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# Sinonasal Cancers: Diagnosis and Management

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Additional information is available at the end of the chapter

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## Abstract

Sinonasal cancers are rare tumors constitute 3% of head and neck cancers. These include malignancies of the nasal cavity and paranasal sinuses (maxillary sinus, ethmoid sinuses, frontal sinus and sphenoid sinus). Patients are often asymptomatic until late in the course of their disease. Tumors of the maxillary sinus are more common than those of the ethmoid sinus or nasal cavity. The workup for patients with suspected paranasal sinus tumors includes complete head and neck CT/MRI with contrast. FDG-PET/CT may be considered in the workup of patients with clinically apparent stage III or IV disease. The most common histology for these tumors is squamous cell carcinoma, others reported includes adenocarcinoma, esthesioneuroblastoma, minor salivary gland tumors, or sinonasal neuroendocrine carcinoma [SNEC]). Surgical resection for all T stages (except T4b, any N) followed by postoperative therapy remains a cornerstone of treatment. However, definitive RT or systemic therapy/RT is recommended for T4b, any N. Locoregional control and incidence of distant metastasis are dependent on T stage, N stage, and tumor histology.

**Keywords:** sinonasal cancers, radiotherapy, surgery, maxilla, ethmoid

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## 1. Introduction

Para-nasal sinuses are small air filled cavities occupying the facial and skull bones and along with nasal cavity, they form a small anatomical space but they are site of origin of histologically diverse group of tumors. These incorporate neoplasms derived from mucosal epithelium, seromucinous glands, soft tissues, bone, cartilage, neural/neuroectodermal tissue, haematolymphoid cells and the odontogenic apparatus.

## 2. Epidemiology

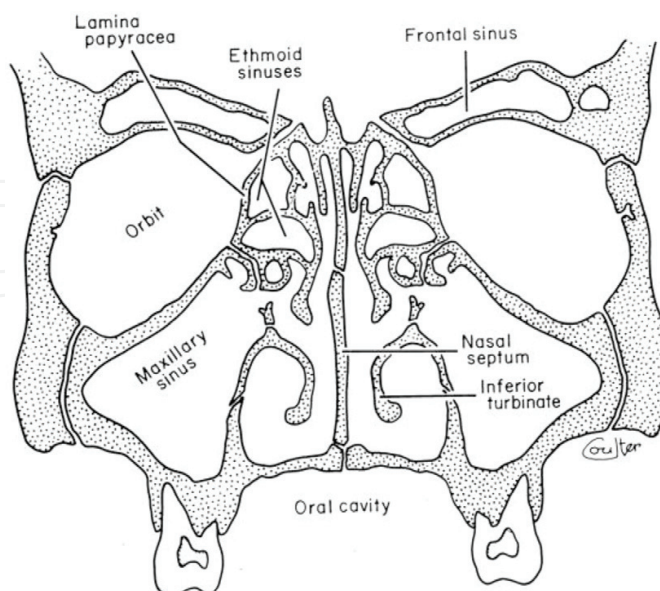
Nasal cavity and paranasal sinus cancers are a group of rare cancers, representing about 5% of all head and neck (H and N) cancer patients. They have an incidence of about 1 case every 100,000, with an average age between 50 and 60 years [1]. About 60% of sinonasal tumors originate in the maxillary sinus, 20–30% in the nasal cavity, 10–15% in the ethmoid sinus, and 1% in the sphenoid and frontal sinuses [2]. The incidence of cancer of the nasal cavity and paranasal sinuses (sinonasal cancer) is low in most of the populations (<1.5/100,000 in men and <1.0/100,000 in women), although higher incidence is seen in Japan and certain parts of China and India [3, 4]. Sinonasal squamous cell carcinoma and intestinal-type adenocarcinoma occur more commonly in men, with a male-to-female ratio of 2:1 in sinonasal squamous cell carcinoma, and up to 6:1 in intestinal-type adenocarcinoma [4, 5].

## 3. Anatomy

The paranasal sinuses are named according to the bones in which they are located: the ethmoid, maxilla, sphenoid, and frontal (**Figure 1**) [6].

### 3.1. Ethmoid complex

This paired complex of sinuses contains 3–18 cells that are grouped as anterior, middle, or posterior, according to the location of their ostia. The *posterior group* drains into the superior meatus above the middle nasal concha; sometimes one or more opens into the sphenoidal



**Figure 1.** A schematic illustration of the relationship between the eye and the paranasal sinuses. The roof of the orbit, the medial wall, and the floor are shared by the frontal, ethmoid, and maxillary sinuses, respectively.

sinus. The *middle group* into the middle meatus of the nose on or above the bulla ethmoidalis and the *anterior group* drains into the middle meatus of the nose by way of the infundibulum.

Since ethmoid sinus is a paired structure, it is connected in midline by cribriform part of ethmoid bone, which also separates it from anterior cranial fossa. Direct extension of the tumor through cribriform plate causes involvement of frontal lobe. A pointed bony landmark called crista galli stretches out from the midline of the cribriform plate upward into the floor of the anterior cranial fossa. The perpendicular plate of the ethmoid bone descends from the cribriform plate forms superior two thirds of the nasal septum. Middle, superior, and supreme turbinates originate from medial wall of each ethmoid labyrinth. Lamina papyracea forms the thin lateral wall, separating the ethmoid cells from the orbit. It forms an easy conduit for tumor spread from ethmoid sinus to orbit. The fovea ethmoidalis is a segment of the ethmoid bone and represents its superior portion which is seen as a continuation of the superior orbital roof to the cribriform plate.

### 3.2. Maxillary sinus

The maxillary sinus is the largest sinus occupying the body of the maxillary bone. The sinus is pyramidal in shape and has three recesses. The alveolar recess lies inferiorly, the zygomatic recess pointing laterally and the infra-orbital recess pointing superiorly. The floor is formed by the alveolar process of the maxilla. The roof is formed by floor of the orbit. It is traversed by infraorbital nerves and vessels. The base of the maxillary sinus forms the inferior part of the lateral wall of the nasal cavity. Anterior wall of the pterygopalatine fossa, also known as the sphenopalatine fossa, forms posterior wall of the maxillary sinus. The anterior sinus wall is the facial surface of the maxilla that is perforated by the infraorbital foramen below the orbital rim. The maxillary sinus drains into the middle meatus by means of the semilunar hiatus. The floor of the maxillary sinus is slightly below the level of the nasal cavity, and it is related to the upper teeth [7].

### 3.3. Sphenoid sinus

Sphenoid sinus is a paired structure that lies in the body of sphenoid bone. They may vary in size and are usually asymmetrical, attributable to the parallel dislocation of the mediating septum. The relationship of the posterior extension of the sphenoid in relation to the sella turcica is variable. With the exception of the sinus roof, the other sinus walls are of variable thickness depending on the degree of pneumatization. The sphenoid sinus is related superiorly to cavernous sinus, sella turcica and its contents, inferiorly to nasal cavity and posteriorly to nasal cavity and posterior ethmoidal cells. Posteriorly it is related to middle cranial fossa and laterally to cavernous sinus and cranial cavity [7].

### 3.4. Frontal sinus

They are paired structures located between the inner and outer tables of the frontal bone. Each opening into the anterior part of the corresponding middle nasal meatus of the nose through

the frontonasal duct. Medially associated with the contralateral frontal sinus, Superiorly, laterally and posteriorly with the frontal bone and frontal lobe and Inferiorly with the orbit [7].

## 4. Etio-pathogenesis

### 4.1. Etiology

The etiologic factors vary by tumor type and location. Occupational exposures to wood and leather dust have been strongly associated with sinonasal cancers [7]. The risk of developing sinonasal cancer also increases with exposure to formaldehyde, in the textile industry and to nickel/chromium compounds [8]. Adenocarcinomas have been associated with wood dust, leather dust, and formaldehyde [9]. The risk is strongest in cases of adenocarcinomas and in sinonasal malignancies. The impact is present after 40 or more years since first introduction and persists after discontinuation. Squamous cell carcinomas have been linked to arsenic and welding fumes [10].

High relative risks of sinonasal cancers (SNC) have been observed for specific chemical exposures and occupational settings, including farming, construction, miners, drillers, blasters, plumbers, machinists, bakers and pastry confectioners, metal industry (chromium and nickel compounds) [11–14]. In contrast to most head and neck cancers, tobacco smoking does not seem to have a key role in the development of sinonasal tumors; nevertheless, evidence suggests that smoking tobacco can increase the risk of SNSCC twofold to threefold [1].

### 4.2. Pathogenesis

Several studies have established a causal role of exposure to hard wood dust and leather in the development of sinonasal cancer. Wood dust is a complex mixture of organic and inorganic components, including genotoxic and carcinogenic factors [15]. Its capacity to induce DNA damage has been attributed in part to its particulate nature, which induces the generation of reactive oxygen species in the cells. Several studies have established a causal role of exposure to hard wood dust and leather in the development of sinonasal cancer, with particular association with intestinal-type adenocarcinoma.

Molecular alterations seen in intestinal-type adenocarcinoma (ITAC) mainly focused on TP53, K-ras and H-ras gene mutations and EGFR or HER2 over-expression. Ras genes were found to be mutated only in rare cases, with conflicting reports about a possible prognostic role [16]. EGFR and HER2 are over-expressed in about 30% of cases [17]. The rate of TP53 mutations in intestinal-type adenocarcinoma is about 60% and it is significantly higher than in squamous cell carcinomas; TP53 mutation rate in ITAC is directly correlated with duration, average and cumulative level of wood dust exposure [18].

In a study by Chernock et al. (81.8%) were diffusely positive for c-KIT, 27.3% cases were positive for EGFR, but none of the cases were positive for HER2/neu [19]. In contrast, in a

### **Malignant epithelial tumors**

- Squamous cell carcinoma
  - Verrucous carcinoma
  - Papillary squamous cell carcinoma
  - Basaloid squamous cell carcinoma
  - Spindle cell carcinoma
  - Adenosquamous carcinoma
  - Acantholytic squamous cell carcinoma
- Lymphoepithelial carcinoma
- Sinonasal undifferentiated carcinoma
- Adenocarcinoma
  - Intestinal-type adenocarcinoma
  - Nonintestinal-type adenocarcinoma
- Salivary gland-type carcinomas
  - Adenoid cystic carcinoma
  - Acinic cell carcinoma
  - Mucoepidermoid carcinoma
  - Epithelial-myoepithelial carcinoma
  - Clear cell carcinoma N.O.S.
  - Myoepithelial carcinoma
  - Carcinoma ex pleomorphic adenoma
  - Polymorphous low-grade adenocarcinoma
- Neuroendocrine tumors
  - Typical carcinoid
  - Atypical carcinoid
  - Small cell carcinoma, neuroendocrine type

### **Soft tissue tumors**

- Malignant tumors
  - Fibrosarcoma
  - Malignant fibrous histiocytoma
  - Leiomyosarcoma
  - Rhabdomyosarcoma
  - Angiosarcoma
  - Malignant peripheral nerve sheath tumor
- Borderline and low malignant potential tumors
  - Desmoid-type fibromatosis
  - Inflammatory myofibroblastic tumor
  - Glomangiopericytoma
  - (Sinonasal-type haemangiopericytoma)
  - Extrapleural solitary fibrous tumor
- Benign tumors
  - Myxoma
  - Leiomyoma
  - Haemangioma
  - Schwannoma
  - Neurofibroma
  - Meningioma

### **Haematolymphoid tumors**

- Extranodal NK/T cell lymphoma
- Diffuse large B-cell lymphoma
- Extramedullary plasmacytoma
- Extramedullary myeloid sarcoma
- Histiocytic sarcoma
- Langerhans cell histiocytosis

### **Benign epithelial tumors**

- Sinonasal papillomas
  - Inverted papilloma
  - (Schneiderian papilloma, inverted type)
  - Oncocytic papilloma
  - (Schneiderian papilloma, oncocytic type)
  - Exophytic papilloma
  - (Schneiderian papilloma, exophytic type)
- Salivary gland-type adenomas
  - Pleomorphic adenoma
  - Myoepithelioma
  - Oncocytoma

### **Tumors of bone and cartilage**

- Malignant tumors
  - Chondrosarcoma
  - Mesenchymal chondrosarcoma
  - Osteosarcoma
  - Chordoma
- Benign tumors
  - Giant cell lesion
  - Giant cell tumor
  - Chondroma
  - Osteoma
  - Chondroblastoma
  - Chondromyxoid fibroma
  - Osteochondroma (exostosis)
  - Osteoid osteoma
  - Osteoblastoma
  - Ameloblastoma
  - Nasal chondromesenchymal hamartoma

### **Neuroectodermal**

- Ewing sarcoma
- Primitive neuroectodermal tumor
- Olfactory neuroblastoma
- Melanotic neuroectodermal tumor of infancy
- Mucosal malignant melanoma



Germ cell tumors	Secondary tumors
<ul style="list-style-type: none"><li>• Immature teratoma</li><li>• Teratoma with malignant transformation</li><li>• Sinonasal yolk sac tumor (endodermal sinus tumor)</li><li>• Sinonasal teratocarcinosarcoma</li><li>• Mature teratoma</li><li>• Dermoid cyst</li></ul>	

**Table 1.** Classification of nasal and paranasal sinus tumors (modified by the World Health Organization histological classification of nasal and paranasal sinus cancer) [23].

study by Takahashi et al., sinonasal squamous cell cancer (SCC) is associated with increase in number of EGFR and HER2 copies in about 40 and 20% of the cases, respectively, with their occurrence being mutually exclusive. Expression of these biomarkers is seen in 82% of the cases, usually indicating a worse outcome [20].

There is increasing evidence that the human papillomavirus (HPV) is associated with a subset of sinonasal carcinomas. HPV has been detected in about 30% of sinonasal carcinomas [21]. HPV 16 seems to be the most frequent HPV type. The identification of HPV in sinonasal carcinomas has important clinical implications, because the presence of HPV could be a prognostic factor associated with a favorable outcome [21].

4.3. Pathological classification

The most-common subtypes of epithelial tumor are sinonasal squamous cell carcinoma, which predominantly occur in the maxillary sinus and nasal cavity, and intestinal-type adenocarcinoma (ITAC), which almost exclusively arise in the ethmoid sinus (Table 1) [22].

5. Pattern of spread

The pattern of spread of maxillary sinus cancers varies with the site of origin. Suprastructure tumors extend into the nasal cavity, ethmoid cells, orbit, pterygopalatine fossa, infratemporal fossa, and base of skull. Infrastructure tumors often infiltrate the palate, alveolar process, gingivobuccal sulcus, soft tissue of the cheek, nasal cavity, masseter muscle, pterygopalatine space, and pterygoid fossa [24].

Lymphatic drainage from the nasal cavity and paranasal sinus occurs in two directions, anterior, and posterior [25]. The anterior mucosal and vestibular skin drainage is by way of lymphatic channels traveling to the facial, parotid, or submandibular groups of nodes, then to the superior deep cervical nodal chain, primarily level II. The posterior lymphatics course posteriorly to a plexus anterior to the torus tubarius, posterior to the retropharyngeal nodes, and inferiorly to the posterior and superior deep cervical nodes [26]. Studies have demonstrated that SCC is associated with a high incidence of nodal metastasis, neck failure and inferior disease-specific survival rate [27, 28].

## 6. Clinical presentation

The majority of maxillary sinus tumors present with nasal fullness, stuffiness, obstruction, epistaxis, rhinorrhea, pain, paresthesia to tooth mobility, tooth loss, proptosis, diplopia, and lacrimation [29].

Owing to the nonspecific and the often relatively mild nature of the symptoms at early stages of disease, sinonasal malignancies have a prolonged diagnostic latency [29].

## 7. Diagnostic evaluation

Inspection and palpation of the orbits, nasal and oral cavities, and nasopharynx can provide preliminary determination of tumor extent. Bimanual palpation is important in assessing contiguous extension of nasal vestibule lesions and in identifying buccinator and submandibular nodal involvement.

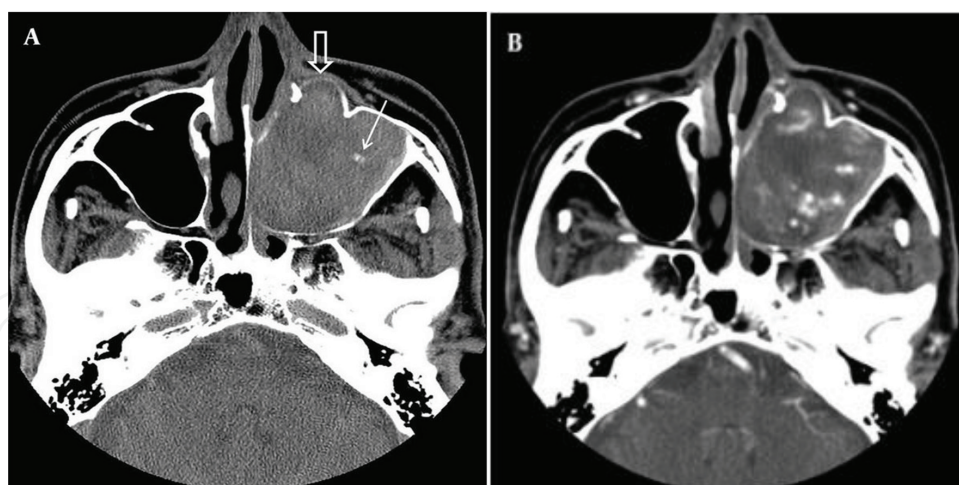
For a suspected sinonasal expansile mass, the clinical examination is incomplete without a nasal endoscopy by flexible and/or rigid endoscopes. Nasal endoscopy allows direct visualization of the lesion and may help in differentiating an inflammatory polyp from a neoplasm, benign or malignant. A unilateral expansile mass with an irregular surface, necrotic areas, and contact bleeding ought to be considered as suspicious and potentially suggestive of malignancy.

Endoscopic evaluation may also allow, especially in those cases not completely filling the nasal fossa, identification or suggestion of the possible site of origin of the lesion, its local extension and to assess the presence of satellite lesions. Oral cavity should also be examined to check for loosening of teeth to rule out involvement of alveolar process of maxilla in cases of maxillary sinus malignancy or any oro-nasal/oro-antral fistula; maxillary sinus tumours may also present as a submucosal swelling at level of the cheek, gingiva-buccal sulcus. A recent history of an otherwise unexplainable tooth extraction or mobility should also be considered.

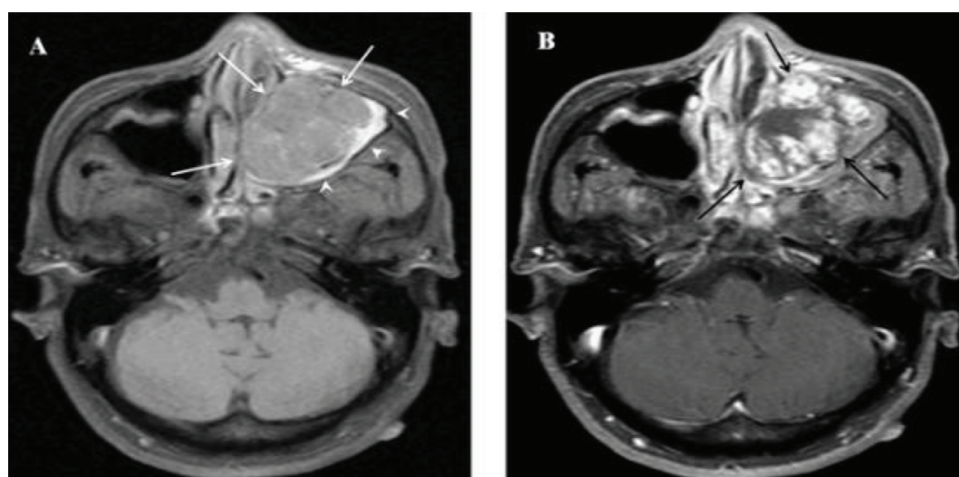
Although the incidence of cervical lymph node involvement is relatively low in sinonasal malignancies, but all cervical lymph node stations must be palpated. The lesions involving the oral mucosa and/or with aggressive histologic behaviour show high risk of lymphatic spreading (i.e., sinonasal undifferentiated carcinoma, high-grade olfactory neuroblastoma). In these cases, clinical evaluation of the neck must be completed by ultrasound so as confirm any neck swelling and metastasis to neck nodes must be confirmed by fine needle aspiration cytology.

Clinical examination of cranial nerves (from I to VI) should be also performed. Malignancies of ethmoid sinus or maxillary sinus can present with alteration of eyeball positioning due to orbital invasion, which can present with proptosis with or without diplopia, due to orbit compression, intraorbital extension or extrinsic muscle involvement. The infraorbital nerve (branch of the maxillary division of the trigeminal nerve) can also be affected especially in lesions extending into the pterygopalatine fossa and/or masticatory space, resulting in sensory disturbances of the cheek. Involvement of cavernous sinus or orbital apex can lead to visual disturbances due to optic nerve infiltration.





**Figure 2.** (A) Nonenhanced axial CT scan shows a large, soft tissue mass in the nasal cavity and maxillary sinus, on the left side. (B) Enhanced axial CT of the lesion shows an inhomogeneously enhancing soft tissue mass.



**Figure 3.** (A) Axial scan shows T1-weighted image with intermediate signal intensity lobulated mass lesion (white arrows) in the left maxillary sinus. Obstructed left maxillary sinus have high signal intensity sinonasal secretions (arrowheads). (B) Enhanced T1-weighted image shows heterogeneous intense enhancement (black arrows).

In the diagnosis of paranasal sinuses tumors MR imaging is a vital tool in the diagnosis of these lesions and is used in conjunction with computed tomography to precisely delineate the extent of neoplasms and involvement of the skull base, the orbits (**Figures 2 and 3**) [30]. The involvement of fine bone structures is best evaluated with contrast-enhanced computed tomography (CECT). CECT provides excellent details about the thin bony paranasal sinuses walls separating the ethmoid from the anterior skull base and the orbit [31].

### 7.1. Biopsy

Transnasal biopsy is preferred for tumors arising from or extending into the nasal cavity or nasopharynx. Some paranasal sinus tumors may be more easily sampled using transoral procedures or an open Caldwell-Luc approach.

8. Staging

The American Joint Committee on Cancer (AJCC) staging system for the nasal cavity and paranasal sinuses (8th edition, 2017) is depicted in **Tables 2–8** [32] (mucosal melanoma of the nasal cavity and paranasal sinuses are not included).

T category	T criteria for maxillary sinus
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues. Floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

Table 2. T staging for maxillary sinus.

T category	T criteria for ethmoid sinus and nasal cavity
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Moderately advanced local disease Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus

Table 3. T staging for ethmoid sinus and nasal cavity.

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)

N category	N criteria
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or metastasis in any node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) with clinically overt ENE (ENEC)

Table 4. Clinical regional lymph nodes.

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral or contralateral node 3 cm or less in greatest dimension and ENE(+); or a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)

Table 5. Pathological regional lymph nodes.

M category	M criteria
M0	No distant metastasis (no pathologic MO; use clinical M to complete stage group)
M1	Distant metastasis

Table 6. Distant metastasis.

Stage 0	Tis	N0	Mo
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	Mo
	T1–3	N1	M0
Stage IVA	T4a	N0–2	M0
	T1–3	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Table 7. Anatomic stage/prognostic groups.

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Table 8. Histologic grade (G).

9. Prognostic factors

Patient-specific factors (primarily prognostic for survival) include age and performance status. Disease specific factors (primarily prognostic for locoregional control) include location, histology, and locoregional extent (reflected in TNM stage), and perineural invasion. Independent of the treatment type used, the prognosis of patients with sinonasal carcinomas is poor, with an overall 5-year survival rate of 30–50% [33]. The 5-year survival rates depend on disease stage and drops from 80% in patients with T1 disease to 30% in patients with T4 tumors [34]. Extensive local disease involving the nasopharynx, base of skull, or cavernous sinuses markedly increases surgical morbidity as well as increases local recurrence often within 2 years of follow up [35].

10. Treatment option overview

Treatment should be individualized based on location and extent of disease, patient performance status, stage of tumor, histopathologic subtype of tumor and availability of local

expertise; because of the rarity of these tumors, consideration should be given to referring patients to centers with experience in their management.

Studies have shown that surgery gives the best results. Early infrastructure lesions may be cured by surgery alone, but, for most other cases, RT is given postoperatively even if margins are negative. Adjuvant Chemo-radiotherapy should be considered for a positive margin. The extension of cancer to the skull base, nasopharynx, or sphenoid sinus contraindicates excision [29, 30, 36].

### 10.1. Surgery

Surgery can produce excellent control rates for T1 and T2 tumors and is generally the mainstay of treatment.

However for T2 tumors, radiation therapy along with surgery is recommended. In patients undergoing radical surgery, it not only removes the bulk of the tumor but also re-establishes the drainage of involved sinus. It can be further followed by postoperative radiotherapy depending upon the stage of the tumor. Radical neck dissection or elective neck radiation therapy is prescribed only for the patients presenting with positive neck nodes. The incidence of lymph node metastases is generally low (approximately 20% of all cases).

Intracranial extension of tumor (i.e., anterior cranial fossa in cases of involvement of cribriform plate in ethmoid sinus tumors), cavernous sinus, or the pterygoid process; infiltration of the mucous membranes of the nasopharynx; or nonresectable lymph node metastases are relative contraindications to surgery [26, 27].

Maxillary sinus and ethmoid sinus tumors often present as locally advanced disease (large T3 or T4) and are commonly managed with surgery and postoperative radiation therapy. Ethmoid sinus carcinomas can be treated with radiation alone or with concurrent chemotherapy to avoid structural or functional deficits [37].

Surgical approaches include fenestration with removal of the bulk tumor, which is usually followed by radiation therapy or block resection of the upper jaw. Surgery generally involves medial maxillectomy and en bloc ethmoidectomy. A craniofacial approach is required if tumor extends superiorly to the ethmoid roof or olfactory region. A combined craniofacial approach, including resection of the floor of the anterior cranial fossa is used with success in selected patients [38].

Surgical exploration may be required to determine operability. Destruction of the base of skull (i.e., anterior cranial fossa), cavernous sinus, or the pterygoid process; infiltration of the mucous membranes of the nasopharynx; or nonresectable lymph node metastases are relative contraindications to surgery.

### 10.2. Chemotherapy

Few studies have investigated the role of neoadjuvant chemotherapy in the management of advanced cancer of the PNS [39, 40]. Intra-arterial cisplatin in combination with intravenous paclitaxel and ifosfamide in patients with locally advanced carcinoma of the PNS was studied



at MD Anderson Cancer Center to determine the efficacy, organ-preservation rate, and safety. Despite better organ preservation rates, generous toxicity was also reported [41]. Further study of the role of neoadjuvant chemotherapy in patients with SCC of the PNS is warranted to determine whether the response (or lack of same) to neoadjuvant chemotherapy can help in the choice of definitive treatment [42].

Concurrent chemo-radiation therapy can also be used for patients with medical conditions that preclude surgery if those patients have good performance status. Depending on the patient’s performance status and renal function, single-agent cisplatin or carboplatin can be used concurrently with external beam radiation for locally advanced, unresectable squamous cell carcinoma [43].

10.3. Radiation therapy

RT treatment planning includes the entire maxilla, the adjacent nasal cavity, the ethmoid sinus, the nasopharynx, and the pterygopalatine fossa. All or part of the orbit is included in patients with extension into or near the orbit. Target volume definition is aided by the use of treatment planning CT combined with image-fusion MRI.

When using conventional definitive fractionation, the primary tumor and involved lymph nodes (i.e., high-risk sites) generally require a total of 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction) [44]. When using hyperfractionation, high-risk sites generally require up to 81.6 Gy (1.2 Gy/fraction) [45]. In contrast, elective irradiation to low-risk and intermediate-risk sites requires 44 Gy (2.0 Gy/fraction) to 63 Gy (1.6–1.8 Gy/fraction), depending on the estimated level of tumor burden, and on whether 3-D conformal RT or IMRT is used.

For 3-D conformal RT and sequentially planned IMRT, suggest 44–50 Gy (2.0 Gy/fraction). For concurrent chemoradiation the dose is typically 70–70.2 Gy (1.8–2.0 Gy/fraction) in 5 fractions. Higher doses of postoperative RT alone (60–66 Gy), or with systemic therapy, are recommended for the high-risk features of extracapsular disease and/or positive margins (Table 9) [46].

Postoperative RT	<ul style="list-style-type: none"><li>• T3-T4 primary disease</li><li>• Microscopic margins &lt; 5 mm (irrespective of intra-operative revision or additional postresection sampling of the surgical site)</li><li>• &gt;1 additional features at primary:<ol style="list-style-type: none"><li>1. High-grade disease</li><li>2. Peri-neural invasion (PNI)</li><li>3. Lymph-vascular invasion (LVSI)</li></ol></li><li>• Lymph node involvement at pathology<ol style="list-style-type: none"><li>1. ≥2 lymph nodes</li><li>2. Any lymph node &gt; 3 cm (N2+)</li><li>3. Level IV-V LN positive</li><li>4. Extracapsular extension (ECE)</li></ol></li></ul>
Preoperative RT	<ul style="list-style-type: none"><li>• Locally advanced cancer for downstaging of disease</li></ul>
Concurrent chemoradiotherapy	<ul style="list-style-type: none"><li>• Positive (inked) margin</li><li>• Extracapsular extension</li></ul>

Table 9. Indications of radiation therapy.



### 10.3.1. *Simulation and daily localization*

The patient is simulated in supine position with head extended and the head and neck are immobilized. If possible, shoulders should also be immobilized to ensure accurate patient setup on a daily basis especially when an extended-field IMRT plan is used. To spare the tongue from high dose nasopharyngeal region, a bite block can be used.

CT scan with IV contrast using 3 mm thickness should be performed from the top of the head including the brain to the carina. 5 mm thickness can be reconstructed below the clavicle to the level of the carina.

Image registration and fusion applications with MRI and PET scans should be used to help in the delineation of target volumes, especially for regions of interest encompassing the gross tumor, skull base, brainstem, and optic chiasm.

## 10.4. **Complication of treatment**

Complications of surgery include failure of the split thickness skin graft to heal, trismus, CSF leak, meningitis, parasinusitis and hemorrhage.

The most frequent and significant complications of RT involve the eye [47, 48]. When only a portion of the ipsilateral eye is irradiated (the medial one third), it is possible to preserve vision in the majority of patients. When there is extensive disease in the orbit, however, the entire eye is irradiated to a high dose with almost certain loss of vision. A few patients will experience a transient CNS syndrome that includes vertigo, headaches, decreased cerebation, and lethargy [49]. Other rare complications are aseptic meningitis, chronic sinusitis, or serous otitis media.

## 11. **Results of treatment**

The management of PNS cancers remains a major challenge in oncology. A major problem in patients with carcinomas of the PNS is that most tumors are highly advanced at the time point of diagnosis.

For single-modality therapies, outcome is generally poor. Amendola et al. compared surgery versus definitive radiation on 39 patients and found no statistically significant differences in survival at 3 and 5 years, with a 5 year survival rate of 31 and 35% for resection and RT, respectively. Later, combined modality treatment was considered superior [50]. A number of reports have demonstrated some improvement in outcome with combined modality therapy. A report by St. Pierre and Baker based on treatment responses of 61 patients treated with surgical resection alone, definitive RT or combined treatment, showed a clear benefit for patients receiving combined surgery [51].

Clinical outcomes of postop patients with carcinomas of the paranasal sinuses and nasal cavity according to decade of radiation treatment were compared at Memorial Sloan-Kettering Cancer Center. In this study, 46% patients were treated by conventional radiotherapy; 35% patients by three-dimensional conformal radiotherapy; and 18% patients by intensity-modulated

radiotherapy. The 5-year overall survival rates were 52%, local control rate was 62%, and disease-free survival was 54%, respectively. There were no significant differences in any of these parameters with respect to radiotherapy technique. The 5-year overall survival rate for patients treated in the 1960s, 1970s, 1980s, 1990s, and 2000s was 46, 56, 51, 53, and 49%, respectively. The observed incidence of severe late toxicity was 53, 45, 39, 28, and 16% among patients treated in the 1960s, 1970s, 1980s, 1990s, and 2000s, respectively [52].

In the past, the main concern in the radiotherapeutic treatment of PNS tumors was treatment-related toxicity. The introduction of IMRT now allows application of high doses to complex target volumes, while the surrounding OARs can be spared and toxicity may be reduced. Over the last years, IMRT has been implemented widely into the clinical routine. Duthoy et al. compared IMRT with conventional RT in 39 patients with PNS cancers. In the comparison between the IMRT and conventional RT groups, no significant differences were found for LC and OS [53].

Dose conformality to the target volume and conformal avoidance of the organs at risk achieved through IMRT may provide better local control and less optic toxicity compared to conventional radiotherapy technique. Image-guided radiation therapy (IGRT) has also been introduced to complement these approaches in ensuring the safe delivery of a highly conformal treatment, by facilitating convenient and frequent imaging of the patient anatomy throughout the treatment course [54].

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