasmic clearing (hematoxylin and eosin, original magnification ×20).

Fig. 7. Pathologic examination of a high-grade ENB. (A) Poorly defined lobules with hyperchromatic nuclei with absence of fibrillary matrix and Homer-Wright rosettes (hematoxylin and eosin, original magnification ×4). (B) Frequent mitosis, anaplasia, marked nuclear pleomorphism, absence of fibrillary matrix and Homer-Wright rosettes, frequent necrosis (hematoxylin and eosin, original magnification ×20).
Cohen and colleagues,\textsuperscript{29} at MD Anderson Cancer Center (MDACC), reviewed the pathologic findings of 12 previously diagnosed cases of ENB and were able to confirm diagnosis in only 2. Misdiagnoses included 2 cases of melanoma, 3 cases of NEC, 3 cases of pituitary adenoma, and 2 cases of SNUC. The change in diagnosis would have lead to a significant alteration in the patient’s original treatment plan in 8 of the 10 patients.

Immunohistochemistry demonstrates that greater than 90\% of ENB cells are neuron-specific enolase positive. Approximately 80\% of cases are positive for S-100, staining cell nests, and synaptophysin.\textsuperscript{30} Cytokeratin AE1/AE3 and epithelial membrane antigen are typically negative with ENB.\textsuperscript{18} SNUC demonstrates greater pleomorphism than ENB, may contain enlarged nucleoli, and isEMA positive and S-100 negative.\textsuperscript{1}

Kim and colleagues\textsuperscript{31} examined 17 ENB specimens for staining with bcl-2, p53, MIC-2, and N-myc. Of note, 70\% of specimens were positive for bcl-2. All specimens were negative for N-myc. MIC-2 and p53 staining was noted in only one specimen. The results suggested a potential survival advantage and improved response to chemotherapy with bcl-2 positivity in patients with ENB, yet this finding was not statistically significant.

In patients with regional lymphadenopathy, fine needle aspiration can be considered a diagnostic aid. Mahooti and Wakely\textsuperscript{1} reviewed 6 fine needle aspiration samples for cytopathologic features of ENB and noted specimens were typically nonspecific. However, if fibrillar neuropil was identified in the context of a patient with an established diagnosis of ENB, the confirmation of metastatic spread could be confirmed with cytometry. The histologic findings noted on aspirates can be mistaken for rhabdomyosarcoma, Ewing sarcoma, lymphoma, extracranial meningioma, poorly differentiated NEC, or pituitary adenoma.

**Clinical Staging**

There are 2 major clinical staging systems for ENB. The Kadish staging system,\textsuperscript{32} originally reported in 1976 with the pretreatment assessment of 17 patients with ENB, has traditionally been the one most commonly reported. Proposed by Morita,\textsuperscript{28} and later used by Jethanamest and colleagues,\textsuperscript{5} a modification to the initial 3-tier Kadish staging system was created that included an additional stage for patients who had distant metastases at the time of diagnosis (stage D). Tumors are staged based on their anatomic involvement (Box 3).

The Kadish system has been shown to correlate with survival.\textsuperscript{5,27,33–35} A criticism of the Kadish system is that it fails to completely stratify patients. Very few patients actually present at stage A and a wide spectrum of presentations can be grouped within stage C. Reports that were published before the addition of stage D with the modified

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**Box 3**

**Modified Kadish tumor staging**

- **Stage A:** Limited to the nasal cavity
- **Stage B:** Involves the paranasal sinuses
- **Stage C:** Extends outside the sinonasal cavity, including involvement of the base of skull, orbit and intracranial cavity
- **Stage D:** Distant metastases at diagnosis

*Data from Refs.\textsuperscript{7,10,11}
system allowed patients with intracranial extension and distant metastases to be initially staged identically. An additional weakness cited in the Kadish system was that it did not allow for stratification of patients with pathologic adenopathy.\textsuperscript{14}

It should be noted that radiologic staging and tumor grading are not directly related. In one report, only 14\% of Kadish A tumors were low grade based on Hyams’ grading.\textsuperscript{9}

Dulguerov\textsuperscript{17,36} proposed a TNM style of staging system for ENB that allowed for the inclusion of nodal status (Box 4). Some authors have commented that the Dulguerov classification more closely correlates with survival and recurrence.\textsuperscript{14}

**TREATMENT**

The rarity of presentation and lack of controlled trials have resulted in a wide variation in the management of ENB. As a general rule, sinonasal malignancies are best managed with a multidisciplinary approach. There is a sufficient body of evidence to suggest that for advanced-stage ENB, such as Kadish C lesions, a combined modality approach improves disease free survival (DFS) and overall survival (OS) compared with surgery or radiation alone.

For Kadish A lesions, the consensus for treatment approach diverges significantly and monomodality care has been explored. Surgical management has evolved beyond open approaches to now include endoscopic management options. Radiation has expanded to include approaches that now use proton therapy. Controversy continues to exist relative to the role of chemotherapy, the most appropriate agents to use, and the timing of administration. The following section provides a review of the published literature as it applies to these various issues.

**Surgical Management**

Most of the literature examining the treatment of ENB consists of retrospective institutional reviews. Surgery, primarily using a craniofacial resection (CFR) approach, has been the traditional treatment modality in the initial care of these patients.\textsuperscript{37} Exposure is obtained through a coronal scalp incision and bifrontal craniotomy (Fig. 8) from above and through a lateral rhinotomy facial incision with potential extension under the ipsilateral eyelid (Weber-Ferguson approach) from below. This approach can allow for excellent exposure and en bloc resection of the tumor (Fig. 9). Reconstruction typically involves placement of a pericranial flap to create a vascularized flap separation

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**Box 4**

**Dulguerov TNM staging**

| T1 | limited to the sinonasal cavity excluding the sphenoid sinus |
| T2 | involves the cribiform plate or sphenoid sinus |
| T3 | involves the orbit or anterior cranial fossa without dural involvement |
| T4 | tumors with intracranial involvement |
| N1 | any lymph node metastasis |
| M1 | any distant metastasis |

of the nasal cavity from the intracranial contents (Fig. 10). Criticisms of this approach include cosmesis-related concerns from the mid-facial incision and frontal lobe trauma from intraoperative retraction.

Shah and colleagues reported on 23-year experience with the use of CFR at Memorial Sloan-Kettering Cancer Center in 115 consecutive patients for malignant tumors of the anterior skull base. The 5- and 10-year DSS rates for ENB (14/115) were 100%. The need for orbital exenteration was associated with a reduction in survival in the group overall. Absolute contraindications to CFR were considered involvement of the cavernous sinus and carotid artery.

Alternative open approaches include the transglabellar-subcranial approach and the transfrontal sinus approach. Pioneered by Raveh and associates in 1998, the subfrontal approach provides wide exposure to the cribriform plate for en bloc resection but avoids facial incisions and lessens the need for frontal lobe retraction. This is accomplished by removing the nasal root and supraorbital rims with a bifrontal craniotomy. With this approach the clival-sphenoidal region can be viewed, allowing for potential optic nerve decompression and exposure to the medial aspect of each

Fig. 8. Exposure to the site of the cribriform plate from a craniotomy approach before resection.

Fig. 9. Operative specimen from craniofacial resection demonstrating frontal lobe/dura resection with cribriform plate bisecting the midpoint of ENB and lateral paranasal sinus anatomy inferiorly (including lamina papyracea, septum, and middle turbinates).
cavernous sinus. In the report of their 13-year experience with the technique in 104 patients, 8 specifically for ENB, Raveh and colleagues reported a low complication rate for cerebrospinal fluid (CSF) leak (2.9%), flap necrosis (1.9%), pneumocranium (1.9%), and epidural infection (1.9%).

Ward and colleagues reported on the use of the subcranial approach in 15 patients with ENB (Kadish B, 13; C, 2). None of the patients experienced a decrease in the Karnovsky performance status after surgery. Median time to recurrence in the study was 82.1 months. Patients who underwent surgery alone had 5- and 15-year DFS rates of 26.7% and 0%, respectively. Individuals who underwent surgery and adjuvant radiation therapy had 5- and 15-year DFS rates of 83.3%. As a result, the authors concluded that low-grade disease and negative margins were not sufficient to warrant foregoing postoperative radiation therapy.

Kane and colleagues performed a Kaplan-Meier analysis reviewing 205 published reports, which included 956 ENB patients, on the treatment outcomes. In contrast to the findings of other studies, no difference in survival was noted for patients who underwent surgery alone versus surgery and adjuvant radiation therapy at 5 (78% vs 75%) and 10 years (67% vs 61%) (P = .3). Univariate analysis demonstrated a negative impact on survival in patients who were Kadish stage C, Hyams grade 3 or 4 lesions, or older than 65 years. The authors concluded that unimodal and combined modality treatment options demonstrated equivalent survival. This finding was also noted with Kadish C and Hyams grade 2 to 4 tumors; however, consideration for the use of chemotherapy was advocated for patients with high-grade ENB. Of note, the median follow-up within the review was only 3 years.

Resto and colleagues reported on 16 patients at Johns Hopkins Hospital during a 17-year period who underwent CFR as part of their treatment of ENB. Complete surgical resection was achieved in 62% patients. Adjuvant radiation was used in the setting of positive margins. In cases of complete resection with negative margins, 80% of patients demonstrated no evidence of disease at a mean follow-up of 5.6 years.
The transfrontal sinus approach, as described in 14 patients by Ducic, is considered a minimally invasive modification of the subfrontal approach that eliminates the need for craniotomy and orbitonasal osteotomy. Patients with a well-pneumatized frontal sinus and limited superior and lateral extent of tumor are capable of complete resection of ENB and require a smaller scope of reconstruction. It also differs from the subfrontal approach in that it is not necessary to reestablish the nasal root position, address lacrimal drainage, and perform canthal repositioning.

Endoscopic Management

CFR has traditionally entailed a craniotomy (superior approach) with a transfacial incision (inferior approach) using a lateral rhinotomy. With the evolution of endoscopic sinus surgery, substitution of the lateral rhinotomy with an endoscopic approach for the inferior resection cuts has been a significant improvement in the traditional technique for appropriate cases. One of the earliest reports detailing this approach for ENB was in 1997. Endoscopic techniques have progressed to the use of purely endoscopic approaches for early-stage lesions with limited anterior skull base involvement. As experience has grown with tumor resection and dural repair, endoscopic skull base surgeons have become more aggressive with the purely endoscopic approach. In 1999, Stammberger and colleagues reported one of the first series of patients, including 8 with ENB, to undergo endoscopic resection with no evidence of disease at a mean observation time of 37.2 months.

In a retrospective review from MDACC, Hanna and colleagues reported on the endoscopic resection of sinonasal cancers from 1992 to 2007. Within the group, 93 patients underwent endoscope-only resection and 27 underwent an endoscope-assisted CFR. ENB was the primary diagnosis in 17% of the patients. Two-thirds of the patients who had an endoscope-only approach had stage T1 or T2 disease, whereas 95% in the endoscope-assisted group had advanced-stage tumors (T3 or T4). No survival difference was noted between the 2 groups. It was considered that acceptable outcomes were achieved with an endoscope-only approach for selected low-grade/early-stage malignancies with appropriate adjuvant therapy. Their indications for adjuvant radiation therapy were high-grade tumors, advanced T stage, bone invasion, perineural spread, intracranial extension, dural or brain involvement, or positive margins. For patients undergoing radiation, 90% were treated with intensity-modulated radiation therapy (IMRT) to optimize tumor dose and minimize toxicity to local structures.

Castelnuovo and colleagues examined the use of endoscopic techniques in the treatment of ENB in a series of 10 patients of various staging (Kadish A, 3; B, 5; C, 2). En bloc excision was possible only for smaller lesions and piecemeal resection was required for larger tumors. Microscopic negative margins were obtained in all patients. Duraplasty was performed as needed dependent on the extent of resection. Most of the patients (9/10) underwent adjuvant radiation therapy. No recurrences were noted at a mean follow-up of 38.1 months. The authors advocated conversion to an open approach if a negative margin resection is not possible during an endoscopic approach and emphasized the importance of selection criteria.

Gallia and colleagues reported on the use of a purely endoscopic approach in 8 patients with ENB at Johns Hopkins Hospital. Their technique uses 2 surgeons, an otolaryngologist and neurosurgeon, with a 3- and 4-handed technique. During the procedure, a lumbar drain is placed and a neuronavigation system is used. Resection involves initial debulking of tumor to gain access to the tumor margins, followed by maxillary antrostomies, ethmoidectomies, sphenoidotomies, and frontal sinusotomies. Next, septal transfixation incisions are made and the ventral skull base is exposed from the planum sphenoidale to the frontal sinus. With tumor resection, circumferential
contiguous intraoperative margins are taken with the goal of obtaining negative margins. Reconstruction is performed with a nasal septal flap or dural/dermal inlay grafting. All patients in this series underwent postoperative radiation therapy and have demonstrated no evidence of disease with a mean follow-up of 27 months.

A meta-analysis reviewing the treatment options of 361 patients (from 1992 to 2008) demonstrated an equivalent survival rate for patients undergoing endoscopic surgery compared with those who had open CFR. Additionally, it was also noted that patients who underwent any surgery, as part of their care, experienced a significant benefit in disease-free outcome and survival compared with patients treated with nonsurgical modalities. The authors concluded that endoscope-only and endoscope-assisted surgery was a valid treatment method with comparable survival to open surgical techniques. Criticisms of the study include that the analysis did not control for Kadish staging, limited follow-up (<5 years), and the bias inherent in retrospective reviews of institutional experiences.

Contraindications to using an exclusively endoscopic approach include involvement of the facial soft tissues. Relative contraindications include highly vascular tumors, the need for orbital exenteration, significant intracranial/intraparenchyma involvement, and lateral extension into the infratemporal fossa. Complete surgical resection remains the expectation of the surgical procedure chosen and if not possible with endoscopic techniques should be considered a contraindication to using this approach.

Complications from endoscopic resections are related to extent of tumor resection and the creation of a connection between the sinonasal cavity and intracranial contents. If an endoscopic dural resection is performed, failure to adequately reconstruct this defect can result in a CSF leak and potential meningitis. Folbe and colleagues reported a CSF leak rate of 17% in their series of 23 patients. Other potential complications include frontal sinusitis, dacrocystitis, epistaxis, and chronic crusting from large areas of mucosal injury.

Randomized controlled clinical trials comparing the efficacy of CFR, endoscope-assisted, and purely endoscopic techniques are unlikely to ever occur. The ultimate goal of endoscopic resection remains the same as with open craniofacial resection: complete resection with a limited associated morbidity. Independent of technique, negative margins should be pursued and abandoned only if critical neurovascular structures are involved, such as the optic nerves or the internal carotid artery. In an editorial on the topic endoscopic resection for ENB, Snyderman advocated that until major skull base centers have treated adequate numbers with endoscopic technique with extended follow-up, open surgical procedures should remain the standard for care.

**Combined Modality Therapy - Surgery and Radiation Therapy With or Without Chemotherapy**

A common theme in the treatment of ENB is the importance of combined modality therapy. The way in which therapy is delivered may differ between institutions; however, the use of surgery in combination with radiation, with or without chemotherapy, remains the standard of care.

Controversy does exist over the need for adjuvant radiation therapy for patients with Kadish stage A lesions that are resected with negative margins. Of interest, in the original report describing the staging that carries his name, Kadish advocated for adjuvant radiation therapy for stage A ENB secondary to concerns over local recurrence. The use of adjuvant radiation to reduce the risk of local recurrence, independent of the margin status of resection, is a widely accepted concept.

In a meta-analysis examining 26 studies (from 1990 to 2000) with 390 patients, Dulguerov and colleagues attempted to assess for new developments in the
treatment of ENB. The authors established that tumor stage (Kadish or Dulguerov), histopathologic grade (Hyams’ classification), and treatment modality (surgery with or without adjuvant therapy) were important determinants of DFS. Five-year OS within the group was 45%. Based on the review of this group of patients, they concluded that surgery with adjuvant radiation therapy was the optimum treatment strategy for ENB.

In contrast, Platek and colleagues, performing a SEER database review (from 1973 to 2006) of 511 patients with ENB came to a different conclusion. The 5-year OS for surgery with adjuvant radiation therapy, surgery alone, and radiation therapy alone were 73%, 68%, and 35% respectively ($P<.01$). At 10-years post-treatment, the authors concluded there was no significant improvement experienced in survival with the addition of radiation to surgery. A prior report by Jethananest also showed no benefit of adjuvant radiation therapy in OS.

Despite this question of survival benefit with the routine use of adjuvant radiation, the practice standard of several institutions that have reported their retrospective experiences is to include adjuvant radiation or chemoradiation in their treatment algorithms.

Levine and colleagues described the surgical management of 35 patients with ENB during a 21-year period. At diagnosis, 62.9% of patients had Kadish stage C disease and 6% presented with regional lymphadenopathy. Patients were treated with standard CFR and adjuvant radiation with or without chemotherapy (vincristine and etoposide). The local recurrence rate was 14.3% and occurred at an average of 6 years after diagnosis; 25.7% developed cervical metastases and the rate of distant metastatic spread was 11.4%. DFS was 80.4% at 8 years.

Dias and colleagues reported on 36 patients with ENB in a 17-year review. Most patients were treated with surgery and adjuvant radiation or radiation alone. The rate of neck metastasis (early and late) was 14%. The authors noted that Kadish staging correlated with DFS and the development of regional or distant metastasis significantly affected prognosis. CFR with adjuvant radiation therapy was associated with the best 5-year DFS (86%).

Diaz and colleagues, reporting the 22-year experience at the MDACC, reviewed the treatment of 30 patients with ENB. In the group, 77% were treated with surgery and adjuvant radiation therapy. The 5- and 10-year OS rates were 89% and 81%, respectively. Relapse-free survival and OS in early-stage (Kadish A/B) lesions was 100%. All of the recurrences in the series occurred in Kadish C patients with a mean time to recurrence of 4.67 years. Salvage was considered successful in prolonging survival in this group. The authors advocated complete surgical resection with postoperative radiation therapy regardless of initial Kadish stage.

Smee and colleagues, reviewing a group of 24 patients with ENB, attempted to use neoadjuvant chemotherapy to direct subsequent treatment. All newly diagnosed patients with surgically resectable disease underwent 2 to 4 cycles of cisplatin/etoposide (cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1, 2, and 3 every 3 weeks) and were then reimaged and rebiopsied. If both parameters were negative, patients would proceed to radiotherapy as definitive local treatment. If either were positive, patients underwent surgery with adjuvant radiation therapy. Only 2 of the initial 6 patients were locally controlled with this approach and avoided surgery. As a result, the authors did not advocate this form of neoadjuvant chemoselection and believed surgery and adjuvant radiation was required to achieve the best local control.

Jiang and colleagues reviewed the treatment of 25 patients with invasive intracranial ENB. The worse survival rates were seen in the subgroups of patients who did not undergo surgery. Without any treatment, no patient lived longer than 1 year. Patients treated with standard CFR (opposed to endoscopic resection) with postoperative radiation therapy (with or without chemotherapy) had the best prognosis, with OS
rates of 100%, 88%, and 66% at 1, 3, and 5 years. In a review by Arigiris and colleagues\textsuperscript{26} of 16 patients, 50% of whom had brain involvement at diagnosis, similar findings and recommendations were made for combined modality treatment with complete surgical resection.

Gruber and colleagues\textsuperscript{35} examined the use of radical radiation therapy (with dosing up to 73 Gy) in the primary treatment of ENB in 28 patients. The authors concluded that primary radiation could not replace surgery and recommended complete surgical resection, followed by high-dose radiation therapy (median dose, 60 Gy) and simultaneous chemotherapy. When surgery was included in care, patients experienced a significantly better local progression-free survival and DFS than did patients treated with radiation alone.

In one of the largest retrospective reviews, Ozsahin and colleagues\textsuperscript{48} examined the outcomes of 77 patients with nonmetastatic ENB from the Rare Cancer Network. On univariate analysis, favorable prognostic factors included Kadish stage A/B, T1 to T3 tumors, N0 status, “curative surgery,” negative or microscopic positive resection margins (R0/R1), and radiation dosing to 54 Gy or greater. Favorable prognostic factors on multivariate analysis included T1 to T3 tumors, N0 status, R0/R1 resection, and total radiation dose to 54 Gy or greater. Median follow-up was 72 months. For the entire group, the 5-year local-regional control was 62% and OS was 64%. The authors advocated combined modality treatment and suggest that novel chemotherapeutic strategies and alternative radiation dosing should be investigated in an attempt to improve local control.

**Radiation Therapy**

Monomodality “radiation-alone” protocols have generally been reserved for patients considered inappropriate for surgery or with selected small lesions below the cribriform plate (Kadish A). Meta-analysis and SEER data reviews have shown decreased survival in patients with ENB receiving monomodality radiation therapy compared with combined modality care.\textsuperscript{6,17}

Radiation therapy used in combination with chemotherapy before surgical resection has been shown to be an effective adjunct in a combined modality care plan.\textsuperscript{11} Preoperative radiation has advocated as a tool to aid in orbital preservation and decrease gross tumor volume with invasive tumors.\textsuperscript{50,51} Adjuvant radiation can improve local control after surgery, decreasing local recurrence rates in one study from 71% to 17%, as well as decrease the risk of regional recurrence.\textsuperscript{52} The timing of radiation, before or after surgery, does not seem to impact the benefit it offers to local disease control.\textsuperscript{14}

Nichols and colleagues\textsuperscript{13} reported on the use of proton beam radiation after CFR in 10 patients with ENB with predominantly Kadish stage C disease. With a median follow-up of 52.8 months, 5-year DFS and OS rates were 90% and 85.7%, respectively. Proton beam radiation was considered safe and effective with ENB and potentially less toxic than photon radiation because of the capacity to lower radiotoxicity to critical adjacent structures (brain, optic nerve, orbit).

In a more aggressive combination of proton therapy with neoadjuvant chemotherapy, Fitzek and colleagues reported on the multimodality treatment of malignant neuroendocrine tumors of the sinonasal tract using high-dose proton-photon radiotherapy. In this series of 19 patients, which included patients with ENB 9 and NEC 10, most tumors were Kadish stage C (15/19). Treatment included 2 cycles of cisplatin/etoposide followed by high-dose proton-photon radiotherapy to 69.2 cGy equivalents using 1.6–1.8 cobalt-Gray equivalents per fraction twice daily in a concomitant boost schedule. Responders (68%) received 2 additional adjuvant courses of chemotherapy. Nonresponders underwent surgery. The actuarial 5-year survival
was 74%. The authors noted that secondary to the precision of the radiation delivered with stereotactic guidance, no radiation-induced visual loss was observed.53

Role of Chemotherapy

A definitive role for the use of chemotherapy in the treatment of ENB has not been explicitly defined, but there is an abundance of evidence to support its use in a multimodality approach. Whether chemotherapy is best used as a neoadjuvant regimen or as an adjuvant treatment in combination with radiation remains a topic of debate. Chemotherapy has been generally accepted for patients with ENB with high-grade, recurrent, or unresectable disease.12

Some of the most cited evidence for the use of chemotherapy in the treatment of ENB comes from the experience of University of Virginia Health System. Patients with Kadish stage A or B disease received preoperative radiation therapy, whereas patients with Kadish stage C disease (22/50) were treated with preoperative sequential chemoradiation. Surgery in both settings was standard CFR. The preoperative sequential chemotherapy involved 1 cycle of cyclophosphamide (650 mg/m²) and vincristine (1.5 mg/m²) with the addition of doxorubicin in a select group of patients. In patients who experienced a good response, a second cycle given. In the series overall, a 5- and 15-year DFS rate of 86.5% and 82.6%, respectively, was noted with a mean follow-up of 93 months. Recurrence occurred in 17 (34%) with a mean interval to recurrence of 6 years. In patients with a locoregional recurrence (12/17), 41% were capable of undergoing successful salvage surgery.54

The authors based their treatment regimen on a philosophy that ENB has biologic characteristics similar to those of other chemosensitive tumors of neural crest origin such as high-grade NEC and primitive neuroectodermal tumor.50,54 A similar consideration led to the use of 2 neoadjuvant cycles of cisplatin (33 mg/m² daily) and etoposide (100 mg/m² daily) before definitive proton therapy (45 Gy during 5 weeks) for 9 patients with ENB and NEC by Bhattacharyya and colleagues55. After treatment, 8 of 9 patients achieved a complete response and avoided surgical resection. In contrast, Smee and colleagues49 described the unsuccessful use of neoadjuvant cisplatin/etoposide as a predictive tool for selecting nonsurgical candidates with ENB.

The combination of cisplatin and etoposide represents a popular regimen that has been successfully used in the neoadjuvant and adjuvant setting. A review from the Mayo Clinic, involving 12 patients with Kadish stage C high-grade ENB, examined the use of adjuvant cisplatin and etoposide after complete surgical resection. Six patients received adjuvant chemotherapy with radiation and 6 received only postoperative radiation. The addition of adjuvant chemotherapy improved median time to relapse from 10.5 to 35 months yet did not significantly affect OS.56 Neoadjuvant cisplatin/etoposide, CFR, and adjuvant chemoradiation with IMRT have also been described with successful use in a Kadish C patient with frontal lobe invasion.57 Use of neoadjuvant chemoradiation (with cisplatin/etoposide) demonstrated a complete pathologic response in 2 Kadish stage C patients who underwent subsequent CFR.58

Kim and colleagues59 described the use of 4 cycles of neoadjuvant etoposide (75 mg/m²), ifosfamide (1000 mg/m²), and cisplatin (20 mg/m²) (VIP) in 11 previously untreated patients with ENB. The induction regimen demonstrated a partial response in 64% of patients and complete responses in 18%. Radiation therapy was used in partial responders and surgery with radiation was offered for nonresponders. Other reports have failed to demonstrate a significant response to neoadjuvant use of the VIP regimen.60

Presentation of ENB in younger patients is frequently associated with advanced-stage presentations and has provoked interest in chemotherapy-associated regimens in an attempt to potentially limit the extent of surgical intervention. Mishima and
colleagues\textsuperscript{61} reviewed the care of 12 treated patients with adolescent-onset ENB. Most patients enrolled had advanced-stage disease (Kadish staging A, 1; B, 1; C, 6; D, 4). Patients were treated with 2 cycles of chemotherapy (cyclophosphamide, doxorubicin, vincristine with continuous-infusion cisplatin, and etoposide), radiation therapy, and peripheral blood stem cell transplantation (PBSCT). A partial response was seen in 75\% after induction chemotherapy and 50\% experienced a complete response after radiation with or without PBSCT. All patients undergoing PBSCT experienced a CR.

Bisogno and colleagues\textsuperscript{10} reported on the experience of 9 patients (age 0.9–18 years, median 9.9) who were identified by the Italian Association of Pediatric Hematology and Oncology registry. Local invasion was extensive at diagnosis in all patients. Complete surgical resection was considered challenging but the addition of chemotherapy (vincristine, doxorubicin, ifosfamide, actinomycin D or vincristine, doxorubicin, and cyclophosphamide alternated with the cisplatin-etoposide combination) and radiotherapy (48.5–60 Gy) enabled tumor control in 8 patients. With a median follow-up of 13.4 years (range 9.2–22.9), 7 patients were still alive.

Novel approaches have been described using various chemotherapeutic combinations with unique presentations and settings. Gupta and colleagues\textsuperscript{62} reported a patient, incapable of obtaining CFR, in whom limited endoscopic excision was performed after 6 cycles of cisplatin, etoposide, and bleomycin and radiation therapy (56 Gy). The patient was free of recurrence at 5 years posttreatment.

Kiyota and colleagues\textsuperscript{63} reported on 12 patients with advanced or metastatic ENB treated with irinotecan and docetaxol and radiation therapy (1 photon, 6 protons). The 7 patients with advanced locoregional disease treated with CRT had a 2-year survival of 100\%. The authors noted that younger patients had a better response to therapy.

Management of the Neck

Cervical lymph node metastases are infrequent at presentation for patients diagnosed with ENB with reported rates between 5\% and 10\%.\textsuperscript{11,17,52,64} The natural history of ENB requires long-term follow-up as many patients (18–33\%) may subsequently develop regional lymph node metastases. Demiroz and colleagues\textsuperscript{52} reported regional recurrence in 27\% of their series with a median time to regional failure of 74 months. The lymphatic vessels of the lateral cribriform plate and anterior nasal cavity pass superficially to join the external nasal skin. Nodal metastases are found most commonly in level II, but metastases have also been seen in levels IB, III, and IV and in retropharyngeal nodes. Bilateral or contralateral spread is also common and should be considered during treatment planning.\textsuperscript{52,54}

Patients who present with N\textsubscript{1} disease have a clinically and statistically worse prognosis. Dulguerov and colleagues\textsuperscript{17} noted that N\textsubscript{1} patients (5\%) at initial presentation were less likely to be treated successfully compared with patients with N\textsubscript{0} disease (29\% vs 64\%). These findings were reinforced by Jethanamest showing only a 40\% DSS at 5 years for patients with N\textsubscript{1} disease, which was significantly less than that for patients with N\textsubscript{0} disease.\textsuperscript{5}

Monroe and colleagues\textsuperscript{64} examined the rationale for elective neck radiation in ENB as regional failure correlates with prognosis for distant failure and DFS. In their study, 22 patients with ENB were treated, 2 had positive neck disease at presentation, and 11 of the remaining 20 underwent elective neck radiation. No patients developed regional disease after elective treatment; however, 4 of the remaining 9 who did not receive elective neck treatment developed regional disease. The authors suggest these findings justify elective regional nodal XRT in Kadish B and C patients.

Demiroz and colleagues\textsuperscript{52} report regional failure in 27\% of cases in their series with a median time to failure of 74 months. They use their data to support the consideration
of elective treatment in the N0 neck. Of their 7 neck failures, only 3 could be salvaged. Salvage rates for isolated neck metastases range between 27% and 80%. Currently, there are no good data to show that elective neck treatment improves survival, and some authors argue that isolated, late neck recurrences are easily salvaged. Given the relatively high reported rates of late regional failures and limited morbidity-associated IMRT, elective neck radiation may warrant consideration in patients with high-grade Kadish C disease.

Management of Recurrence

Local recurrence of ENB can occur more than a decade after definitive treatment. The rate of local recurrence depends on the primary treatment. Lund and colleagues report a 17% local recurrence rate for all patients. A study from the University of Michigan showed 10 of 14 (71%) patients treated with surgery alone developed a local recurrence within 5 years, whereas 2 of 12 (17%) treated with surgery followed by radiation had local recurrences at 72 and 115 months. Of the 12 patients with local recurrence 7 were capable of salvage treatment that included surgery. Success of salvage treatment of local disease depends on the extent of disease and location of recurrence. Careful follow-up examination with rigid nasal endoscopy is of great importance because early recurrences may be successfully treated by endoscopic resection.

For intracranial recurrence, a report of an intracavitary chemotherapy wafer placed in the field of a recurrent ENB undergoing re-resection showed acceptable results. Gliadel is a biodegradable polymer of carmustine (BCNU) allowing for the controlled release and local delivery of the chemotherapeutic agent with minimal systemic side effects.

Lymph node metastases are uncommon at presentation, but up to 27% of patients with ENB will develop neck disease. A meta-analysis reviewing 33 articles revealed 137 of 678 (20.2%) patients developed neck metastases and 79 (61.7%) of those were recurrences that presented 6 months or later after initial diagnosis. Salvage rate for these recurrences, defined by 1 year of DFS, was 31.2%. Combined therapy with surgery and radiation increased salvage rates compared with either treatment alone (OR 8.6 vs 3). Additional reports confirm these findings in the setting of recurrence showing an advantage in DFS for combined modality therapy versus monomodality treatment.

Distant metastasis occurs to brain, bone, lungs, viscera, trachea, and heart. Distant disease may develop in up to 10%. One study reported the development of distant metastases at a mean of 13.4 months after primary treatment. Despite the poor prognosis of distant metastatic disease, when possible, salvage therapy can offer symptom palliation and extend overall survival. Gabory and colleagues reported that 3 of 28 patients developed distant metastases at 6-, 168-, and 243-month follow-up.

McElroy and colleagues reviewed a series of 10 patients with recurrent ENB. Cisplatin-based chemotherapy was noted to be active in advanced high-grade ENB and was considered a reasonable choice for systemic therapy. Mean duration of regression was noted to be 9.3 months.

Complications

Treatment of ENB is not without significant procedure- and therapy-related morbidities. Complications, short and long term, vary with the therapeutic intervention used and are more likely when extensive local invasion is seen at initial presentation. Levine and colleagues reported a central nervous system complication rate of 25.7% (1 patient with elevated intracranial pressure, 2 with pneumocephalus, 5 with CSF leaks) in patients who underwent CFR. Orbital complications were encountered
in 22.9% and included epiphora, radiation-associated cataracts, radiation keratopathy, and transient diplopia with cranial nerve IV dysfunction. Shah and colleagues reported an operative mortality of 3.5% with 115 consecutive patients undergoing limited or extended CFR. The major complication rate was 35% (frontal bone osteomyelitis, local sepsis, delayed return of neurologic function, meningitis) and 4 patients died as a result of perioperative complications.

Kryzanski and colleagues reported on 58 patients undergoing surgery for a midline anterior skull base lesions (including 4 ENB, 29 meningioma) that required a craniotomy or craniofacial approach. Most of the patients underwent a narrow 2-piece biobritofrontal craniotomy. Dura was typically repaired before the nasal cavity was entered in an attempt to prevent infection. Their complication rates were 2% for CSF leak, 2% for meningitis, 3% for bone flap necrosis, and 3% for symptomatic pneumocephalus. No deaths occurred and no reoperations for CSF leak were necessary. There were no new permanent neurologic deficits experienced by patients beyond anosmia. The authors concluded that transcranial approaches for anterior skull base lesions can be associated with low complication rates.

Bisogno and colleagues reported on 9 pediatric patients (age 0.9–18 years, median 9.9) with ENB treated with neoadjuvant chemotherapy, surgery, and adjuvant chemo-radiation therapy. Treatment-related complications included 4 patients with subsequent endocrinologic dysfunction (hypogonadism, hypothryoidism), and 4 patients experienced craniofacial growth impairments (hypoplasia).

LONG-TERM RECOMMENDATIONS

Multiple authors have advocated extended follow-up because of the average time to recurrence. Follow-up for ENB patients that extends longer than 15 years after the completion of treatment is recommended.

Routine clinical examination augmented with nasal endoscopy should be expected during reevaluation. Abnormal findings on clinical examination, including new-onset lymphadenopathy, should provoke a low threshold for biopsy. Follow-up imaging with contrast-enhanced MR imaging at 4-month intervals for the first 1 to 3 years, then every 6 months for 3 years, and followed by every 9 to 12 months thereafter has been advocated (Fig. 11).

**Fig. 11.** MR imaging coronal (A) and sagittal (B) cuts after craniofacial resection with pericranial flap reconstruction for a Kadish C ENB.
SUMMARY

For selected presentation, endoscope-assisted craniofacial resections and “endoscope-only” resections have demonstrated success with long-term results comparable to those of conventional open craniofacial resection techniques. Most series advocate combined modality therapy (surgery and radiation therapy with or without chemotherapy) in the management of ENB. Neoadjuvant chemotherapy has been advocated for locally invasive and advanced-staged ENBs and has demonstrated the capacity to significantly decrease gross tumor volume before definitive surgery and/or radiation. Elective management of the neck in patients with ENB remains a controversial topic. Early surgical salvage of patients with regional recurrence is possible in a portion of patients. ENB requires long-term follow-up (>10 years) given the extended time to local and regional recurrence.

REFERENCES
