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TOPIC REVIEW

Management of olfactory neuroblastoma, neuroendocrine carcinoma, and sinonasal undifferentiated carcinoma involving the skullbase

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Abstract

Introduction Sinonasal tumors that harbor neuroendocrine histologic features include olfactory neuroblastoma (previously known as esthesioneuroblastoma), sinonasal neuroendocrine carcinoma, and sinonasal undifferentiated carcinoma. These tumors represent a diverse spectrum of clinical behavior and as such require histology-specific management. Herein, we review the management of these sinonasal tumors with neuroendocrine features and discuss fundamentals of multi-modality care for each histology. An emphasis is placed on olfactory neuroblastomas, given their relative frequency and skullbase origin.

Methods A comprehensive literature review on contemporary management of olfactory neuroblastoma, sinonasal neuroendocrine carcinoma, and sinonasal undifferentiated carcinoma was performed.

Results Management of sinonasal tumors with neuroendocrine features can include surgical resection, radiation therapy, and/or chemotherapy. Due to their site of origin, these tumors can frequently involve the skullbase, which can require site-specific care. The optimal treatment modalities and the sequence in which they are performed are largely dependent on histology. In most cases, olfactory neuroblastoma is best managed with surgical resection followed by radiation therapy. Sinonasal neuroendocrine carcinomas represent a variety of histologic phenotypes (carcinoid, atypical carcinoid, small cell, and large cell), which determine the optimal treatment modality. Finally, sinonasal undifferentiated carcinoma is likely best managed by induction chemotherapy with subsequent therapy dictated by the initial response.

Conclusions A team approach to multi-modality care is essential in the treatment of olfactory neuroblastoma, sinonasal neuroendocrine carcinoma, and sinonasal undifferentiated carcinoma. Early biopsy, histologic diagnosis, and comprehensive imaging are critical to determining the appropriate management paradigm.

Keywords Esthesioneuroblastoma · Neuroendocrine carcinoma · Olfactory neuroblastoma · Sinonasal undifferentiated cancer

Introduction

Sinonasal malignancies are infrequent but challenging to manage cancers with an incidence of approximately eight cases per million [1]. Among these, olfactory neuroblastoma (ONB, previously known as esthesioneuroblastoma), sinonasal neuroendocrine carcinoma (SNEC), and sinonasal undifferentiated carcinoma (SNUC) represent tumors with a spectrum of neuroendocrine histologic characteristics (Table 1) [2]. Common presenting symptoms include nasal obstruction, facial pain, and/or epistaxis. These tumors originate in the sinonasal cavity and frequently involve the skullbase. Malignant histology in the skullbase location require multi-disciplinary care that includes medical oncologists, neurosurgeons, head and neck surgeons, pathologists and

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Table 1 Categories of sinonasal tumors with neuroendocrine histologic features

Tumor type	Subtypes	Differentiation	Other notes
Olfactory neuroblastoma		Well- to Poorly-differentiated	Follows Hyams histologic grading
Neuroendocrine carcinoma	Carcinoid	Well-differentiated	
	Atypical carcinoid	Moderately-differentiated	
	Small cell	Poorly-differentiated	
	Large cell	Poorly-differentiated	Rare subtype (< 40 cases reported)
Sinonasal undifferentiated carcinoma		Poorly-differentiated	± neuroendocrine differentiation

radiation oncologists. Among these tumors, ONB arise from a neuroectodermal origin, while SNEC and SNUC share an epithelial phenotype. Although rare, experience with these tumors at higher-volume centers have led to improvements in management over time. Furthermore, the varied biologic characteristics of these tumors require different management paradigms that are histology-specific.

Management of olfactory neuroblastoma

Olfactory neuroblastoma is a rare tumor that arises from the olfactory neuroepithelium below the cribriform plate and accounts for 3% of all sinonasal neoplasms [2]. Due to this site of origin, ONB naturally involves the skullbase. ONB is frequently locally invasive and has the capacity for locoregional and distant metastasis. Primary management typically includes surgical resection followed by local radiotherapy. Advanced disease at presentation can require the addition of chemotherapy and some groups favor utilizing induction chemotherapy for selected patients with high Hyams grade tumors and extensive local or regional disease [3]. Finally, recurrence requires multi-disciplinary salvage therapy based on its distribution (locoregional versus distant).

Diagnosis and staging

Initial workup of nasal masses suspicious for ONB should include thorough physical (including neurologic) exam and computed tomography (CT) and magnetic resonance imaging (MRI) of the sinuses. CT imaging of the neck is also essential to evaluate for nodal involvement. Some centers routinely utilize positron emission tomography (PET)-CT to screen for nodal or distant metastases, although this practice is not uniform [4]. The cornerstone of diagnosis for ONB is nasal endoscopy and biopsy. This allows for appropriate confirmation of histology and disease-specific treatment planning. We generally recommend that biopsy of a mass suspicious for malignancy be performed under general anesthesia. Regardless, histopathologic diagnosis of high-grade ONB can be challenging and may need to be referred to an experienced center. Prior study at M.D. Anderson Cancer Center demonstrated that among 12 consecutive patients referred with an outside diagnosis of ONB, 10 were misdiagnosed upon expert review [5]. These included misdiagnosed pituitary adenomas (3), SNEC (3), sinonasal melanoma (2), and SNUC (2). Recent data have suggested that PET-CT may help to distinguish between ONB and SNUC [4]. Future diagnosis and substratification may take into account molecular and/or genetic characteristics such as DNA methylation patterns, however their significance has not been validated to date [6, 7].

Once a diagnosis of ONB is established, tumors may be stratified by histologic and clinical staging systems. Hyams grading is a histologic scale developed in the 1980s at the Armed Forces Institute of Pathology (Table 2) [8]. Several recent studies have demonstrated that increased histologic grade significantly predicts worse disease free and overall

Table 2 Hyams histologic grading system for olfactory neuroblastoma

Microscopic feature	Grade 1	Grade 2	Grade 3	Grade 4
Architecture	Lobular	Lobular	± Lobular	± Lobular
Pleomorphism	Absent/slight	Present	Prominent	Marked
Neurofibrillary matrix	Prominent	Present	May be present	Present
Rosettes	Homer-Wright	Homer-Wright	Flexner-Wintersteiner	Flexner-Wintersteiner
Mitoses	Absent	Present	Prominent	Marked
Necrosis	Absent	Absent	Present	Prominent
Glands	May be present	May be present	May be present	May be present
Calcification	Variable	Variable	Absent	Absent

Adapted from [8]

Table 3 Kadish-Morita and AJCC staging systems for olfactory neuroblastoma

System	Stage	Feature
Kadish-Morita*	A	Limited to the nasal cavity
	B	Extends to the paranasal sinuses
	C	Extends to cribriform plate, skullbase, orbit, or intracranial cavity
	D	Cervical or distant metastases
AJCC**	T1	Tumor confined to the ethmoid sinus with or without bone erosion
	T2	Tumor invades two subsites in a single region or extends to involve an adjacent region, with or without bony invasion
	T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
	T4a	Tumor invades any of the following: anterior orbit, skin or nose/cheek, anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
	T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

*Adapted from [12]

**Adapted from [13]

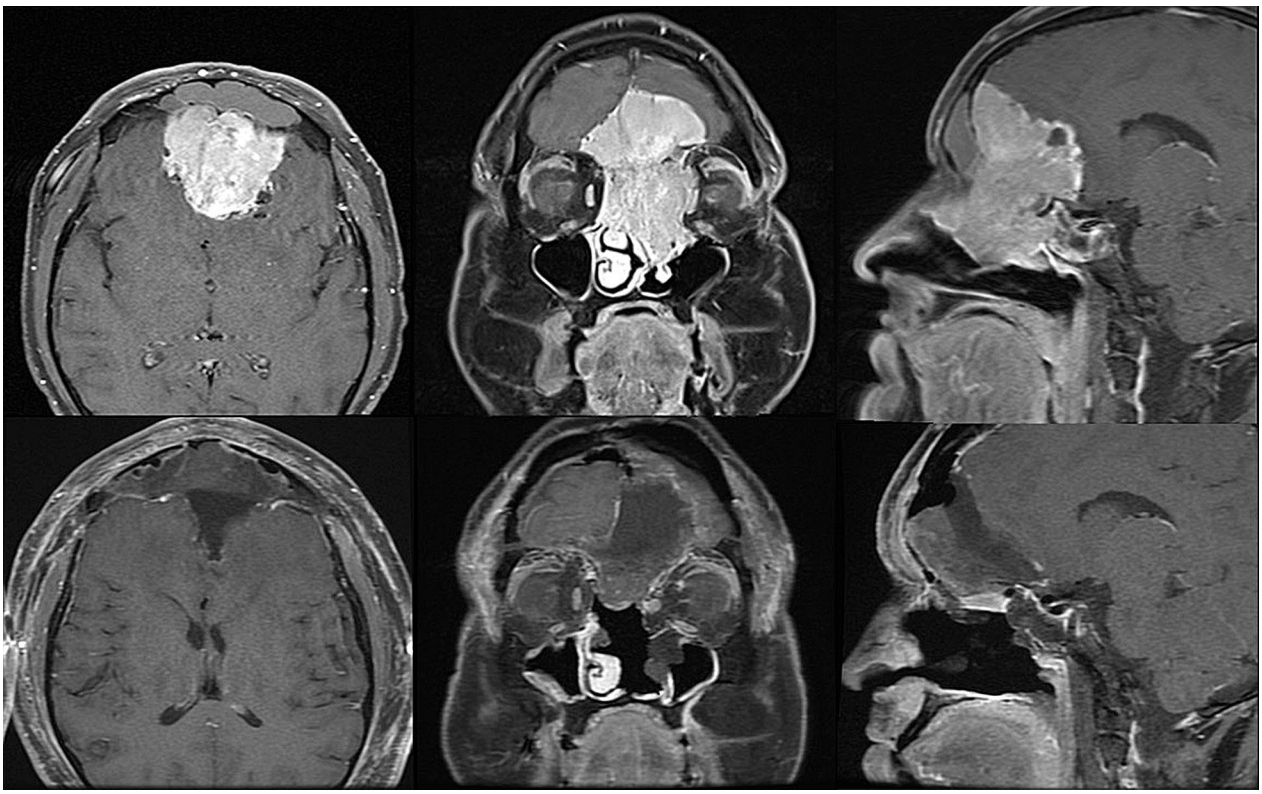

Fig. 1 Axial (top left), coronal (top middle), and sagittal (top right) T1 post-contrast magnetic resonance imaging of a 36-year-old patient with a Hyams grade 2, Kadish-Morita stage C olfactory neuroblastoma with brain and orbital invasion. Cranio-endoscopic resection resulted in gross total resection with negative margins (bottom). Of note the perioribital margin was found to be negative on the right, however there was sub-periorbital membrane extension on the left that was extraconal with minimal orbital fat invasion. This orbital invasion was excised to negative margins

survival in patients with ONB [9, 10]. A clinical staging system was proposed by Kadish in 1976 and updated by Morita in 1993 (Table 3) [11, 12]. Several studies have demonstrated a trend between Kadish-Morita stage and survival, however this has not been proven to be a significant predictor [10]. Alternate staging systems include American Joint Committee on Cancer (AJCC) staging (TNM) and a staging system proposed by Dulguerov (Table 3) [13, 14].

Surgical management

After pathologic confirmation, surgical resection is typically the first step in management of ONB. Due to the epicenter of these tumors in the anterior cranial fossa, a combined transcranial and transfacial approach has traditionally been used to achieve *en bloc* removal. First described in 1963 by Ketcham, craniofacial resection (CFR) can be very effective in total resection of ONB (Fig. 1) [15]. A multicenter, cooperative study analyzed the outcomes of CFR among 151 patients with ONB and found that negative margins could be achieved in 85% [16]. This cohort of patients underwent heterogenous adjuvant and neoadjuvant therapies, with 5-year overall survival of 78%. Thirty-two percent of patients experienced surgery-related complications with 20% experiencing central nervous system complications.

Endoscopic resection of ONB has gained popularity over the past two decades. This approach offers direct visualization of tumor origin, less soft tissue dissection and/or brain retraction, and potentially shorter hospital stays. This approach can even be used to address appropriately selected cases that involve the dura or brain [17]. Unlike open craniofacial approaches, this approach requires piecemeal resection to remove tumor through the limited nasal corridor. Despite this inability to perform an *en bloc* resection, in appropriate patients, endoscopic surgery has been shown to provide similar oncologic results (progression-free and overall survival) as combined cranio-endoscopic resection for a variety of sinonasal malignancies, including ONB [18]. Specific limitations of a pure endoscopic approach include tumors that directly involve the lacrimal sac, the skin or soft tissues of the face, supra-orbital extension past the fovea ethmoidalis, extensive dura or brain parenchymal involvement that may be better managed with a craniofacial or cranio-endoscopic approach.

Surgery for ONB is most effective when negative margins are achieved. This has been shown to be a consistent independent predictor of outcome by multiple studies irrespective of the adjuvant or neoadjuvant treatment schema and/or transdural tumor invasion [16, 19]. For early stage disease (Kadish A/B), recent study has evaluated the value of resection of the cribriform plate, dura, and olfactory bulb, respectively [20]. Among these, only resection of the cribriform plate was found to have a significant impact on survival outcome. Limiting resection to this extradural compartment reduces the risk of CSF leak and intracranial complications. Finally, for patients with a clinically-negative neck (N0), no data exist to support elective neck dissection, however neck dissection should be performed when nodal disease is present (N+) [21].

Radiation therapy

Apart from select cases of early Kadish stage, low Hyams grade tumors with negative surgical margins, surgical resection should be followed by postoperative radiation therapy [20]. Meta-analysis by Dulguerov and colleagues analyzed survival outcomes by treatment modality and found that among all treatment combinations patients who received surgery and radiation had the best outcome [14]. Patients in this group had 65% 2-year disease-free survival, compared with 48% for surgery alone and 37% for radiation alone. More recent study analyzed long-term outcomes for Stage T3/T4 ONB and found significantly improved disease-specific survival in patients who underwent surgery and postoperative local radiation compared with surgery alone [21].

While the value of local postoperative radiotherapy has been established, the benefit of elective nodal irradiation (ENI) in ONB patients with a clinically negative neck is still debated. Recent study has shown that ENI can reduce the rate of nodal relapse [22]. With ENI, 5-year regional control was 100%, compared with 82% without ENI. Despite this finding, a survival benefit was not observed among patients who underwent ENI.

Chemotherapy and induction therapy

Chemotherapy, particularly as a neoadjuvant therapy has been advocated for advanced stage ONB and high Hyams grade tumors. This built upon a protocol for preoperative radiotherapy reported by the University of Virginia [23]. Overall response rates to induction chemotherapy are reported in the range of 67% to 82%, with high Hyams grade tumors noted to be particularly chemo-sensitive [3]. Pediatric patients appear to have an even higher response rate with up to 50% of patients achieving complete response [24]. Most of the other studies reported in the literature are small and use a variety of chemotherapeutic agents, including chemoradiation and precluding generalization of results [25, 26]. Protocols have included cisplatin + etoposide (EP), cyclophosphamide + doxorubicin + vincristine (CAV), and cisplatin + etoposide + ifosfamide (VIP). Recently, targeted therapies have been successfully applied to ONB in single patients, including sunitinib, which blocks multiple tyrosine kinases, and cetuximab, which blocks epidermal growth factor receptor (EGFR) [27, 28]. Finally, a subset of ONB have been demonstrated to express immune checkpoint molecules such as programmed cell death ligand 1 (PD-L1), suggesting that immunotherapeutic approaches may have utility in appropriately-selected patients [29]. These strategies represent promising disease-specific treatments for ONB, but require larger study.

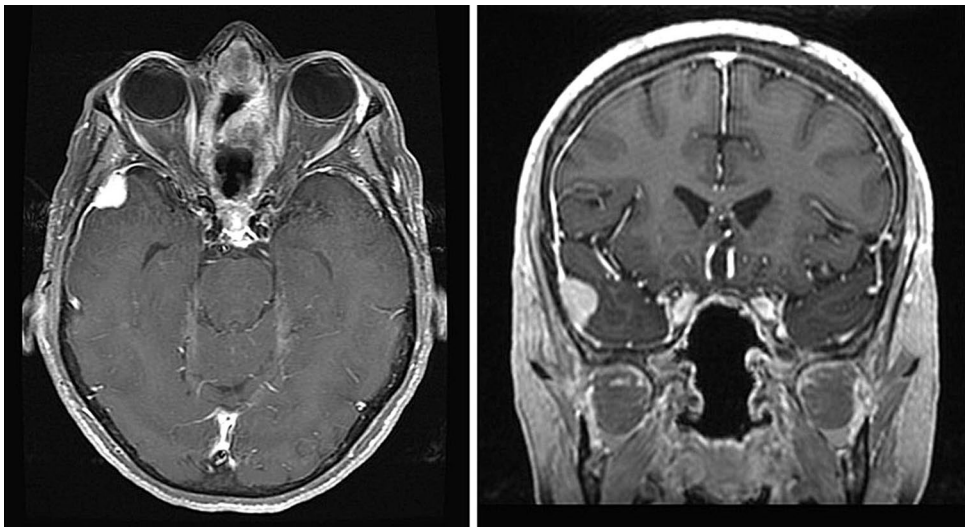

Fig. 2 Axial (left) and coronal (right) T1 post-contrast magnetic resonance imaging of a 56-year-old patient with a Hyrams grade 2 olfactory neuroblastoma who had undergone craniofacial resection with postoperative radiotherapy 7 years earlier for a Kadish-Morita stage C tumor. Surveillance imaging detected a right perisylvian dural-based lesion that was resected without difficulty. Histopathology confirmed metastatic olfactory neuroblastoma

Salvage therapy

Long-term follow-up of patients with ONB has demonstrated that nearly half of patients will eventually recur despite receiving definitive therapy (median 6.9 years to recurrence) [21]. Nearly 20% of patients recur locally, nearly 20% of patients recur regionally, and 10% of recur at distant sites. Treatment for local recurrence can include repeat surgery, radiation therapy, or chemotherapy. Treatment for regional recurrences can include neck dissection, radiation, or chemotherapy [22].

Distant metastases most frequently involved the spine, brain, or leptomeninges [21]. We have found that non-contiguous meningeal metastases have a predilection for the peri-Sylvian dura (Fig. 2). Solitary metastases may be treated with surgical excision, however we have also found that these lesions are responsive to stereotactic radiosurgery.

Management of sinonasal neuroendocrine carcinoma

Sinonasal neuroendocrine carcinoma (SNEC) is an exceptionally rare tumor with less than 300 cases reported [30]. These tumors most commonly occur in the ethmoid sinus, nasal cavity, or maxillary sinus [31]. SNECs may be roughly divided into well-differentiated tumors (carcinoid), moderately-differentiated tumors (atypical carcinoid) and poorly-differentiated tumors (small cell and large cell variants) (Table 1) [2]. Diagnosis and staging follows the same principles as for ONB, starting with comprehensive imaging and endoscopic biopsy. AJCC guidelines are used for staging of SNEC (Table 3) [13].

The small number of reported patients and diverse treatments used have limited the ability to clearly define optimal management paradigms for SNEC [32]. For laryngeal neuroendocrine carcinomas, tumor differentiation status defines ideal treatment [33]. In these cases, well- and moderately-differentiated lesions are best treated with surgery, whereas poorly-differentiated lesions are best treated with chemo- and radio-therapy. Conversely, for SNEC however, the degree of differentiation has to date not been demonstrated to significantly impact ideal treatment approach [30, 34]. Regardless, it has been shown that a multi-modality approach is likely beneficial for SNEC across most histologic phenotypes. Meta-analysis of SNEC has shown a significant benefit for surgery among patients with well- and moderately-differentiated tumors [30]. Among patients with small cell histology (poorly-differentiated), only chemotherapy as a monotherapy predicted poor outcome. This outcome may have been influenced by the stage of disease encountered at presentation (i.e. unresectable or metastatic).

Among lower-grade tumors, many studies do not differentiate between well- and moderately-differentiated SNEC. However it has been suggested that well-differentiated tumors may be adequately treated with surgery alone, whereas moderately-differentiated tumors may benefit from surgery followed by radiation therapy [30]. Given their aggressive nature, poorly-differentiated lesions likely benefit from systemic therapy, although the utility of chemotherapy as either a neoadjuvant or concurrent postoperative strategy has not been established. Combination therapy with etoposide (a topoisomerase inhibitor) and cisplatin (platinum-based) has been a cornerstone of small cell cancer therapy and has been shown to be effective against a variety of histologically-similar neuroendocrine cancers [35]. Fitzek and colleagues described a neoadjuvant regimen of etoposide/cisplatin for 9 patients

with SNEC, with responses in 7 patients [36]. In this study however, SNECs were not segregated by differentiation and tumors with mixed histologies were included. Another study from University of North Carolina included 2 patients with lower-grade SNEC that received induction chemotherapy [37]. Both patients had a partial response to chemotherapy and had no evidence of disease at long-term follow-up. This report also included 2 patients who underwent chemotherapy as a postoperative strategy with concurrent radiotherapy—both with objective responses.

Despite these limitations of prior studies a reasonable strategy for SNEC may include surgery alone for resectable well-differentiated tumors, surgery followed by radiation therapy for moderately-differentiated tumors, and induction chemotherapy followed by definitive therapy (surgery versus consolidative radiation/chemo) for poorly-differentiated tumors.

ENI may play a role in the management of SNEC as regional recurrences can occur in as many as 25% of patients [31]. In an analysis of patients with moderately- and poorly-differentiated SNEC, regional treatment failures were observed only amongst patients who did not undergo ENI. Finally, salvage therapy for SNEC should involve a multi-disciplinary approach and may depend on the location and extent of the recurrence.

Management of sinonasal undifferentiated carcinoma

SNUC is an aggressive epithelial cancer that can harbor neuroendocrine histologic features. Given their malignant clinical behavior these tumors often present at an advanced stage, with 10–30% demonstrating regional nodal metastases at the time of presentation [38]. Because of this aggressive phenotype there is controversy regarding optimal management with a likely role for induction chemotherapy as first-line therapy, followed by locoregional treatment as necessary.

Diagnosis and staging

Diagnosis and staging follow the same principles as ONB and neuroendocrine lesions, including MRI and CT (head and neck), as well as endonasal biopsy. When a histopathologic diagnosis of SNUC is made, clinicians may consider obtaining chest CT or positron emission tomography (PET) imaging to identify distant metastases at the time of presentation [39].

Clinical staging for SNUC typically follows AJCC criteria (Table 3) [13]. Regardless, given the sinonasal origin of these tumors, some authors have applied the Kadish system to staging of SNUCs [40].

Management paradigms for SNUC

The optimal management paradigm for SNUC remains controversial. The initial experience with SNUC was reported by Levine and colleagues at the University of Virginia who suggested a treatment paradigm of chemotherapy followed by radiation therapy and then surgical resection [40]. Standard treatment consisted of cyclophosphamide, doxorubicin and vincristine (CAV) given in 3 cycles at 3-week intervals. In this early cohort, there were several long-term responders. Additionally, 2 of 8 patients demonstrated no response to CAV and were switched to cisplatin and etoposide, with one long-term responder.

Given the paucity of large clinical series, other groups have differed significantly in management. Notably, at the University of Florida, a protocol of surgical resection with curative intent is followed by radiotherapy, similar to standard therapy for ONB [38]. In their series of 15 patients, they found the role of chemotherapy to be "unclear".

As many patients with SNUC initially present with regional or distant metastases and/or unresectable local disease, several centers have adapted to a protocol of induction chemotherapy followed by definitive radiation therapy and concurrent chemotherapy [41]. This may be followed by surgery as salvage therapy.

At M.D. Anderson Cancer Center, our preferred approach has been to utilize induction chemotherapy for all patients

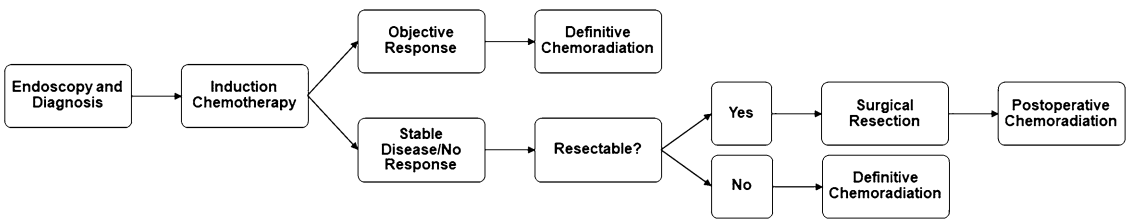

Fig. 3 Proposed management of sinonasal undifferentiated carcinoma based on response to induction chemotherapy

and to use the response to this initial therapy as a guide for definitive locoregional therapy (Fig. 3) [42]. Analysis of this cohort included the largest series of patients with SNUC reported to date. In patients with a complete or partial response after induction chemotherapy, application of definitive concurrent chemo-radiotherapy appears to confer a survival advantage compared with patients who undergo surgery. Conversely, in patients with stable or progressive disease, surgical salvage results in greater survival compared with chemo-radiotherapy alone.

Induction chemotherapy

Induction chemotherapy has several distinct advantages when applied to patients with SNUC. First, as many of these patients present with or are susceptible to distant metastasis, early systemic therapy is advantageous in addressing all sites of disease. Second, as SNUCs are often fast-growing and invasive, surgical resection may be incapable of achieving complete resection at the time of presentation. Potential cytoreduction achieved by induction chemotherapy increases the likelihood of complete surgical resection and possibly the results of definitive radiation. Finally, induction chemotherapy alone may result in a complete response in a small subset of patients [40, 42]. Modern induction chemotherapy regimens are similar to the salvage regimen described by Levine and colleagues [40]. We typically recommend platinum-based combination therapy with etoposide and cisplatin in 3 week cycles. For patients with renal dysfunction, peripheral neuropathy, or hearing loss, carboplatin is substituted for cisplatin. Among 95 patients who underwent this induction chemotherapy regime (1–5 cycles), 6% demonstrated a complete response, 61% demonstrated a partial response, 23% demonstrated stable disease, and 10% demonstrated progressive disease [42]. Sixty of the 95 patients (63%) in this cohort presented with skullbase invasion. Notably, the presence of skullbase, dural, and/or brain invasion at presentation was not a significant predictor of overall or disease-specific survival in this cohort.

Radiation therapy

Radiation therapy often comprises a component of definitive locoregional therapy for SNUC. Based on the aggressive nature of this pathology, high doses have been associated with greater local control and survival. Al-Mamgani and colleagues found that local control was 75% in the group that received > 60 Gy versus 44% for the group that received ≤ 60 Gy [43]. Similar results were reported by Gamez and colleague for 5-year overall survival based on radiation dose (73% with > 60 Gy versus 21% with ≤ 60 Gy) [44]. Both groups found improved survival with more conformal intensity-modulated radiotherapy (IMRT) compared with conventional techniques. The incidence of complications related to skullbase location was low with optic neuropathy in 5% of patients and cerebral radiation necrosis in 2.5% [44]. The overall incidence of complications reduced over time with more conformal techniques.

Elective neck irradiation for SNUC is less controversial than for ONB given the high frequency of regional spread. Kim and colleagues reported regional recurrence in 3 of 5 patients who presented with an N0 neck and did not receive ENI [45]. Based on these and more recent studies, ENI has been recommended for most patients with high-risk T4 disease, even if they present with an N0 neck [43]. The University of California, San Francisco group applied ENI for 15 of 17 patients with an N0 neck and found a regional recurrence in only 1 of the 15, but only after distant metastases had occurred [43].

Surgery

In general, surgical techniques for SNUC follow those appropriate for ONB and other neuroendocrine tumors. Resection with open and/or endoscopic techniques has been suggested by some groups as the optimal initial strategy for SNUC—typically followed by radiation therapy. Tanzler and colleagues reported the outcomes of 15 patients who underwent definitive therapy with resection followed by radiotherapy [38]. Three-year locoregional control was 65% and disease-specific survival was 77%. Finally, endoscopic techniques appear to be useful in appropriately selected patients, although principles of oncologic resection and attainment of negative margins should still be the goal [46].

Salvage therapy

Patterns of treatment failure were studied in 21 patients with SNUC treated generally with definitive surgery and radiation at UCSF [47]. Within this group, one third developed a local recurrence and one third developed a distant metastasis (4 patients lung, 2 distant brain, 1 bone). This rate appears to be lower for patients who undergo induction chemotherapy followed by definitive chemo-radiation (83% distant metastasis-free survival at 5 years) [42]. Salvage therapy options should be weighed in the context of location, extent of disease, prior treatments, and overall goals of care. As this may include surgery, radiation therapy, and/or chemotherapy, a multidisciplinary team approach is a must.

Conclusions

Olfactory neuroblastoma, sinonasal neuroendocrine tumors, and sinonasal undifferentiated tumors comprise a broad spectrum of disease that share neuroendocrine histologic features and a location that frequently involves the skullbase. Given their location and invasive behavior, multidisciplinary histology-specific management, including oncology, radiation oncology, head and neck surgery, and neurosurgery is critical to optimizing outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict on interest.

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