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The Contemporary Management of Cancers of the Sinonasal Tract in Adults

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Abstract

Sinonasal malignancies make up less than 5% of all head and neck neoplasms, with an incidence of 0.5–1.0 per 100,000. The outcome of these rare malignancies has been poor while significant progress is being made in management of other cancers. This review aims to describe the incidence, causes, presentation, diagnosis, treatment and recent developments of malignancies of the sinonasal tract. The diagnoses that we cover in this review include sinonasal undifferentiated carcinoma, sinonasal adenocarcinoma, sinonasal squamous cell carcinoma, and esthesioneuroblastoma, which are exclusive to the sinonasal tract. In addition, we will also cover malignancies that are likely to be encountered in the sinonasal tract - primary mucosal melanoma, NUT carcinoma, and extranodal NK/T Cell lymphoma. For the purpose of keeping this review as concise and focused as possible, we have excluded sarcomas or malignancies that can be classified as salivary gland neoplasms.

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Keywords

rare diseases; head and neck neoplasms; paranasal sinus neoplasms; sinonasal carcinoma

Introduction

Sinonasal malignancies make up less than 5% of all head and neck neoplasms, with an incidence of 0.556 per 100,000 individuals per year. (1) While outcomes of other cancers of the head and neck have significantly improved over the past decade, the outcomes of sinonasal malignancies have been relatively stable. (2) This is likely related to, at least in part, the exclusion of sinonasal malignancies from most clinical studies testing therapeutic agents for head and neck cancer patients. (3) The scope of this review is to cover incidence, mortality, survival, causes, presentation, diagnosis, treatment, and ongoing developments in malignancies that occur in the sinonasal tract. We include malignancies that are exclusive to the sinonasal tract such as sinonasal undifferentiated carcinoma, sinonasal adenocarcinoma, sinonasal squamous cell carcinoma, and esthesioneuroblastoma. Additionally, we include other malignancies that can occur in the sinonasal tract but are not classified as sarcomas or salivary gland neoplasms. This includes tumors that are seen most often in the sinonasal region such as primary mucosal melanoma, NUT carcinoma, and extranodal NK/T Cell lymphoma. We have specifically emphasized the management of these tumors due to the lack of specific protocols due to paucity of data. Nasopharyngeal carcinoma is not included in this review because of its distinct anatomical presentation.

The histology of the sinonasal tract is diverse. The nasal vestibule at the entrance of each nostril is composed of keratinized squamous epithelium, and like the skin, has sweat glands, hair follicles, and sebaceous glands. Approximately one to two centimeters into the nose at the limen nasi this epithelium transitions to a ciliated pseudostratified columnar epithelium, also called the Schneiderian epithelium, which lines most of the nasal cavity and paranasal sinuses. This lining is like that of the lower respiratory tract and contains submucosal seromucous glands. The mucus membrane of the paranasal sinuses is thinner than that of the nasal cavity and has fewer seromucous glands. The olfactory mucosa is located over the cribriform plate and the superior third of the nasal septum. This mucosa consists of specialized olfactory neuronal cells that protrude from the mucosa alongside columnar sustentacular epithelial cells. (4,5)

Presentation and evaluation of a sinonasal malignancy

Clinical presentation

Early symptoms are non-specific and include nasal obstruction most commonly, along with epistaxis, facial pain, or persistent rhinorrhea. (6,7) Locally advanced disease has more localizing symptoms such as proptosis, diplopia or cranial neuropathy, chronic rhinosinusitis, or headache. (6) Symptoms of advanced disease correlate to location and extent of disease. Tumors advancing towards the anterior cranial fossa via the cribriform plate or the orbit cause anosmia or proptosis, whereas tumors extending to the lateral bony wall into the cavernous sinuses cause neuropathy of cranial nerves III, IV, VI, V1, and V2,

leading to diplopia and paresthesias of the face. When the tumor invades the middle cranial fossa, patients experience paresthesias of the lower face or trismus due to involvement of cranial nerve V3 or invasion of the pterygoid muscles. Because many of the early symptoms are associated with common benign states such as allergies, most patients with these tumors tends to be diagnosed when it is locally advanced, or even metastatic. (8)

Initial evaluation

Clinical examination of patients with the above symptoms should include, complete head and neck exam including all mucosal surfaces and assessment of cranial nerves. An endoscopic exam is necessary to visualize the extent of the tumor in the sinonasal area, as well as obtain tissue for histopathological examination. This is usually followed by imaging. Computed tomography (CT) and magnetic resonance imaging (MRI) can be used alone or in combination depending on the clinical context. CT is helpful for examining bony landmarks and erosion and is important for the use of image guidance during surgery. MRI is helpful for soft tissue differentiation, specifically about invasion of the orbit, intracranial structures (dura, brain, cavernous sinus), perineural spread, infratemporal fossa and facial soft tissues. MRI can also provide higher resolution of the tumor itself. Relevant nuclear imaging for a subset of sinonasal malignancies will be discussed in the context of individual disease entities in the respective sections below.

Staging of sinonasal malignancies is as per the American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classifications for cancer of nasal cavity and paranasal sinuses. (9) T-staging varies based on the location of the tumor, with separate T staging for maxillary sinus and nasal cavity/ethmoid sinus. It is based on the depth of invasion and degree of destruction of surrounding structures. N-staging is based on regional nodal status, clinically or pathologically. While most tumors share common staging, certain diseases like ONB and mucosal melanoma have unique staging systems, as discussed in their respective sections of this article. Table 1 summarizes the TNM staging of sinonasal malignancies outside ONB and mucosal melanoma.

Sinonasal Squamous Cell Carcinoma

Incidence and patient demographics

Sinonasal squamous cell cancers (SNSCC) are the most common sinonasal malignancy, making up about 3% of head and neck cancers. (10) Within sinonasal malignancies, sinonasal squamous cell carcinoma is the most common, making up 61% of cases. (11) A recent study examined 4,994 cases of SNSCC between 1973 and 2009, as documented by the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program, which revealed that the overall incidence rate was 0.36 cases per 100,000 population per year. There was a male-to-female incidence ratio of 2.26:1 and almost 80% of patients were older than 55 years old. The incidence rate has steadily declined over the last 30+ years. Trend analysis showed annual percentage change (APC), which is the percentage change in incidence rate over time, of -2.63% for male SNSCC incidence and -1.69% for female SNSCC incidence during the same period. (8)

Pathophysiology

SNSCC is a complex disease, and its pathogenesis is poorly understood. Occupational exposure to several industry compounds, such as wood dust, leather dust, glue, chrome, nickel, formaldehyde, arsenic, welding fumes, and multiple compounds in the textile industry, has been reported to increase the risk of SNSCC. (12) A case-control study by Hayes (13) revealed a strong association between SNSCC and tobacco use (relative risk of 3.1) with a dose-response relationship, especially for recent tobacco users. Fukuda et al (14) revealed similar evidence to support tobacco smoke exposure as a risk factor. In addition to environmental exposures, a meta-analysis also showed a strong prevalence of HPV in SNSCC. (15)

Squamous cell cancers in several anatomic locations, including the oropharyngeal region, are well known to be linked to human papillomavirus (HPV) and recent studies support a potential causative role for the virus in SNSCC as well. Recent studies have revealed that around 31% of SNSCC patients had HPV-positive tumors from 770 cases of SNSCC with known HPV status. (16,17) These patients with HPV-positive SNSCC were significantly younger than HPV-negative patients. HPV-positivity was associated with a higher 5-year OS, like squamous cell carcinoma of the oropharynx. Another observation that is often discussed is the association of SNSCC with inverted sinonasal papilloma (ISP). Lawson et al. (18) reviewed all studies evaluating the association between HPV and ISP and hypothesized that low-risk HPV may induce ISP formation which then disappears as infected cells die while high-risk HPV causes dysplastic ISP and squamous cell carcinoma. The College of American Pathologists do not recommend routine HPV testing in non-oropharyngeal primary tumors of the head and neck due to undetermined prognostic significance. (19)

In 2017, the WHO included human papillomavirus-related multi-phenotypic sinonasal carcinoma (HMSC) as a new subtype of non-keratinizing squamous cell carcinoma of the sinonasal tract. This entity, first described in 2013, has favorable clinical outcome despite aggressive histomorphology. (20) HPV status is commonly defined by p16 overexpression of tumor and morphologically is described as basaloid proliferation with focal areas of squamous differentiation. A systematic review by Zupancic et al. (21) reported 79 cases of HMSC, of which 77 (97.5%) occurred in the sinonasal cavity and 2 cases in the breast and tonsils respectively. Of the tumors originating in the sinonasal cavity, none had regional metastasis.

The contribution of genetic abnormalities to the pathogenesis of SNSCC is poorly understood. *TP53* mutations in the tumor have been described in 80% of SNSCCs. (22) Patients with *TP53* mutations in their SNSCC tended to have worse 3 years OS (43.8% vs 84.1%). (23) *KRAS* mutations are rarely detected in SNSCCs, however they are seen in almost all cases associated with Oncocytic Sinonasal Papilloma (OSP). (24) 50% of ISP converting into malignancy have an *EGFR* 20 exon mutation, and overall *EGFR* mutated SNSCC has worse prognosis (25,26) Amplification of *FGFR1* has been reported in approximately 20% SNSCC, *SOX2* amplification has been reported in 37% of SNSCCs and was associated with a higher incidence of disease recurrence. (27) Also, *VEGFR* gene overexpression has been detected in ~50% of SNSCCs. (28)

Presentation

The most common site of SNSCC is the maxillary sinus (~60%), followed by the nasal cavity (25%) and ethmoidal complex (15%). (29,30) Like most sinonasal malignancies, diagnosis of SNSCC most often occurs at an advanced stage due to nonspecific symptoms early in the disease, with >80% of patients reportedly presenting with at least stage T3 disease. (31)

Pathology

Histologic diagnosis of SNSCCs can be challenging due to relative rarity, a large miscellany of different possible histology, and overlapping appearance of other malignancy or inflammatory disease. Both keratinizing and nonkeratinizing types of squamous cell carcinoma are encountered. (32) In 1 to 7 percent of cases, SCC is seen embedded within ISP, and are classified as IP-associated SCC (IP-SCC). A recent retrospective review that was performed on 52 sinonasal tumors showed 21% of these patients had discrepancies between preliminary pathology and post-surgical diagnosis, with alteration in management in all cases with a change in histologic diagnosis. (33,34) These findings support the general recommendation to provide the pathologist with abundant material to emphasize the importance of second-opinion review by subspecialized pathologists to minimize diagnostic error. Figure 1 shows an H&E slide of a representative SNSCC originating from an ISP.

Imaging

SNSCCs are characterized by aggressive bony destruction of the adjacent sinus walls. Invasion of the contralateral sinonasal area, orbital wall, infratemporal fossa, and skull base is sometimes observed. Therefore, a combination of CT and MRI provides the most accurate assessment of tumor extent. Due to its high spatial resolution, CT is required to visualize the structural changes and reabsorption of thin bone structures and should be utilized when malignancy is suspected. Gadolinium-enhanced MRI is valuable to assess soft tissue involvement, which can otherwise resemble other conditions such as lymphoma, necrosis, inflammatory, mucus retention, and fibrosis. (29,35,36). Evaluation of apparent diffusion coefficient (ADC) values on MRI is a promising way to differentiate benign ISPs from IP-SCCs which are associated with a loss of convoluted cerebriform pattern and lower ADC values. (37) ADC values are also useful in differentiating sinonasal lymphoma as the ADC values of maxillary SNSCCs are typically higher than those for lymphoma.(35) PET-CT is also widely used as an alternative to MRI since there appears to be a correlation between different histopathologic types of sinonasal tumors and SUV values. PET-CT can be used as “metabolic biopsy” to characterize sinonasal malignancy. Figure 2 shows PET-CT of SNSCC arising from ISP. Not surprisingly, the authors found overlap in fluorodeoxyglucose (FDG) uptake values among some histologic subgroups. Therefore, a surgical biopsy is necessary. (38) PET-CT has also been used as a prognostic tool. A retrospective study described that absence of pathologic FDG uptake at the first post-treatment PET-CT was associated with better OS. (39)

Current treatment

Surgery is a potentially curative treatment for resectable SNSCCs with the goal of complete resection and achieving negative margins. Due to the proximity of the nasal cavity and paranasal sinuses to critical structures, complete resection can be prohibitively morbid. For example, radical surgeries such as craniofacial resection, ethmoidectomy, sphenotomy, or total maxillectomy are associated with high morbidity, adverse effect on function, and disfigurement. The surgical approach, including endoscopic or open surgery, should be selected based on tumor location and local extension.

A large retrospective study by Jafari et al (40) identified 7,808 patients with SNSCC who were treated with different approaches and highlights the importance of negative surgical margins. 31.1% of patients who underwent surgery had positive surgical margins (PSM) and of those cases, around half had microscopic PSM and the rest had macroscopic PSM. Compared to nonsurgical treatment, negative surgical margins (NSM) and microscopic PSM were associated with improved survival. The benefit of surgical treatment was not seen in the macroscopic PSM group, particularly in advanced stages, including nodal metastasis. The median OS was 90.5 months, 56.7 months, 38.4 months, and 36.4 months for patients with NSM, microscopic PSM, macroscopic PSM, and nonsurgical therapy, respectively. Risks and benefits should be discussed before electing to proceed with surgery, particularly for patients with advanced stage disease. Patients should be counseled that surgery might not improve OS when compared with nonsurgical therapy if gross total resection is not achieved, and that surgery bears inherent risks.

In clinically node negative disease, elective neck dissection (END) remains controversial. In a retrospective study of 1120 patients using the National Cancer Database (NCDB), 220 patients (19.6%) underwent END. The occult metastasis rate in the END cohort was 12.7% and in propensity score-matched cohorts END did not correlate with OS (HR 0.971, 95% CI 0.677–1.392). (41)

To achieve negative surgical margins, the use of induction chemotherapy has been investigated as part of multimodal treatment. In the past decade, multiple studies have shown promising results of induction chemotherapy by improving morbidity, function/organ preservation, and overall survival. (42–46) A large retrospective study by Abdelmeguid et al (47) included 123 locoregionally advanced SNSCC patients who were treated with platinum-based induction chemotherapy as part of their overall treatment. 88.6% of patients received platinum with taxanes with or without another agent, and the rest received platinum-based doublet regimens without a taxane. Seventy patients (56.9%) achieved at least a partial response, and stable disease was seen in 32 patients (26.0%), whereas 21 patients (17.0%) had progressive disease. The 2-year OS of patients who had at least stable disease after induction chemotherapy compared with those who had progressive disease was 68.2% vs 33.3%, a statistically significant difference. More importantly, before treatment, 66.7% of patients had orbital invasion, but only 18.3% required orbital exenteration at the time of surgery. These data support the hypothesis that induction chemotherapy is associated with an improved OS and better chance of organ preservation.

The data on neoadjuvant chemoradiation in SNSCCs is scarce. Robin et al (48) conducted a large retrospective multivariate analysis of 11,160 patients with sinonasal cancer using the National Cancer Data Base and found those who received neoadjuvant treatment had a higher likelihood of achieving a negative surgical margin and better OS than those who did not, but this group also included patients who received any form of neoadjuvant treatment (including chemotherapy or radiotherapy alone). Another retrospective study by Fernstrom et al (49) suggested that neoadjuvant chemoradiotherapy can be beneficial to patients with locally advanced disease to decrease surgical morbidity, but does not improve OS. However, prospective clinical studies studying the exact role and benefit of neoadjuvant chemoradiotherapy are needed.

Adjuvant intensity-modulated RT (IMRT) after complete resection is considered the standard treatment for pT2-T4 SNSCCs, aiming to decrease the incidence of local recurrence. A handful of retrospective studies have indicated that control rates with surgery and adjuvant radiotherapy ranged between 50 and 85%. (50–52) Compared to conventional 2D and 3D techniques, IMRT for the management of unresectable T4 paranasal sinus and skull base malignancy may help preserve organ function and minimize toxicity. (53) Intensity-modulated particle therapy (IMPT) such as protons and ¹²C-carbon ions are also being investigated for these patients and allows the design of a sharp dose gradient to a well-defined depth, leading to much higher radiobiological effectiveness and reduced dependence on tissue oxygenation. (54) A retrospective study by Zhang et al revealed that in comparing proton radiation therapy (PRT), IMRT, and carbon ion radiation therapy (CIRT), CIRT appeared to provide significant improvement in 3-year OS of 75.1% compared to 66.2% for PRT and 63.8% for IMRT in nasal cavity and paranasal sinuses malignancies. (55) However, no prospective studies have been published to confirm the superiority of CIRT. Concurrent platinum-based adjuvant therapy is often delivered to further optimize tumor control. The aim is two-fold, both radiosensitization and targeting of residual disease in cases of positive margins, with high-risk features, such as nodal, perineural or lymphovascular invasion. (29) The dose and schedule of cisplatin typically used is either 100mg/m² every 3 weeks or 30–50 mg/m² weekly. Carboplatin can be considered if the patient is ineligible for cisplatin. (56,57)

Definitive chemoradiation therapy is employed for patients with unresectable tumors or for those who do not choose to undergo surgery. The chemotherapy is platinum-based as above delivered using the same schedule described above in the adjuvant setting. Radiation is typically delivered in the form of IMRT, although IMPT can be used as an alternative to IMRT, concurrent with chemotherapy. Currently, there are no prospective data comparing these two forms of radiation. A phase II study investigating the efficacy and toxicity of intensity-modulated or proton radiation therapy for locally advanced sinonasal malignancy is ongoing. (58)

For locoregional recurrence, salvage surgery or re-radiation is generally recommended, if possible. Otherwise, palliative systemic chemotherapy is considered the treatment of choice. (59–61) Orlandi et al (62) reported that patients with locally advanced sinonasal cancers treated with palliative chemotherapy achieved significantly improved OS compared to those without. Palliative regimens were either platinum-, anthracycline-, taxane-,

and/or alkylating-agent-based (e.g., temozolomide or ifosfamide) in different combinations. However, there was no treatment-related subgroup OS analysis in SNSCCs. The role of immunotherapy is still not defined as most of these patients are excluded from HNSCC immunotherapy clinical studies. (63) However, Riobello et al (64) have demonstrated membranous expression of PD-L1 by the cancer cells in 34% of SNSCC cases and by immune infiltrating cells in 45%, which might indicate a potential benefit from immunotherapy. Figure 3 demonstrates an algorithm for the management of SNSCC.

Prognosis/Surveillance

The 5-year overall survival (OS) has been around 50% in the past three decades partly due to high rates of local recurrence. (65–67) Patients with nasal cavity SCC have increased 5-year relative survival rates compared to patients with SCC of the maxillary, ethmoid, frontal, and the sphenoid sinuses. (48,67) Additionally, male sex, older age, higher T and N stage, and poorer tumor grade portend a poor prognosis. (68) Recurrence is as high as 56% at 5 years and 5-year OS is 50%. (69) Patients who survive after multimodal treatment should continue to undergo clinical (endoscopy) and radiological (CT, MRI, PET) examinations for at least 5 years given the high recurrence risk, as per head and neck cancer guidelines. (70) Optimal timing of surveillance in sinonasal malignancy is ill defined and 70% of clinicians follow the NCCN guidelines for head and neck cancer. (70) The frequency and length of follow-up should be individualized based on histology and grade.

Recent or ongoing developments/research

Few clinical studies for HNSCC are actively enrolling patients with SNSCC. However, there are studies for SNSCC, specifically evaluating IMRT and PRT for sinonasal malignancies ([NCT01586767](#)). (58) In addition, a phase II study is underway evaluating the response of docetaxel, cisplatin, and fluorouracil (TPF) in previously untreated Stage II-IV SNSCC ([NCT00707473](#)). (71)

Sinonasal Adenocarcinoma

Incidence and patient demographics

Adenocarcinoma is the second most common type of sinonasal cancer after squamous cell carcinoma. International data from public cancer registries suggests that it accounts for approximately 27% of all sinonasal malignancies. (72) The incidence of sinonasal adenocarcinoma (SNAC) has remained stable over the 40 years from 1973 to 2013.

Overall incidence based on SEER data from 1973 to 2013 was 0.44 per million, with men making up 58.2% of the cohort. The median age was 64 at diagnosis. The widespread use of nasal endoscopy and radiologic studies may have allowed earlier diagnosis leading to improved survival. (2)

Presentation

The most common sites of origin are the ethmoid sinuses and the nasal cavity, which account for more than half of the cases. An MD Anderson cohort of 66 patients noted 37.9% originated from the ethmoid sinus, 36.4% from the nasal cavity and 19.7% from the

maxillary sinus.(73) Tumor extension to the skull base, sphenoid sinus, dura, brain, orbit, or cribriform was seen at diagnosis causing related symptoms.

Pathophysiology

A wide range of histopathology findings is seen in SNAC, which can be divided into the salivary type and non-salivary type. The non-salivary type can be further subdivided into the intestinal type and non-intestinal type (low grade and high grade). (74) The risk factors for sinonasal adenocarcinoma have been identified based on reports of environmental exposure in affected patients. Low-grade non-intestinal SNAC has no known association with environmental exposures. For intestinal-type SNAC, there is a notable association with long-term exposure to wood dust. Workers with occupational exposure to hardwood dust show incidences that are 1,000 times those of the general population. Wood dust exposure was observed in 20% of SNAC cases within a historic cohort with an exposure period of 40–43 years. (74) In a more recent cohort of 66 patients seen at a single institution in the US, smoking and alcohol consumption were the most common exposures and reported in 30 (45%) and 45 (68%) patients respectively. Only three patients reported exposure to wood dust. (75) The carcinogenic compound from wood dust exposure has not been identified but a possible role of tannins is suspected. (74)

Pathology

Low-grade non-intestinal adenocarcinoma (LGNIA) encompasses a heterogeneous morphology with exophytic masses with crowded back-to-back glandular complex configurations in papillary or microcystic patterns. They also lack necrosis, increased mitotic activity and nuclear polymorphism, which differentiate them from high-grade non-intestinal adenocarcinoma. (76) Intestinal-type SNAC mimics the appearance of the normal or neoplastic large and small intestine and cannot be differentiated from metastatic colorectal carcinoma based on histology alone. Both intestinal-type SNAC and colorectal carcinoma express CK20, CDX-2, MUC2, and villin. The presence of CK7 may be suggestive of intestinal-type SNAC. (74) TP53 is the most common genetic alteration seen in 40–50% cases. (26) Other notable differences are seen at the molecular level, where SNAC is associated with *MET* gene amplification, and colorectal carcinoma is associated with *KRAS* and *BRAF* mutations. (77)

Two other rare entities are sinonasal renal cell-like adenocarcinoma and ETV6 rearranged SNAC. (76) The former is a clear cell variant of LGNIA and was included as a new tumor entity in the 4th edition of the WHO classification of sinonasal tumors. It expresses *CK7*, *CAIX*, *DOG-1*, and *SOX10*, and is negative for *CK20* and *PAX-8*, findings that help to distinguish it from metastatic renal cell carcinoma. ETV6 rearranged sinonasal adenocarcinoma has tubular proliferations with rare apocrine features, and is strongly positive for *CK7*, *GCDFP-15*, *DOG-1* and *SOX-10*, weakly and focally positive for *S100* and negative for *GATA-3* and mammaglobin. They are associated with ETV6/receptor tyrosine kinase gene fusions, like ETV6-NTRK3 or ETV6-RET. Both ETV6-rearranged and LGNIA have an indolent clinical course.

Imaging

Imaging and staging of SNAC are similar to SNSCC.

Current treatment

Local control and prevention of locoregional recurrence are the main treatment objectives in SNAC. Disease-related death is typically attributed to local recurrence, which occurs in approximately half of cases. Lymph node spread and distant metastases are uncommon and occur in approximately 8% and 13% of cases, respectively. Most published reports are retrospective studies with heterogeneous disease characteristics, making evidence-based conclusions difficult. (73,75,78,79)

The mainstay of treatment is surgical resection with curative intent. There are no prospective studies comparing surgery alone to other treatments. For tumors involving the ethmoid sinus, surgery with or without radiation had a survival advantage compared to radiotherapy alone in a retrospective study of 418 patients. (75) Different surgical approaches are reported with endoscopic resection having a survival advantage; however, bias is present with patient selection for this approach favoring smaller, lower stage tumors.(78) Prophylactic dissection of cervical lymph nodes is not recommended in SNAC. In a retrospective study of sinonasal malignancies diagnosed at two academic centers from 1975 to 1994, 5 of 386 patients had lymph node involvement at diagnosis.(79) None of the five lymph node positive patients had SNAC, with four of the five patients having squamous cell carcinoma and one patient having undifferentiated carcinoma.

Most case series report the use of preoperative or postoperative radiotherapy, but there are no prospective studies. In retrospective series, patients treated with radiotherapy alone are more likely to have locally advanced unresectable tumors and the outcomes are not comparable to surgery. Adjuvant radiotherapy is also more likely to be given in higher-grade tumors or cases with positive margins. In a review of 66 patients treated at MD Anderson Cancer Center from 1993 to 2009, 24 patients (36.4%) were treated with surgery alone and 26 (39.3%) were treated with surgery and radiation with or without chemotherapy.(73) The rest received either surgery with chemotherapy, only radiotherapy or no treatment at all.

Several chemotherapeutic agents are reported to be effective for SNAC. Cisplatin and 5-FU were associated with a 37% overall response rate in the neoadjuvant setting. The complete response rate was 15% and partial response was seen in 22%.(80)

Prognosis/Surveillance

SEER analyses suggest 5-year survival improved over time from 49.6% between years 1973 and 2006 to 63.8% between years 1973 to 2013. (65,81) SNAC appears to have improved survival outcomes compared with SNSCC. The 5-year disease-specific survival (DSS) is 63% for SNAC, which is higher than 53% for SNSCC. (73) Paranasal sinus involvement, age > 75 years, black race, advanced stage, and high-grade tumors have been identified as poor prognostic factors for patients with SNAC. (73,82) Survival is variable from cure in early stages to poor prognosis in higher stage patients; specific factors that were found to

be significant in a multicenter study by Choussy et al. (75) included the size of the lesion (specifically T4 disease), lymph node involvement, and extracranial extension.

Patients who are at high risk are more likely to have a local recurrence than distant metastases. Therefore patients who undergo treatment should have interval ENT evaluation examination.

Recent or ongoing developments/research

There is a single ongoing study evaluating IMRT and PRT for sinonasal malignancies irrespective of pathology. (58)

Sinonasal Neuroendocrine Carcinoma

Incidence and patient demographics

Like all sinonasal malignancies, sinonasal neuroendocrine carcinoma (SNEC) is exceedingly rare at 2% of sinonasal malignancies. (11) In an analysis of the SEER database, the incidence rate was 0.012 cases per 100,000 in 1986, and 0.0077 cases per 100,000 in 2011. (83) The mean age at diagnosis was 55.8 years, and males were predominant with 60% of cases. The most common site for SNEC in the SEER database was the nasal cavity followed by the ethmoid sinus. (83)

Presentation

Like most sinonasal malignancies, the symptoms at presentation are non-specific. Lower-grade SNEC can be locally aggressive and cause localized symptoms, while poorly differentiated SNECs can metastasize outside the sinonasal cavity and skull base. (84,85) Small cell NEC has been associated with paraneoplastic syndromes causing SIADH, SIADH, and Lambert- Eaton Syndrome. (85)

Pathophysiology

There is no information available about the etiology and pathophysiology of SNEC. This is likely due to the rarity of the disease.

Pathology

Typically, neuroendocrine carcinomas (NEC) show histologic features of neuroendocrine differentiation with patterns comprising nests, ribbons, festoons, glands and rosettes, and solid areas. They also are positive for broad-spectrum keratin antibodies and neuroendocrine markers like CD56/N-CAM (diffuse) with synaptophysin and/or chromogranin (focal/variable) and dense-core, small membrane-bound cytoplasmic vesicles by electron microscopy. (86,87) The 2017 WHO classification of neoplasms of the head and neck identified four different subtypes of SNECs - carcinoid tumor, atypical carcinoid tumor, poorly differentiated neuroendocrine carcinoma of small cell type and poorly differentiated neuroendocrine carcinoma of large cell type. (88)

There is likely a correlation between grade and prognosis in SNEC, though due to low incidence, the evidence is not definitive.(87) Small cell SNEC and large cell SNEC are aggressive with a 5-year survival of patients of 20.8 % and 21.7%, respectively. (89)

There is some similarity in the mutation profiles of aggressive sinonasal SNEC and small cell carcinoma of the lung with mutations of *TP53* and *RBI*, up-regulation of *BCL2* signaling, and activation of *MYC* and *PI3K* pathways. (90) This suggests that additional studies of this rare histologic type are required to better define the mutational landscape of SNEC.

Imaging

Imaging and a staging workup are similar to other sinonasal malignancies. There is no definitive recommendation about the use of Gallium-DOTATATE PET/CT in SNEC but there have been some studies evaluating their utility in low-grade SNEC where there was no radiotracer uptake on FDG PET/CT. (91)

Current treatment

The ideal treatment for SNEC is still unknown. Surgical management is likely appropriate for carcinoid. But there is no consensus among physicians treating higher grade SNEC about the sequencing of surgery, radiotherapy, and chemotherapy. Babin et al (92) developed a protocol using response to induction chemotherapy as a marker of tumor response, and this approach has been validated by other studies showing response to chemotherapy as a sign of favorable prognosis. (84) Chemotherapy utilized included platinum along with etoposide. If there was a good response, or surgery was not possible after 2 cycles, the protocol recommended radiotherapy followed by additional cycles of chemotherapy. If there was a poor response but resection was possible, the recommendation was to proceed with surgery followed by adjuvant radiation and complete 4–6 cycles of chemotherapy. Figure 4 outlines treatment algorithm for the SNEC.

Prognosis and surveillance

The 5-year disease-specific survival (DSS) rate for SNEC ranges from 50 to 70%. Treatment failure can be a locoregional or distant in high-grade SNEC. (83,93) The median overall survival was 32 months. (83) As expected, survival was better for lower grade and stage SNEC. The DSS was longer for primary nasal cavity tumors, followed by maxillary sinus and ethmoid sinuses, possibly due to nasal cavity tumors being symptomatic earlier. (93) The best survival was noted for sphenoid sinuses SNEC, for unclear reasons; this observation may be the result of random error due to the small sample size.

Surveillance of these patients depends on the grade of SNEC. Low-grade SNEC can be followed by ENT examinations, whereas higher-grade SNEC like small cell variant should undergo serial imaging to detect distant metastasis. This recommendation is based on recommendations for small cell carcinoma of the lung, due to a lack of prospective post-treatment surveillance data in patients with SNEC.

Recent or ongoing developments/research

There are no current active clinical studies for patients with SNEC.

Sinonasal undifferentiated carcinoma (SNUC)

Incidence and patient demographics

SNUC is an extremely rare carcinoma that makes up 5% of all sinonasal malignancies.(11) It was first described in 1986 as a highly aggressive carcinoma of the nasal cavity and paranasal sinuses that originates from the Schneiderian epithelium or nasal ectoderm. This pathologic diagnosis originated from a small case series of eight patients diagnosed between 1975 and 1985. (94) Since the original description, 318 total cases were documented from 1973 to 2010 in the SEER Program, with an approximate annual incidence rate of 0.02 per 100,000. There was a higher incidence in males than females (0.03 vs 0.01 per 100,000 per year). (95) The median age at which patients present is 50–60 years. (96) Overall, SNUC has become somewhat of a catchall diagnosis for all undifferentiated sinonasal malignancies. (97)

Pathophysiology

The risk factors and etiology of SNUC are still unknown. Possible associations with tobacco use and with certain environmental/work exposures have been reported. Seven of the eight patients in the original 1986 paper by Frierson et al. had prior exposure to tobacco (no median pack-year history available). One worked in the coal industry, and another worked in the chrome plating industry and was exposed to sulfuric acid, chromic acid, nickel, zinc, copper, and metallic dust. (94) Nickel refinery workers (98) and softwood exposed furniture workers may also be at a higher risk. (99)

There is controversy surrounding other potential risk factors associated with SNUC, particularly the role of Epstein-Barr virus (EBV). One study by Lopategui et al (100) identified EBV RNA in seven of the eleven SNUC patients from Asia but none of eleven Western SNUC patients. However, a subsequent study of 36 SNUC patients from Taiwan (where EBV is endemic) found no SNUC patients with EBV. (101) Additional studies failed to confirm any association between EBV and SNUC. (102)

Clinical presentation

One systematic review of 140 patients reported that patients presented with common symptoms like nasal obstruction (20.0%), epistaxis (17.1%), diplopia or other visual symptoms (15.0%), or headache (12.1%). Since these are generally aggressive tumors, orbital involvement was seen in 42.9% of patients. (103) In a retrospective study of TNM stage at diagnosis in 128 patients, the majority met the criteria for Stage IV disease (72.9%). Common sites of metastases include bone, cervical lymph nodes, lung, brain, and liver. (103–107)

Pathology

Grossly, SNUCs present as a large, fungating tumor with poorly defined margins. They are locally aggressive tumors invading surrounding structures and lead to bone destruction.

There is a high risk of regional and distant metastasis – with the rate varying from 5–16% of regional and 20–30% of distant metastasis. (108)

Histologically, as their name implies, SNUCs are truly undifferentiated as they lack any clear lineage pattern by histology and immunophenotyping, and is a diagnosis of exclusion. (109) It lacks S-100 but expresses certain epithelial type cytokeratins like CK 7, 8 and 19. (110) The cells are small to medium-sized, pleomorphic, and arranged in ribbons, sheets, large nests, trabeculae, and an organoid pattern. There is scant cytoplasm, hyperchromatic nuclei, prominent nucleoli, and homogenous chromatin. Further, there may be necrosis, lymphovascular and perineural invasion, and a high mitotic rate. (110,111) There has been an evolution of the definition of SNUC from being a wastebasket for any unclassifiable sinonasal malignancy to a specific entity. (86,112) Figure 5 shows histopathology of SNUC.

Immunohistochemically, SNUC appears to have variable positivity for pan-cytokeratin (anti-cytokeratin monoclonal antibodies 1 and 3 (AE1/AE3)), low molecular weight cytokeratin (CAM 5.2), and cytokeratin 8 (CK8). There was a suggestion of association with *p16* and *KIT* (CD117), however, this has been questioned. Wadsworth et al. (113) postulate that p16 may simply be the epithelial tract staining that can be seen normally in sinonasal tissue and not truly indicative of SNUC, as there was absence of HPV DNA expression. (114) Further, Chernock et al. (115) did not find any activating mutation nor gene amplification that led to the expression of *KIT* in SNUC. There was no reactivity seen with CK5/6, p40, HER2/neu, (116), lymphoma markers (CD45), sarcoma markers (CD99, desmin, and myogenin), and melanoma markers (MelanA and HMB45). Finally, there may be some expression of neuroendocrine markers like NSE, CD56, synaptophysin, and chromogranin; however, Thompson et al (117) states that there is no corresponding neuroendocrine morphology.

Takahashi et al. (118) performed a gene expression analysis between SNUC and SNSCC and found 7 genes related to DNA repair, synthesis, and cell division that completely distinguished between the two entities. The genes with greater expression in SNUC were *CLCA2*, *ARID2*, *MAP1LC3A*, *SMAD4*, *HELLS*, *MAPKAPK5-AS1*, and *KRT16*; *CLCA* was the most differentially expressed between the two groups. SNUC has been linked to somatic mutations in *SMARCB1* (*INI-1*), *SMARCA4* (*BRG1*), and isocitrate dehydrogenase 2 (*IDH2*). (119) Both *SMARCB1* (on chromosome 22q11.2) and *SMARCA4* (on chromosome 19) genes encode for subunits of the SWItch/Sucrose Non-Fermentable (SWI/SNF) protein complex, which regulates transcription and chromatin remodeling. (120) *SMARCB1* deficiency was seen in nine of 142 (6%) cases in a study by Bishop et al. (121) and only a total of 89 cases of *SMARCB1* deficiency have been reported thus far. (122) *SMARCA4* deficiency was seen in ten patients in one study by immunostaining. (123) *IDH2 R172X* mutations have also been associated with SNUC. Mito et al. (124) found ten of sixteen (62.5%) SNUC cases with *IDH2* mutations, Jo et al. (125) found six of the eleven cases (54.5%) on targeted next-generation sequencing, and Dogan et al (126) found variants in 14 of the 17 analyzed cases (82.4%) of SNUC. In their study, Dogan et al. studied 12 *IDH2*-mutated cases and found co-existing *TP53* mutations in five cases (41.7%), *CDKN2A/2B* loss-of-function in four (33.3%), *MYC* amplification in four (33.3%), and *SETD2* mutations in three (25%). (126,127)

Imaging

Imaging typically shows a large mass with local invasive growth. On CT imaging, SNUC tumors are noncalcified and can lead to sinus obstruction. On MRI, signal intensity was found to be isointense to muscle on T1- weighted images, iso- to hyperintense on T2, and heterogeneous enhancement was seen with gadolinium. (128) Figure 6 demonstrates an MRI with local invasion of SNUC into the base of the skull.

Staging for SNUC uses either the American Joint Committee on Cancer or the Modified Kadish staging system. The Modified Kadish system places patients in stages from A-D with A being limited to nasal cavity and D being regional or distant metastasis. (129)

Current treatment

Given the aggressive nature of SNUC, and involvement of the brain or eye, treatment can be quite difficult. A multimodal approach is typically favored incorporating surgery and radiation therapy with or without chemotherapy. (130) Patients treated with all three modalities had better outcomes when the dose of radiotherapy was 60 Gy. (131) In one meta-analysis, locoregional control with trimodality therapy was 63.9% as compared to bimodality regimens 49.2% and surgery alone at 31.3%. (132) However, in another meta-analysis comparing survival, trimodality was not superior to double modality treatment but combination therapy was still superior to single modality. (133)

There is no clear curative treatment for patients with SNUC. Case studies and retrospective studies help formulate the acceptable treatment options available for SNUC. Surgical resection remains a major component of treatment along with radiation therapy and chemotherapy. Previously, the gold standard was open craniofacial resection, with coronal or transfacial incisions and craniotomy, which has been replaced by endoscopic endonasal or craniofacial resection. (129) Radiation therapy is a critical component in the treatment of SNUC leading to improved survival. (134) Within radiation, intensity-modulated radiotherapy (IMRT) of at least 60 Gy as compared to conventional radiotherapy (CRT) was associated with improved overall survival, decreases toxicities, and improved 3- year recurrence-free survival. (130,135)

Finally, systemic chemotherapy is almost always included as part of the therapy regimen. Typically, cisplatin, etoposide, 5-FU, docetaxel, and paclitaxel are employed. The optimal sequence of these treatments is unclear but Amit et al (136) used induction chemotherapy to guide further management of SNUC in 95 treatment-naïve patients. In this study, patients first received platinum-based doublet regimen: cisplatin (60–80 mg/m² on day one) followed by etoposide (100 to 120 mg/m²) or docetaxel (75 mg/m²) on days 1–3, every 21 days for one-five cycles (median three) prior to locoregional therapy. Response to this regimen was used to prognosticate patients, and further develop plans. As per their observation, patients with favorable responses to induction therapy did better than those with unfavorable responses. Patients who had a favorable response who were treated with combination chemoradiotherapy did better than patients who underwent surgery followed by adjuvant radiotherapy with or without chemotherapy. The hypothesis for this observation is that surgery might delay definitive radiotherapy which these patients need. Moreover,

patients who had an unfavorable response to induction chemotherapy did better with surgery compared to definitive chemoradiation. Figure 7 summarizes recommendations on the management of SNUC.

Prognosis and surveillance

SNUC is an aggressive malignancy that confers a poor prognosis. These cancers tend to be locally recurrent and frequently metastasize leading to morbidity and mortality. The SEER database showed a median survival of 22.1 months, with a 5-year survival rate of 34.9%. (95)

Data on prognosis and survivorship varies considerably. 5-year survival estimates vary from 6.25% to 74% in different series. Five-year survival rates following surgery, radiation, or combination of surgery and radiation were 38.7%, 36.0%, and 39.1%, respectively. (95)

The evidence-based recommendations for post-treatment surveillance are limited by the rarity of the disease and poor overall survival. We recommend surveillance with multidisciplinary follow-up for treated patients.

Recent or ongoing developments/research

Currently, ongoing studies are exploring the use of proton beam therapy for SNUC. In one multi-institutional study by Yu et al, (137) 69 patients underwent either uniform scanning or pencil-beam scanning PBT with a median dose per fraction of 2.0 Gy and found this to be a safe, equivalent, and possibly less toxic option than even IMRT.

Other strategies include the use of RADPLAT, which refers to radiation followed by intra-arterial infusion of cisplatin and thiosulfate. Noticewala et al (138) proposed this given the success of the strategy in other similar head and neck cancers (HNC). Elective neck treatment (irradiation or lymph node dissection) for patients with clinically node-negative disease leads to a lower risk of regional recurrence (OR 0.38 and 95% CI 0.25–0.58) compared to observation alone; however, the impact on overall survival is not clear. (139)

Primary Mucosal Melanoma

Incidence and patient demographics

Primary Mucosal Melanoma (PMM) is a rare disease and accounts for 0.03% of all cancer diagnoses. (140) Only 1.3% of all melanomas originate in the mucous membranes, but 70% of mucosal melanomas originate in the head and neck, with an increasing incidence over time. (141–143) The most common head and neck sites of origin for PMM are the nasal cavity and paranasal sinuses, followed by the oral cavity. (144) Between 1988 and 2010, the SEER database has 924 cases of head and neck PMM, of which 50% were nasal, 24% were sinus, 22% were oral and the rest were pharyngeal. (145)

For epidemiological purposes, most studies have considered all mucosal melanomas as one entity, including anogenital and vulvovaginal MM. The overall incidence is known to be 2.3 per million, which is significantly lower than for cutaneous or ocular melanoma. (145) The average age of patients diagnosed with PMM is 70 years, compared with 65 years for

cutaneous melanoma. (146,147) The incidence increases exponentially with age without a plateau, and with no gender difference.(145) Like cutaneous melanoma, PMM is also more common in Caucasians, but these represent a smaller proportion of all melanomas than in other racial groups, due to a greater incidence of cutaneous melanoma in Caucasians.

Pathophysiology

The etiology and pathogenesis of PMM are unknown, and its association with pre-existing mucosal nevi is controversial. PMM is not related to racial pigmentation or sun exposure, unlike the more common cutaneous melanoma. (140,148) It has been conjectured that the close anatomic proximity of all the common sites in the head and neck region may reflect an embryological predisposition to PMMs. There is also speculation that PMM arises from pigment producing cells and Schwann cells found in the mucous membranes. (149) In addition, like other sinonasal malignancies, inhaled and ingested carcinogens may be linked to the pathogenesis of sinonasal, pharyngeal, and laryngeal PMMs, but these claims have never been confirmed with robust studies. (150–152)

Presentation

In addition to sinonasal symptoms, a pigmented lesion might be seen on ENT examination when patients present with symptoms. Rarely, a non-pigmented lesion may be seen. (153) These macules are asymmetric and irregular which differentiates them from melanosis.

Pathology

On histopathology, since PMMs usually present at advanced stages, they are seen as nodular neoplasms rather than as flat in situ lesions. (140) When PMM cells contain melanin, the histological diagnosis is straightforward, and can be confirmed using immunohistochemistry. When melanin is scarce or absent, then immunohistochemistry is required to make a diagnosis. PMMs commonly express S-100 protein and melanocytic markers, including MART-1/Melan-A, tyrosinase, HMB-45, and MITF. (154) In Figure 8, H&E-stained sections of a sinonasal melanoma show sheets of pigmented tumor cells, as well as intermixed lymphocytes.

The molecular mechanisms that cause PMM are still largely unknown. The understanding of molecular pathways leading to malignant transformation of melanocytes will lead to more specific and successful therapies. (140) Notably, an increased frequency of *c-KIT* aberrations in PMM compared to cutaneous melanoma is shown in multiple studies. (155–160) These aberrations can be either somatic mutations or overexpression of unmutated *KIT*, which regulates the activity of MITF (microphthalmia-associated transcription factor) which is essential for melanogenesis and melanocyte function. (161) *MITF* can also be amplified in cutaneous melanomas, especially in the head and neck. (162)

While the discovery of *BRAF* mutations led to the successful development of BRAF inhibitors for the treatment of cutaneous melanoma, their role in PMM is limited due to a low prevalence of these mutations. *BRAF* mutations are seen in less than 10% of PMM cases, and while the incidence in sinonasal tract PMM is unavailable, the number is not believed to be high. (155,156,163,164) Another common genetic alteration in cutaneous

melanoma is inactivation of the *CDKN2A* locus, which encodes the tumor suppressor protein *p16/INK4A* which is known to cause familial cases of melanoma, unrelated to sun exposure. (140,165) While 50% of PMMs were associated with loss of p16 expression, *CDKN2A* mutations, and/or loss of heterozygosity for *CDKN2A*, these abnormalities do not confer a worse prognosis in PMM, unlike in cutaneous melanoma. (158,166–170)

Imaging

MRI of PMMs exhibit low-signal intensity on T2-weighted images and enhancement on precontrast T1-weighted images. (140) In addition, since melanoma has high fluorodeoxyglucose (FDG) avidity, PET/CT plays an important role in staging these patients. In Figure 9, a PET-CT shows nodal metastasis in a patient after resection of primary sinonasal melanoma.

Staging of these tumors remains challenging, and there are multiple ways to stage the disease. (9,140) The American Joint Committee on Cancer (AJCC) staging for head and neck mucosal melanoma (mmTNM) is available and did not exist before 2010. To account for the aggressiveness of the disease, the primary tumor is designated either T3 or T4 based on the depth of invasion. This is a modification of the TNM staging developed by AJCC for carcinoma of the nasal cavity and sinuses (carTNM). (171,172) Ballantyne (173) described a method of classification where stage I includes localized lesion, stage II includes regional lymph node metastases, and stage III includes distant metastases. Even though this method is simple, it does not account for the depth of invasion of the disease. Prasad et al. (174) proposed another staging system based on the level of invasion of tissue compartments within the mucosa. Level 1 included in situ disease, level 2 included superficially invasive disease invading up to the lamina propria, and level 3 includes deeply invasive melanomas.

In a head-to-head comparison, Michel et al (175) compared survival between 3 staging systems for sinonasal PMMs -- the Ballantyne staging system modified by Prasad, the AJCC mmTNM, and the AJCC carTNM, and concluded that carTNM was the only staging system that significantly correlated with OS ($p = .012$) and DFS ($p = .041$). However, more recently, Gras-Cabrerizo et al. (176) performed a comparison of staging systems and concluded that the correlation between survival and tumor stage was better with mmTNM staging. The AJCC 8th edition recommends this classification system for staging PMM of the head and neck.

Current treatment

Complete surgical resection with uninvolved surgical margins is the mainstay of initial treatment. Patients with positive margins have a 21-fold increased risk of death and decreased survival. (177,178) Like most sinonasal malignancies, negative margins may not be achievable due to the need to preserve vital organs. If there is local recurrence without distant disease, salvage surgery is an option, but there is a significant chance of distant disease in a large majority of patients with local recurrence. Even though surgical resection with curative intent offers the best chance at survival, more than half of the patients ultimately develop distant metastases. (179) Elective dissection of the neck is recommended only in the treatment of non-sinonasal PMMs where lymph node metastases

are more common. In oral PMM regional lymph node metastases is seen in 25% of cases at presentation and in 42% during the course of disease. The rate is only 6% at presentation and 20% during the course of the disease in sinonasal PMMs. (180)

Another topic of controversy is the role of sentinel lymph node biopsy in patients with clinically node-negative disease. Prinzen et al. (181), found sentinel lymph node (SLN) biopsy was an accurate staging tool, and their two SLN biopsy negative patients remained regional or distant disease-free, while two of three SLN biopsy positive patients developed distant metastases within the first year.

Radiation therapy may have a role in the adjuvant setting following surgery, or as primary treatment in patients who are not surgical candidates. In a study by Temam et al (182), postoperative radiotherapy was associated with better local disease-free survival in a historic dataset of head and neck PMMs treated between 1979 and 1997. However, patients who received postoperative radiotherapy developed distant metastasis more rapidly than patients who did not; although this observation is potentially confounded by the fact that patients who received postoperative radiotherapy had more locally advanced tumors than those who did not. This association was also noted in other retrospective studies. (183,184) A systematic review of the published literature showed a moderate survival benefit of postoperative radiation most likely due to reduced local recurrence. (185) Most experts agree that patients with a high risk of local recurrence, including patients with extracapsular disease, two or more lymph nodes involved, large nodes (3 cm or more), positive or close margins, or patients with residual disease, should receive postoperative radiotherapy. (186) A retrospective analysis by Moreno et al. (187) showed that patients with a total dose of 54 Gy or more had a lower recurrence rate compared to patients who had a total dose of 30–50 Gy. They also found that standard fractionation was associated with a lower locoregional failure rate compared to hypofractionation.

There have been very few clinical studies on systemic treatments for advanced head and neck mucosal melanoma patients, and the treatment of these patients is based on small case series. These few studies have failed to show a significant survival benefit with chemotherapy. (180) Older studies report response to chemotherapy in 7 of 15 patients with use of different combination regimens that included interferon alpha-2b, interleukin-2, cisplatin, vinblastine, dacarbazine, and/or temozolomide. The median time to progression for these patients was 10 months, and the median overall survival was 22 months. (188) A more recent study concluded that adjuvant chemotherapy with temozolomide and cisplatin resulted in lower risk of relapse and metastasis in resected mucosal melanoma when compared to high-dose IFN-a2b. (189)

Like cutaneous melanoma, immune checkpoint inhibitors are being used for the treatment of metastatic PMMs. Studies by Shoushtari et al (190) and Moya-Plana et al (183) have demonstrated an ORR of 23% and 20%, respectively. In another post hoc analysis of KEYNOTE-001, 002, and 006 evaluating the outcomes of pembrolizumab in mucosal versus non-mucosal melanomas, the ORR in mucosal melanoma patients was 19% in contrast to non-mucosal melanoma patients with an ORR of 33%. The median OS for these patients was 11.3 months. The lower response rate in PMMs could be because of

lower PD-L1 expression. (192) CheckMate 067 explored 5-year outcomes of melanoma, and a subset analysis of 79 mucosal melanoma patients showed poorer long-term efficacy in comparison to patients with cutaneous melanoma. The study also noted that the combination of nivolumab and ipilimumab was superior to single agent nivolumab or ipilimumab. (193)

In addition, PMMs also have a lower prevalence of BRAF and NRAS (12%) mutations which limits the use of BRAF kinase inhibition treatment. PMMs have demonstrated increased c-KIT aberrations. Curtin et al (155) found 21% of patients with PMMs carry KIT mutations, and 61% overexpress c-KIT, supporting the use of imatinib as a therapeutic option in patients with c-KIT driven PMM. Beadling et al reported similar mutation profiles (194) with only 15.6% of patients with PMM having a c-KIT mutation and 26.3% having increases in copy number. Hodi et al (195) conducted a multicenter phase II study of imatinib in metastatic mucosal, acral, or chronically sun-damaged melanoma with c-KIT aberrations, and they concluded that imatinib is effective in tumors harboring KIT mutations, but not in tumors with KIT amplification only. They found a significantly different disease control rate between patients with wild type or mutant KIT, in favor of patients with KIT-mutant melanoma, but no statistical difference in overall survival. Current American Society of Clinical Oncology (ASCO) guidelines recommend enrolling patients in a clinical study if available, otherwise, using the treatment guidelines of cutaneous melanoma. (196) Figure 10 summarizes recommendations on the management of PMMs.

Prognosis/Surveillance

The median survival for sinonasal PMMs is 26 months, with a 5-year survival rate of 22%. (197) Even when matched for stage at diagnosis, the prognosis of PMM is significantly worse than cutaneous melanoma. Most patients with PMMs of the nasal cavity have localized disease, whereas PMMs in the paranasal sinuses are usually more advanced, which confers a less favorable prognosis for the latter site. (187,198) Ethmoid and maxillary sinus PMMs have the worst prognosis amongst all sinonasal PMMs because of frequent infiltration into the skull base, orbit, or facial tissue and thus, the difficulty to obtaining clear surgical margins. (199)

Only 10–20% of sinonasal PMMs have cervical lymph node metastases at presentation, and less than 10% have distant metastases. (140) But over time, an additional 20% can develop nodal metastases, and 40–50% develop distant disease in the lungs, brain, bone, and liver. (200) PMMs are also characterized by early and repeated recurrences. (140) Stanimirov Rossi et al (201) described two different types of sinonasal PMMs- unilocular and multilocular, and the latter were associated with an unfavorable disease-free survival.

These patients need surveillance in accordance with patients with cutaneous melanoma, in addition to local examination of the ear, nose and throat.

Recent or ongoing developments/research

Most clinical studies that include patients with metastatic mucosal melanoma are basket studies in which patients with Stage IV disease are enrolled irrespective of primary tumor site, based on biomarkers suggesting response to a particular regimen. The role of neoadjuvant immunotherapy is being investigated due to the high rates of systemic relapse

even when negative margins are achieved. (191) There is one trial investigating neoadjuvant chemotherapy in head and neck mucosal melanoma ([NCT 03313206](#)). (202)

The majority of clinical studies of mucosal melanoma are based in China due to the high prevalence of acral and mucosal melanoma in this region. Currently, several clinical studies are investigating neoadjuvant and adjuvant therapies in mucosal melanoma. (202–204)

Nuclear protein in the testis (NUT) Carcinoma

Incidence and patient demographics

Nuclear protein of the testis (NUT) carcinoma, previously known as NUT midline carcinoma (NMC) was first identified in 1991 as a thymic carcinoma with a unique chromosome translocation at t(15;19) (q15;p13) not seen in thymic carcinomas. (205) Initially, the name NMC was used given because that carcinoma was typically found in midline structures (mediastinum, head, and neck). (206) However, as more anatomic structures outside of the midline became involved, the nomenclature has shifted away from NMC to NUT carcinoma, as per the World Health Organization's classification. (207)

The exact incidence of NUT carcinoma in the head and neck is unknown. Lee et al (208) have found a total of 105 reported cases of NUT since the first case was reported in 1991. Among head and neck cancers, which collectively refers to all cancers of the oral cavity, salivary glands, larynx and pharynx as well as nasal cavity and paranasal sinuses, NUT has an unclear prevalence rate, ranging from 1.9% to 17.9% of undifferentiated carcinomas of the head and neck. Lee et al (208) examined immunohistochemical and histological features in 362 cases previously classified as poorly differentiated or undifferentiated carcinomas of head and neck origin and found the prevalence of NUT carcinoma to be 2.9% among poorly differentiated carcinomas and 12.5% among undifferentiated carcinomas. The location was predominantly in the sinonasal tract (73.4%), followed by the larynx (7.3%), pharynx (4.6%), salivary gland (11.0%), and finally oral cavity (3.7%) (208) However, there have been reports of NUT carcinoma originating at other anatomical sites including the pelvis (209), kidney (210), larynx, maxillary gingiva, orbital cavity (211), lung (212), pancreas (213), and bone (214).

Patients can present with NUT at any age (0.1– 81.7 years) with a female predominance (1.5:1). (215) In one study of 119 patients, the median age was found to be 23 years (216) similar to other studies reporting a median age of 17.6– 25 years. (217,218)

Pathophysiology

These aerodigestive carcinomas, are associated with chromosomal rearrangement of the nuclear protein in testis midline carcinoma family member 1, also known as *NUTM1* or *C15orf55*, located on chromosome 15q14. Two case reports from 1991 (one in a 22-year-old and the other in an 11-year-old female) detailed the translocation at t(15;19)(q14;p13.1). (219) This translocation leads to the formation of a 6.4-kb fusion oncogene, between *NUT* and bromodomain protein family member 4 (*BRD4*) creating the chimeric-gene (*BRD4-NUT*) where exon 11 of *BRD4* fused to exon 3 of *NUT*. This fusion is seen in nearly two-thirds of all NUT cases. *NUT* may also fuse to other bromodomain members, including

BRD2, *BRD3*, and *BRDT*. About one-third of fusions will involve *BRD3*. (220) There are other (less frequently seen) fusion partners including the Zinc Finger-Containing Proteins (*ZNF532* and *ZNF592*), MAX Dimerization Protein 4 and 1 (*MGA*, *MXD4*, and *MXD1*), CCL6 Corepressor Like 1 (*BCORL1*), Nuclear Receptor Binding SET Domain Protein 3 (*NSD3*), (221) and Capicua Transcriptional Repressor (*CIC*). (222)

NUT is expressed in the testis, but the exact function of the gene is unclear. Bromodomains are key players in transcription, histone acetylation, and chromatin remodeling. (223) The fusion of BRD and NUT leads to uncontrolled cell growth and restricts epithelial differentiation via transcription suppression and histone hypoacetylation. The NUT portion of the complex binds to p300, a specific histone acetyltransferase (HAT), to chromatin and propagates the formation of megadomains that are actively transcribed. These megadomains then express specific oncogenes. (224–226) There is also acetylation of p53 via this pathway (binding of p300), and thereby suppression of TP53. (227)

Unlike other HNCs that have possible associations with certain environmental factors, there are currently no identified exposures (including smoking) that have been linked with NUT. Furthermore, there has been no link seen between NUT and EBV or HPV. (227,228)

Presentation

The malignancy often affects midline structures, and in the sinonasal cavity, it can present with sinonasal symptoms. (229) More local symptoms can occur as other structures are also involved. Typically, patients will present at more advanced stages and therefore will have metastases to lymph nodes, bone, or pleura. (230)

Pathology

Routine hematoxylin and eosin histopathology alone cannot reliably diagnose NUT carcinoma as there is no distinguishing feature and it is frequently mistaken for other undifferentiated or poorly differentiated carcinomas. (222) Cells are small to medium-sized and monomorphic, with indistinct to clear cytoplasm, prominent nucleoli, and areas of abrupt squamous differentiation. There may be areas of spindled cells and keratin pearls. Given the aggressive nature of NUT, there are also vast areas of necrosis. (231) Given the gene fusion, the diagnosis can be made using fluorescence in situ hybridization (FISH), reverse-transcriptase polymerase chain reaction (RT-PCR), or next-generation sequencing (NGS). FISH is superior to RT-PCR as it can detect all variants, whereas RT-PCR can only detect BRD-3 or BRD4-NUT tumors. (218)

Stelow (231) found most NUT carcinomas to be immunoreactive with antibodies to p63, CK20, and sometimes CD34. Finally, the diagnosis can also be made via immunohistochemistry with a novel rabbit monoclonal antibody (C52B1) to NUT, which has a sensitivity of 87% and a specificity of 100%. (232)

Imaging

Bair et al (233) outlined that NUT appears to be a hypoattenuating heterogeneously enhancing infiltrative mass with poorly defined margins on CT. It has also shown necrosis

and calcification along with invasion into adjacent structures, with a predilection for central airways and vascular structures. On MRI, a heterogeneous mass with predominantly hypointense signal on T-1 weighted images and hyperintense on T-2 weighted images has been described. FDG PET/CT is recommended to evaluate for metastatic disease. Figure 11 shows MRI and PET imaging of the brain in a patient with NUT midline carcinoma with brain invasion and retropharyngeal adenopathy.

Current treatment

Currently, there is no gold standard treatment for NUT carcinoma. Mainstay remains surgical resection, radiation therapy, and possibly chemotherapy. (234)

Surgery is frequently the first line for resectable disease as it is associated with both improved progression-free survival and overall survival. Chau et al. found that surgery with or without postoperative chemoradiation or radiation were critical components in overall survival. The study also found that chemotherapy or radiation therapy alone was insufficient. (215)

Chemotherapy options for NUT include monotherapy or combinations including 5-fluorouracil, actinomycin D, bleomycin, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, etoposide, gemcitabine, ifosfamide, S-1, vinblastine, vincristine, and vinorelbine. (216) Case reports have found some benefit when using alkylating agents, cisplatin, and taxanes. (220) There are no head to head comparisons between agent and combinations.

Finally, there has been some development in the utilization of targeted histone deacetylase inhibitor (HDACi) therapy. As previously mentioned, the BRD-NUT fusion protein leads to hypoacetylation and thereby transcription repression. HDACis work to reverse that process. Schwartz et al. have found promising results in xenograft models with growth inhibition and survival benefits. Two HDACi are approved by the Food and Drug Administration (FDA) - romidepsin and vorinostat. In one study, vorinostat induced squamous differentiation and growth arrest in a ten-year-old with NUT carcinoma. The therapy had to be discontinued due to thrombocytopenia.(225) In another case report, vorinostat induced a decrease in lymphadenopathy and tumor lesion, but again, was discontinued due to thrombocytopenia. (235)

Prognosis/Surveillance

Prognosis is poor with median survival time from diagnosis estimated at 6–7 months. (236) In one retrospective review of 48 cases, median progression-free survival was estimated to be 6.6 months (range of 4.7– 8.4) and median overall survival was 9.7 months (range of 6.6– 15.6). (215) Another review of 54 patients found median survival to be 6.7 months, with a two-year PFS of nine percent, and two-year overall survival to be nineteen percent. (237) Chau et al (238) performed a retrospective review of all known cases of head and neck NUT carcinoma and found 40 patients. They found no statistically significant difference in PFS or OS by age, gender, tumor location, size, histology, presence of neck lymph node involvement, or *BRD4-NUT* translocation. However, they did find that presence of distant metastasis was associated with 2-year PFS and 2-year OS of 0%. Contradicting the

results though, French et al (217) found that individuals with non BRD4-NUTM1 fusions (BRD3-NUTM1 or NSD3-NUTM1 fusions) have a better prognosis, independent of the extent of metastatic disease.

Recent or ongoing developments/research

There has also been some discussion about the utility of BET inhibitors in NUT carcinoma. These work by binding to the acetyl-lysine binding pocket of BD1 and BD2, or the bromodomain that all BET proteins contain. JQ1, a thieno-triazolo-1,4-diazepine, is one of the earliest BETi that works to accelerate squamous differentiation and inhibit the cellular proliferation driven by BRD4. (239) Using mouse xenografts, Beesley et al. found that the efficacy of JQ1 on NUT carcinoma might depend on the presence of a BRD4 translocation. (240) Similar results have been seen for Birabresib in mice, with a success rate of 79% tumor growth inhibition in one study. (241) In one Phase Ib study using Birabresib, three of ten patients achieved a partial response to the therapy. These treatments carry toxicities including anorexia, diarrhea, headache, fatigue, nausea, and thrombocytopenia. (242) Another BRDi, Molibresib, was evaluated in 19 patients with NUT carcinoma in a phase I study and showed no complete responses and two (11%) confirmed partial responses. (243) Likely, these BET inhibitors will need to be used in combination with other agents.

There is one current study for patients with NUT where a novel BET inhibitor, ZEN003694, is being used in combination with etoposide and cisplatin ([NCT05019716](#)). (244)

Extranodal NK/T cell lymphoma

Incidence and patient demographics

Extranodal NK/T Cell Lymphoma (ENKTCL) is another rare malignancy, accounting for 3% of T-cell lymphomas in USA, Canada, and Europe with higher incidence seen among Asian Pacific Islanders or people of Hispanic ethnicity. (245) ENKTCL is even more common in East Asia and Latin America representing 15% and 13% of all T-cell lymphomas, respectively. (246)

Data from 797 patients with ENKTL patients from SEER was reported between 2001 to 2014, the median age at diagnosis was 53 years, and males tended to be younger at diagnosis. The annual incidence rate of the disease in the US was 0.07 per 100,000. (247) As expected from international data, the incidence was higher in US Hispanics with a recent incidence of 0.16 per 100,000. The malignancy most commonly presents with disease in the head and neck, with 52.6% cases in the nasal cavity and the sinuses, followed by 15.3% in the upper aerodigestive tract.

Pathophysiology

Although the exact pathogenesis of ENKTCL is unclear, EBV has been implicated in association with this disease entity across all ethnic groups. (245) Possible mechanisms include EBV-infected NK cells and their microenvironment producing IL-2, IL-9, and IL-10 to promote proliferation and overexpression of the latent membrane protein 1 (LMP1) which

is oncogenic. (248,249) Another plausible mechanism is activation of NF- κ B pathway that inhibits apoptosis and thereby increases the survival of cells. (246,250)

Presentation

The most common presentation is nasal obstruction due to chronic rhinosinusitis, followed by ulcerative necrosis of the upper aerodigestive tract and the face. Most patients have localized disease (Ann Arbor Stage I/II) with rare cases of disseminated disease, and the majority lack B symptoms. (251)

Pathology

The diagnosis of ENKTCL is confirmed by biopsy. Histopathology shows an atypical lymphoid proliferation with an angiocentric pattern, and angiodestruction. (246) Most cases are positive for CD2. Cytoplasmic CD3, CD56, cytotoxic granules (granzyme-B, TIA-1) indicate NK cell origin. In addition, CD4, CD8, T-cell receptors (TCR) are expressed variably. (251) Figure 12 shows H&E and several immunostains of a biopsy of from a patient with ENKTL. Positivity for LMP-1 immunostains is also necessary to confirm the diagnosis and may help to differentiate it from other T-cell lymphomas, which are EBV negative. (246,251) Plasma EBV DNA measured with RT-PCR is also associated with tumor load and serial EBV DNA monitoring is used to assess response and detect recurrence. (252,253)

There likely is a role of somatic mutations in the pathogenesis of ENKTCL. Activating *JAK3* mutations are seen in 35% cases, in addition to *STAT3* and *STAT5B* mutations. (254,255) In addition, mutations of the *DDXX3X* gene have been identified which participates in RNA translation initiation and assembly in ribosome and spliceosome. (256) Deletions in tumor suppressor genes such as *TP53*, *PRDM1*, *FOXO3*, and *HACE2* have been noted in some cases of ENKTCL. (256–258) Some studies have correlated environmental exposures and socioeconomic status with the risk of developing ENKTCL. (246)

Imaging

CT or MRI are acceptable to define the local extent of disease, but for sensitive detection of metastases, a PET/CT should be performed. (252) Figure 13 below shows an MRI of nasal NK/T Cell lymphoma. Bone marrow involvement is uncommon, but aspirate and biopsy can be considered for evaluation, though PET/CT may also be able to detect bone marrow disease. (259,260)

Current treatment

The treatment of ENKTCL is based on retrospective studies and phase II studies. For localized disease, radiotherapy with chemotherapy is considered the standard of care. Radiotherapy by itself has been associated with a higher relapse rate, and the addition of anthracycline therapy to radiotherapy did not result in improvement of survival outcomes. (261,262) This poor response is thought to be due to NK-cells expressing very high P-glycoproteins concentrations causing a multidrug resistance (MDR) phenotype. (263) Therefore, non-MDR-dependent drugs have been used in treating NK/T cell lymphomas.

Kim et al (264) compared concurrent chemoradiotherapy with cisplatin followed by VIDP chemotherapy to dose-intensified CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) followed by radiotherapy, and found significantly improved OS and PFS with the concurrent chemoradiotherapy regimen. This was also studied by Yamaguchi et al. (265) where they found that concurrent radiotherapy and 3 courses of dexamethasone, etoposide, ifosfamide, and carboplatin produced improved survival compared with CHOP. L-asparaginase was found to be effective for relapsed/refractory NK/T-cell lymphomas, after which its use up front was investigated in many studies, with radiotherapy sandwiched between infusions. (266) The different regimens studied were LVP (l-asparaginase, vincristine, and prednisolone), with an ORR of 89% and CR rate of 81%, GELOX (gemcitabine, l-asparaginase, and oxaliplatin) with an ORR of 96% and CR rate of 74%, and SMILE (dexamethasone, methotrexate, ifosfamide, l-asparaginase, and etoposide) with an ORR of 90% and CR rate of 69%. (267–269) SMILE was associated with treatment-related mortality of 7%. (269) L-asparaginase has been associated with allergic reactions including anaphylactic shock, and Erwinia asparaginase can be used as an alternative. (252)

For advanced-stage or relapsed/refractory NK/T-cell lymphoma, combination chemotherapy remains the treatment of choice. The SMILE regimen used for these patients showed an ORR of 80%, 93%, and 25% in stage IV, relapsed, and primary refractory diseases and CR rate of 40%, 64%, and 0% after 2 cycles. (270) Another regimen used for patients with refractory/relapsed disease was AspaMetDex (l-asparaginase, methotrexate, and dexamethasone) with an ORR and CR rate of 78% and 61%, respectively. Once remission is achieved, these patients might benefit from allogeneic hematopoietic stem cell transplant, but prospective data is not robust. (271) Figure 14 details a treatment algorithm for patients with ENKTL.

Prognosis/Survivorship

The survival of patients with ENKTCL is relatively poor with a median OS of 20 months after diagnosis, but it varies significantly based on the stage of disease, age, and nodal disease site. (247) the overall survival (OS) was reported to be around 42% while the 5-year progression-free survival (PFS) was only 29%. (272) A prognostic index for patients with ENKTL was developed using retrospective data called prognostic index for natural killer cell lymphoma (PINK). (273) Four independent risk factors are incorporated: age greater than 60 years, stage III/IV disease, distant lymph-node involvement, and non-nasal type disease. The patients were stratified into low-risk (no risk factors), intermediate-risk (one risk factor), or high-risk (two or more risk factors) groups. Low, intermediate, and high-risk groups had a 3-year OS of 81% (95% CI 75–86), 62% (95% CI 55–70), and 25% (95% CI 20–34), respectively. In the same study, 328 patients had EBV DNA levels available, and a score called PINK-E was developed. Low (zero or one risk factor), intermediate (two risk factors), and high risk (three or more risk factors) were associated with an OS of 81%, 55%, and 28% respectively.

Disease surveillance uses plasma EBV DNA titers from RT-PCR, along with symptom-guided imaging. There are no guidelines on duration or frequency of surveillance but there have been late relapses reported up to 29 years after initial remission. (274) Thus, lifelong

surveillance is recommended. These patients with late relapses have a prognosis similar to primary ENKTL, rather than relapsed/refractory disease. (275)

These patients face significant compromise in quality of life with radiation in the head and neck region, in addition to long-term toxicity from chemotherapeutic agents used in treatment. In addition, they are at increased risk of the development of treatment-related acute myeloid leukemia. (247)

Recent or ongoing developments/research

There are abundant clinical studies available for patients with ENKTL. Trials are studies investigating immune checkpoint inhibitors in early-stage disease, with or without other agents. (276–278) HDAC inhibitors such as Chidamide are also being investigated in several studies. (276,279) More studies are investigating newer regimens and combinations for relapsed/refractory ENKTL and advanced ENKTL. (280–285) Table 2 lists selected clinical studies for patients with ENKTL.

Esthesioneuroblastoma (Olfactory neuroblastoma, ONB)

Incidence and patient demographics

Esthesioneuroblastoma, or olfactory neuroblastoma (ONB), is a rare tumor arising from the olfactory neuroepithelium in the sinonasal cavity that extends to the anterior skull base. (286) ONB comprises 2–6% of all sinonasal tumors and affects four people per ten million in the population. (286–288) The estimated incidence is 0.04 per 100,000 people. (286) ONB affects men and women equally and has a bimodal age distribution with peaks in the second and sixth decades.

Pathophysiology

The etiology of ONB is unclear, and no clear genetic or environmental risk factors have been isolated. A case report described the association of ONB with chronic wood dust exposure. (289) Animal studies have correlated ONB development with nitrosamine compound exposure, (290,291) and retrovirus exposure, (292) however, these associations have not been described in humans.

Presentation

Patients with ONB often present with symptoms related to direct effects of the nasal mass. Tumors are often slow growing and local symptoms are most common. (293) Delayed diagnosis is common and is made on average six months after the onset of symptoms (15). (294) Cervical adenopathy due to nodal metastasis may be a presenting symptom in 9–22% of patients with a new ONB diagnosis. (295)

Paraneoplastic syndromes that have been described in ONB cases include Cushing syndrome from ectopic adrenocorticotropin syndrome, (296,297) syndrome of inappropriate anti-diuretic hormone, (297,298) catecholamine secretion induced hypertension, cerebellar degeneration, and clonus-myoclonus-ataxia and humoral hypercalcemia of malignancy. (297)

A nasal exam may not reveal the mass unless endoscopy or imaging is utilized as the tumor can be localized high in the nasal cavity. Upon viewing, the mass may appear as a vascular, gray or red polypoid lesion. Imaging prior to biopsy is recommended to avoid swelling or bleeding from the tumor that may impact imaging findings.

Pathology

Histopathological diagnosis usually follows imaging. There is no specific immunohistochemical marker; however, ONBs are typically positive for S-100, chromogranin, and synaptophysin, and negative for cytokeratin, desmin, vimentin, actin, glial fibrillary acidic protein, UMB45 and common leukocyte antigen. For poorly differentiated tumors, electron microscopy can visualize dense core neurosecretory granules and microtubules, neurofilaments and rare synapses although it is rarely used for diagnostic purposes. There is marked heterogeneity within esthesioneuroblastoma tumors. Pathology may range from low grade, reflecting a more indolent malignancy to rarely, a high-grade tumor representing a highly aggressive cancer. (286,299) Genomic sequencing of ONB tumors is limited, and mutations in *TP53*, *c-kit*, *PDGFR-b*, *EGFR*, *FGF-FGFR1* signaling, Sonic hedgehog pathway; apoptosis-related pathways (*Bcl-2*, *TRAIL*) and neoangiogenesis (*VEGF*; *KDR*) have been identified. (300)

The Hyams grading system is used to grade tumors from I to IV based on pathologic findings such as mitotic activity, preservation or disruption of lobular architecture, necrosis, and presence of rosettes. (301) Grades I and II are considered low-grade lesions and grades III and IV are high grades. Light microscopy on low-grade tumors reveals well-preserved lobular architecture below an intact mucosa, with tumor cells arranged in nests. The tumor cells appear characteristically as small, blue, and round cells consistent with the neuroendocrine origin. In up to one-third of samples a rosette or pseudorosette pattern can be found.(286,302) However, in high-grade ONB, there is often a sheet-like pattern of growth with disrupted architecture. For this reason, high-grade ONB has been challenging to distinguish from other high-grade small cell sinonasal malignancies. The use of immunohistochemistry for high-grade ONB is helpful to distinguish it from neuroendocrine carcinoma, sinonasal undifferentiated carcinoma (SNUC), large cell neuroendocrine carcinoma, mucosal malignant melanoma, rhabdomyosarcoma, Ewing sarcoma/PNET, and other metastatic tumors.(286,302)

Hyams grade has been shown to correlate with prognosis. Median five-year overall survival for low-grade lesions ranges between 56–80% compared to 20–40% for high-grade lesions. (303,304) Analysis of cases from the SEER database data confirmed the prognostic impact based on tumor grade, where a 10-year overall survival of 64–67% was found in low-grade tumors compared to 34–40% in high-grade tumors. (305,306) Figure 15 shows a low-grade ONB with Hyams grade I.

Imaging

CT or MRI shows a characteristic radiographic appearance of a bilobed, or dumbbell-shaped mass at the cribriform plate. (286) Additional imaging is often not indicated unless there are symptoms of distant metastatic disease. If clinical suspicion is present or the biopsy

reveals high-grade features, PET CT or somatostatin receptor-based imaging is used, given olfactory neuroblastomas typically express somatostatin receptors. (307,308) Figure 16 shows DOTATE PET and MRI in a patient with ONB in the right nasal cavity with extension into the right ethmoid air cells and epidural intracranial involvement along the cribriform plate.

There are two staging systems for ONB: the Kadish system and Dulguerov system. The Kadish system was created in 1976 and originally had three stages, and has, since then, been modified to include four stages. In Stage A, the tumor remains in the nasal cavity; in stage B it extends into the paranasal sinuses; in stage C the tumor extends outside of the paranasal sinuses (involving the dura); and staged where regional lymph nodes or distant metastases are present. (304) Most patients present with stage C (53–61%) followed by stage A or B (34–39%), with only 8–9% presenting with stage D. (295,309) Later, the Dulguerov system was created to mirror the tumor, nodes, metastasis (TNM) system used in other malignancies. In this system, tumors range from T1 through T4 with advanced T stages representing more invasive tumors: T1 involves the nasal cavity and paranasal sinuses excluding the sphenoid, T2 extends into the cribriform plate, T3 extends to the orbit and anterior cranial fossa and T4 invades into the brain. Nodal staging is N0 or N1, if cervical lymph node metastasis is present. M0 or M1 reflect if distant metastatic disease is present. (299,310) The Kadish staging system is more commonly utilized given that it preceded the Dulguerov system in creation. (304) There is also no consensus regarding which staging system is a better prognostic tool. Data from two comparative studies have resulted in conflicting findings. (310)

An important consideration is within the Kadish stage C group that includes tumors with dural extension. This subgroup within Kadish stage C with dural invasion has a worse prognosis as dural invasion is a known predictor for recurrence and metastasis. Possibly, in those with dural involvement outcomes may be better predicted with the Dulguerov system. (311,312)

Current treatment

ONB is most often treated with surgery plus radiation therapy given the radiosensitive nature of the tumor and high risk of local recurrence.(313) Surgery alone or radiation alone is typically reserved for those who have a contraindication to combined treatment or, are a poor surgical or radiotherapy candidate. Further, nasal cavity and paranasal sinuses are reportedly difficult sites in which to ensure adequate surgical margins, and so adjuvant radiation is often recommended even after negative margins are obtained. (313) Craniofacial or transfacial approaches are most employed given cranial cavity extension or other local extension. Resection of the ipsilateral cribriform plate, crista galli, overlying dura and olfactory bulb are performed to help reduce recurrence rates. Less favored is the endoscopic rhinotomy approach given high rates of local recurrence but can be considered for a T1 tumor or Kadish A lesion, where the tumor is limited to the nasal cavity. (299,301,314)

In those patients presenting with N1 disease in cervical lymph nodes, treatment most commonly involves surgical resection of the primary tumor and cervical nodes, followed by radiation, if possible, to both sites. (295,315) In the absence of nodal positivity at diagnosis,

elective neck surgery is usually not performed although it may be considered for high-grade disease or tumors that invade the dura. (316,317) If relapse involving the neck occurs later, salvage surgery with or without radiation therapy is performed and is successful in achieving remission in up to one-third of patients.(318)

Radiation therapy is administered adjuvantly after surgery. In theory, tumor shrinkage may be obtained with neoadjuvant radiation and result in a smaller resection, however similar to radiation effects in other malignancies, post radiation changes result in unclear tumor margins and resection becomes challenging. Adjuvant radiation to a total of 55–65 Gy, is used most often using a stereotactic approach to minimize damage to surrounding healthy structures. (319) Other current radiation techniques utilize proton beam and intensity-modulated radiotherapy approaches.(320–322)

Chemotherapy is not typically given outside of palliative intent in distant metastatic disease. Neoadjuvant chemotherapy has been explored, however with unclear benefit. This was described in a series of patients with Kadish stage C disease, defined as tumors extending beyond the paranasal sinuses. These patients were given neoadjuvant cyclophosphamide and vincristine, with or without doxorubicin, followed by neoadjuvant radiation to 50 Gy total then surgery. Five and 10-year overall survival outcomes were similar to other studies of similar stage C disease that did not incorporate chemotherapy. (323) Chemotherapy combinations such as cisplatin and etoposide for high-grade tumors, similar to regimens used in other small cell malignancies are often employed in the advanced stage setting. Other regimens have been used including irinotecan plus docetaxel, and single agent treatments with doxorubicin, ifosfamide, vincristine or temozolomide have also been reported.(324,325)

Systemic treatment for distant or recurrent disease with targeted treatments has been reported. Durable responses have been observed with tyrosine kinase inhibitors such as sunitinib and pazopanib, mammalian target of rapamycin inhibitors, and epidermal growth factor receptor (EGFR) inhibitors. (326) Peptide receptor radionuclide therapy (PRRT), based on somatostatin receptor expression by ONB cells, has been used in later line treatments for progressive disease and described in case reports. (327)

Prognosis/Surveillance

The overall 5- and 10-year survival rates were 62.1% and 45.6%, respectively. (293) Per staging, five-year overall survival rates for Kadish stage A, B and C tumors are 75–91%, 49–71%, and 38–47%. (286,328) Since the introduction of Kadish stage D, the overall mean survival time for patients with stage A disease was 145.6 months (95% CI, 129.0–162.2), 149.5 months (95% CI, 119.0–180.0) for those with stage B disease, 72.5 months (95% CI, 32.3–112.7) for those with stage C disease, and 53.7 months (95% CI, 27.3–80.0) for those with stage D disease. (293) Similarly trending, the overall survival rates at 10 years for patients with stage A disease was 83.4%, stage B disease was 49%; for stage C disease was 38.66%; and for those with stage D disease was 13.3%.

One report noted earlier Kadish stage A conferred a worse 5-year overall survival compared to Kadish stage B, however, this was thought primarily due to lack of adjuvant radiation

therapy and higher number of positive surgical margins in the stage A group. (329) Similarly, outcomes using the Dulguerov system show a higher T category associated with worse five-year overall survival: T1 with 81%, T2 93%, T3 59% and T4 48%. (313) Local and locally advanced ONB without distant metastasis is curable. However, the presence of nodal metastasis, and using only radiotherapy was associated with a worse prognosis. (293)

The risk for local recurrence is up to 20–40% at ten years after initial treatment. This highlights the need for ongoing long-term surveillance. (313) Optimal surveillance is not defined, however one protocol described obtaining a baseline MRI brain and maxillofacial 2–4 months after treatment, then repeating at 4–6-month intervals for 5 years, then annually for a lifetime. History and physical exams should coincide with the above schedule and additional imaging should be guided by symptoms or exam findings. (330)

Recent or ongoing developments/research

Research is centered on developing a universal staging system, defining the role of nodal dissection in high-risk node-negative patients, and exploring the role of systemic treatments. Currently, a phase II study is evaluating the role of Bintrafusp Alfa in recurrent/metastatic ONB ([NCT05012098](#)). (331) In addition, there are studies on the use of DOTATATE based imaging in the diagnosis and management of SSR positive tumors, including ONB ([NCT04081701](#)). (332)

Survivorship issues in sinonasal malignancies

Survivorship and surveillance of patients with sinonasal malignancies is not defined clearly. They do require multidisciplinary involvement from diagnosis to follow-up. (333) Individual surveillance plans are discussed in every section, and includes serial imaging of the sinonasal area. (334) In addition to medical oncologists, radiation oncologists and head and neck surgeons, involvement from speech-language pathologists, audiologists, dentists, and nutritionists is valuable. Follow up is essential to facilitate early diagnosis of recurrence and to help patients deal with survivorship issues. Immediate issues include rehabilitation after radiation and surgery to the sinonasal cavity. Comprehensive nutritional assessment is necessary to ensure recovery. Delayed issues include development of radiation induced soft tissue sarcomas, hypothyroidism and damage to organs from surgery or radiation.

The risk factors for some sinonasal cancer types are also common with several other head and neck malignancies, and smoking cessation is essential to prevent additional primary malignancies. (334)

Future of sinonasal malignancies

Given the poor overall survival for a majority of patients with sinonasal malignancies these limitations, until most effective ways are available, increasing awareness for early detection is the only way to decrease morbidity and mortality from sinonasal malignancies. Some efforts include cancer registries for rare diseases to provide a large database with patient information, treatment variables, and outcomes available for providers to contribute to and learn from. (335) Another effort includes development of multi-national clinical studies for

patients to allow accruing significant number of patients to allow for meaningful testing of treatment approaches. Therefore, initiatives like the International Rare Cancer Initiative can expand the reach of clinical studies for these rare diseases. A challenge for studies for such rare cancers is the comparison of treatment regime to standard of care that does not exist is always challenging. A possible solution to these problems with cancer registries and clinical studies for rare diseases is to have multi-national institutions maintain a well-constructed prospective registry. (335) One such group is the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group, which is a collaborative group for Surgical Oncologists and Sarcoma professionals who aim to provide better evidence for patients with retroperitoneal sarcoma. The Head and Neck Cancer International Group is also one such group that aims to promote and conduct high quality clinical studies to improve outcomes in patients. At this point, they do not have clinical studies for rare cancers, but a platform like this is perfect for international cooperation for rare tumors, and it is one of the goals of the group. (336) While there are only a handful of studies for these patients, table 3 does list open clinical studies for patients with sinonasal malignancies.

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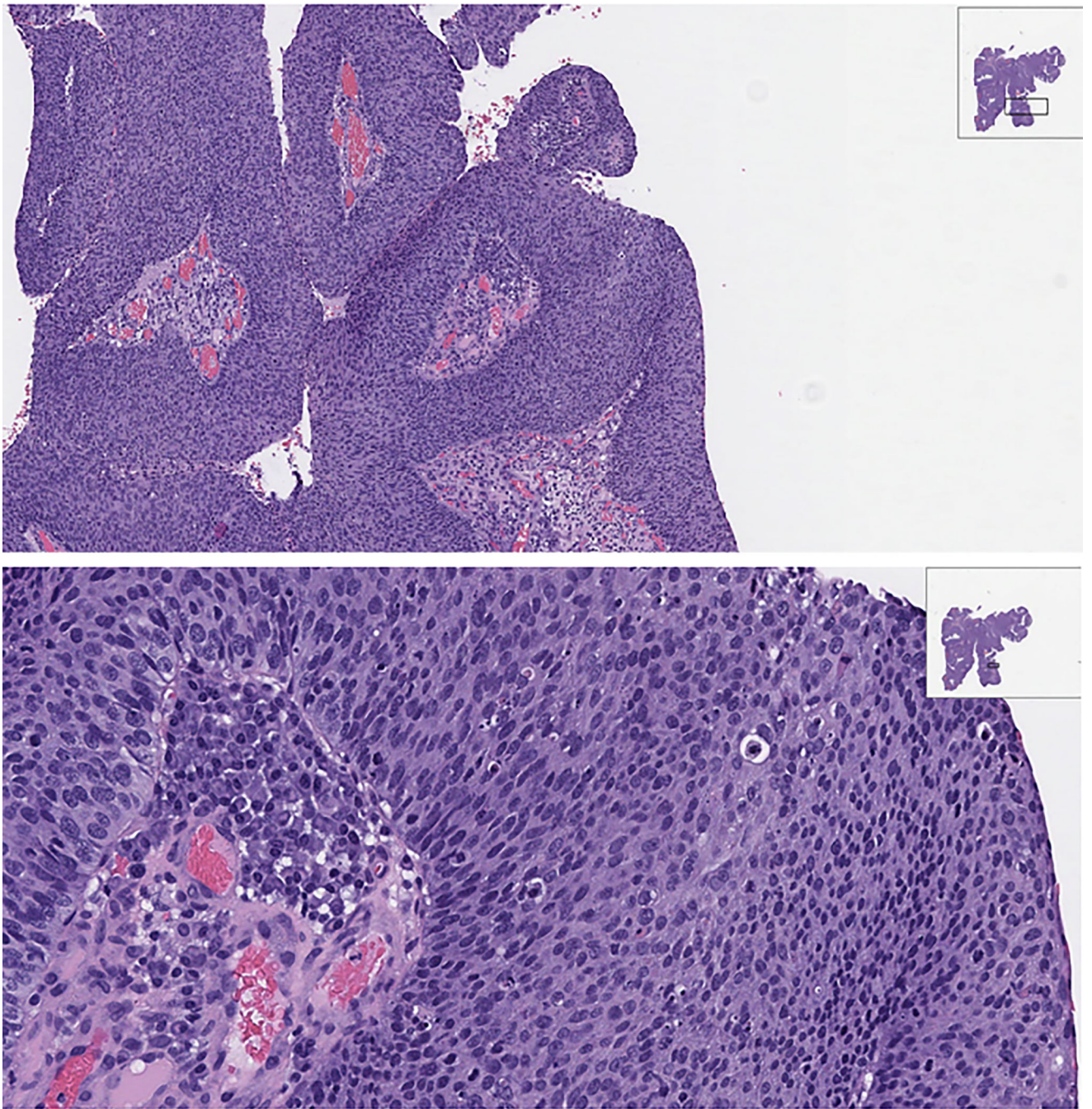


Figure 1:
H&E of Sinonasal Squamous Cell Carcinoma originating from an inverted papilloma

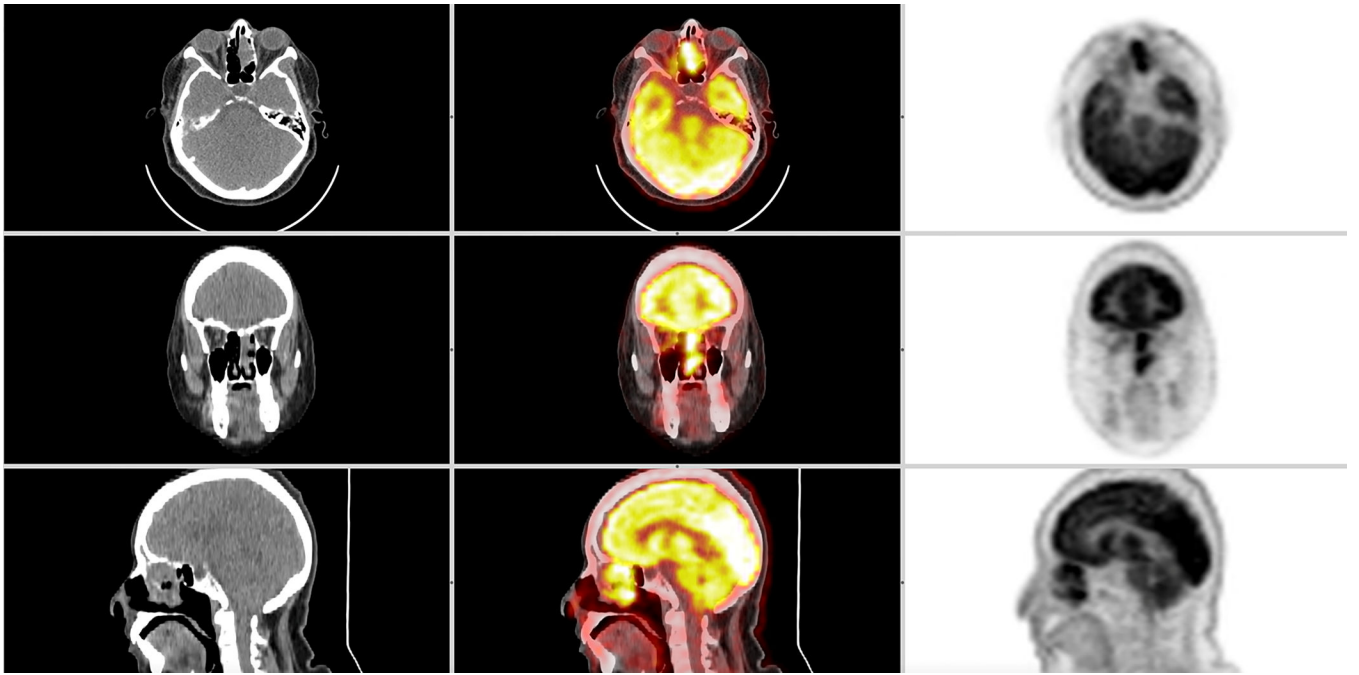


Figure 2:
PET/CT of Sinonasal Squamous Cell Carcinoma originating from an inverted papilloma

Sinonasal Squamous Cell Carcinoma

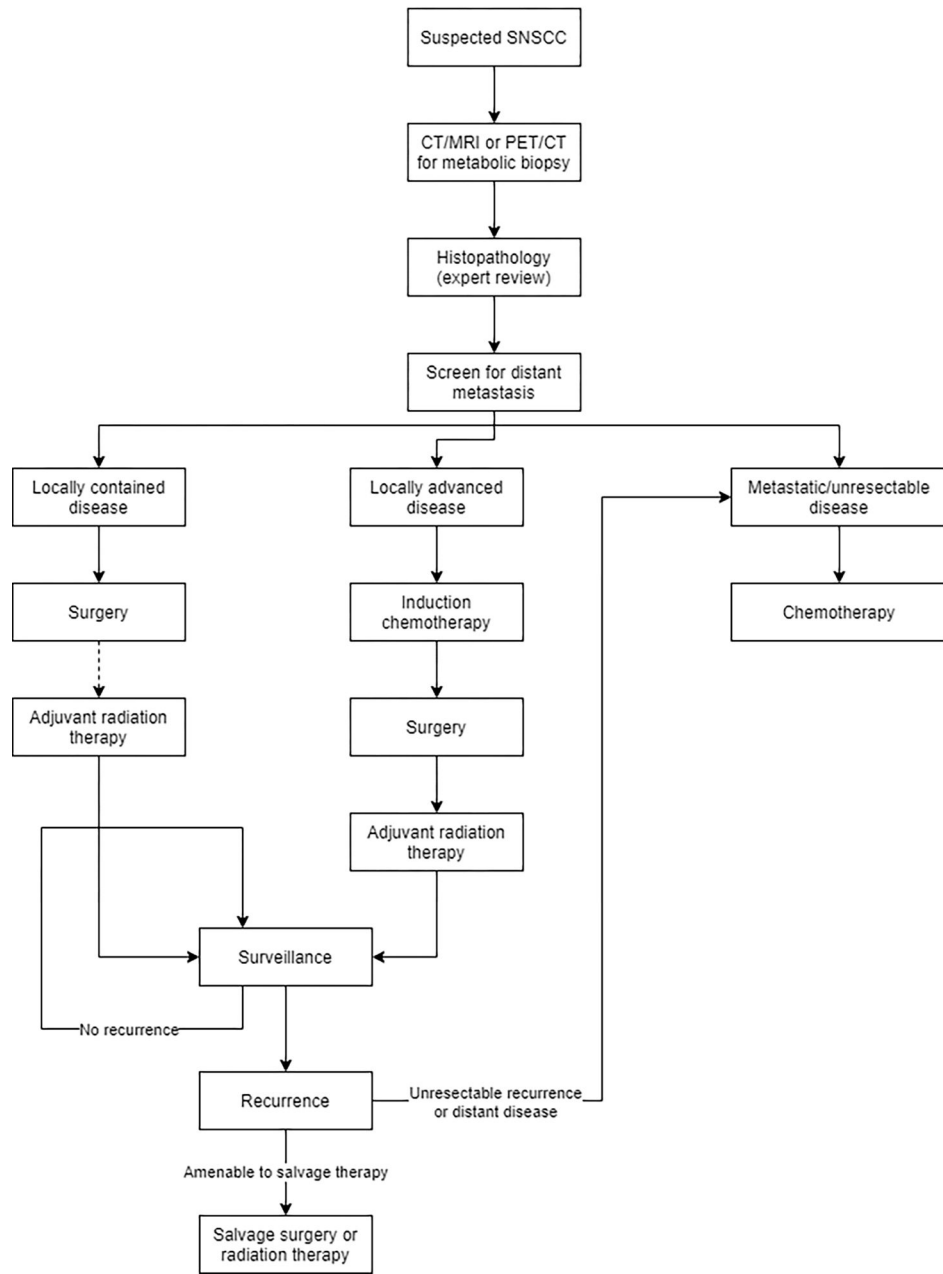


Figure 3: Authors algorithm summarizing management of Sinonasal Squamous Cell Carcinoma

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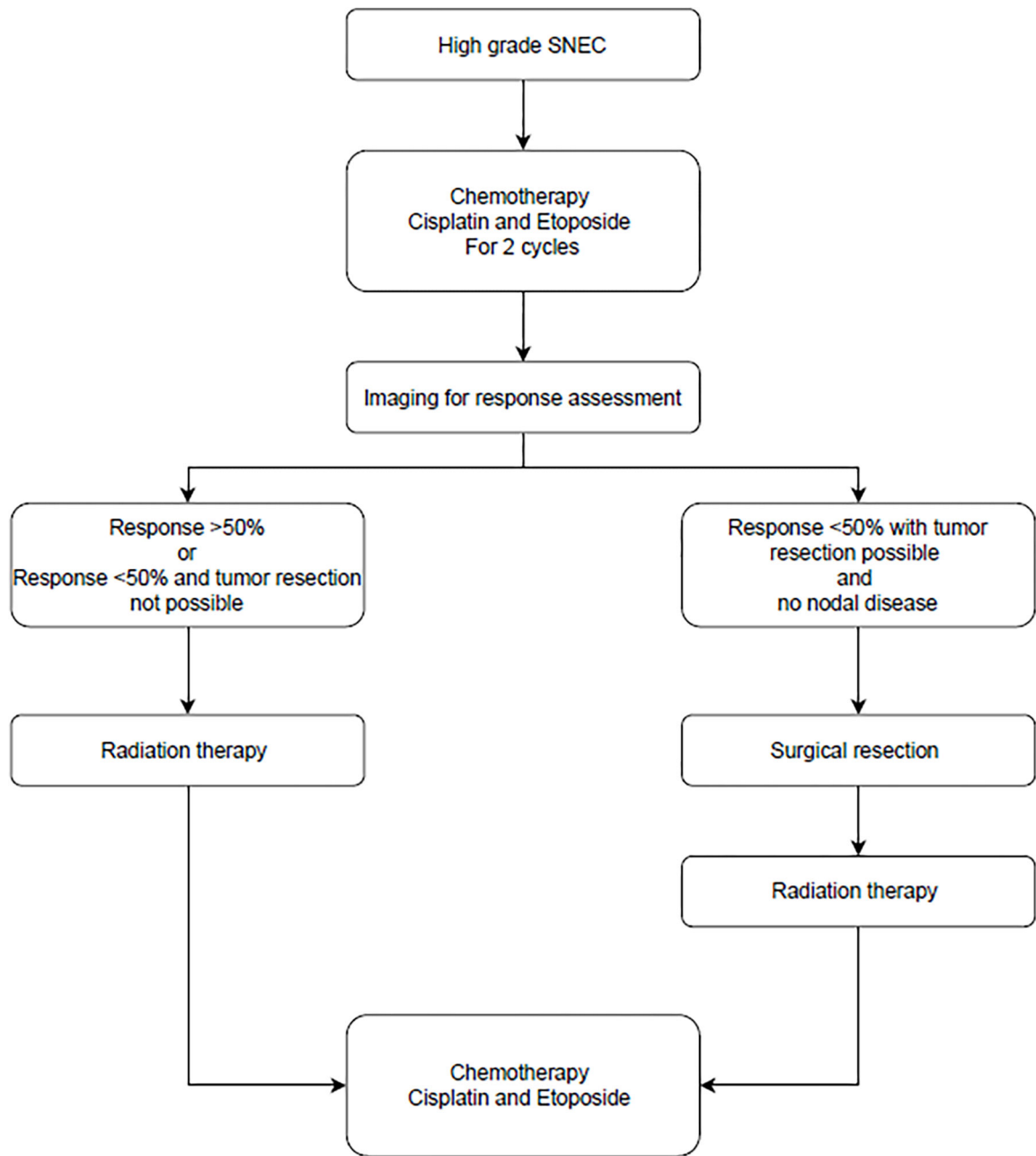
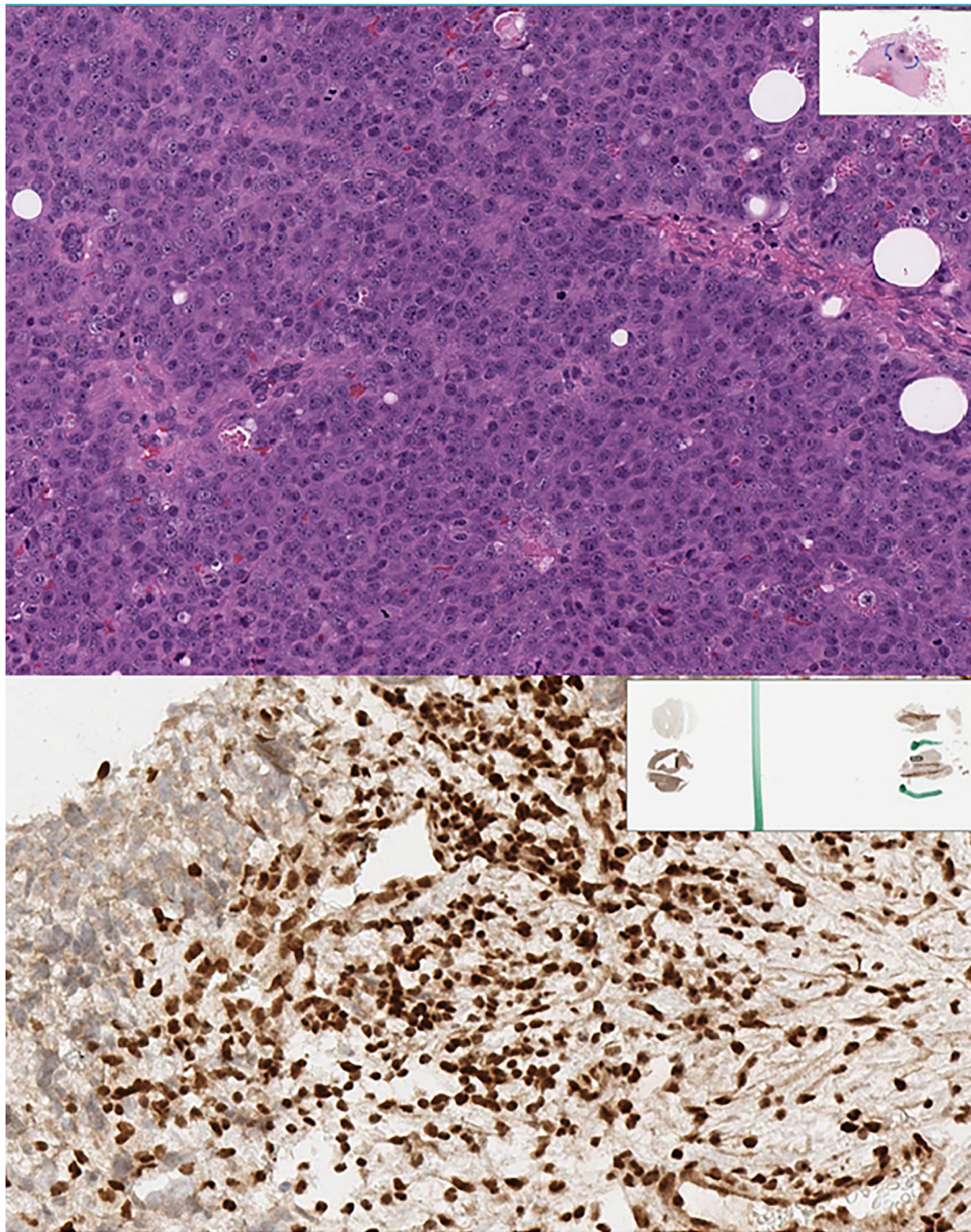


Figure 4:
Authors algorithm summarizing management of Sinonasal Neuroendocrine Carcinoma



A. H&E

B. INI-1

Figure 5:
A. H&E stain of Sinonasal Undifferentiated Carcinoma showing undifferentiated cells B. Loss of INI-1 staining seen in Sinonasal Undifferentiated Carcinoma

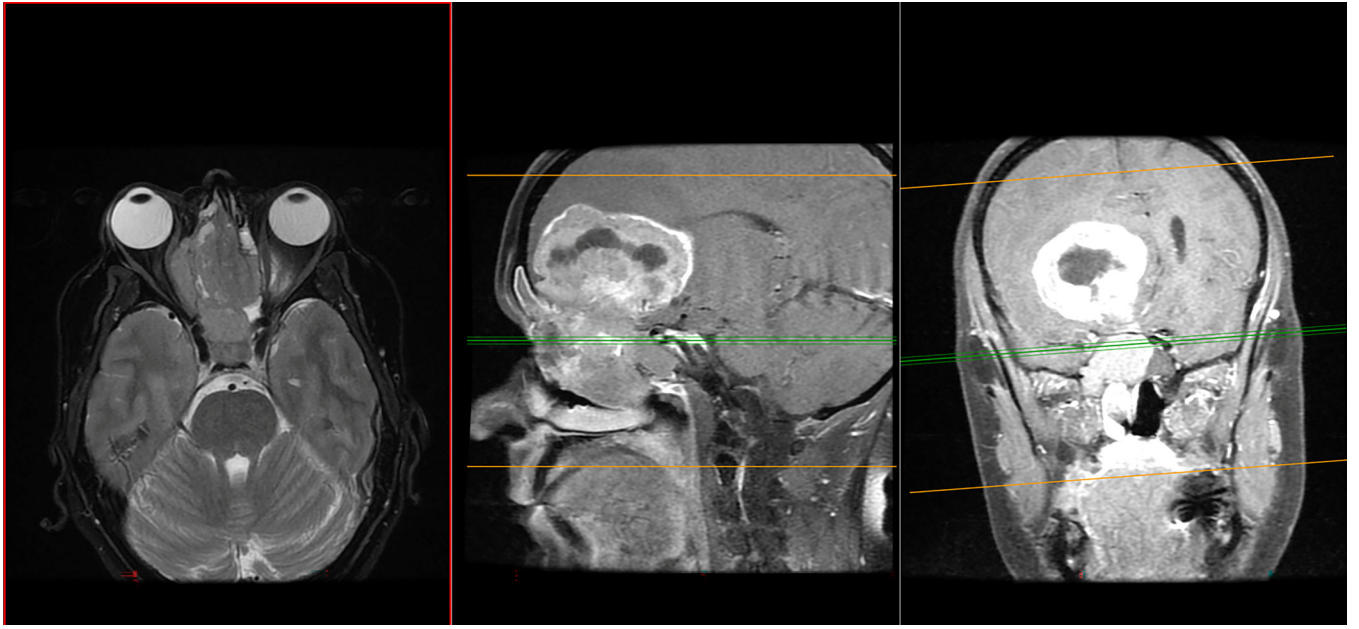


Figure 6:
MRI with local invasion of Sinonasal Undifferentiated Carcinoma

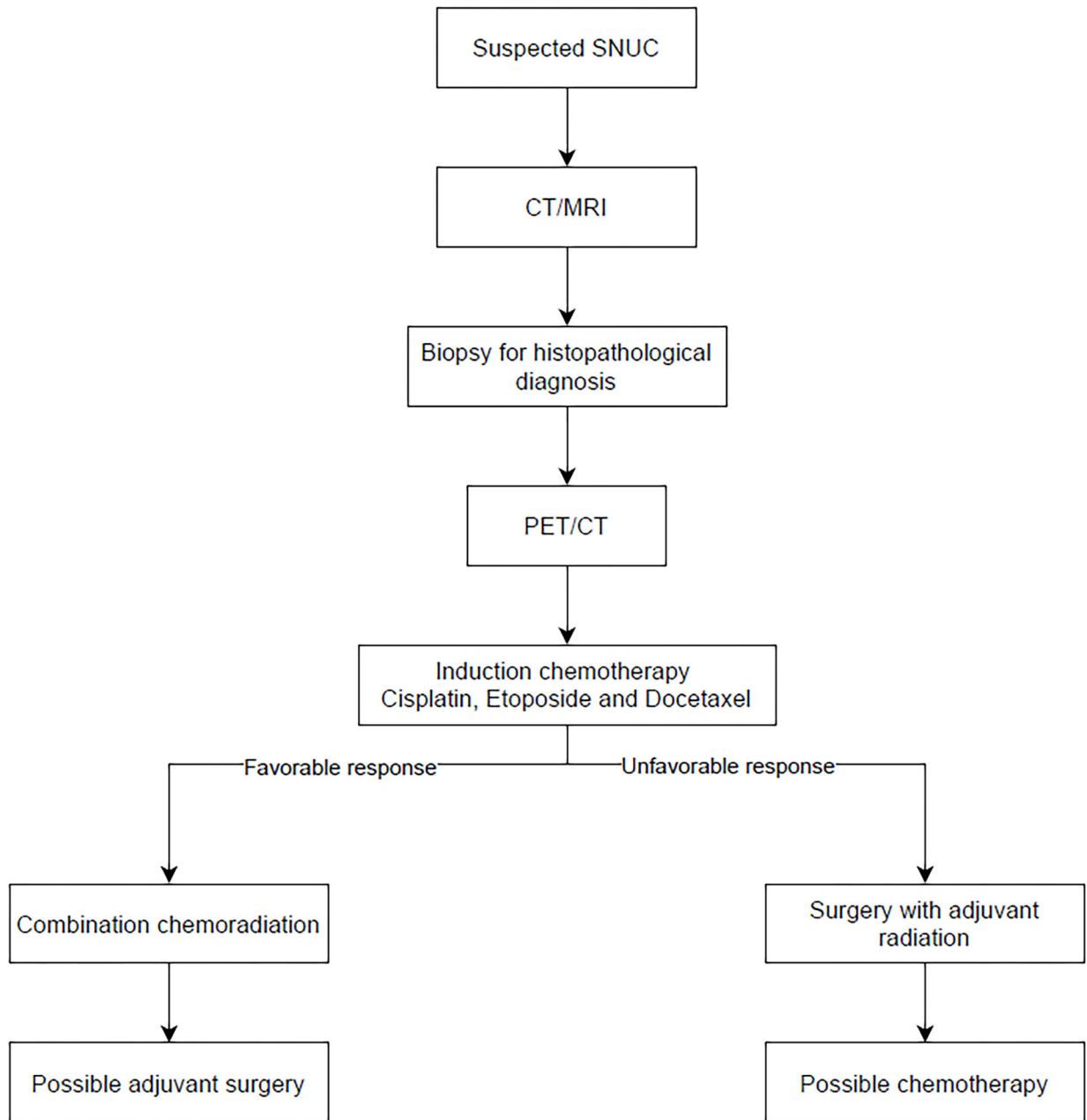
Sinonasal Undifferentiated Carcinoma

Figure 7:
Algorithm summarizing management of Sinonasal Undifferentiated Carcinoma

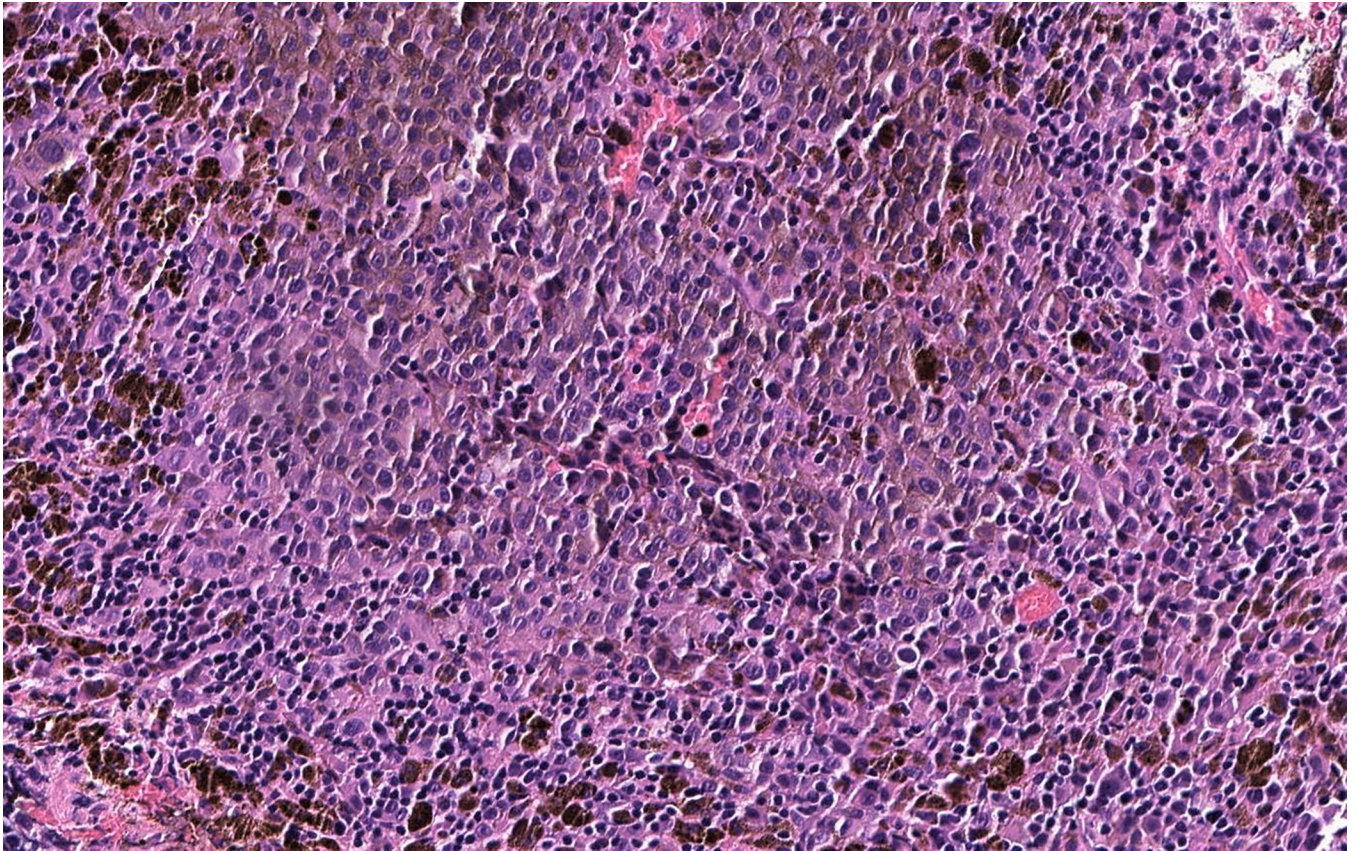


Figure 8:
H&E of sinonasal melanoma with sheets of tumor cells, many of them loaded with melanin pigment, as well as intermixed lymphocytes

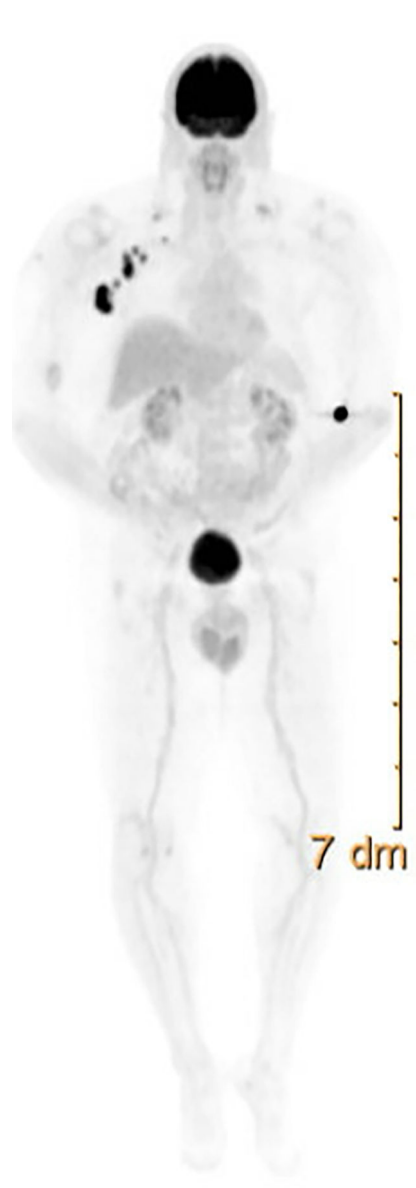


Figure 9:
FDG-PET showing axillary lymphadenopathy in a patient with primary mucosal melanoma after primary resection

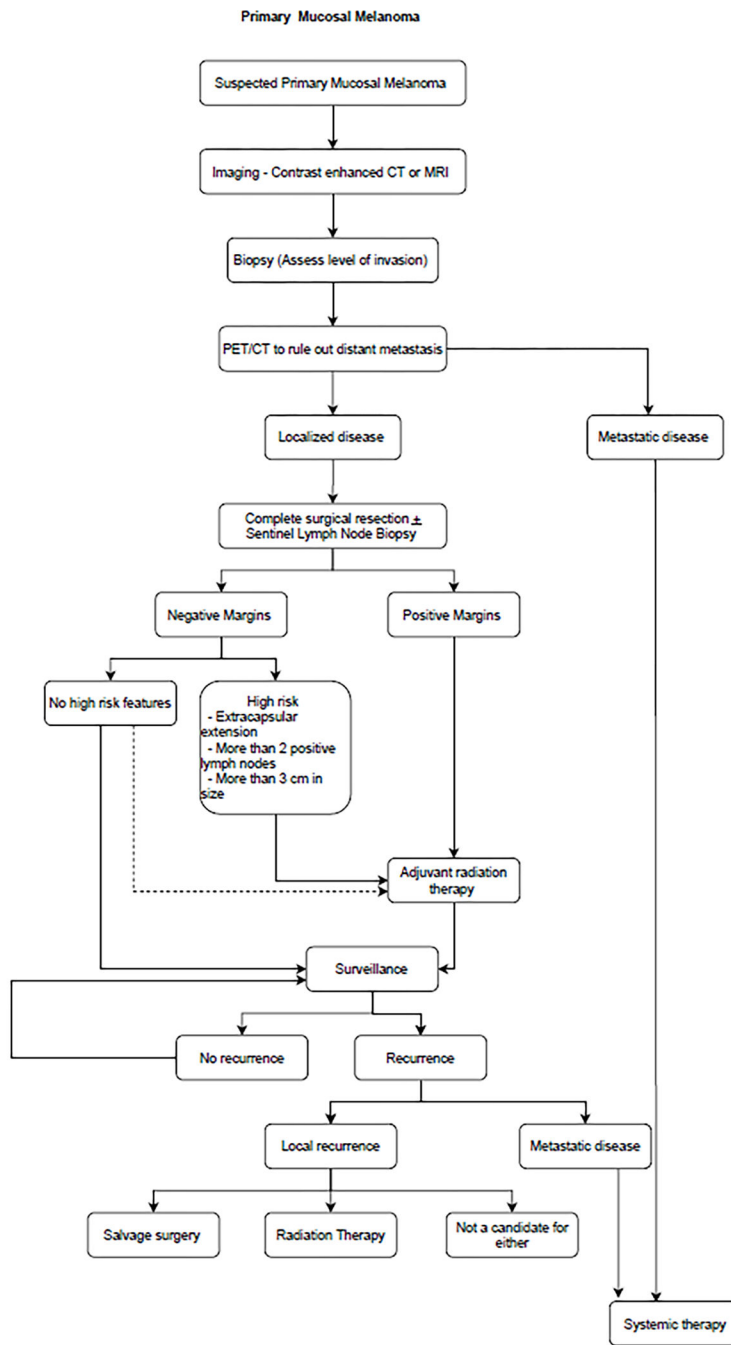


Figure 10: Authors algorithm summarizing management of Primary Mucosal Melanoma

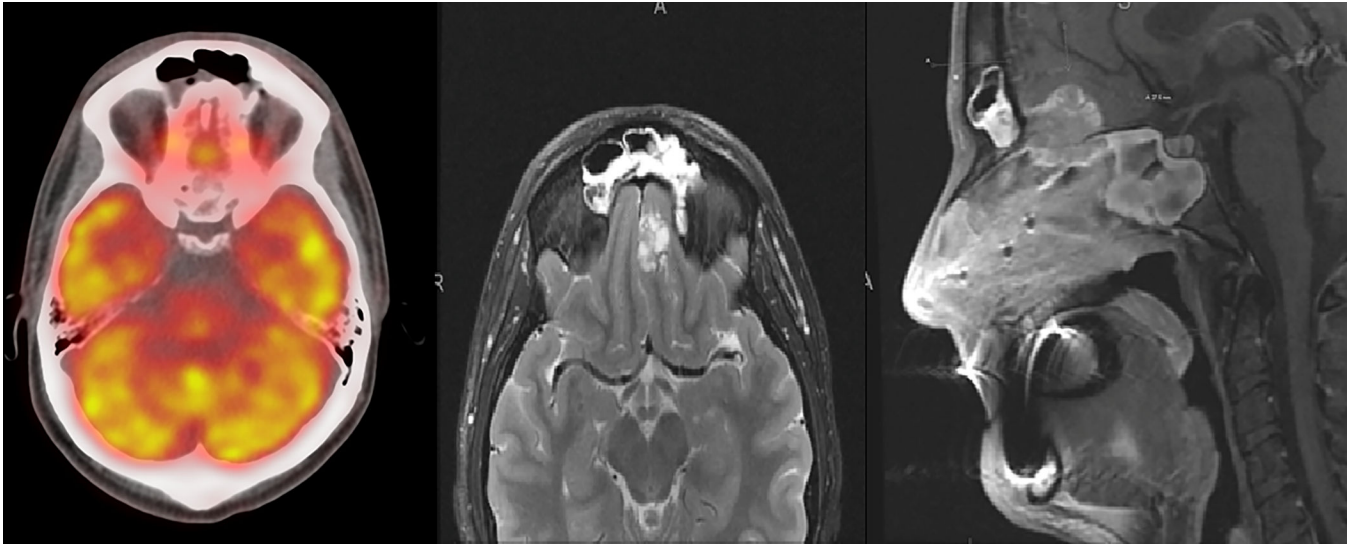


Figure 11: MRI and PET imaging of the brain in a patient with NUT midline carcinoma with brain invasion and retropharyngeal adenopathy.

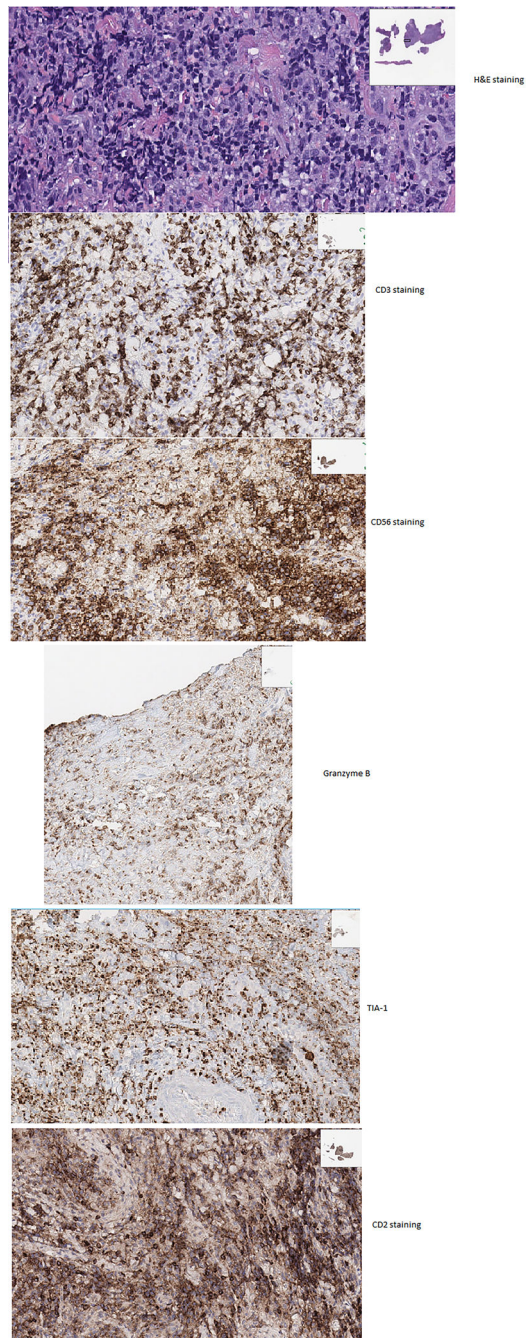


Figure 12:
H&E and different immunostains in a biopsy sample with NK/T Cell Lymphoma

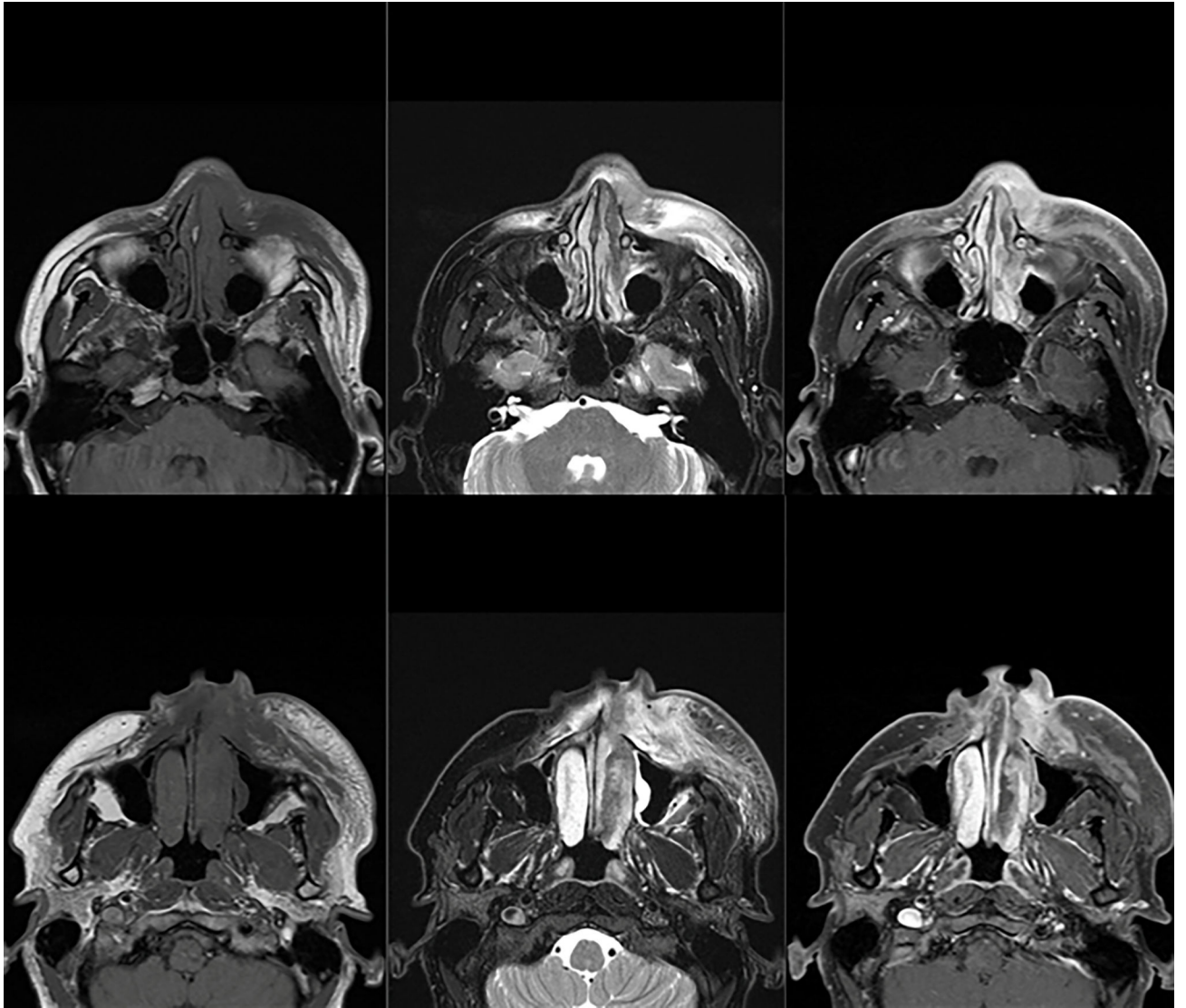


Figure 13:
MRI with nasal NK/T Cell Lymphoma

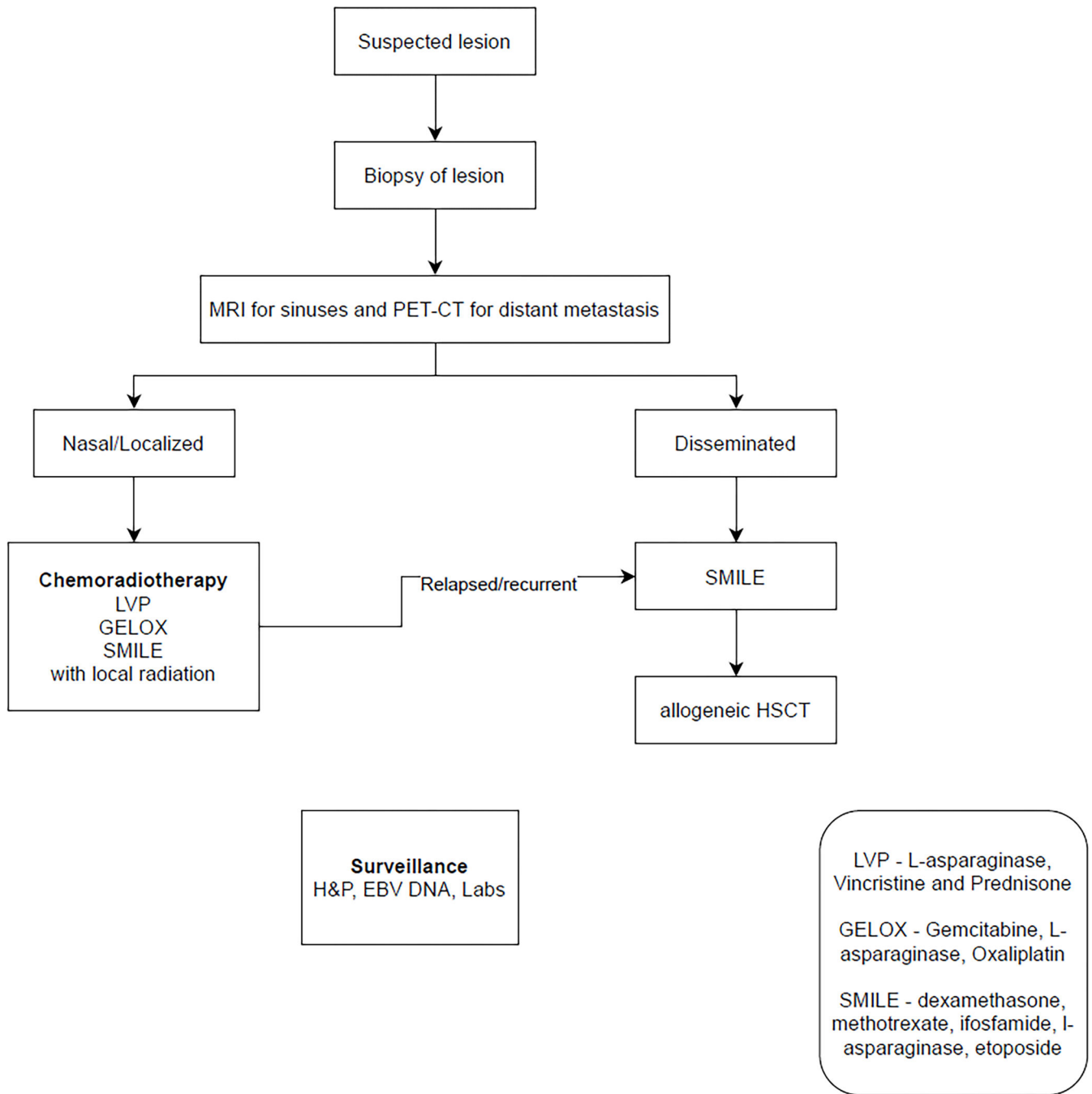


Figure 14: Algorithm summarizing management of NK/T Cell Lymphoma

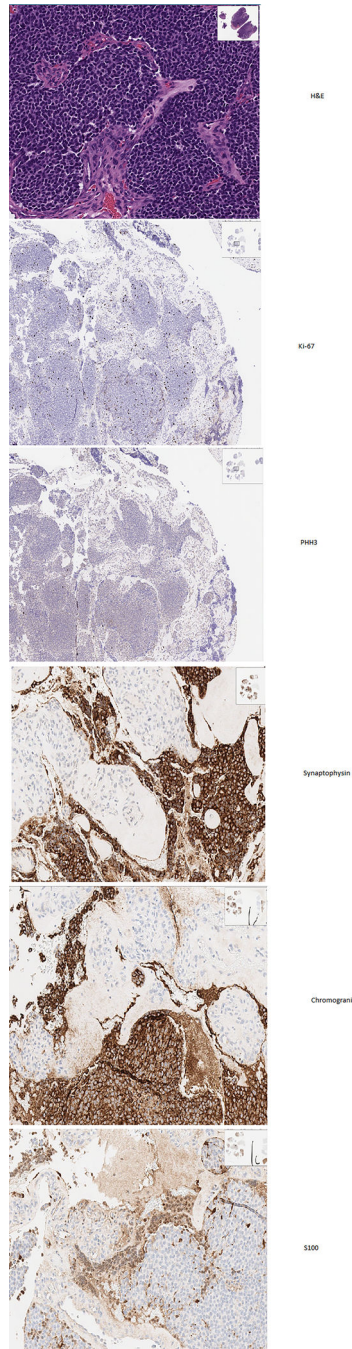


Figure 15: Esthesioneuroblastoma histology in H&E with Hyams grade I, with Ki67 7%, with PHH3, synaptophysin, chromogranin and S100 positivity.

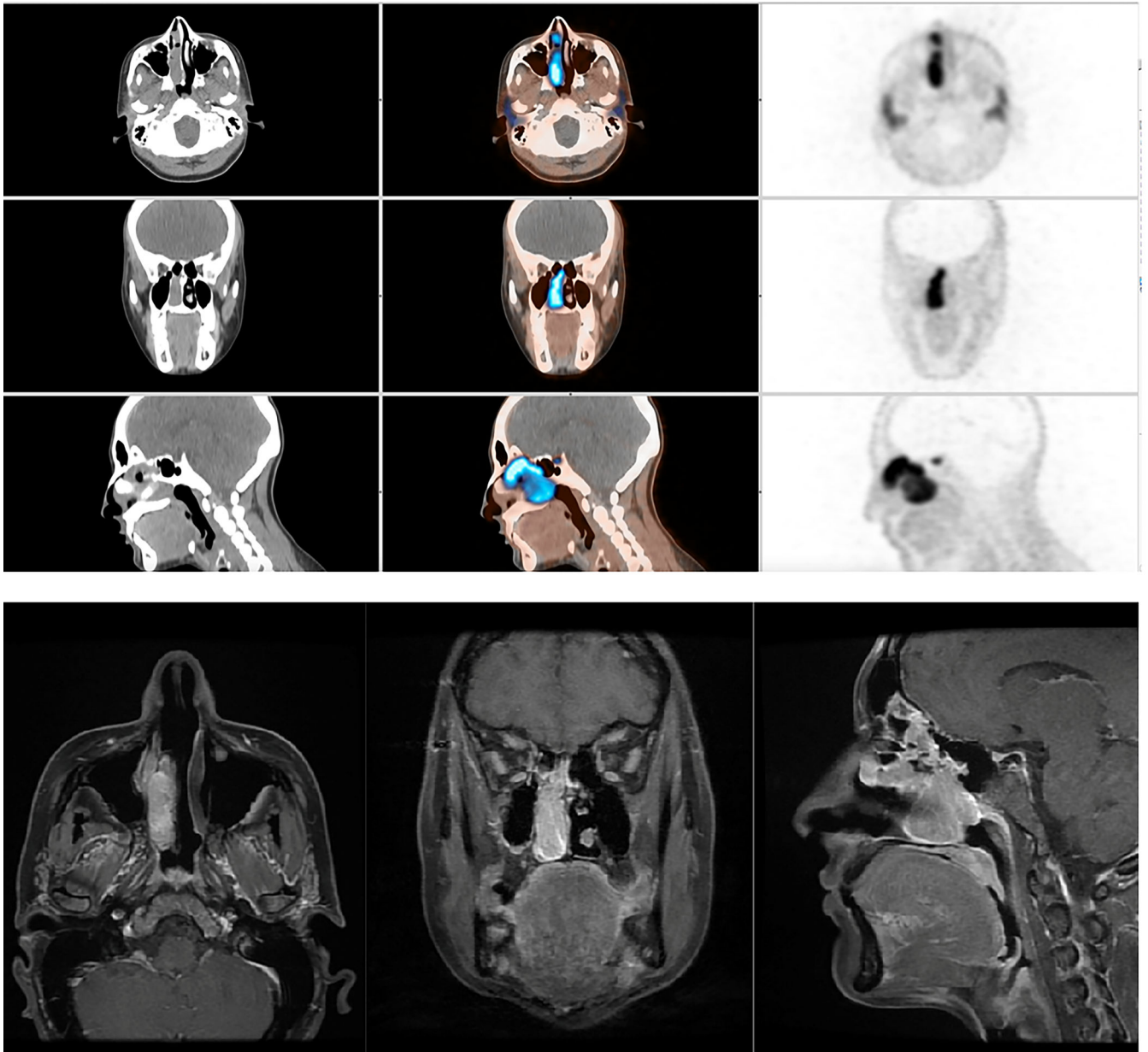


Figure 16:
DOTATE PET and MRI in a patient with Esthesioneuroblastoma in the right nasal cavity mass with extension into the right ethmoid air cells and epidural intracranial involvement along the cribriform plate.

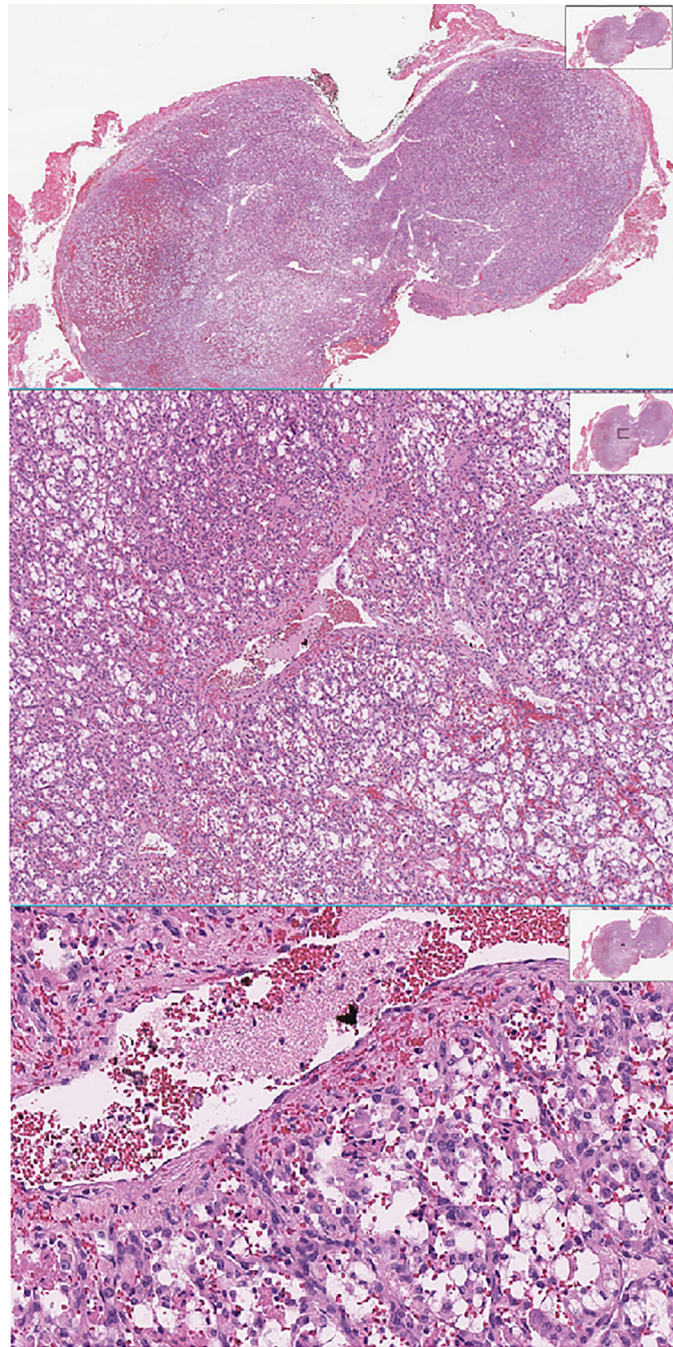


Figure 17:
H&E of paraganglioma showing pink epitheloid cells with round hyperchromatic nucleus.

Table 1:TNM staging of sinonasal malignancies as per AJCC 8th edition

TNM Staging	Nasal cavity/Ethmoid Sinus	Maxillary Sinus
T-stage		
Tis	Carcinoma in situ	
T1	tumor limited to one subsite (septum, floor, lateral wall, or vestibule (edge of naris to mucocutaneous junction of nasal cavity); left or right ethmoid sinus)	tumor limited to maxillary sinus mucosa (no bone erosion/destruction)
T2	tumor involving two subsites in one region or extending to involve an adjacent region in the nasoethmoidal complex	tumor with bone erosion/destruction, including extension into hard palate and/or middle meatus, excluding structures in a higher T category
T3	Tumor invades any of the following: <ul style="list-style-type: none"> • medial wall or floor of orbit • maxillary sinus • palate • cribriform plate 	Tumor invades any of the following: <ul style="list-style-type: none"> • bone of posterior wall of maxillary sinus • subcutaneous tissues • floor or medial wall of orbit • pterygoid fossa • ethmoid sinuses
T4a	Tumor invades any of the following: <ul style="list-style-type: none"> • anterior orbital contents • skin of nose or cheek • minimal extension to anterior cranial fossa • pterygoid plates • Sphenoid sinus • Frontal sinus 	Tumor invades any of the following: <ul style="list-style-type: none"> • anterior orbital contents • skin of cheek • pterygoid plates • infratemporal fossa • cribriform plate • sphenoid sinus • frontal sinus
T4b	Tumor invades any of the following: <ul style="list-style-type: none"> • orbital apex • middle cranial fossa • dura • brain • cranial nerves other than maxillary division of trigeminal nerve (V2) • nasopharynx • clivus 	
N-stage		
N0	no regional node metastases	
N1	metastasis in single ipsilateral node, ≤ 3 cm, and no extranodal extension (ENE(-))	
N2a	metastasis in single ipsilateral node, >3 cm and ≤ 6 cm, and ENE(-); or metastasis in single ipsilateral node, ≤ 3 cm, and ENE(+)	
N2b	metastasis in multiple ipsilateral nodes, all ≤ 6 cm, and ENE(-)	
N2c	metastasis in bilateral or contralateral nodes, all ≤ 6 cm, and ENE(-)	
N3a	metastasis in a node, >6 cm, and ENE(-)	
N3b	metastasis in single ipsilateral node, >3 cm, and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes any with ENE(+); or single contralateral node of any size and ENE(+)	

Table 2:

Selected clinical studies for patients with Extranodal NK/T Cell Lymphoma

NCT #	Condition	Title	Intervention
NCT03671850		VT-EBV-N for Treatment of Severe in EBV Positive Extranodal NK/T Cell Lymphoma Patients	VT-EBV-N (EBV-CTL) is a cytotoxicity T lymphocyte
NCT03246750	Newly diagnosed Extranodal NK/ T-cell Lymphoma	B-MAD Chemotherapy in Newly diagnosed Extranodal NK/ T-cell Lymphoma	Brentuximab vedotin and methotrexate/ L-asparaginase/ dexamethasone
NCT03728972	Newly diagnosed Extranodal NK/ T-cell Lymphoma	Study of Pembrolizumab in Patients With Early-Stage NK/T-cell Lymphoma, Nasal Type	Pembrolizumab
NCT04602065	Relapsed/Refractory Extranodal NK/T Cell Lymphoma (Nasal Type)	Evaluation of Safety and Efficacy of IBI318 Monotherapy for Relapsed/Refractory Extranodal NK/T Cell Lymphoma (Nasal Type) Study	IBI318(Recombinant human anti-PD1/PD-L1 bispecific antibody)
NCT04096690	Advanced Stage NK/T-cell Lymphoma	Anti-PD-1 Antibody Combined With Pegaspargase in the Treatment of Advanced Stage NK/T-cell Lymphoma	Pegaspargase, Anti-PD-1 monoclonal antibody
NCT04279379	Relapsed/Refractory or Advanced NK/T-cell Lymphoma	Sintilimab and Decitabine for Patients With Relapsed/ Refractory or Advanced NK/T-cell Lymphoma	Sintilimab and Decitabine
NCT04484506	Newly diagnosed Extranodal NK/ T-cell Lymphoma	Pegaspargase-COEP Chemotherapy Combined With Radiotherapy for Extra-nodal NK/T Cell Lymphoma	Pegaspargase, cyclophosphamide, vincristine, etoposide, prednisone
NCT04405375	Relapsed/Refractory or Advanced ENKTCL	GPED Regimen for Relapsed/Refractory or Advanced ENKTCL	Gemcitabine, Pegaspargase, Etoposide, Dexamethasone
NCT04509466	Any ENKTCL	Clinical Study of Liposomal Mitoxantrone Hydrochloride Injection Combined With Pegaspargase in the Treatment of NK/TCL	Liposomal mitoxantrone hydrochloride and Pegaspargase
NCT04365036	Newly diagnosed Extranodal NK/ T-cell Lymphoma	A Multicenter, Phase 3, Randomized Study of Sequential Chemoradiotherapy With or Without Toripalimab (PD-1 Antibody) in Newly Diagnosed Early-Stage Extranodal Natural Killer/T Cell Lymphoma, Nasal Type (ENKTL)	Toripalimab, Pegaspargase, Gemcitabine, Oxaliplatin, Definitive intensity-modulated radiotherapy (IMRT)
NCT04127227	Newly diagnosed advanced extranodal natural killer/T-cell lymphoma, nasal type	Sintilimab With P-GemOx Regimen for Newly Diagnosed Advanced Extranodal Natural Killer/T-cell Lymphoma, Nasal Type	Sintilimab, pegaspargase, gemcitabine, oxaliplatin
NCT04511351	Stage I/II Extranodal Nasal NK/T-cell Lymphoma	Radiotherapy Combined With GDP With or Without Chidamide in Stage I/II Extranodal Nasal NK/T-cell Lymphoma	Chidamide, Gemcitabine, Cisplatin, Dexamethasone
NCT04414969	Early Stage of NK/T Cell Lymphoma	Anti-PD-1 Antibody Combined With Peg-Asparaginase and Chidamide for the Early Stage of NK/T Cell Lymphoma	Anti-PD-1 Antibody, Peg-Asparaginase, Chidamide
NCT03936452	Untreated stage I-II Extranodal NK/T Cell Lymphoma	Combined Treatment of Sintilimab, Peg-aspargase Plus Anlotinib in NK/T Cell Lymphoma	Sintilimab, Peg-aspargase, Anlotinib
NCT05058755	Refractory Extranodal NK/T-cell Lymphoma	Tislelizumab Combined Treatment in Refractory Extranodal NK/T-cell Lymphoma	Tislelizumab, azacytidine, lenalidomide Or Tislelizumab, etoposide, pegaspargase
NCT04004637	Relapsed refractory CD7+ NK/T Cell Lymphoma	CD7 CAR-T Cells for Patients With R/R CD7+ NK/T Cell Lymphoma, T-lymphoblastic Lymphoma and Acute Lymphocytic Leukemia	CD7 CAR-T cells infusion

Table 3:

Clinical studies for patients with sinonasal malignancies

NCT #	Condition	Title	Intervention
NCT05151588	Sinonasal Carcinoma	Induction Chemotherapy and Tazemetostat for Locally Advanced SMARCB1-deficient Sinonasal Carcinoma	docetaxel, cisplatin, 5-FU and tazemetostat followed by surgery or radical chemoradiation and maintenance tazemetostat
NCT00707473	- Locally Advanced Nasal Cavity and Paranasal Sinus Squamous Cell Carcinoma - Nasal Cavity and Paranasal Sinus Poorly Differentiated Carcinoma - Sinonasal Undifferentiated Carcinoma	Docetaxel, Cisplatin and Fluorouracil in Treating Patients With Previously Untreated Stage II-IV Nasal Cavity and Paranasal Sinus Cancer	Induction Therapy With Docetaxel, Cisplatin and Fluorouracil
NCT01586767	Any sinonasal malignancy	Intensity-Modulated or Proton Radiation Therapy for Sinonasal Malignancy	Proton radiation therapy, Intensity-modulated radiotherapy
NCT04081701	Esthesioneuroblastoma	68-Ga DOTATATE PET/MRI in the Diagnosis and Management of Somatostatin Receptor Positive CNS Tumors. (DOMINO-START)	Ga68-DOTATATE-PET/MRI
NCT04318717	Mucosal Melanoma of the Head and Neck	Pembrolizumab and Hypofractionated Radiation Therapy for the Treatment of Mucosal Melanoma	Pembrolizumab, Hypofractionated radiation therapy during first 2 cycles
NCT03241186	Resected mucosal melanoma	Ipilimumab and Nivolumab as Adjuvant Treatment of Mucosal Melanoma	Ipilimumab and Nivolumab
NCT04622566	Resected mucosal melanoma	Lenvatinib and Pembrolizumab in Resectable Mucosal Melanoma	Neoadjuvant Lenvatinib and Pembrolizumab, followed by maintenance Pembrolizumab
NCT03313206	Resectable Head and Neck Mucosal Melanoma	Neoadjuvant Treatment Associated With Maintenance Therapy by Anti-PD1 Immunotherapy in Patients With Resectable Head and Neck Mucosal Melanoma (IMMUQ)	Pembrolizumab
NCT05019716	Advanced, metastatic or unresectable NUT Carcinoma	Testing the Safety and Efficacy of the Addition of A New Anti-cancer Drug, ZEN003694, to Chemotherapy Treatment (Etoposide and Cisplatin) for Adult and Pediatric Patients (12–17 Years) With NUT Carcinoma	BET Bromodomain Inhibitor ZEN-3694, Cisplatin, Etoposide
NCT03313206	Resectable head and neck mucosal melanomas	Phase II Multicentric Study: Efficacy Evaluation of Neoadjuvant Treatment Associated With Maintenance Therapy by Anti-PD1 Immunotherapy on Disease-free-survival (DFS) in Patients With Resectable Head and Neck Mucosal Melanoma	Pembrolizumab

Table 4:

Summary of incidence, molecular expression, prognosis and treatment of sinonasal malignancies

Disease entity	Incidence	Molecular expression	Prognosis
Sinonasal Squamous Cell Carcinoma	61% of sinonasal cancers	TP53, EGFR, FGFR1, SOX2 amplification, microsatellite instability, KRAS rarely	5-year OS 50%
Sinonasal Adenocarcinoma	27% of sinonasal cancers	ETV6 fusions rarely seen	5-year OS 66.7%
Sinonasal Neuroendocrine Carcinoma	2% of sinonasal cancers	mutations of TP53 and RB1, up-regulation of BCL2 signaling, and activation of MYC and PI3K pathways	5-year DSS 70.2%
Sinonasal Undifferentiated Carcinoma	5% of sinonasal cancers	<i>IDH2</i> mutations, <i>P53</i> mutations, <i>CDKN2A/2B</i> loss-of-, <i>MYC</i> amplification <i>SETD2</i>	5-year OS 34.9%
Primary Mucosal Melanoma	Rare (< 1%)	KIT, BRAF, loss of p16 expression, CDKN2A mutations, and/or loss of heterozygosity for CDKN2A	5-year OS 22%
NUT Carcinoma	Rare (< 1%)	Translocations involving the NUT gene on 15q14, TP53 suppression	2-year OS 0%
Extranodal NK/T Cell Lymphoma	Rare (< 1%)	JAK/STAT activation, mutations of DDX3X, dmutations in tumor suppressor genes such as TP53, PRDM1, FOXO3, and HACE2	5-year OS 42%
Esthesioneuroblastoma	2–6%	TP53, c-kit, PDGFR-b, EGFR, FGF-FGFR1 signaling, Sonic hedgehog pathway; apoptosis-related pathways (Bcl-2, TRAIL) and neoangiogenesis (VEGF; KDR)	5-year OS 62%