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# Modern Treatment Outcomes in Sinonasal Malignancies

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**Abstract**
*Purpose of the Review* This manuscript reviews the current management of sinonasal malignancies based on their histology.
*Summary* The diagnosis of sinonasal malignancies can be challenging, thus requiring a thorough histological analysis using immunohistochemistry and molecular studies, which requires a team that includes an experienced head and neck pathologist. Accurate histopathological analysis and thorough tumor staging, with upfront identification of prognostic factors, more so if the tumor demonstrates high-grade differentiation and an advanced disease stage, help to tailor the patients' treatment plan. Management of sinonasal malignancies is best accomplished in centers with experience treating these pathologies, with a multispecialty tumor board or planning conference that guides individualized patients' treatment planning. Multidisciplinary input and interdisciplinary cooperation are of utmost importance, as multimodal management strategies including locoregional treatments (i.e., surgery or radiotherapy such as IMRT and heavy ion radiotherapy, whether carbon ion or proton beam) and systemic treatments (i.e., chemotherapy, targeted therapy, immunotherapy) are aimed at improving the overall patient survival and locoregional disease control rates, thus shifting the management treatment paradigm for these malignancies with the aim to minimize patient morbidity, improving long-term survival, and ultimately with intention to achieve disease cure. Growing reported evidence suggests that, in "well-selected patients," outcomes following endoscopic endonasal resection of sinonasal malignancies are comparable, and may be even superior, to traditional "open craniofacial resection."

**Keywords** Sinonasal · Malignancy · Endoscopic · Surgery · Chemotherapy · Radiotherapy · Targeted therapy

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## Introduction

Sinonasal malignancies are rare tumors accounting for 3–5 % of head and neck cancers; however, they include a wide spectrum of histological subtypes with different biological behaviors. Thus, choosing an optimal management, as well as the subsequent analyzing of the patients oncological outcomes yielded by different treatment regimens, is challenging. The current literature offers many differing combinations of treatments with confounding results, resulting in controversies regarding the optimum management of these tumors; thus, no standard treatment protocols

have been so far available. Over the past decade, the acceptance of endoscopic endonasal technique to manage sinonasal malignancies, coupled with the emergence of novel radiation therapies and targeted therapies, has shifted the management paradigm of these complex tumors. Moreover, this manuscript reviews recent publications including larger series of patients with longer follow-up, and analyzing outcomes based on histology instead of bundling all the tumors based on their sinonasal location have provided more accurate data. This review discusses the current management of sinonasal and anterior skull base malignancies based on their histological differentiation.

## Treatment Outcomes Based on Tumor Biology

### Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the most common malignant tumor of the sinonasal tract, arising most frequently in the antrum (60 %) followed by the ethmoid sinuses [1••]. Of note, SCC originating in the paranasal sinuses is associated with a worse prognosis than those originating in the nasal cavity [2].

Management of SCC depends on the disease stage, location, and histologic differentiation. Great attention is paid to its histologic differentiation as it has been shown to determine its biological behavior. Histologic variants include verrucous, papillary, spindle cell or sarcomatoid, basaloid, and adenosquamous, and this subtyping can also affect prognosis [3]. According to the Surveillance, Epidemiology and End Results (SEER) database review from 1973 to 2009 by Vazquez et al., when comparing the different histological variants of SCC to conventional SCC in the sinonasal tract, they reported the following:

- In the setting of advanced-stage disease, sinonasal verrucous, papillary, and basaloid carcinomas were associated with improved prognosis.
- Adenosquamous and spindle cell carcinoma had poor prognosis.
- Prognosis was similar for all variants in early stages.

It should be noted that the SEER database allows for large-sample population-based studies; however, it has well-known informational biases, such as inaccuracy of staging, lack of detailed data of the surgery (i.e., extent of resection, open vs endoscopic, management of the neck), details of the radiotherapy, and no information regarding whether or not the patient received chemotherapy.

Human papilloma virus (HPV) infection when associated with SCC, especially the non-keratinizing variant, portends to a better prognosis than SCC not associated with HPV. However, current studies are inconclusive regarding the optimal management for patients with SCC associated with SCC; thus, to date, testing for HPV is not indicated for sinonasal malignancies [4].

Standard treatment for SCC of the sinonasal tract includes a complete surgical resection (i.e., tumor free margins) with adjuvant postoperative radiotherapy or concurrent chemoradiotherapy. Traditionally, sinonasal tumor surgical ablation has been managed via open craniofacial resection; however, over the past two decades, an endoscopic endonasal resection, or combined cranioendoscopic resection, has become an acceptable alternative. In a series published by de Almeida et al. [5], including 27 patients treated with definitive endoscopic surgery (70 % of the patients' tumors were staged T4, and 2 of 34 patients had brain invasion), the 5-year overall survival (OS) and disease-free survival (DFS) were 78 and 62 %, respectively. In this series, the authors reported a positive surgical excision margin rate of 19 % [5]. A meta-analysis by Rawal et al. showed that the 2- and 5-year OS rates after endoscopic endonasal resection are comparable and even superior to those obtained with a traditional craniofacial resection [6••].

In the setting of SCC related to inverted papilloma, Karligkiotis et al. reported a 5-year OS of 66.8 % and a disease-specific survival (DSS) of 71.2 % [7]. These authors identified that poorer outcomes accompanied advanced pT classification (pT3 or greater), high-grade lesions, resection via combined cranioendoscopic approach, and recurrent disease [7].

Adjuvant radiotherapy is indicated in most patients with nasal and paranasal SCC; however, its use is imperative in patients with close or positive margins, involvement of critical areas such as the frontal sinus, the sphenoid sinus, anterior skull base (with or without dural invasion), lamina papyracea or periorbita, and the nasopharynx [7]. Some studies suggest that using proton therapy for sinonasal SCC following gross total resection yields better local control rates than conventional radiotherapy or intensity-modulated radiation therapy (IMRT) [8, 9]. Concurrent chemotherapy with platinum-based agents is indicated in patients with factors associated with a poor prognosis such as positive surgical margins and perineural and lymphovascular invasions.

Elective neck irradiation is controversial; however, data suggest that it should be considered in advanced disease (T3 or T4), given the high risk of cervical lymph nodes involvement (23 %) [10••]. Others recommend elective neck irradiation only for maxillary sinus SCC, especially if there is extension to the skin or oral cavity [11]. Selective neck dissection for the N0 neck was shown to increase locoregional control rate but not OS. Management of the

neck is discussed in each paragraph based on each tumor histology [11].

Hirakawa et al. evaluated the role of neoadjuvant chemotherapy, showing superior outcomes in patients who responded to the treatment (at least 50 % reduction) when compared to non-responders or patients who did not receive neoadjuvant chemotherapy. In this study, responders to neoadjuvant chemotherapy had statistically better OS, DFS, locoregional control, and freedom from distant metastasis regardless of staging [12].

Two favored approaches for advanced-stage poorly differentiated SCC are advocated:

- Induction chemotherapy using taxane- and platinum-based agents or taxanes and 5-fluorouracil followed by definitive chemoradiation,
- Or neoadjuvant chemotherapy followed by surgery and adjuvant chemoradiation [10••].

Selection of these management protocols often depends on what structures are likely to be sacrificed during a primary resection and subsequent morbidity.

## Adenocarcinoma

Adenocarcinomas of the sinonasal cavity may be broadly divided into intestinal-type (ITAC) and non-intestinal-type (NITAC). Their current management is based on tumor stage and more importantly on histological grade and the p53 status [10••].

Standard management for ITAC includes surgery followed by radiation therapy. However, single modality treatment with surgery alone is recommended for early-stage (pT1) and low-grade adenocarcinoma with no change in DFS and OS [13]. Multimodal management, including surgery followed by postoperative radiotherapy, is recommended for advanced-stage disease (pT3–pT4), positive surgical margins, and high-grade adenocarcinoma regardless of the stage of disease [13]. Proton therapy following gross total resection has shown promising results compared to conventional radiotherapy or IMRT with superior local control rates for adenocarcinoma (80 vs 50–60 %) [8].

Compared to open techniques, endoscopic endonasal surgery provides similar oncological outcomes, while associated with less morbidity; thus, it is considered the surgical treatment of choice in select patients [6••, 14, 15]. It should be considered, however, that adenocarcinomas related to frequent exposure to wood dust or leather tanning chemicals carry the risk of multifocal lesions, as the entire sinonasal mucosa is exposed to the same carcinogens. Therefore, bilateral resection, including involved and uninvolved sides, is prudent [10••]. Although controversial, given the risk of leptomeningeal spread (5.4 %), Nicolai et al. suggested prophylactic brain irradiation in high-grade lesions with intracranial extension [15]. Conversely, ITAC's risk of spread of to the cervical lymph nodes is 7 %; therefore, elective treatment of the N0 neck is not recommended [10••].

Concurrent chemotherapy regimens based on cisplatin, fluorouracil, and leucovorin are highly effective for ITAC with a wild-type or functional p53 protein [15]. In addition, a subset of ITACs, found mostly in woodworkers, showed a high expression of EGFR on immunophenotyping, suggesting the possibility for anti- EGFR therapies [16].

Nicolai et al. reported an overall event-free survival (EFS) of 85.2, 73.3, and 71.7 % at 1, 3, and 5 years, respectively, with an OS of 93.0, 80.5, and 68.8 % at 1, 3, and 5 years, respectively. OS and EFS were negatively affected by histological grade, T stage, dural and brain involvement, and positive surgical margins [15]. In a SEER review analysis of frontal sinus malignancies, adenocarcinoma carried the worst prognosis [17].

A retrospective study published by Camp et al. analyzed whether the location of the first surgical treatment had an impact on outcomes. They compared "patients primarily treated at a tertiary referral center" with "patients primarily treated at a regional hospital," finding a significant difference in recurrence-free survival. In a group of patients with similar T stage, those treated at a tertiary referral center had a superior survival (67 %) than patients treated at a regional hospital (48 %). Therefore, these authors advocate that adenocarcinoma of the paranasal sinuses should only be treated by centers with adequate volume and expertise [18].

## Olfactory Neuroblastoma

Olfactory neuroblastoma (ONB) arises from the neural olfactory epithelium and could be considered as an intermediate lesion between a pure neural neoplasm such as neuroblastoma and a neuroendocrine epithelial tumor such as neuroendocrine carcinoma [19, 20]. This sharing and overlap of clinical and histological features lead to a broad clinical differential diagnosis and a challenging histopathological analysis. ONB can be confused with several other "small blue round cell tumors" of the sinonasal cavity such as sinonasal undifferentiated carcinoma (SNUC), sinonasal neuroendocrine carcinoma (SNEC), pituitary adenoma, mucosal melanoma, lymphoma, and rhabdomyosarcoma [19]. Therefore, a thorough pathological review by an experienced pathologist is warranted.

Currently, treatment of ONB should be based on both the Kadish–Morita staging and Hyams pathological grading; although their optimal treatment remains controversial, both have been used for decades worldwide. We followed the instruction reviewing current literature. Surgery followed by radiotherapy is favored by most skull

base centers. Proton therapy following resection has shown promising results with superior local control rates [8]. Endoscopic endonasal resection is an accepted technique in the management of ONB. A recent meta-analysis comparing endoscopic to open craniofacial resection showed that endoscopic approaches were associated with improved OS in all patients, even those with advanced stage (Kadish C/D) and grade (Hyams grade III/IV) [6••, 20, 21].

Chemotherapy's role, whether used as neoadjuvant or adjuvant, remains undefined. Neoadjuvant chemotherapy is primarily reserved to downstage the tumor, minimize the extent of brain and orbital manipulation during surgery, and as a radiosensitizer [22].

## Management of the Neck

Large-scale series have shown rates of primary or delayed neck involvement ranging from 15 to 33 % [23]. When not clinically evident, neck involvement may be detected using PET/CT scan or CT scan with contrast, and may include levels I, II, III, and IV as well as the retropharyngeal nodes and the parotid lymph nodes [23–25]. If a neck dissection is planned as part of the initial treatment, the senior authors recommend staging the sinonasal and neck surgeries by first removing the skull base ONB, followed by the neck dissection 1–2 weeks later. This avoids the possibility of brain swelling sometimes associated with the injury or postoperative thrombosis of a dominant internal jugular vein (or bilateral).

Prophylactic management of the N0 neck is controversial; however, prophylactic irradiation seems prudent in patients with ONB staged as Kadish C–D or graded as Hyams 3–4. Tumors with these advanced stage or grade have a greater than 20 % probability of late cervical metastasis, which carry a poor prognosis despite aggressive treatment [24, 26, 27].

A multi-institutional study suggested that patients with high-grade (Hyams III/IV) disease have a higher chance of primary neck involvement, whereas patients with positive surgical margins had a higher risk of delayed neck involvement [24]. This study concluded that adjuvant therapies such as radiotherapy with or without chemotherapy should be considered in patients with primary neck disease given their overall poorer prognosis, and prophylactic neck therapy should be considered in patients with high Hyams grade and positive surgical margins. Naples et al. found that neck recurrence is associated with Kadish staging; thus, the rate of late neck metastasis is significantly higher in Kadish B and C ONB [26]. However, this association has not been proven in all series. Banuchi et al. reported the experience in the Memorial Sloan Kettering Cancer Center, finding no association between nodal metastasis and Kadish staging. Despite their findings, they recommended elective irradiation to the neck to optimize locoregional control with the understanding that this intervention does not prolong OS [23]. It should be noted that due to risk of cross over lymphatics, bilateral neck radiation therapy is recommended for these tumors.

## Recurrent and/or Metastatic Disease

Stabilization of recurrent or metastatic ONB has been achieved using targeted therapy such as sunitinib mesylate, cetuximab, imatinib mesylate, bevacizumab, temozolomide, as well as somatostatin analogs [28]. However, these therapies were described in case reports on a case-by-case basis and have not been standardized.

Bell et al. reported the experience of the MD Anderson Cancer Center (MDACC), including 124 patients with ONB. These ONB were staged as Kadish A in 16 %, B in 33 %, C in 48 %, and stage D in 3 % of the patients. Most patients (62 %) had low-grade or Hyams I/II tumors, 21 % had high-grade or Hyams III/IV tumors, and 17 % were not graded. Their 5- and 10-year OS were 75 and 55 %, respectively, and the DFS was 60 and 40 % [19].

## Sinonasal Neuroendocrine Carcinoma

Neuroendocrine carcinomas of the sinonasal cavity (SNEC) are exceedingly rare tumors. According to the WHO, they are divided as carcinoid tumor, atypical carcinoid, small-cell carcinoma—neuroendocrine type, neuroendocrine carcinoma—not otherwise specified, and combined small-cell carcinoma (neuroendocrine type) with non–small-cell carcinoma (usually adenocarcinoma or squamous cell carcinoma) [22]. Recent reviews described the presence of large-cell neuroendocrine carcinoma of the head and neck [29]. Both small- and large-cell carcinomas are poorly differentiated and considered as high-grade tumors [19]. Some classify small- and large-cell carcinomas separately, given that their management and outcomes differ [20].

SNEC is a highly aggressive malignancy usually presenting at advanced stages (81 % present with stage III or IV) [30] with frequent local recurrences and a high incidence of distant metastases (47.6 %) [10••]. Currently, the recommended management for SNEC consists of neoadjuvant chemotherapy, mainly with cisplatin and etoposide or 5 FU, followed by either concurrent chemoradiation or surgical resection followed by adjuvant radiation therapy with or without chemotherapy [10••, 20, 31]. Response of the tumor to induction chemotherapy predicts its prognosis, and a complete response portends improved survival at 3 years [19, 20]. Concurrent chemoradiation is favored, if there is more than 50 % reduction of the tumor after induction chemotherapy or if there is less than 50 %

reduction but the tumor is unresectable. Less than 50 % reduction in tumor volume indicates the need for surgery provided that the patient is an acceptable surgical candidate and the tumor is resectable [30].

Predictors of poor outcomes include skull base and orbital involvement, and tumors originating outside of the nasal cavity [19]. Mitchell et al. reported the experience at MDACC which yielded 5-year OS and DFS of 66.9 and 43.8 %, respectively; however, the authors did not distinguish between the different histopathological subtypes [32]. A systematic review of the literature for patients with small-cell carcinoma of the nasal and paranasal area by Rivero et al. identified 80 patients of whom 46.3 % were alive at 30.8 months of mean follow-up, and 49 % had developed local, regional, or distant metastasis, with a median time of 9 months [30].

### Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinoma (SNUC) is an extremely aggressive high-grade malignancy that usually presents at a locally advanced T stage. Its histogenesis is unclear, and it may have neuroendocrine or Schneiderian origin [19]. SNUC has overlapping histological features with high-grade ONB and SNEC. Given the prognostic and therapeutic consequences, it is of utmost importance that the pathological diagnosis is established and confirmed by an experienced head and neck pathologist, and that consultations for second opinion are requested as needed. Of interest, recent studies have suggested that HPV may play a pathogenic role in SNUC with a prevalence ranging from 0 to 64 % [33].

The primary treatment and sequence of multimodal therapy are debatable. However, some clinical observations are universally accepted. SNUC is exquisitely chemosensitive, thus suggesting that systemic therapy may be of benefit in improving locoregional control and may influence distant metastasis. SNUC also seems to be radiosensitive.

Patients who present with early-stage disease can be treated with surgery followed by chemoradiotherapy or radiotherapy alone [31]. However, most patients present at an advanced stage [34] and are best managed with combination of chemotherapy and radiation therapies. In our experience, even seemingly small tumors frequently have extensive microscopic extension making it near impossible to clear the surgical margins; thus, we favor chemoradiation for most tumors. If the disease is extensive and associated with significant intracranial extension, neoadjuvant chemotherapy may be used to avoid irradiating or reduce the radiation dose of critical structures such as optic nerves, chiasm, and brain, followed by concurrent chemoradiation. Others have suggested surgery followed by adjuvant radiotherapy of SNUC [10••, 19]. In addition, targeted therapy against the human epidermal growth factor 2 (HER2) using lapatinib has shown promising results in in vitro and in vivo (mice) experimental settings on SNUC cell line [35].

In a population-based analysis of 328 patients with SNUC, the OS at 2, 5, and 10 years were 43, 30, and 25 %, respectively. While 51.2 % of this cohort of patients were staged Kadish C, and 18.6 % were staged Kadish D, the extent of their surgery and whether or not the patients received chemotherapy are not clear, given that the study is a SEER database analysis [34].

Other series report 5-year OS ranging from 63 to 74 % [36••, 37]. In a series of 21 patients reported by Al-Mamgani et al., high T stage, use of two- instead of three-modality treatment, presence of dural or orbital invasion, and omission of surgical treatment were significantly correlated with poor local control.

In a SEER population-based analysis of 141 patients by Ahn et al., 22 % had nodal involvement in the neck (mode of diagnosis not specified). Stage and size of the SNUC were not correlated with nodal involvement at the time of diagnosis. Common involved levels included I, II, and III, thus suggesting a potential benefit of elective neck dissection [38].

### Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a salivary gland tumor with a tendency for perineural spread and bony invasion, thus frequently presenting with extension into the skull base, cavernous sinus, and cranial cavity as well as involvement of cranial nerves. Among the nasal and paranasal sites, ACC arises most commonly in the maxillary sinus.

Of notice, a recently described HPV-related squamous cell carcinoma with adenoid cystic-like features can be confused with ACC; thus, it should be included in the differential diagnosis [39]. Given it rarity and recent description, it is not known whether its management and prognosis should be different from other SCC.

The recommended management of ACC consists of surgery followed by postoperative radiotherapy. The addition of chemotherapy to date has demonstrated no role in the management of localized sinonasal ACC. The goal of surgery is to radically resect the tumor with negative microscopic margins; however, a "gross tumor resection" is often the achieved goal, given the ACC propensity for perineural invasion. The rate of occult neck metastasis is 10 %, and elective neck dissection does not improve the 5-year OS, DFS, regional control, and distant metastasis [40].

Lupinetti et al. reported OS and DSS rates at 5 years, for patients with sinonasal ACC, of 62.9 and 70.9 %, respectively, with a local recurrence rate of 56 %. However, their survival rate [3-, 5-, and 10- year survival] seems better

than that of other sinonasal malignancies reviewed in this manuscript [41]. Carbon ion and proton radiotherapy have shown promising results as adjuvant therapies for the local control of ACC and for inoperable cases [8, 42]. Pretreatment methionine-PET scan may prognosticate the therapeutic efficacy of heavy particle therapy such as carbon ion for these patients [43].

## Sarcomas

Sarcomas are a heterogeneous group of malignancies that rarely arise in the sinonasal cavities. Their clinical behavior depends on their histology, which is extremely complex. Furthermore, sarcomas often require immunohistochemical and genetic analysis to identify the correct subtype of tumor, as well as their grade. Primary sarcomas of the sinonasal tract include rhabdomyosarcoma, fibrosarcoma, malignant nerve sheath tumors, angiosarcomas, leiomyosarcomas, chondrosarcomas, osteosarcomas, malignant solitary fibrous tumors, and others.

The French Sarcoma Group concluded that grade and histological type significantly impacted OS (5-year OS = 62 %) and metastatic risk (5-year metastasis-free survival = 73 %), with rhabdomyosarcoma being the most common and having the poorest prognosis [44].

Rhabdomyosarcoma is staged differently from other malignancies based on the histological type (embryonal, alveolar, and botryoid), TNM staging, and clinical group. The clinical group is defined based on the extent of disease and the extent of removal during the initial surgery. Using this information, patients are divided into low-, intermediate-, and high-risk groups which help determine the optimal treatment [45].

The optimal sequence of therapy for sarcomas is still undefined, and the literature contains great controversies. However, surgery is considered as the primary treatment of sinonasal sarcomas, even if negative margins cannot be achieved. Surgical excision is a predictive factor for complete response, although radiotherapy is usually necessary for local control [22, 44].

Bossi et al. recommended surgical excision with wide margins as the mainstay of treatment for adult soft tissue sarcomas as well as chondrosarcomas and osteosarcomas [36••]. A SEER analysis of 51 patients with fibrosarcoma revealed that surgery, with or without adjuvant radiotherapy, is the best treatment, yielding a 5-year OS rate of 71.7 % [46].

Ewing's sarcoma or primitive neuroectodermal tumor (PNET) occurs in a younger population, and the optimal treatment option consists of neoadjuvant chemotherapy followed by radical surgery with adjuvant radiotherapy [10••].

## Hemangiopericytoma

Hemangiopericytoma is a rare tumor of the sinonasal cavity of vascular origin and is better termed glomangiopericytoma. This tumor has a low risk of distant metastasis but has a tendency to recur locally and is radioresistant and chemoresistant. Hence, the optimal treatment option is endoscopic surgical excision as a single modality with wide margins if possible [10••].

## Mucosal Melanoma

Mucosal melanoma (MM) of the sinonasal cavity is a very aggressive tumor with poor outcome, high propensity to recur, and metastasize. To this effect, the American Joint Commission for Cancer (AJCC) staging system classified the T stage for MM omitting T1 and T2, thus starting at as T3 and continuing to T4a and T4b. However, the carTNM (2009 AJCC TNM classification for carcinomas of the nasal cavity and sinuses) seems to provide the most reliable prognostic information [47•, 48].

Surgery is considered the main treatment option; however, given the high risk of recurrence [10••], it is best to avoid aggressive radical surgery that would include the removal of critical structures, and preferably use a minimally invasive endoscopic approach [8, 49]. Furthermore, Lund et al. hypothesized that aggressive surgery might lead to a severe disturbance in the immune system, subsequently promoting recurrence or rapid systemic dissemination [50].

Adjuvant radiotherapy seems to improve local control; however, it is unclear if it improves OS [49]. Positive or close surgical margins are recognized as a factor that increases the rate of local recurrence, thus indicating adjuvant radiotherapy [47•]. Lombardi et al. also advocated adjuvant radiotherapy in the presence of involvement of critical structures (i.e., dura) and cervical metastases [49]. Elective treatment of the neck is usually not performed given that the risk of nodal disease is low both at the time of presentation (5–10 %) and throughout the course of the disease (20 %) [47•].

In view of the rarity of sinonasal MM, multimodality systemic therapy is advocated, and includes chemotherapy, immunotherapy, and biochemotherapy (defined as systemic administration of a chemotherapeutic agent and at least one biological agent in the same cycle), all of which have been extrapolated from the management of metastatic cutaneous melanoma. Biochemotherapy is gaining acceptance as a first-line treatment in a multimodality approach for locally advanced sinonasal MM, and there is some evidence suggesting that it may improve survival rates [36••, 49]. Furthermore, a good response to biochemotherapy is a good prognostic factor for long-term survival [36••].

Genetic profiling of MM identified frequently altered genes and molecular pathways that can be used for targeted therapy. The main focus is on c-KIT gene, an oncogene that codes for a transmembrane protein with tyrosine kinase activity with alterations found in up to 40 % of sinonasal MM [36••]. Thus, MM may respond to c-KIT

**Table 1** Summary of management, 5-year OS, and DFS for the major sinonasal malignancies

| Sinonasal malignancy | Early stage management | Late stage management | Management of the cN0 neck | 5 year DFS (%) | 5 year OS (%) | Comments |
|---|---|---|---|---|---|---|
| SCC | – Single modality (Surgery or RT)<br>– Dual modality if margins are close or positive (Surgery + RT) | Multimodality based on differentiation:<br>– Well differentiated: surgery with neoadjuvant chemoradiation<br>– Poorly differentiated: induction chemo followed by surgery and/or chemoradiation | N0: ENI recommended in T3-4 (23 % risk) or if maxillary sinus is involved | 62 | 66.8–78 | – Role of HPV in management is unclear |
| Adenocarcinoma | – Low grade:<br>Single modality surgery with or without RT<br>– High grade: dual modality surgery + RT | High grade or positive margins: dual modality surgery + RT | N0: risk of occult neck disease is 7 %. Not recommended | 79–85.2 | 68.8 | P53 status: consider neoadjuvant chemotherapy |
| Olfactory neuroblastoma | – Low grade:<br>Single modality surgery with or without RT<br>– High grade:<br>Dual modality surgery + RT | Dual or triple modality:<br>Surgery + CRT | N0: risk of occult neck disease is 15–33 %. Recommended in high grade, positive surgical margins, Kadish B and C. | 75 | 60 | |
| SNEC | Dual modality: surgery followed by RT or concurrent chemoradiation | Multimodality:<br>Induction chemotherapy followed by: surgery or concurrent chemoradiation (If good response to induction chemotherapy) | N0: not recommended | 43.8 | 66.9 | |
| SNUC | Dual therapy: Surgery followed by RT | Multimodality:<br>Neoadjuvant chemotherapy followed by either:<br>– Concurrent chemoradiation or<br>– Surgery with adjuvant RT | N0: risk of occult neck disease is 10–30 %. | 64 | 30–74 | |
| Adenoid cystic carcinoma | Dual therapy:<br>Surgery followed by RT | Dual therapy:<br>Surgery followed by RT | N0: risk of occult neck disease is 10 %. Not recommended | | 62.9 | |
| Mucosal melanoma | | – Resectable: Surgery, preferably endoscopic if no contraindication followed by adjuvant RT<br>– Unresectable: Biochemotherapy followed by surgery followed by adjuvant RT with or without biochemotherapy | N0: risk of occult neck disease is 5–10 %. Not recommended | 39 | 14–56 | |

*cN0* clinically N0 neck, *RT* radiotherapy, *ENI* elective neck irradiation, *HPV* human papilloma virus

inhibitors such as imatinib, sorafenib, dasatinib, or sunitinib [47•]. Agents that enhance cancer immunity such as ipilimumab, an anti-cytotoxic T-lymphocyte antigen-4 monoclonal antibody, recently showed improved survival rates in patients with metastatic cutaneous melanoma; however, its role in MM is yet to be defined [47•].

Five-year DFS for MM of the head and neck ranges between 14 and 48 %, and the 5-year OS ranges between 14 and 47 % [47•]. However, these numbers include oral MM. Studies limited to sinonasal MM report 5-year OS ranging between 26.9 and 38.7 % [10••]. Lund and Wei reported a 5-year OS and DFS of 56 and 39 %, respectively; however, their 10-year OS and DFS were 0 % [22]. Independent predictors of outcome include clinical stage, margin status, tumor thickness greater than 5 mm, and lymphovascular invasion on light microscopy. Other cited factors associated with a worse prognosis include amelanotic melanoma, the presence of more than 10 mitotic figures per high-power fields and/or ulceration, age above 70 years, occurrence of nodal and distant metastasis, and higher Ki-67 scores [47•].

### NUT Midline Carcinoma

NUT midline carcinoma (NMC) is a recently described aggressive epithelial tumor, and as its name suggests, it affects sites along the midline of the body, the most common being the mediastinum and the sinonasal tract. It affects both children and adults and is defined by the presence of a chromosomal rearrangement involving the nuclear protein in testis (NUT) gene on chromosome 15q14, along with other genetic alterations identified through either immunohistochemical or molecular means. These are necessary for the diagnosis [51]. NUT midline tumors are part of the long list of sinonasal "small round blue cell tumors"; hence, the differential diagnosis include ON, lymphoma, MM, rhabdomyosarcoma, and Ewing sarcoma. NUT tumors have been most often misdiagnosed as SNUC or SCC [51].

Clinically, NMC is a highly aggressive chemo- and radioresistant tumor with a bad prognosis and an 80 % mortality rate within the first year of diagnosis [52]. However, the presence of a defining translocation makes targeted therapy the ideal current treatment. Trials involving agents such as bromodomain inhibitors and deacetylase inhibitors are currently ongoing [39, 53].

### Hematolymphoid Tumors: Lymphoma and NKT Cell Lymphoma

Sinonasal lymphoma is a rare tumor accounting for 1.5 % of all lymphomas, and the most common subtypes involving the sinonasal tract are non-Hodgkin (NHL) B cell lymphomas and extranodal natural killer/T-cell lymphoma nasal type (ENKTCL), along with other rare entities [53]. It is staged according to the Ann Arbor staging system, and the main treatment consists of chemotherapy and targeted therapy such as rituximab (anti-CD 20) with or without radiotherapy. Aggressive localized disease warrants radiotherapy, and more evidence emphasizes its role for ENKTCL [54, 55]. The role of surgery is limited to obtaining a biopsy specimen for histological and molecular analysis as well as to exclude persistent disease [10••].

A series published by the UCLA group showed a 5-year OS and DFS rates of 53 and 49 %, respectively, regardless of the histological subtype [54]. In a SEER database analysis, NHL-mature B-cell lymphomas carried the best prognosis among sinonasal malignancies (5-year DSS = 64.3 %) with a worse prognosis for lesions overlapping multiples subsites compared to nasal cavity alone [2]. Diffuse large B-cell lymphoma carried a better prognosis when compared to ENKTCL regardless of gender, age, stage, and treatment modality [56].

## Conclusion

The diagnosis of sinonasal malignancies is challenging, thus requiring a thorough histological analysis by an experienced head and neck pathologist. The care of sinonasal malignancies is best accomplished in centers with "ample experience" managing these pathologies through the interaction of a multispecialty tumor board or planning conference that includes otolaryngologists, head and heck surgeons, neurosurgeons, radiation oncologists, medical oncologists, neuroradiologists, and ophthalmologists for optimal individualized treatment.

There is growing evidence demonstrating that in adequately selected patients, endoscopic endonasal resection of sinonasal malignancies is comparable, and in some cases, even superior to open craniofacial resection. However, it is important for the oncologic skull base surgeon to be able to perform an open approach, as many tumors will require a surgical approach and resection that is beyond the reach of an endoscopic endonasal approach and, occasionally, the surgeon may need to convert an endoscopic to an open approach.

Multimodal management strategies including systemic treatment such as chemotherapy, targeted therapy, immunotherapy, and local treatment using surgery or radiotherapy such as IMRT and heavy ion radiotherapy (carbon ion and proton beam) is improving overall survival and local control rates, thus shifting the paradigm of management of these malignancies. A recent large systematic review and meta-analysis showed that compared with photon therapy, charged particle therapy (Protons and

Carbon ions) could be associated with better outcomes for patients with malignant diseases of the nasal cavity and paranasal sinuses [57••]. A thorough staging and upfront identification of factors of bad prognosis, especially high-grade and advanced-stage diseases help tailor the optimal treatment plan. Table 1 summarizes the management, 5-year OS, and DFS for the major sinonasal malignancies (Table 1).

The role of neoadjuvant chemotherapy, targeted therapy, HPV and other molecular markers, heavy ion radiotherapy, and endoscopic endonasal surgery is yet to be fully defined using prospective studies and standardized retrospective case series. Investigators are encouraged to collaborate in the form of prospective multi-institutional studies in order to understand the best management and natural history of these rare and complex tumors.

#### Compliance with Ethical Guidelines

**Conflict of Interest** Dr. Ralph Abi Hachem, Dr. Andre Beer-Furlan, Dr. Ahmad Elkhatib, Dr. Sanjeet Rangarajan, Dr. Daniel Prevedello, Dr. Dukagjin Blakaj, Dr. Aashish Bhatt, and Dr. Ricardo Carrau, declare that they have no conflicts of interest.

**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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- • Of importance
- •• Of major importance


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