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Olfactory Neuroblastoma: Treatment Strategies for Advanced Disease

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Abstract

Purpose of Review This review seeks to synthesize emerging literature and expert management recommendations of olfactory neuroblastoma (ONB), a rare sinonasal neuroendocrine malignancy.

Recent Findings The rare nature of ONB and variability in extent of disease at presentation make formal recommendations and trials challenging—particularly as it pertains to advanced disease. Margin-negative surgical resection, including craniofacial and/or endoscopic approaches, when feasible, followed by radiation treatment performed with a multi-disciplinary care team remains the standard of care, with some evidence for chemotherapy in advanced disease. Salvage surgery and radiation for nodal metastases may provide extended periods of recurrence-free survival.

Summary Management of ONB should include nuanced radiographic and anatomic staging followed by aggressive margin-negative surgical intervention coupled with radiation and possibly chemotherapy. Ongoing surveillance should be undertaken, even in patients with presumed definitive treatment due to high risk of delayed recurrence.

Keywords Olfactory neuroblastoma · Esthesioneuroblastoma · Treatment of advanced neuroendocrine disease · Hyams · Kadish

Abbreviations

ONB	Olfactory neuroblastoma
MIBG	Metaiodobenzylguanidine
SEER	Surveillance, Epidemiology, and End Results
IMRT	Intensity-modulated radiation therapy
CSF	Cerebrospinal fluid

Introduction

While commonly known as esthesioneuroblastoma, its now formal World Health Organization name is olfactory neuroblastoma (ONB), a neuroectodermal malignancy arising from olfactory epithelium. The clinical presentation is often insidious due to the indolent and slow growing tumor phenotype, possibly creating falsely low incidence rates, but best estimates suggest 0.4 cases per 1,000,000 individuals—less than 5% of all sinonasal malignancies [1–9]. There is a significant age variance, with median age of 53 (range 30–70), with a slight male sex predominant distribution (59% male vs 41% female) [1–9].

Presentation

Local mass effect, anosmia, nose bleeds, and nasal obstruction are the most common presenting symptoms of ONB [1–10]. Most of the symptoms are non-specific and often lead to a delay of diagnosis. In rare cases, ONB may have paraneoplastic phenomenon that can mimic pituitary disease (Cushing syndrome, humoral hypercalcemia, syndrome of inappropriate anti-diuretic hormone, hyponatremia), hypertension, or additional CNS pathology (opsoclonus-myoclonus-ataxia, and cerebellar degeneration) [10–14]. Rarely, a patient may initially present with palpable cervical lymphadenopathy.

Diagnosis

A well-coordinated multidisciplinary team is critical to high value care, with pre-operative evaluations frequently by otorhinolaryngology, neurosurgery, ophthalmology, radiation oncology, and oncology. A thorough physical examination, including outpatient nasal endoscopy, as well as CT scan

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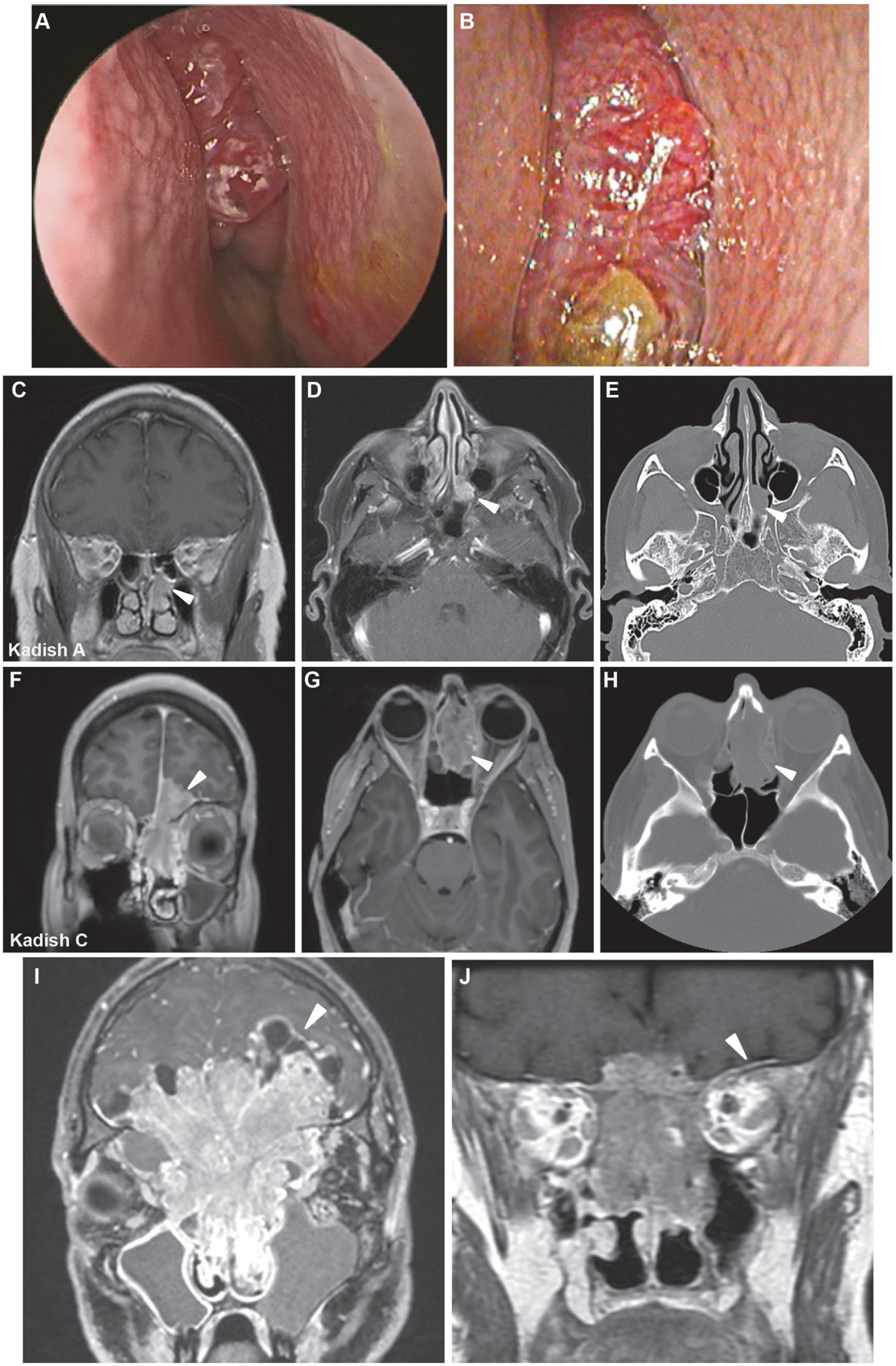
A
B
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◂**Fig. 1** Endoscopic image with 30-degree endoscope of left olfactory cleft mass that was biopsied and proven to be ONB (**A–B**). Coronal (**C**) and axial (**D**) T1-weighted MRI with gadolinium contrast highlight Kadish A stage ONB with disease confined to the nasal cavity (white arrow). Axial bone windowed CT (**E**) highlights mild local disruption of nasal cavity architecture but minimal bony changes (white arrow). Coronal (**F**) and axial (**G**) T1-weighted MRI with gadolinium contrast highlight Kadish C stage ONB with disease that extends beyond the paranasal sinuses and in this case into the intracranial space (white arrow). Axial bone windowed CT (**H**) highlights broader erosion of the nasal septum and larger disruption of local nasal architecture (white arrow). Coronal (**I**) T1-weighted MRI with gadolinium contrast: ONB that demonstrates intradural invasion can develop adjacent peritumoral cysts (white arrow) with adjacent brain—which can demonstrate mild to moderate enhancement and are somewhat unique to ONB. Coronal (**J**) T1-weighted MRI with gadolinium contrast: Lateral extent of ONB invasion is important to determine when planning surgical approach. Invasion laterally along the anterior skull base and superior to the orbit (white arrow) may be challenging to reach with an endoscopic-only approach and may benefit from addition of an open craniotomy component

and brain MRI, should be obtained. On endoscopic evaluation, the lesion often appears polypoid, firm, and with a reddish-brown color—biopsy in the clinic is often performed to aid in histopathologic diagnosis (Fig. 1A, B). Head CT scans are helpful in demonstrating the scope of bony destruction, and a contrasted scan may highlight important vascular structures—particularly carotid arteries. A nuclear medicine scan may also be helpful, as these lesions are metaiodobenzylguanidine (MIBG)-avid, to help distinguish from other olfactory/planum pathology, namely, meningiomas, although paragangliomas and medullary thyroid carcinomas are also MIBG-avid. In a routine clinical practice, however, MIBG scans are used infrequently.

Radiographic Features and Staging

Often, patients may obtain head CT scans initially due to associated easier access and lower screening cost than MR imaging. The masses are centered on the superior olfactory recess and grow to fill the ethmoid air cells, either unilaterally if small, or commonly bilaterally. On bony CT windowing, the lesions erode surrounding bone, notably the cribriform plate, lamina papyracea, and fovea ethmoidalis, and may have sparse calcifications throughout the mass as well. Very rarely, they can produce hyperostosis [15]. As the mass erodes through the cribriform plate superiorly, they often become intracranial and take on a dumbbell shape when viewed on coronal reconstructions. On CT soft tissue windows, the lesions have mild attenuation and often homogenously enhance if given contrast.

Contrasted MR imaging is the best modality for evaluating the extent of the mass itself and is critical for tumor staging. The lesion is usually hypointense on T1-weighted images and iso to hyperintense on T2, with occasional accompanying cystic structures and mucoceles due to sinus obstruction. With larger tumors, there are sometimes central areas of tumor necrosis or hemorrhage, but often the tumors are homogenously enhancing. The tumor is often locally invasive, and fat saturation sequences may help distinguish invasion vs abutment of periorbital fat. Often, MR imaging may distinguish between intradural invasion but can be challenging without definitive surgical correlation (Fig. 1C–H). When they do involve intradural invasion, these lesions can develop adjacent peritumoral cysts with adjacent brain—which can demonstrate mild to moderate enhancement and are somewhat unique to ONB (Fig. 1I) [16]. While characteristic features may be identified in many ONB cases, several other lesions could be considered in the differential diagnosis depending on the radiographic characteristics, which may include sinonasal undifferentiated carcinoma, squamous cell carcinoma, adenocarcinoma, inverted papilloma, meningioma, primitive neuroectodermal tumors/Ewing sarcoma, and lymphoma.

During diagnostic evaluation, tumor staging is critical to aide decision-making. There is some variability, but most studies quote < 20% of presenting ONBs have accompanying metastases, with cervical lymph nodes being the most frequent location. A larger Surveillance, Epidemiology, and End Results (SEER) database study found regional lymph node metastases of 9% [17]. As such, workup may include additional neck physical exam and cervical/neck imaging, often MRI, but PET-CT may also be considered. Indeed, ONB is upstaged in 36% of cases due to added PET-CT scans [18]. In addition, PET-CT may be useful for post-treatment evaluation and further disease classification [19]. As a general guideline, any patient with Kadish C disease or evident modified Kadish stage D should undergo PET-CT prior to finalizing a treatment plan.

Several systems have been utilized and studied for ONB staging, without a formally accepted gold standard. The first system was proposed by Kadish et al. in 1976 [20] and later modified by Morita and colleagues in 1993 [8], which subdivides tumor groups into four categories: (A) confinement to the nasal cavity, (B) extends into the paranasal sinuses, (C) extends beyond paranasal sinuses, and (D) cervical lymph node spread or distant metastases (Fig. 1C–H, Table 1). In addition to patient age, Kadish/modified Kadish has some correlation with outcomes and survival [3, 6, 21•]. In a National Cancer Database review, Konuthula et al. found discordance between groups A and B, which was not accounted for by treatment; however, the survival between groups A and C was relatively similar, with a major expected drop off in survival with the metastatic disease group D [21•]. It should be noted that most patients present with some form of ethmoidal disease involvement, making category A disease rare and often difficult to

Table 1 Staging systems for olfactory neuroblastoma (American Joint Committee on Cancer (AJCC))

Kadish staging	
A	Tumor confined to nasal cavity
B	Tumor involves nasal cavity and at least one paranasal sinus
C	Tumor extension beyond nasal cavity and into paranasal sinuses, with involvement of cribriform plate, skull base, orbit, or intracranial cavity
Modified Kadish staging	
A	Tumor confined to nasal cavity
B	Tumor involves nasal cavity and at least one paranasal sinus
C	Tumor extension beyond nasal cavity and into paranasal sinuses, with involvement of cribriform plate, skull base, orbit, or intracranial cavity
D	Tumor with metastasis to cervical lymph nodes or distant sites
Dulguerov staging	
T1	Tumor involvement of nasal cavity and/or paranasal sinuses, excluding sphenoid or most superior ethmoid cells
T2	Tumor involvement of nasal cavity and/or paranasal sinuses, including sphenoid with extension to/erosion of cribriform plate
T3	Tumor extending into orbit or protruding into anterior cranial fossa without dural invasion
T4	Tumor with brain involvement
AJCC tumor (T) ethmoid staging	**Definition**
T1	Tumor restricted to any one sub-site, with/without bony invasion
T2	Tumor invasion of two sub-sites in a single region or extension to adjacent region within nasoethmoid complex, with/without bony invasion
T3	Tumor invasion of medial wall or orbit floor, maxillary sinus, palate, or cribriform plate
T4A	Tumor invasion of: anterior orbital contents, skin of nose or cheek, anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4B	Tumor invasion of: orbital apex, dura mater, brain, middle cranial fossa, cranial nerves except V2, nasopharynx, or clivus
AJCC overall staging	
0	Tis, N0, M0; tumor is only in top layer of cells lining inside of nasal cavity or ethmoid sinus and has not grown deeper. No lymph node involvement (N0) or metastases (M0)
I	T1, N0, M0; tumor has grown deeper, but only in one part of nasal cavity or ethmoid sinus, with or without bone involvement
II	T2, N0, M0; tumor has grown into more than one part of nasal cavity or ethmoid sinus, or located in both the nasal cavity and ethmoid sinus
III	T3, N0, M0; tumor has grown into eye socket, palate, cribriform plate, and/or maxillary sinus OR T1 to T3, N1, M0; tumor may have extended outside nasal cavity or ethmoid sinus, cancer has spread into a single lymph node (< 3-cm diameter) in neck with same laterality of tumor (N1)
IVA	T4A, N0 or N1, M0; tumor has extended into anterior eye socket, skin of nose or cheek, sphenoid or frontal sinus, or pterygoid plates OR T1 to T4A, N2, M0: tumor may or may not extend outside of nasal cavity or ethmoid sinus and may be moderately advanced (T4A) has spread to a single lymph node in neck with same laterality of tumor, larger than 3 cm but less than 6-cm diameter OR has spread to one or more lymph node in neck with less than 6 cm. diameter OR has spread to a single lymph node in neck with same laterality as tumor, but is 3 cm or smaller with extranodal extension (N2)
IVB	T4B, Any N, M0; tumor is growing into back of eye socket, brain, dura, clivus, middle cranial fossa, certain cranial nerves, or nasopharynx (T4B). Cancer may or may not have lymph node metastases (any N) OR Any T, N3, M0; tumor may or may not extend into structures outside nasal cavity or ethmoid sinus (any T) and has either spread to one least one lymph node larger than 6 cm, spread to single lymph node with same tumor laterality and is larger than 3 cm with extranodal extension or growing in multiple lymph nodes on either side
IVC	Any T, any N, M1; tumor may or may not extend into structures outside the nasal cavity or ethmoid sinus and may or may not extend to nearby lymph nodes, but has spread to distant parts of the body (M1)

identify. There are two additional classifications based on more conventional oncologic tumor/nodal/metastasis (TNM) staging by the American Joint Committee on Cancer (AJCC) and articulated towards ONB by the American Academy of Otolaryngology-Head and Neck Surgery, as well as the commonly used modification from Dulguerov and Calcaterra [4, 22]. The AJCC modification focuses on local, regional, and distant areas of disease as outlined in Table 1.

While none of these systems are universally accepted and utilized, they have been compared. A study by Joshi et al. employed the National Cancer Database of 883 ONB patients and showed superiority of TNM tumor staging system in predicting long term survival and outcomes [23]. Another systematic review study by Arnold et al. demonstrated slight superiority of the modified Dugeurov system, compared to the Kadish system, at predicting disease-free survival and overall survival [24]. That said, nodal status and presence of metastases are common delineators that do demonstrate reproducible outcomes on multivariate analysis, as do patient age, patient frailty, and hospital volume [23]. Unsurprisingly, the best predictor of long-term survival among the staging systems is presence of nodal/metastatic disease, which is typically the mediator for mortality, rather than local uncontrolled disease [25•, 26].

In addition to radiographic and anatomic features, ONB is also graded to assess phenotype using the Hyams grading system [27]. The Hyams grading system uses histopathology to categorize tumors from grade 1 through 4, with increasing nuclear pleomorphism, mitotic activity, and necrosis with increasing grade. Additionally, decreasing fibrillary matrix is associated with increasing grade. As may be hypothesized, worse Hyams grade correlates relatively well with many prognostic characteristics [3, 4, 28]. A meta-analysis from Dulgeurov and colleagues found overall 5-year survival rates of 56% for Hyams grades I–II and 25% for grades III–IV [3]. Laboratory real-time PCR assessment for human achaete-scute homolog (hASH-1) messenger MRI has also been investigated to aid in the diagnosis of ONB vs other poorly differentiated sinonasal tumors [29].

Conventional Management

The rare nature of this disease, coupled with a paucity of high-level clinical trials on disease management, makes wide variations in practices. Furthermore, the initially asymptomatic nature of disease progression often means the tumors may be quite large at presentation, extending into various cranial spaces. That said, the mainstay of current management strategies is surgical intervention—mainly gross total surgical resection with negative margins. The surgical approach selection, which will be discussed in more detail in later sections, has traditionally been guided by the size and compartment involvement of tumor, often involving combined "open" and "endoscopic" approaches. While we will cover the nuances of differential treatments and patient subcategorization in coming sections, an article by Chao et al. highlights the fundamental principle—5-year local control was achieved in 87% of patients undergoing surgery and radiation, whereas only 51% control rates with isolated primary chemoradiation [30•]. Interestingly, surgical margin status did not influence local tumor control in this study.

Surgical Selection

In addition to surgeon experience and expertise, the extent of disease plays a major role in surgical approach selection and should be tailored accordingly. The various staging systems, which may be helpful in pre-operative counseling and discussions with patient/family, may also guide surgical approach selection based on the sinus, intracranial, and neck spaces needed to be encountered.

For primary disease, "open" approaches have traditionally dominated the selection of surgical approach—typically a bifrontal craniotomy with craniofacial resection to allow a subfrontal approach to the anterior skull base, as well as occasionally craniofacial and ophthalmologic corridors. In modern skull bas centers, most "open" approaches are also coupled with an endoscopic endonasal approach to clear intranasal margins and to help facilitate skull base reconstruction.

Endoscopic endonasal and transmaxillary (Caldwell-Luc) approaches have advanced significantly and therefore have being increasingly utilized for primary surgical modality, particularly for less locally invasive disease, although the extent of resection using endoscopy has continued to progress [31, 32]. Often, the extent of disease and a desire for margin-negativity may drive a combination of approach techniques. Most modern data support the efficacy of an endoscopic piecemeal approach for carefully selected tumors with equivalent or improved outcomes compared to stage-matched tumors undergoing resection via open approaches, when negative margins can be obtained [33–36]. However, open and combined open/endoscopic approaches continue to play an important role when tumor involves dura laterally over the orbit, high along the frontal sinus or when reconstructive opens are limited endonasally (Fig. 1J). An open approach may particularly be utilized with intracranial, intraorbital, cavernous sinus, and frontal sinus extent of disease depending on individual patient anatomy. Current literature rates of the 5-year overall survival ranging from 55 to 89% and disease-free survival ranging from 46 to 83% for open-based approaches [2, 9, 37, 38]. Endoscopic approaches, when directly compared with open approaches, have been linked with improved 5-year progression free survival, overall survival, lower rates of local recurrence, and lower

complications and may be utilized as the mono-surgical management in thoughtfully selected patients [39, 40].

Adjuvant Therapy

In our practice, surgery alone is usually reserved for small, non-invasive, and non-metastatic disease with widely negative surgical margins—often Kadish A-B and low Hyams grade, although this practice is variable around the country (Fig. 1C–E). However, mixed prognostic distinction between staging systems and relative high rates of local recurrence often led to many centers to opt for some form of planned adjuvant therapy—usually radiation [9]. Radiation has been trialed as a monotherapy independent of surgery and has moderate success for controlling small local disease but has poor outcomes for most ONBs and should not be considered the standard of care except in rare circumstances [41]. The most common adjuvant radiation modalities employed today are intensity-modulated radiation therapy (IMRT) and proton beam therapy—which may result in reduced radiation effect to radiosensitive structures such as optic nerves, pituitary gland, cerebrum and brain stem, and retina. Indeed, a large systematic review and meta-analysis found that overall the 5-year survival and disease-free survival were higher in charged particle vs photon therapy; however, no major differences were found at longest follow-up [42]. However, locoregional control was slightly higher at longest follow-up for charged particle therapy. In a further subgroup analysis, proton beam therapy had improved disease-free survival and locoregional control at longest follow-up [42]. It should be noted that the rare nature of ONB makes more direct treatment comparisons impractical to perform and therefore studies have not directly evaluated whether proton beam or IMRT is superior.

In addition, there has been variable support for elective cervical nodal radiation, with decreased rates of long-term nodal spread, albeit with significant morbidity [43]. Alternatively, many centers do not electively treat clinically N0 necks, instead utilizing salvage neck dissection or radiotherapy for cases of delayed regional spread with excellent long-term disease control [44••].

Chemotherapy is not commonly incorporated as an initial adjuvant therapy paradigm at many centers, particularly for non-advanced disease. However, it is often indicated in combination with radiotherapy in the adjuvant setting for aggressive tumor features such as high Hyams grade, positive surgical margins, or metastatic disease. Several relatively small, and often retrospective, studies have trialed induction and neoadjuvant chemotherapy with mixed results, including the use of platinum-based agents, etoposide, and/or cyclophosphamide [5, 45–50]. Induction chemotherapy remains as an option in locally advanced tumors to improve the chances of obtaining a negative-margin resection or as part of an orbital preservation strategy.

Retrospective, non-randomized single center reports have found modest individual improvements in various outcome measures with chemotherapy; however, a larger SEER analysis found no convincing support for utilizing chemotherapy for improving disease free or overall survival [45, 47–49, 51, 52]. The most common agents utilized are cisplatin, or other platinum-based agents, along with etoposide, as it remains a well-characterized regimen for other high-grade neuroendocrine carcinomas. However, additional chemotherapy agents have been utilized, including case reports for additions of doxorubicin, ifosfamide, vincristine, and temozolomide [47, 53–55].

Treatment of Advanced Disease

A major delineator in the treatment of advanced ONB is when the surgical team feels that a margin-negative resection cannot be accomplished. This may be due to the extent of local invasion, distant nodal/metastatic disease, or patient preferences and individual considerations. Indeed, disease-free survival is roughly cut in half with nodal or metastatic disease present at diagnosis, and about 9% of patients present with orbital involvement and 36% with intracranial invasion [56•]. Surgical debulking is certainly not standard of care but may play an occasional role in ameliorating patient symptoms in unresectable or metastatic cases. Beyond obvious limitations of surgically controlling nodal/metastatic disease, locally advanced disease may similarly prove challenging due to indistinct margins and invasion into sensitive structures such as the orbit, brain, and intracranial neurovascular structures—not only making for poorly controlled disease, but suboptimal cosmetic and quality of life outcomes.

For the rare ONB patients with locally advanced tumors in which negative margins are unlikely to be achieved or would require orbital exenteration, our current institutional practice is to consider induction chemotherapy, prior to a planned surgical resection. Candidly, when our institution reviewed its modern series of ONB, only six patients fell into this category, and only five went on to surgical resection of some form. Three of the five patients responded to induction treatment, with four patients achieving margin-negative status [50]. However, three patients had disease recurrence after surgery, and two died as a direct result of disease progression; the patient who did not undergo initial surgery passed away 12 months after diagnosis. Surgery was undertaken at a median of 7 months, all five underwent bifrontal craniotomies, and two were combined with cranio-endoscopic approaches. One patient was margin-negative on intraoperative frozen section, but later was deemed positive on permanent pathologic assessment.

There have been a handful of other studies that also reported on induction chemotherapy for advanced ONB. One of the larger trials, a cohort of 23 patients, had a response rate of 74% to induction chemotherapy, but individual outcomes for this subcohort were not distinguished [57]. In another series of twenty ONB patients with advanced sinonasal tumors, 12 patients underwent treatment with neoadjuvant cisplatin/carboplatin and etoposide for two cycles—those with radiographic responses underwent attempted gross total resection, whereas non-responders underwent radical chemoradiation [58]. Only one out of eleven patients with pretreatment "non-resectability," referring to an inability for gross total resection with negative margins, demonstrated a change to become "resectable." Two-year progression-free survival was 91.7%, but the median follow-up was only 1.7 years. This study would suggest that neoadjuvant chemotherapy is not reliably beneficial to improve rates of surgical cure in advanced disease. However, another study evaluating similar induction chemotherapy regimen in fifteen patients found a higher response in high Hyams grade lesion (78%), with three patients avoiding orbital exenteration and five-year disease-free and overall survival rates of 71% and 78%, respectively [49]. Ten of the fifteen patients had objective response to chemotherapy—with substantially correlated improved outcomes of both survival and preservation of the orbit [49].

A series of 32 patients by Loy et al. evaluated treating patients with Kadish stage C using preoperative combined chemoradiation, using cyclophosphamide, vincristine, and selected doxorubicin, followed by surgical craniofacial resection [7]. Seventeen patients (53%) developed recurrent disease at a mean of 6 years, and seven underwent successful subsequent salvage surgery without remnant of disease recurrence at a mean follow-up of 93 months. Non-platinum-based chemotherapies have also been tried, including a series of twelve patients with advanced ONB were primarily managed with primary chemotherapy of irinotecan and docetaxel, with five patients previously undergoing radiation and the radionaïve undergoing subsequent radiation after chemotherapy, mostly proton beam [53]. Younger patients (< 50 years) fared better; in all patients, median progression-free and overall survival was 13.6 and 36.6 months, with a median follow up of 22 months.

In the past decade, there remains interest in targeted chemotherapy for advanced ONB—using tumor genetics to guide treatment; however, most reports are case series, trials remain relatively small, and there is no consensus on the regimen or timing [59, 60, 61••]. In addition, due to the rarity and often difficulties discriminating between ONB and other sinonasal tumors with neuroendocrine differentiation, they are often combined in the published literature, further muddying the interpretation towards making clinical practice recommendations. That said, there is an emerging appreciation for distinct genome-wide methylation variations in ONB, particularly compared to non-ONB sinonasal malignancies, as well unique tumor expression of targetable ligands such as PD-L1, TSC1, and SUFU, which provide more focused therapy by repurposing available chemotherapy agents against these targets [59, 60, 61••].

Around one in ten patients present with metastatic disease at presentation, mostly to cervical lymph nodes [17, 62••]. Advancements in our understanding of anterior skull base dural lymphatic channels, which drain into cervical lymph nodes, provide a better understanding for the pathophysiology of nodal metastases. Indeed, patients with anterior skull base dural invasion had a 50% rate of cervical metastases, while on 22% of those without dural invasion had similar nodal disease—which had strong correlation with decreased survival and outcomes [63].

The management of non-localized disease is particularly challenging, with approximately 5-year survival rates cut in half (29 vs 64%). If distant metastases are present, treatment is often more focused more on palliation and disease control rather than curative strategies [17, 25•]. Due to the elevated risk of developing distant metastatic spread with current cervical nodal disease, and overall associated poor outcomes, there has been some studies evaluating elective neck radiation as part of the primary treatment paradigm [44••, 64]. A large study from Jiang et al. examined 71 patients between 1970 and 2013 with clinically N0 ONB and performed elective cervical radiation in 22 (31%) [64]. In the elective neck radiation group, they found that no patients develop nodal disease at 5 years, compared to 18% with new nodal disease in those without elective nodal radiation. However, this regional control did not translate to increase disease-free or overall survival. In a long-term outcomes study by Abdelmeguid et al. with a median follow-up of 75 months, patients that received elective nodal irradiation demonstrated a 6.4% neck recurrence rate, compared to 34.4% in those that did not receive it [65]. Prophylactic neck radiation does come with considerable adverse risks, including confluent mucositis, esophageal injury, salivary gland dysfunction, and long-term declines in physician, social, and emotional functioning [66, 67]. In another trial from our institution by Peacock et al., it was found that patients initially managed with nodal radiation has excellent control with salvage surgery and radiation when regional cervical metastatic disease occurred, which was found in 41% of patients by 10 years, with more than doubled increases in local recurrence-free survival compared to salvage surgery alone (80% vs 35%) [44••].

Even in patients that undergo initial "definitive" surgical resection and treatment, distant metastases still occur in 12% of patients at a median of 15 months and a 6-month overall metastasis-free survival rate of 63% [68]. Metastatic disease to the spine and thecal sac had the best overall survival with

6-month survival of 80%, while visceral organ mets having the worst 6-month survival of 52%. Patients with aggressive triple therapy of surgery, chemotherapy, and radiation had the best overall survival compared to monotherapy or no treatment, with likely treatment biases that confound broader interpretation (PMID: 36900297).

Emerging Therapy

Conducting clinical trials in ONB is challenging due to disease rarity, so assessing small series and trials using novel treatment agents is a challenge and is often anecdotal. Molecular targeted therapies, such as sunitinib, have been discussed as possible agent to be used in cases with treatment failure, with one report of 15 months disease stability, with some histologic evidence for positive targeting of PDGFR [69]. Pre-clinical studies have identified activation of sonic-hedgehog pathways in ONB, which has been hypothesized to be a druggable target, with one study showing cyclopamine improved tumor cell control [70]. Other trials are working to evaluate peptide receptor radioligand therapy, particularly in metastatic disease. Most are single case reports, but one larger study of seven patients found partial response in 4 patients, disease stabilization in 2, and early progression in another—with an observed increase in rates of cerebrospinal fluid (CSF) leaks [71–74].

Post-Treatment Considerations and Surveillance

Complications are relatively high with both major surgical approach techniques. The extent of disease is associated with increased risk of operative morbidity and mortality, with common open adverse events including CSF leak, intracranial hematoma, infection including meningitis, seizures, frontal lobe edema and cognitive dysfunction, and incisional dehiscence—particularly with added adjuvant therapy. These complications can occur in rates as high as 20–60% of cases [3, 7, 9, 37, 40, 75]. Endoscopic techniques have similar risks of CSF leak, intracranial hematoma, and infection including meningitis but carry less risk of increasing frontal lobe edema through retraction and seizures; however, nasal complications can occur—including nasal crusting, septal perforation, sinus infections, and breathing dysfunction [76].

Use of induction chemoradiation has been shown to have minimal risk of adverse effects in small series [7]. However, chemotherapy-related toxicities have been documented to occur—including leukopenia, neutropenia, febrile neutropenia, thrombocytopenia, and anemia, among others [53, 58]. Patients with post-operative CSF leaks that previously received chemotherapy or radiation do not have increasing rates of repair failure [77]. It should be noted, as has been discussed above, that these are rare tumors with relatively low overall complication rates, making detecting complication causation is challenging; however, none of the major treatment modalities seem to have significant adverse side effect profiles.

There are no outlined surveillance protocols, and individualization should be undertaken—with a major priority on avoiding patients lost to follow up. Even patients with presumed definitive disease develop distant metastasis by 10 years at a rate of around 12%, with improved outcomes with salvage systemic treatment [38, 68]. Directed MRI surveillance of the maxillofacial and brain area should be considered standard, potentially every 6–12 months as clinically indicated. There is no good evidence for cervical nodal surveillance, but should be considered well, particularly as disease is often missed on physical exam and patients may not be symptomatic. Systemic surveillance, with PET-CT or modalities, may also be considered. Other disease processes are exploring serum surveillance of disease using tumor cell-free DNA, exosomes, circulating tumor cells, and other tumor-related systemic biomarkers that may also be useful, but warrant further assessment and validation [78]. Multidisciplinary teams, comprised of oncologists/neuro-oncologists, otorhinolaryngologists, neurosurgeons, radiation oncologists, pathologists, neuroradiology/radiology, and patient support elements including pharmacy, nursing, care management, and physical/occupational therapy, should all be incorporated in pre and post-treatment management of these challenging patients.

Conclusions

ONB is a rare sinonasal malignancy- early identification, and aggressive negative-margin resection and radiation can lead to enhanced outcomes and survival. Despite nuances in assessing lesions based on staging and grading characteristics, in addition to patient age, there is clear linear correlation with outcomes when viewed in comparison with more invasive, higher grade, and metastatic disease. For all patients with ONB, 5-year overall and progression-free survival are 50–90% and around 50%, respectively, with modest historical improvements corresponding with emergence of better diagnostic and interventional resources. While higher level trials are lacking, the mainstay of ONB advanced disease treatment should be margin-negative surgery and adjuvant radiation, possibly with chemotherapy, to improve disease-free and overall survival; however, long-term outcomes remain relatively guarded even with initial presumed definitive intervention.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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