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Olfactory neuroblastoma

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Abstract

Originating from the olfactory neuroepithelium, olfactory neuroblastoma is a rare malignant tumor of the nasal cavity that typically affects adults between the ages of 35 and 70. Clinical presentation predominantly consists of nonspecific symptoms such as nasal obstruction, nasal drainage or epistaxis, thus illustrating the need for a thorough diagnostic workup. In addition to a complete head and neck examination, rigid nasal endoscopy, biopsy and imaging are necessary to establish a definitive diagnosis as well as plan for treatment. Computed tomography (CT) and magnetic resonance imaging (MRI) are the primary imaging modalities utilized to assess for bony invasion and soft tissue involvement, respectively. Hyams grading system provides a histologic assessment of disease severity while various staging systems correlate severity of disease to anatomic location/progression. Treatment relies on both surgical intervention and radiation. In addition, ongoing research trials are investigating therapeutic targets. Given the risk of recurrence, extended post-treatment surveillance remains necessary.

Keywords: Olfactory neuroblastoma, esthesioneuroblastoma, sinonasal tumors, malignancy endoscopic sinus surgery, radiation therapy

INTRODUCTION

Initially described in 1924 by Berger *et al.*, esthesioneuroblastoma, now widely referred to as olfactory neuroblastoma, is an uncommon malignant tumor of the nasal cavity that originates from the sensory

olfactory neuroepithelium[1]. It accounts for 2% to 6% of nasal cavity and paranasal sinus cancer cases with an incidence rate of 0.4 per million population[2-5]. Most cases occur in individuals aged between 35 and 70 years with a mean age of presentation of 53 years[6]. There is a moderate male predominance with a male-to-female ratio of 59 to 41[6].

Diagnosing olfactory neuroblastoma involves a nasal cavity examination and a tissue biopsy. While there is no universally employed staging system, the Kadish and Dulguerov systems are commonly used[7,8]. Imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan are particularly valuable for assessing regional and distant metastases, and staging.

The behavior of olfactory neuroblastoma varies widely, ranging from less aggressive, slowly growing tumors with extended survival to highly aggressive malignancies, characterized by rapid recurrence and spread of cancer to distant sites[9]. This diversity in tumor severity, coupled with its rarity and the limited data regarding genetic and molecular alterations, leads to some uncertainties surrounding the best practices for management[10]. Currently, treatment involves surgery, radiation therapy, and/or chemotherapy followed by long-term surveillance to monitor treatment outcomes and recurrences[11].

Ultimately, this chapter explores the clinical characteristics, diagnostic modalities, staging, treatment options, outcomes, and recent advances in our understanding of this disease.

CLINICAL PRESENTATION

Olfactory neuroblastoma typically manifests with a variety of nonspecific symptoms, with nasal obstruction manifesting as the most prevalent symptom. This is primarily attributed to the space-occupying effect of the nasal cavity mass. Obstruction or local invasion of adjacent structures explains other common symptoms, including the paranasal sinuses (headache, facial swelling), the nasolacrimal duct (epiphora), cribriform plate (anosmia), eustachian tube (middle ear effusion, otalgia, recurrent acute otitis media), and orbit (diplopia, proptosis, other visual changes)[12-14]. Alongside nasal obstruction, patients may experience other symptoms, including nasal discharge, epistaxis, and/or varying degrees of pain[15]. Due to the anatomic etiology of these symptoms, patients will report ineffective trials of medical therapy prior to referral to the appropriate specialist. Rigid nasal endoscopy commonly reveals a unilateral, polypoid, glistening firm pink-gray mass with irregular and friable mucosa. Given its sensory neuroepithelial olfactory cell origin, the mass often occupies areas in which these cells reside: the superior portion of the nasal septum and olfactory cleft, superior nasal concha, roof of the nose, and cribriform plate of the ethmoid sinus[16]. Rarely, olfactory neuroblastoma has been noted to originate in the nasopharynx or sphenoid sinus[16-18]. Hypervascularization of the tumor is common, consistent with the common complaint of epistaxis.

While relatively rare, olfactory neuroblastoma can give rise to paraneoplastic syndromes secondary to excess hormone production. Such syndromes include ectopic adrenocorticotropic hormone (ACTH) syndrome[19,20], hypercalcemia[21], hyponatremia[19], syndrome of inappropriate antidiuretic hormone (SIADH)[22], and various neurological paraneoplastic syndromes[23]. Rare reports of atypical presentations such as oral paresthesia and tooth laxity as the only presenting symptoms further add to the clinical heterogeneity of olfactory neuroblastoma[24]. Ultimately, these nonspecific symptoms may result in misdiagnosis, delaying definitive diagnosis and appropriate management[4]. Thus, it is imperative to execute a thorough diagnostic workup.

DIAGNOSTIC WORKUP

Upon initial presentation to an otolaryngologist, thorough physical examination serves as the critical first step. Physical examination requires baseline, head and neck, neurologic and ophthalmologic examination as well as nasal endoscopyIt is prudent to perform a detailed head and neck examination as rates of cervical nodal metastasis at the time of diagnosis range from 5% to 8.7% of cases[6,25,26]. Furthermore, there are significant outcome differences in treatment success for patients with nodal disease compared to those without cervical metastasis which further highlights the significance of evaluating nodal involvement[4].

In addition to physical examination, imaging plays an essential role in the diagnosis, staging and management of olfactory neuroblastoma. The first-line protocol for imaging consists of both CT and MRI with and without contrast[27]. CT is utilized to delineate possible osseous involvement of the cribriform plate, orbit and sinuses while MRI will detail soft tissue involvement in the sinonasal cavities, orbit, meninges, brain parenchyma and perineural invasion[28]. Following initial diagnosis, these imaging studies are needed to initiate preoperative planning and management and assess regional and distant disease. While the cervical lymph nodes are the most common site of metastasis, additional sites include the breast, lung, bone, prostate, abdomen, or central nervous system either by intracranial extension through the cribriform plate or seeding of the cerebrospinal fluid (CSF)[29,30].

The appearance of olfactory neuroblastoma on imaging is nonspecific and can be confused with other skull base or intracranial masses such as meningiomas[27]. However, notable features on imaging include a dumbbell-shaped mass spanning across the cribriform, with CT illustrating a heterogeneous mass exhibiting bony erosion notably at the cribriform, while MRI shows a T1 hypointense and T2 isointense mass, which clearly distinguishes it from that of secretions[27,31]. With intracranial extension, peritumoral cysts at the tumor brain interface are characteristic findings. [18F]-Fluorodeoxyglucose (FDG) PET may be used in evaluation of advanced disease or to evaluate treatment response. Recently, the use of [68Ga]-DOTATATE PET was found to be superior to FDG PET due to the tumor's increased expression of somatostatin receptors (SSTRs), which serve as a molecular target and are well-illustrated on whole-body [68Ga]-DOTATATE PET scans[28,32,33]. Nonetheless, the anatomic extent of the tumor is critical to the staging of these cancers, which impacts prognosis and survival outcomes.

HISTOPATHOLOGY

Following physical examination and review of imaging, diagnostic biopsy remains the gold standard for definitive diagnosis. The biopsy can be performed in the office under local anesthesia or in the operating room under general anesthesia. This decision depends on a patient's bleeding risk and the tumor characteristics.

Prior to determining whether an in-office or intraoperative biopsy can be performed, both the patient's bleeding risk and the tumor's vascularity must be assessed. If a patient is on anticoagulation, the provider must contact the patient's cardiologist, hematologist or prescribing physician to establish appropriate timing to hold and resume anticoagulation in the preoperative and postoperative setting[34]. To assess tumor vascularity, imaging modalities such as Doppler ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA), and fluorescence angiography are used to identify cerebral vascular blood supply and its relationship to the tumor. Should the tumor be in the posterior sinonasal space and or noted to be highly vascular on imaging, then biopsy should be performed in the operating room.

Doppler ultrasonography is a noninvasive, portable and relatively affordable imaging modality that offers real-time visualization of cerebral vascularity without radiation exposure[35]. Color Doppler ultrasonography provides color mapping of cerebral vasculature and flow velocity[36]. When paired with contrast agents, color Doppler ultrasonography may help delineate blood flow of both large and small vessels feeding the tumor, which may not be as easily discernible with traditional ultrasonography alone[36,37]. More recently, color Doppler ultrasonography has been utilized intraoperatively in resection of various skull base pathologies such as pituitary adenomas and meningiomas[37-39]. However, its use remains limited given operator-dependent results[35].

Both CT and MRI provide essential information on the tumor's relationship to adjacent bony landmarks and soft tissue structures, respectively. Contrasted CT and MRI also help identify critical vascular structures such as the intracranial portion of the internal carotid and its proximity to the lesion. However, these conventional modalities may not fully capture the tumor's vascularity as intricately as would CTA and MRA. Both detail the cerebral vasculature with high-resolution images during specific arterial and venous phases, which allows the surgeon to determine if pre-biopsy or preoperative embolization is warranted[40]. As both CTA and MRA offer equivalent results, the choice of CTA versus MRA depends on whether the patient meets the criteria to undergo the respective study[41]. Furthermore, if CTA or MRA indicates a high risk of internal carotid artery (ICA) injury, then a balloon test occlusion (BTO) may be necessary to identify collateral cerebral blood flow should the patient experience an ICA injury intraoperatively[40].

Lastly, fluorescence angiography can be employed as an adjunct intraoperative tool to help identify tumor vascularity. Initially applied by neurovascular surgeons for use on patients with intracranial aneurysms or intracranial dural fistula malformations, indocyanine green (ICG) has been used in endoscopic endonasal surgery to assist with identification of vascular structures, nasoseptal flap (NSF) viability and tumor identification[42-44]. ICG is administered intravenously and provides real-time identification of tumor vascularity. Thus, its use is limited to intraoperative applications. Ultimately, utilizing the imaging modalities in the setting of a patient's coagulation history can help guide biopsy, thus allowing for both biopsy and surgical resection planning.

Histologic assessment of well-differentiated specimens reveals a lobular architecture of small, round, blue cells with uniform nuclei with salt-and-pepper chromatin and small or absent nucleoli[14,27]. In addition, these well-differentiated masses are characterized by a typically low mitotic rate, high nucleus-to-cytoplasm ratio and poorly defined cytoplasm[15,27,45]. Physical arrangements of these cells include Flexner-Wintersteiner rosettes, glandular rings with a true lumen, or Homer-Write pseudorosettes[14]. On the other hand, poorly differentiated tumors exhibit a less defined architecture with increased pleomorphism, higher mitotic rate, and necrosis, thus making it difficult to distinguish from other sinonasal masses. Inevitably, immunohistochemistry (IHC) staining remains of the utmost importance as it narrows the differential diagnosis and rules out other sinonasal tumors presenting in a similar fashion (i.e., Ewing's sarcoma, mucosal melanoma, rhabdomyosarcoma, sinonasal lymphoma, sinonasal undifferentiated carcinoma and sinonasal neuroendocrine carcinoma)[14,15,27,45]. Notable positive markers include the expression of S100-protein positive sustentacular cells and neuroendocrine markers such as neuron-specific enolase, synaptophysin, and chromogranin. However, desmin, myogenin, vimentin, actin melanoma, myogenic and Ewing sarcoma markers are negative[46]. Ultimately, histology evaluation not only determines definitive diagnosis but also establishes the foundation for pathologic grading.

Developed at the Armed Forces Institute of Pathology, the Hyams staging system [Table 1] was described in 1988 as a histologic grading system of olfactory neuroblastoma[47]. This staging system categorizes the

Table 1. Hyams histologic grading system

Grade	I	II	III*	IV*
Architecture	Lobular	Lobular	±	±
Mitotic rate	0	Low	Moderate	High
Nuclear pleomorphism	Absent	Slight	Moderate	Marked
Rosette	±	±	True rosettes	None
Necrosis or calcifications	Absent	Absent	Mild	Extensive

*High grade.

severity of disease into four grades, ranging from well differentiated (Grade I) to least differentiated (Grade IV) based on microscopic features such as architecture, pleomorphism, neurofibrillary matrix, rosettes, mitoses, glands and presence of necrosis or calcifications[48]. Hyams I-II are designated as low-grade tumors whereas Hyams III-IV are considered high-grade tumors[49].

STAGING

In 1976, Kadish *et al.* proposed a clinical staging system to classify disease based on the anatomic extent of tumor by separating disease location into four groups: A, B, and C[7,27]. Morita *et al.* later modified the Kadish staging system [Table 2] based on a retrospective analysis of patients treated at the Mayo Clinic between 1951 and 1990, to include group D, which considers cervical or distant metastases[50]. Today, the modified Kadish system serves as the most used clinical staging system with a good predictor of outcomes[27,48,51]. The Dulguerov staging system [Table 3], proposed in 1992, utilizes the TNM classification in conjunction with imaging data, which some oncologists and surgeons have preferred due to recognizing of early cribriform plate involvement in the T2 stage as well as the distinction between intracranial but extradural tumors from tumors with gross brain involvement[27,51]. A recently described modified staging system, the Kadish-International Network For Sinonasal Cancer Research (INSICA), is based on a large international multicenter study conducted in 2022 [Table 4][52,53]. This staging combines Kadish A and B groups and separates group C into those with or without dural invasion, as dural invasion carries a worse prognosis. Further research is necessary to validate this staging system.

SURGICAL RESECTION

Complete surgical resection with negative margins is considered the primary definitive treatment for olfactory neuroblastoma [Figure 1]. Prior to the introduction of the endoscopic approach in 1993, craniofacial resection was primarily used[54]. Historically, open surgical approaches have been associated with high rates of major and intracranial complications[55,56]. Currently, open approach is reserved for more advanced cases not amenable to endoscopic endonasal resection[57]. There has been a shift toward endoscopic resection, and subsequent case series have shown favorable oncological outcomes[57-65]. Moreover, studies have shown that endoscopic endonasal resection has a lower rate of postoperative complications compared to open surgery including lower CSF leaks occurring in 1.0%-10.3% of endoscopic resection cases versus 6.0%-12.7% for open surgery, meningitis in 0%-1.8% *vs.* 4.5%, and death in 0% *vs.* 1.3%-3.2%[63,66-69]. In addition, a 2021 National Cancer Database (NCDB) study reported significantly shorter hospital stays with endoscopic resection (3.8 days) compared to open surgery (7.0 days)[70]. Unilateral resection techniques with olfactory preservation are being explored for tumors with minimal extension and negative margins[60]. Thus, the endoscopic endonasal approach has gradually gained popularity due to the anterior skull base midline origin of olfactory neuroblastoma. However, intracranial or orbital invasion may influence the choice of surgical approach and the sequence of therapy used.

Table 2. Modified Kadish classification

Staging	Description
A	Tumor confined to nasal cavity
B	Tumor extension to paranasal sinuses
C*	Tumor extension beyond the nasal cavity and paranasal sinuses, including involvement of cribriform plate, skull base, intracranial cavity, and/or orbit
D*	Tumor metastasis to cervical lymph nodes and/or distant sites

*Advanced stage.

Table 3. Dulguerov classification system

Staging	Description
Primary tumor	
T1	Tumor involving the nasal cavity and/or paranasal sinuses (excluding the sphenoid), without involvement of the most superior ethmoid
T2	Tumor extending into the nasal cavity and/or paranasal sinuses (including the sphenoid) with extension to or eroding the cribriform plate
T3	Tumor extension into the orbit or protruding into the anterior cranial fossa but no dural involvement
T4	Tumor invading the brain
Lymph nodes	
N0	None
N1	Any evidence of cervical lymph node metastasis
Distant metastasis	
M0	None
M1	Distant metastasis

Table 4. Kadish-INSICA staging system

Staging	Description
Kadish-INSICA A	Tumor confined to nasal cavity and/or paranasal sinuses
Kadish-INSICA B	Tumor extends beyond sinuses but no dural infiltration or nodal/distant metastases
Kadish-INSICA C	Tumor extends beyond sinuses with dural infiltration but no nodal/distant metastases
Kadish-INSICA D	Kadish-INSICA DN: nodal metastasis only
	Kadish-INSICA DM: distant metastases present

INSICA: International Network For Sinonasal Cancer Research.

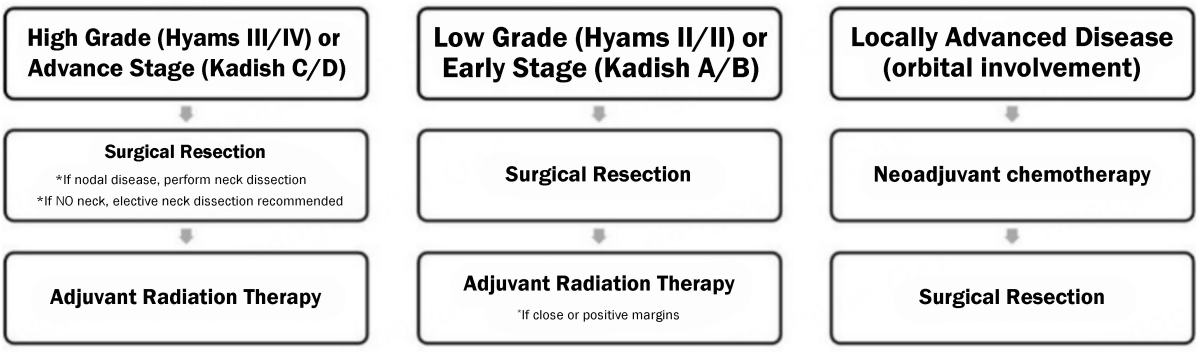

Figure 1. Treatment algorithm for olfactory neuroblastoma.

Locally invasive tumors can be resected with a combined approach involving both endoscopic endonasal resection and a bifrontal craniotomy for the advanced intracranial component[69]. The combined approach has improved local control in advanced-stage olfactory neuroblastoma[59,65,69]. Studies comparing surgical approaches have also supported the advantages of endonasal endoscopic approach, showing benefits in terms of achieving gross total resections, negative margins, less local recurrence, and better disease-free survival and overall survival rates[58,69]. Surgeons should aim to achieve negative margins, which remain a crucial prognostic factor and have a greater impact on survival outcomes than the surgical approach[58]. Reconstruction is commonly performed via a multi-layered approach with grafts placed intradurally or extradurally but intracranially, and flaps placed extracranially. The NSF, an intranasal vascularized flap based on the pedicle of the posterior septal artery, a terminating branch of the sphenopalatine artery, is commonly used if not involved by the tumor. During surgical resection, the surgeon must evaluate the surrounding mucosa through both gross macroscopic assessment via direct visualization and microscopic assessment via intraoperative frozen pathology. Any gross disease should be resected and margins should be cleared prior to consideration of reconstruction. If clearing margins results in compromise of the NSF vascular pedicle or surface area, then alternative reconstructive options such as a lateral nasal wall flap, pericranial flap, free mucosal graft or free flaps may be employed[57,71,72]. Ultimately, reconstruction with a NSF should be deferred given the risks of recurrence with close margins and the potential for delayed recurrence[72-76].

Nonetheless, endoscopic resection and reconstruction with a vascularized flap has been associated with faster recovery, shorter hospital stay, improved neurological, visual, and functional outcomes as well as lower chance of failure during adjuvant radiation therapy[77-81].

ADJUVANT RADIATION AND CHEMOTHERAPY

While primary radiation therapy has been considered, multiple reports suggest better outcomes with postoperative adjuvant radiation therapy, particularly in cases with high-grade tumors[4,82-86]. There is conflicting evidence on the long-term survival benefits of adjuvant radiation therapy for early-stage tumors, Kadish A[83,87]. However, there is greater consensus that advanced-stage (Kadish C and D), high-grade tumors (Hyams III-IV), and tumors with close or positive resection margins require adjuvant radiation therapy[88]. Intensity-modulated radiation therapy (IMRT) is the most used method, as it safely delivers an effective radiation dose and reduces treatment toxicity. Proton beam radiation has shown promise in terms of long-term survival outcomes and reduced radiation-induced toxicity compared to conventional radiation therapy[89].

The role of chemotherapy in olfactory neuroblastoma management lacks definitive evidence but has been explored to improve management outcomes in advanced disease. Acceptable indications for chemotherapy include high histological tumor grade (Hyams grade III or IV), positive or close resection margins, unresectable tumors and metastatic or recurrent tumors[19,90]. Even in predominantly advanced-stage tumors, neoadjuvant chemotherapy followed by radiation therapy for Kadish stage C lesions showed a disease-free survival of 82.6% at 15 years. This regimen employed vincristine and cyclophosphamide[91]. Neoadjuvant chemotherapy is also used as an organ preservation strategy in the setting of significant orbital involvement in order to preserve a functional eye with relatively good oncological outcomes[92]. Adjuvant chemoradiation using a combination of cisplatin and etoposide for Kadish stage C tumors improved the median time of the tumor relapse without a significant effect on overall survival[93].

There are no official treatment guidelines for the pediatric population due to the relatively small cohort size and limited trials documented. In the pediatric population, neoadjuvant chemotherapy followed by surgical

resection and postoperative radiation therapy is the mainstay of treatment for advance stage disease whereas those with low-stage disease are typically treated with surgical resection followed by radiation therapy[94-96]. More prospective trials with larger patient cohorts should be included to further elucidate established treatment protocols for pediatric patients.

MANAGEMENT OF THE NECK

Elective management for cN0 neck in olfactory neuroblastoma is debatable, with varying viewpoints and limited evidence[26,97-99]. Some studies advocate for prophylactic neck treatment in the high-risk group of patients who have high-grade tumors or advanced Kadish stages (B and C)[99,100]. Due to the low incidence of nodal metastasis at the time of presentation and co-morbidities associated with radiation treatment, other investigations suggest conservative management with neck surveillance[26,97,98,101,102]. When patients present with late cervical lymph node metastasis, a multimodality approach consisting of neck dissection and adjuvant radiation illustrated better disease-free survival compared to single modality survival outcomes[102].

Positive cervical lymph node metastasis is considered a known predictor of survival in olfactory neuroblastoma[4,8,83,103]. Overall incidence of nodal metastasis is around 30% of cases, with 5%-8% of patients presenting with nodal metastasis at the time of diagnosis[4,97,102]. The most common lymph nodes affected are level II cervical lymph nodes (90% of cases), followed by levels I/III lymph nodes (50%) and retropharyngeal lymph nodes (40%). Levels IV and V nodal metastasis were reported in high-grade advanced tumors[97]. When addressing cervical metastasis, general consensus recommends a proactive approach with neck dissection followed by adjuvant radiation[4]. However, the extent of neck dissection required remains unclear. Selective neck dissection with further surveillance of the nodal drainage pattern has been suggested[97,104].

PROGNOSIS, LONG-TERM OUTCOMES, AND SURVEILLANCE

Outcome studies have identified several factors associated with better prognosis, which include patients aged 60 or less, female gender, lower histological tumor grade, lower Kadish stage, negative neck metastasis, and achieving total resection with negative margins. These factors collectively contribute to improved survival and treatment outcomes[82,105,106]. In contrast, male patients often present with advanced- and high-grade tumors[106]. These findings provide valuable insights into identifying high-risk patients and assist in determining the need for adjuvant treatments.

Rimmer *et al.* conducted a comprehensive meta-analysis consisting of 95 patients with olfactory neuroblastoma who were treated and followed over a 35-year period showing a 5-year overall survival rate of 83.4% and a 10-year overall survival rate of 76.1%[9,66]. Disease-free survival rates at five and ten years were 80% and 62.8% respectively, with a mean follow-up period around seven years[9]. Local recurrence occurred in 25.3% of patients, with an average recurrence time of around five years. Of these cases, 25% of patients exhibited early recurrence within a year. Late recurrence was reported in 33% of the cases after five years, and 8% after ten years of diagnosis and treatment[9,66]. These findings highlight the importance of long-term surveillance.

Detecting and addressing tumor recurrence extended patient survival by an average of 29 months in those who eventually died and an average of 93 months in patients who were still living by the conclusion of the Rimmer study. In this same investigation, surgical approaches were evaluated. Sixty-five patients underwent craniofacial resection while 30 patients had endoscopic resection. Further analysis of the surgical techniques demonstrated significantly improved overall survival and disease-free survival rates in those who underwent endoscopic resection in comparison to those of the craniofacial resection group. Advanced-stage tumor

presentation was associated with poor prognosis while orbital and dural invasion exhibited significantly worse disease-free survival[53,58,66]. Lechner *et al.* conducted a multicenter retrospective analysis of clinical staging, prognosis and treatment outcomes of 404 patients diagnosed with olfactory neuroblastoma and the role of targeted SSTR therapy[53]. Results highlighted the prognostic implications of stratifying Kadish C patients based on orbital involvement, intracranial extension or dural invasion, revealing that dural invasion serves as a significant prognostic indicator of worse survival outcomes. In addition, among patients presenting with Kadish D staging who were stratified based on cervical nodal disease versus distant disease, those with distant metastasis exhibited significantly worse outcomes, further illustrating the worsened prognosis and shortened survival associated with distant metastatic disease.

Ultimately, long-term surveillance is crucial for all cases of olfactory neuroblastoma due to its tendency for late recurrences which can occur up to 15 years after initial treatment[19,26,107,108]. It is recommended that close monitoring should involve ongoing physical and endoscopic imaging examinations as well as imaging evaluations for at least ten years after treatment. Unfortunately, there are no clear guidelines in place for surveillance recommendations. PET-CT offers great value in detecting recurrences that may not be apparent through other routine imaging methods[109]. However, the advent and increased use of [68Ga]-DOTATATE PET as an imaging modality and surveillance tool have illustrated the benefits and sensitivity of this imaging modality compared to that of routine PET/CT and MRI[28,110,111]. Although these studies involve a small cohort of patients, findings are promising and illustrate the need for larger prospective trials in efforts to develop a standardized guideline recommendation. Nonetheless, long-term surveillance with [68Ga]-DOTATATE PET should be highly considered given its documented superiority in detection of tumors compared to that of PET/CT[53].

FUTURE THERAPEUTIC DIRECTIONS

Olfactory neuroblastoma is increasingly recognized as a heterogenous disease composed of various cell lineage-specific elements from the normal olfactory epithelium. One study performed bulk transcriptomics on 19 olfactory neuroblastomas and found that tumors could be grouped into either neural or basal categories based on cell gene signatures[112]. Follow-up studies have expanded on this notion and provide evidence for tumor cells expressing either known neuronal, sustentacular, or glandular markers[52,113]. It may make sense, then, for a possible combination therapeutic approach to target components of each of these cell type-specific lineages. For example, enhancer of zeste homolog 2 (EZH2) is widely expressed in neuronal cells of olfactory neuroblastoma, helps coordinate normal olfactory neurogenesis, and plays a role in proliferation in other cancers[52]. A future trial of tazemetostat, a Food and Drug Administration (FDA)-approved EZH2 inhibitor, in olfactory neuroblastoma patients, might therefore be a viable, mechanistically-based option. Recently, a mouse model of olfactory neuroblastoma was developed and validated[114]. Interestingly, mouse tumors recapitulated heterogeneity observed in human tumors, including a neural population expressing EZH2; however, it was shown that high-grade olfactory neuroblastoma exhibits plasticity, with the potential to shift between neural and non-neuronal lineages[114]. This emphasizes the potential importance of targeted combination therapies.

Another therapeutic direction involves adapting treatment approaches from better-studied neuroendocrine cancers. A recent study showed that 82.4% of olfactory neuroblastoma cases expressed the SSTR2, which is commonly upregulated in many neuroendocrine cancers[53]. In a pilot cohort part of the larger LUTHREE trial, three metastatic olfactory neuroblastoma patients were treated with an SSTR2-targeted radionucleotide, which was well-tolerated and led to stable disease[53]. Hasan *et al.* documented a retrospective trial with a cohort of seven patients with Kadish D unresectable disease treated with 177Lu-DOTATATE surface SSTRs and noted a median progression-free survival of 17 months and a median

overall survival of 32 months in a setting of relatively mild toxicity profile[115]. This study illustrates the promising utility of targeted receptor therapy for metastatic non-resectable disease. While larger, randomized trials are necessary to determine the efficacy of such targeted therapies over standard-of-care, the idea of borrowing validated treatment approaches from other neuroendocrine cancers may represent a promising path forward.

Finally, with the rapid rise in immunotherapies for solid tumors, there has been interest in the olfactory neuroblastoma immune landscape. Classe *et al.* observed an increase in tumor infiltrating lymphocytes in high grade compared to low-grade tumors[112]. London *et al.* later demonstrated in a cohort of ten olfactory neuroblastomas that 4/10 tumors were positive for the immune checkpoint Programmed death ligand 1 (PD-L1), whereas in metastatic samples, 3/4 tumors stained positive for PD-L1[116]. This prompted a phase 2 trial currently underway, assessing the role of Bintrafusp Alfa, a bifunctional fusion protein targeting PD-L1 and transforming growth factor (TGF)-beta signaling, in recurrent olfactory neuroblastoma[117]. Depending on the outcome, immune checkpoint inhibitor therapy could be a future option for some olfactory neuroblastoma patients.

CONCLUSION

Olfactory neuroblastoma is a rare malignant tumor, originating from the olfactory neuroepithelium. Due to the malignant nature of the tumor, proximity to the brain and orbit, and tendency for cervical lymph node metastasis, a comprehensive clinical assessment should include detailed head and neck imaging, to properly stage the tumor. A multidisciplinary approach involving head and neck surgeons, neurosurgeons, radiation, and medical oncologists should be used for management planning. The surgical management of olfactory neuroblastoma should aim for negative margins using either endoscopic endonasal, open or hybrid approaches. Endoscopic endonasal approach often provides complete surgical resection with lower morbidities compared to open approaches. Advanced tumor stage requires more aggressive treatment strategies with combined surgical approaches and adjuvant or neoadjuvant therapies as olfactory neuroblastoma has shown sensitivity to both chemotherapy and radiation therapy. Given the tumor's tendency for late recurrence, extended post-treatment surveillance remains necessary.

DECLARATIONS

Authors' contributions

Conceived and designed the book chapter: Abi Hachem R
Coordinated various parts of the study: Okafor S, AlShammari S, Helou V, Mitchell M, Finlay JB
Had full access to all the data in the study and took responsibility for the integrity and accuracy of the study analysis: Abi Hachem R, Goldstein B, Jang D
Wrote the article: Okafor S, AlShammari S, Helou V, Mitchell M, Finlay JB
Provided cyclical feedback on the writing process: Abi Hachem R, Goldstein B, Jang D
All authors have reviewed and approved the final manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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