19 ■ SINONASAL TUMORS

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QUICK HIT ■ Sinonasal tumors include a range of malignancies that can develop in the maxillary, ethmoid, sphenoid, or frontal sinuses and in the nasal cavity. Squamous cell carcinoma and adenocarcinoma of the maxillary sinus, nasal cavity, and the ethmoid sinus are the most common.

Table 19.1 General Treatment Paradigm for Sinonasal Tumors

Stage	Treatment Options
Stage I/II	Surgical resection (preferred) and observation (only T1 ethmoid), RT, or chemoRT based on postoperative risk factors OR definitive RT
Stage III/IVA	Surgical resection (preferred) followed by RT or chemoRT based on postoperative risk factors OR definitive chemoRT
Stage IVB	ChemoRT or RT alone

EPIDEMIOLOGY: Sinonasal cancers cover a range of rare malignancies and account for ~3% of all head and neck cancers, with an annual incidence of 1 case per 100,000 people worldwide (~2000 cases).[1] M:F ratio of 1.8:1. Tumors generally develop after age 40 and usually between the ages of 60 and 70. The maxillary sinus is the most common paranasal sinus cancer (60%–70%), followed by nasal cavity (20%–30%), ethmoid sinus (10%–15%), and frontal and sphenoid sinuses (1%–2%). Prevalence is higher in Asia and Africa.

RISK FACTORS: Occupational exposure (including leather tanners, textile, wood dust ACA, and formaldehyde), air pollution, and tobacco smoke. There is some recent evidence that HPV infection can be associated with malignant degeneration of an inverted papilloma.[2] There is also evidence of a connection between EBV virus infection and subsequent development of a sinonasal tract lymphoma.[3] Chronic sinusitis is not causative.

ANATOMY: The paranasal sinuses are air-filled spaces that are located within the bones of the skull and face. They are centered on the nasal cavity and consist of four sets of paired sinuses: maxillary, frontal, sphenoid, and ethmoid.

Maxillary Sinus: Largest paranasal sinus in the shape of a pyramid with the base along the nasal wall and the apex pointing laterally toward the zygoma. The anterior maxillary sinus wall houses the infraorbital nerve, which runs through the infraorbital canal along the roof of the sinus and sends branches to the soft tissues of the cheek. The roof of the maxillary sinus is the floor of the orbit. The posteromedial wall of the maxillary sinus is adjacent to the pterygopalatine fossa, and the posterolateral wall is adjacent to the infratemporal fossa. The maxillary sinus is innervated by branches of V2 (infraorbital nerve and the greater palatine nerves).

Frontal Sinus: Located in the frontal bone superior to the orbits in the forehead. The posterior wall of the frontal sinus separates the sinus from the anterior cranial fossa (much thinner than anterior wall). It is innervated by the supraorbital and supratrochlear nerves of V1.

Sphenoid Sinus: Located in the center of the head in the sphenoid bone and may extend posteriorly as far as the foramen magnum. Innervation of the sphenoid sinus is from V1 and V2 branches.

Ethmoid Sinus: Air cells between the orbits in the ethmoid bone. The ethmoid cells are shaped like pyramids and are divided by thin septa. Lamina papyracea paper-thin bone separate ethmoid cells from orbit.

PATHOLOGY: The most common histology of sinonasal tract tumors is squamous cell carcinoma (~80% of cases). Other common histologies include adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma. Other rarer histologies include SNUC, HMPC, angiosarcoma,

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rhabdomyosarcoma, lymphoma, olfactory neuroblastoma (esthesioneuroblastoma), mucosal melanoma, NUT-midline carcinoma, teratocarcinosarcoma, meningioma, plasmacytoma, and metastasis. Benign etiologies to consider include sinonasal polyposis, choanal polyps, and juvenile angiofibromas.

CLINICAL PRESENTATION: Most patients are asymptomatic or have nonspecific sinonasal symptoms that mimic benign tissue until they invade an adjacent structure and cause more urgent medical attention or more detailed evaluation. Therefore, most patients have locally advanced disease at presentation (a triad of facial asymmetry, palpable or visible tumor in the oral cavity, and visible intranasal disease occurs in ~50% of patients). Common initial symptoms include facial or dental pain, nasal obstruction, and epistaxis. Less common symptoms include cranial neuropathy (extraocular movements or trigeminal nerve symptomatology), chronic sinusitis, facial edema, vision loss, headaches, rhinorrhea, and hyposmia.

WORKUP: History and physical exam with particular attention to cranial nerves and evidence of local invasion. Nasal endoscopy as clinically indicated. Dental consult.

Labs: CBC and BMP.

Imaging: CT sinuses and MRI are both performed to evaluate disease extent and distinguish from benign causes (infection, retained secretions, granulation of scar tissue). CT chest for earlier stage disease and PET/CT for stage III/IV patients. CT provides information about bone invasion and MRI about the involvement of soft tissues, nerves, skull base, and brain, and better differentiation of fluid from solid tumor.

Biopsy: Endoscopic biopsy is typically performed unless tumor is protruding through nasal cavity or oral cavity. Maxillary sinus lesions biopsied intranasally or through gingivobuccal sulcus if tumor extends through the anterior maxilla. Ethmoid sinus lesions are biopsied through endoscopic or transnasal approach in exam under anesthesia. Frontal sinus lesions are biopsied through endoscopic approach or via the frontal recess in the OR as well.

PROGNOSTIC FACTORS: The 5-year OS for patients is 50% for those with local disease, 30% with regional disease, and 15% for those with distant metastatic disease. Favorable prognostic factors: lower T stage (T1/T2 vs. T3/T4), N status (N0 vs. N+), histology (adenocarcinoma vs. squamous cell or undifferentiated), sinus location (maxillary sinus vs. ethmoid sinus). Poor prognostic factors: intracranial extension, infiltration into the pterygopalatine fossa, skull base, dura, cribriform plate, or orbits.

Table 19.2 AJCC 8th Edition (2017): Staging for Maxillary Sinus Tumors

T/M \ N		cN0	cN1	cN2a	cN2b	cN2c	cN3a	cN3b
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone	**I**						
T2	Extension	**II**	**III**	**IVA**				
T3	Invasion[1]							
T4a	Invasion[2]							
T4b	Invasion[3]	**IVB**						
M1	Distant metastasis	**IVC**						

Notes: Extension = extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates, or bone erosion. Invasion[1] = Invasion of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, or ethmoid sinuses. Invasion[2] = Invasion of anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses. Invasion[3] = Invasion of orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus.
N1 = single ipsilateral LN ≤ 3 cm without extranodal extension (ENE), N2a = single ipsilateral LN 3–6 cm without ENE, N2b = multiple ipsilateral LNs ≤ 6 cm without ENE, N2c = bilateral or contralateral LN ≤ 6 cm without ENE, N3a = LN > 6 cm without ENE, N3b = any node with clinically overt ENE.

Table 19.3 AJCC 8th Edition (2017): Staging for Nasal Cavity and Ethmoid Sinus Tumors

T/M \ N		cN0	cN1	cN2a	cN2b	cN2c	cN3a	cN3b
T1	Tumor limited to any one subsite, with or without bony invasion	**I**						
T2	Invasion[1]	**II**	**III**		**IVA**			
T3	Extension							
T4a	Invasion[2]							
T4b	Invasion[3]				**IVB**			
M1	Distant metastasis				**IVC**			

Notes: Invasion[1] = invasion of two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion. Extension = extension to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate. Invasion[2] = Invasion of anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses. Invasion[3] = Invasion of orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus.

TREATMENT PARADIGM

In general, there are no randomized trials to define optimal treatment paradigms due to the rarity, heterogeneity in histology, and variability in site of origin.

Surgery: Resection with either open or endoscopic surgery with the goal of a gross-total resection of involved bone and soft tissue is standard of care. Imaged-guided endoscopic techniques are becoming increasingly popular and are performed by both ENT and neurosurgeons with lower frequencies of surgical complications and decreased morbidity. The endoscopic method was historically criticized because it involves piecemeal resection of tumor (vs. en-bloc resection). However, negative margin status is now known to be the most important factor for local control, and this is equivalent between approaches. Advantages of endoscopic approach over open surgery include no facial incision, no craniotomy, no facial bone osteotomy, shorter hospital stay, and faster recovery time. Endoscopic sinus surgery alone can be used for early-stage lesions or in combination with open craniofacial surgery for locally advanced cases. Contraindications to endoscopic surgery include extensive dural involvement or extension into facial or orbital soft tissues. Prior to surgery, it is important to evaluate the extent of disease with regard to orbital involvement. There are three grades of orbital invasion:

- Grade I—destruction of medial orbital wall.
- Grade II—invasion of the periorbital fat, extraconal.
- Grade III—invasion of the medial rectus, optic nerve bulb, or eyelid skin, which implies breaching of the periorbita/periosteum.

Orbital exenteration should be performed for those with grade III invasion (gross transgression of the periorbita with orbital invasion) since orbital preservation with periosteal resection in cases of incomplete periosteal invasion yields comparable survivals and allows for functional eye preservation. After resection, most patients undergo surgical and/or prosthetic reconstruction to improve cosmesis, function, and quality of life. Complications of surgery include meningitis, hemorrhage, wound infection, abscess, CSF leak, pneumocephalus, trismus, and blindness. Regarding management of the neck, cervical lymph node metastases are typically uncommon for patients with sinonasal cancers (see following). Neck management (RT or neck dissection) should be performed in patients who have documented cervical lymph node involvement or locally advanced disease (T3/T4).

Chemotherapy: Although no prospective randomized trials have been performed in sinonasal cancer specifically regarding CHT recommendations, typically, management is similar to other H&N squamous cell carcinomas. Cisplatin-based CHT given concurrently with RT is recommended in cases of unresectable disease or postoperatively in patients with positive margins and extracapsular spread and can be considered for multiple intermediate risk factors (appropriate for SCC or ACA, but

benefit is unclear for other histologies). For patients with borderline resectable disease, preoperative CHT or chemoRT can decrease tumor size to facilitate surgery. A small prospective series of cisplatin-based induction CHT for patients with T3 or T4 tumors followed by surgery and postoperative RT demonstrated favorable 3-year EFS of 69%[4] and OS of 57%.[4]

Radiation: Typically, postoperative RT (started within 6 weeks of surgery) is used after maximum surgical resection and reconstruction. Definitive RT is recommended for patients with unresectable disease or for medically inoperable patients. Extrapolating from other H&N sites: 60 Gy for completely resected disease, 66 Gy for positive margins, and 70 Gy for unresectable or gross residual disease. In the paranasal sinus area, 1.8 Gy/fraction can be considered if multiple neural structures are treated or if escalating dose to >70 Gy. Refer to PORT Chapter 17 for more detailed information.

■ EVIDENCE-BASED Q&A

SINONASAL TUMORS

■ What is the risk of lymph node involvement?

In general, LN involvement is rare (<15% to 20%) at the time of diagnosis for patients with sinonasal tumors. However, in patients with SCC or poorly differentiated histology, this could be as high as 30%. The risk of lymph node involvement correlates with advanced T classification and inferior involvement of the alveolar ridge, gingivobuccal sulcus, and palate. In retrospective series, adjuvant elective nodal RT is associated with improved LC and RFS in these subgroups.[5–7] Nasal, ethmoidal, sphenoid, and frontal sinus cancers rarely metastasize regionally. The most commonly involved LNs levels are ipsilateral Ib and II, but consider RP and parotid for cancers of the mid-face or with lateral extension; contralateral involvement is rare.

■ What are the toxicities of RT in the current era?

Previous reports had high risks of toxicities to surrounding structures when treating patients with sinonasal cancer including visual complications (chronic pain and vision loss), pituitary dysfunction, osteoradionecrosis, and frontal/temporal lobe necrosis. IMRT has resulted in a decline in these complications without sacrificing LC or OS.[8]

■ Is there a role for proton beam therapy for patients with sinonasal cancer?

PBT has been observed to be safe and efficacious in multiple retrospective series, but prospective validation has yet to be published.

Yu, Multi-Institutional (*Adv Radiat Oncol* 2019, PMID 31673662): RR of 69 patients who underwent curative-intent PBT for sinonasal tumors from 2010 to 2016. Forty-two patients received de novo RT and 27 received re-RT; most common histology was SCC, and median dose was 58.5 GyE. With MFU 26 months, de novo patients experienced 3-yr OS, FFDP, and FFLR rates of 100%, 84%, and 77%, respectively. Re-RT patients experienced 3-yr OS, FFDP, and FFLR rates of 76.2%, 32.1%, and 33.8%, respectively, and also experienced freedom from distant metastasis rate of 47.4%. Late toxicity observed in 15% of patients with no grade >3 toxicities and no incidence of vision loss or symptomatic brain necrosis. **Conclusion: PBT appears safe and efficacious for patients with sinonasal tumors.**

■ Is there a role for charged-particle therapy for patients with sinonasal cancer?

Potentially, to spare the retina and uninvolved brain, but requires prospective investigation.

Patel, Mayo Arizona (*Lancet Oncol* 2014, PMID 24980873): Meta-analysis of 41 studies of nasal cavity and paranasal sinus tumors including 43 cohorts of treatment-naive patients (primary and adjuvant RT) and those with recurrent disease who were treated with CPT and photon therapy. Overall, higher 5-yr OS (RR 1.51, $p = .0038$) and DFS (RR 1.93, $p = .0003$) but no difference in 5-yr LRC (RR1.06, $p = .79$) but was higher in CPT cohort at long-term follow-up (RR 1.18, $p = .031$). Subgroup analysis compared IMRT to CPT showed higher DFS (RR 1.44, $p = .045$) and LRC (RR 1.26, $p = .011$). **Conclusion: CPT may lead to improvements in LRC, DFS, and OS but prospective studies are necessary.**

SNUC

SNUC is a rare, poorly differentiated, rapidly growing malignancy that arises from the mucosa of the nasal cavity or paranasal sinuses. SNUC historically accounted for 3% to 5% of sinonasal carcinomas, but retrospective pathology review in light of recent new histologic classifications (see following) has changed SNUC to a diagnosis of exclusion.[9,10] SNUC is associated with a poor prognosis, generally presenting with locally advanced disease (80% are T4 at presentation) and a high frequency of distant metastases, even when local disease control can be achieved. There are no prospective randomized clinical trials to guide treatment; however, a prospective series from MD Anderson evaluating induction CHT followed by response-adapted local therapy is described in the following. Otherwise, treatment involves surgery with adjuvant chemoRT or definitive chemoRT.

■ What are the outcomes with multimodality therapy in SNUC?

An NCDB analysis suggests combined modality therapy; either chemoRT alone or surgery combined with chemoRT yields the best survival rates.

Kuo, NCDB (*Otol Head Neck Surg* 2017, PMID 27703092): Retrospective NCDB analysis of 435 patients treated from 2004 to 2012. Multivariate cox regression evaluated OS based on treatment when adjusting for other prognostic factors (age, primary site, sex, race, comorbidity, insurance, and TNM stage). Results: OS was 41.5%. On MVA, surgery + chemoRT was associated with significantly higher OS compared to surgery + RT and RT alone. Surgery + chemoRT was not significantly different than chemoRT alone. **Conclusion: Combined modality therapy (chemoRT or surgery + chemoRT) is associated with improved OS vs. other treatment modalities in patients with SNUC.**

■ Is there a benefit to induction CHT in SNUC?

The following study from MD Anderson in the only prospective study to guide therapy for patients with SNUC.

Amit, MDACC (*JCO* 2019, PMID 30615549): Prospective cohort study of 95 patients with treatment-naive SNUC undergoing induction CHT prior to definitive locoregional therapy with either definitive chemoRT or surgery followed by RT or chemoRT; 5-yr DSS was 59% for the entire cohort. For patients with PR or CR after induction CHT, 5-yr DSS estimates for patients treated with chemoRT vs. surgery with post-op RT or chemoRT (not randomized) were 81% and 54%, respectively (log-rank $p = .001$). For patients without at least PR after induction CHT, 5-yr DSS estimates for chemoRT vs. surgery with post-op RT or chemoRT were 0% and 39%, respectively (adjusted HR 5.68, 95% CI 2.89–9.36). **Conclusion: For patients with favorable response after induction CHT, chemoRT was associated with improved OS compared to surgery. However, for patients without favorable response to induction CHT, surgery was associated with improved disease control and OS.**

■ How should the neck be managed in SNUC?

While prospective data are lacking, a meta-analysis of 12 studies demonstrated fewer regional recurrences with elective neck treatment in patients with clinically node negative necks, specifically showing regional failures in 3.7% of patients undergoing elective neck therapy vs. 26.4% in those without (OR 0.2, 95% CI 0.08–0.49, $p = .0004$).[11]

RARE SINONASAL CANCER SUBTYPES

■ What are the recently classified histological subtypes of sinonasal malignancies?

There are several emerging rare histologies of sinonasal malignancy recently characterized in the pathology literature[12;] some of them have not been distinctly classified by the World Health Organization.

HMSC: Rare entity characterized by indolent clinical course despite aggressive appearing histologic morphology with high rates of local recurrence. Mediated by HPV subtype 33 rather than 16, which is common in oropharyngeal HPV-related SCC. Commonly locally invasive at presentation. A retrospective case series of 57 patients demonstrated LR rate of 36.4% among all patients, with LR rates of 40% if PNI+ and 60% if bone invasion.[13] Despite these high rates of LR, there were no nodal recurrences and no cases of disease-specific mortality.

NUT-midline carcinoma: Arises from translocation of the nuclear protein on the testis called *NUTM1* on chromosome 15q14.6. These tumors represent ~2% of sinonasal carcinomas and are observed more in teens and young adults. These are aggressive tumors, with half of patients presenting with locoregional or distant metastases. Treatment involves surgery with adjuvant cisplatin-based chemoRT as previously noted. Prognosis is poor for this almost uniformly fatal disease with MS of 9 months.

SMARCB1 (INI-1)-deficient sinonasal carcinoma: Locally aggressive tumor usually presenting as T4 disease. The name is derived from the deletion of the tumor-suppressor gene *SMARCB1* found on chromosome 22. These tumors often arise in the ethmoid sinus and can demonstrate local invasion into the orbit or anterior cranial fossa. Imaging can demonstrate calcifications and "hair on end" phenomenon suggestive of aggressive periosteal reaction.

Olfactory neuroblastoma (Esthesioneuroblastoma): Small round blue-cell tumor arising from the olfactory epithelium. General treatment paradigm includes aggressive locoregional therapy with endoscopic resection followed by adjuvant RT for Kadish stage B through D patients (Table 19.5). Kadish stage A patients may be observed postoperatively. Standard post-op RT dosing recommended with minimum dose of 54 Gy. The risk of cervical nodal metastasis at diagnosis is 5%, but delayed cervical LN metastasis is common. Prophylactic vs. salvage management of the neck is controversial, but patients with Kadish stage C or Hyams grade III or IV disease are thought to be at higher risk of LN relapse. NCDB analysis demonstrated that prognosis is good for Kadish A–C patients (5-yr OS 80%, 88%, and 77% for stage A, B, and C, respectively) but worse for stage D (5-yr OS 50%).[14] However, a meta-analysis and SEER data demonstrate higher risk of DM and worse OS correlating with higher Hyams grade, suggesting grade is more prognostic than stage.[15,16] Concurrent CHT with cisplatin/etoposide added to adjuvant RT is indicated for positive margins or extranodal extension.

TABLE 19.4 Hyams Histologic Grading System: Esthesioneuroblastoma

Grade I	Prominent fibrillary matrix, tumor cells with uniform nuclei, absent mitotic activity, and no necrosis
Grade II	Some fibrillary matrix, moderate nuclear pleomorphism with some mitotic activity, and no necrosis
Grade III	Minimal fibrillary matrix, Flexner-type rosettes present, more prominent mitotic activity and nuclear pleomorphism, and some necrosis possible
Grade IV	No fibrillary matrix or rosettes, marked nuclear pleomorphism, increased mitotic activity, and frequent necrosis

TABLE 19.5 Kadish Staging System: Esthesioneuroblastoma

Stage	Definition
A	Confined to the nasal cavity
B	Involves the nasal cavity and one or more paranasal sinuses
C	Extending beyond the nasal cavity or paranasal sinuses
D	Regional lymph node or distant metastasis

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