American College of Radiology
ACR Appropriateness Criteria®

NASAL CAVITY AND PARANASAL SINUS CANCERS

Expert Panel on Radiation Oncology–Head & Neck Cancer: Farzan Siddiqui, MD, PhD[1]; Richard V. Smith, MD[2]; Sue S. Yom, MD, PhD[3]; Jonathan J. Beitler, MD, MBA[4]; Paul M. Busse, MD, PhD[5]; Jay S. Cooper, MD[6]; Ehab Y. Hanna, MD[7]; Christopher U. Jones, MD[8]; Shlomo A. Koyfman, MD[9]; Harry Quon, MD, MS[10]; John A. Ridge, MD, PhD[11]; Nabil F. Saba, MD[12]; Francis Worden, MD[13]; Min Yao, MD, PhD[14]; Joseph K. Salama, MD.[15]

Summary of Literature Review

Introduction/Background

The paranasal sinuses consist of the maxillary, ethmoid, sphenoid, and frontal sinuses. They communicate with the nasal cavity in the midline and all structures together form a group of air-filled cavities where cancers can arise, grow, and spread without encountering significant barriers to local extension. Cancers of the paranasal sinuses and nasal cavity are rare malignancies, accounting for 3%–5% of all head and neck cancers and <1% of all cancers [1-3]. The maxillary sinus is the most common site of paranasal sinus cancers (60%–70% of cases), followed by the nasal cavity (20%–30%), ethmoid sinus (10%–15%), and frontal and sphenoid sinuses (1%–2%). These are to be distinguished from skin cancers with deep erosion or nasal vestibule/nasal sill cancers with posterior extension. Due to the air space and cavities in the sinonasal region, these cancers are generally asymptomatic in early stages and are often not diagnosed until they are locally advanced. There are a wide variety of tumor types within the paranasal sinuses and nasal cavity, but as in other locations in the head and neck, squamous cell carcinoma predominates, accounting for >80% of paranasal sinus cancers [2,4]. The 5-year overall survival in patients with squamous cell carcinoma of the paranasal sinuses is approximately 50%, 30%, and 15% among those with localized, regional, and distant disease, respectively [3]. Tobacco use is a significant risk factor for squamous cell carcinomas, and exposure to wood dust, glues and adhesives, and pollutants is associated with adenocarcinomas.

These cancers are relatively rare, resulting in a consequent lack of well-designed prospective trials to guide therapy. Therefore, most treatment recommendations are based on retrospective studies. Unfortunately, these reports have included a mix of disease sites and stages; they often represent varied histologies. Additionally, many of the large retrospective series include patients treated over many decades, with changes in diagnostic imaging, surgical techniques, radiation therapy (RT) techniques and doses, and use of systemic agents further clouding the applicability of these studies. Hence, definitive treatment recommendations regarding a specific subsite with a specific histology are hard to derive. Finally, many studies present significant institutional bias.

Anatomy and Patterns of Spread

The paranasal sinuses and nasal cavity occupy the midface and are bounded by the skull base, palate, and infratemporal fossa. Although the paranasal sinuses have defined boundaries, the degree of pneumatization is widely variable, which can affect the ability of a tumor to invade the surrounding structures. These adjacent structures are generally responsible for the signs and symptoms that prompt evaluation and diagnosis, heralding an advanced stage.

The maxillary sinus is the largest of the paranasal sinuses and is bounded by the floor of the orbit superiorly, the lateral wall of nasal cavity medially, the zygomatic process and deep masseteric space laterally, and the alveolar processes and palate inferiorly. Tumors that invade the orbit lead to proptosis, diplopia, and other visual changes.

[1]Principal Author, Henry Ford Health System, Detroit, Michigan. [2]Co-author, Montefiore Medical Center, Bronx, New York, American College of Surgeons. [3]Panel Vice-chair, University of California San Francisco, San Francisco, California. [4]Emory University School of Medicine, Atlanta, Georgia. [5]Massachusetts General Hospital, Boston, Massachusetts. [6]Maimonides Cancer Center, Brooklyn, New York. [7]University of Texas MD Anderson Cancer Center, Houston, Texas. [8]Radiological Associates of Sacramento, Sacramento, California. [9]Cleveland Clinic, Cleveland, Ohio. [10]Johns Hopkins University, Baltimore, Maryland. [11]Fox Chase Cancer Center, Philadelphia, Pennsylvania, American College of Surgeons. [12]Emory University, Atlanta, Georgia, American Society of Clinical Oncology. [13]University of Michigan, Ann Arbor, Michigan, American Society of Clinical Oncology. [14]University Hospitals Case Medical Center, Cleveland, Ohio. [15]Panel Chair, Duke University, Durham, North Carolina.

Reprint requests to: publications@acr.org

Trismus, facial swelling, tooth pain, and midface or jaw numbness signify spread to the infratemporal fossa, pterygopalatine fossae, or masseteric space. The maxillary sinus can be divided into 2 portions by the imaginary Ohngren line, drawn from the medial canthus to the angle of the mandible. This line separates the maxillary sinus into suprastructure (posterosuperior portion) and infrastructure (anteroinferior portion), a historically important distinction. Although this designation is not part of current staging, it is clinically useful for providing a framework to predict extension outside the sinus cavity and it functions as a general guide to surgical resectability. Lesions originating in the suprastructure more readily invade the nasal cavity, ethmoid sinus, orbit, pterygopalatine fossa, infratemporal fossa, and skull base. Involvement of these structures gives rise to a higher T-stage and may render the tumor unresectable, thus portending a poorer prognosis. Lesions inferior to the Ohngren line tend to invade the soft palate, mandible, buccal mucosa, nasal cavity, and pterygopalatine space. These lesions typically carry a lower T-stage and have a better prognosis because they are more often resectable with uninvolved margins.

Primary nasal cavity tumors often originate on the nasal septum or roof of the nasal vault and will usually fill the airspace on the involved side. The nasal cavity is bounded anteriorly by the mucocutaneous junction with the nasal vestibular skin, posteriorly by the choana, laterally by the turbinates and lateral nasal wall, superiorly by the skull base, and inferiorly by the hard palate. Septal cancers should be carefully distinguished from skin cancers originating from the nasal vestibule/sill. The pattern of cancer spread is typically determined by the site of origin of the tumor. For example, lesions in the superior portion of the nasal cavity can invade the orbit through the ethmoid sinuses and lamina papyracea and the anterior cranial fossa through the cribriform plate, whereas more inferior lesions can invade the maxillary sinuses and the palate. Anteriorly, they can grow into subcutaneous tissue and the overlying skin.

The ethmoid sinuses are in close proximity to critical structures such as those in the orbit, containing the optic nerve laterally and optic chiasm posteriorly, and the base of the skull. The paranasal sinuses are separated from the orbit by the lamina papyracea. The thin lamina allows easy access to the orbit, which can result in diplopia, proptosis, and visual loss from relatively small tumors. Superior extension into the anterior cranial fossa is also easy due to the poor tumor barrier provided by the fenestrated cribriform plate. Superior extension is facilitated by the olfactory nerves, which cross the cribriform plate, providing intracranial access. In addition, ethmoid sinus cancers often extend to involve the adjacent maxillary sinus.

The sphenoid sinus is a midline structure and cancers arising here often extend laterally to involve the adjacent cavernous sinus or orbital apex. The occult nature of these tumors often results in intracranial extension. The frontal sinus resides within the anterior skull and is bounded by the anterior cranial fossa and the tissues of the forehead. The pneumatization pattern is quite variable, even side-to-side in the same patient, and may extend laterally over the orbital roof.

Lymph node involvement at the time of diagnosis is rare for most nasal cavity and paranasal sinus malignancies. The rates are generally below the 15%–20% recommended for elective treatment. However, in patients with squamous cell and poorly differentiated carcinoma of the maxillary sinus, the cumulative macroscopic and microscopic incidence of nodal disease can be as high as 30%. In a report of patients with predominantly T3 and T4 cancers of the maxillary sinus, the regional recurrence rate was 38% in patients with squamous cell and poorly differentiated carcinoma in the absence of elective neck treatment [5]. The most commonly involved lymph nodes are ipsilateral level Ib and level II lymph node groups. Contralateral nodal involvement is very rare. Le et al [6] reported that the overall risk of nodal involvement at diagnosis and on follow-up was 28% for squamous cell carcinoma of the maxillary sinus. The risk of lymph node involvement correlates with advanced T-stage and inferior involvement of the alveolar ridge, gingivobuccal sulcus, and palate. In the above series, all patients with nodal involvement had T3-4 disease. This is in contrast to nasal, ethmoidal, sphenoid, and frontal sinus cancers, which rarely metastasize regionally. Extension outside the confines of the involved sinus (higher T-stage) allows access to more robust lymphatics and may lead to a higher rate of nodal disease. In addition to levels Ib and II, the retropharyngeal nodes need to be assessed for all paranasal sinus tumors and the parotid nodes are potential first-echelon nodes in cases of midface or lateral extension. Nasal cavity cancers also have low nodal metastatic rates, and 1 series of primary nasal cavity cancer reported a rate of subsequent neck recurrence of 7% in patients without neck treatment [7].

Clinical Presentation and Patient Evaluation

The paranasal sinuses and nasal cavity are unique in that they largely consist of air-filled spaces. This allows for insidious growth of a tumor with relatively few obvious symptoms until the tumor reaches an advanced stage after invading adjacent structures. For sinonasal malignancies, presenting symptoms are usually nonspecific and may mimic sinusitis until lesions extend into the surrounding tissues. Common symptoms include nasal obstruction, nasal discharge, epistaxis, a visible tumor mass, facial pain or discomfort, or hypoesthesia of the midface. The diagnosis requires a high index of suspicion [8]. The symptoms and signs resulting from local extension outside the involved sinus can include facial swelling and pain from anterior extension; proptosis, diplopia, and orbital pain with orbital invasion; or toothache, unhealed tooth socket after dental extraction, a mass in the upper gum, or an oroantral fistula from inferior extension.

A full history and physical examination should be performed with emphasis on careful examination of cranial nerve function. Endoscopic nasal examination allows assessment of local extension of the disease. Imaging studies should include dedicated thin-cut multiplanar computed tomography (CT) and magnetic resonance imaging (MRI) of the sinuses. CT offers better information on bone invasion and MRI offers better information about the involvement of soft tissue, nerves, skull base, and brain and better differentiation of fluid from solid tumor. Tissue biopsy must be performed for definitive pathologic diagnosis and careful endoscopic evaluation can be performed at that time.

Prognostic Factors

One of the most important prognostic factors for these tumors is the local extension of the tumor, signified by the American Joint Committee on Cancer T-stage. T3 and T4a tumors are locally advanced by virtue of invasion of structures in the immediate vicinity but are considered surgically resectable. Stage T4b tumors are surgically unresectable as they invade the orbital apex, dura, brain, middle cranial fossa, cranial nerves other than CN V2, nasopharynx, or clivus. The local extent determines the ability to perform a surgical resection with clear margins and the structures that must be sacrificed to achieve them. The potential loss of structures, such as the eye with maxillary sinus cancer, although technically feasible and appropriate, may overwhelm the patient and lead to rejection of surgical management. Adequate counseling must be provided in order to permit informed decisions on the part of the patient.

Other negative prognostic factors for nasal cavity and paranasal sinuses include advanced N-stage, intracranial tumor infiltration, or infiltration of the pterygopalatine fossa, skull base, dura, cribriform plate, or orbits [9-12].

Principles of Management and Treatment Outcomes

Management of nasal cavity and paranasal sinus malignancies should involve a multidisciplinary approach with the inclusion of head and neck/skull base surgeons, neurosurgeons, radiation oncologists, medical oncologists, and neuroradiologists. All cases must be discussed and reviewed by a panel of these experts and the role and sequencing of each treatment modality must be determined. If surgery is to be performed, upfront involvement of the reconstructive team, including plastic surgeons, oral surgeons, and prosthodontists, is also crucial.

Surgery

Surgical resection of the primary cancer remains the primary modality of therapy for paranasal sinus cancers. The type of procedure varies for the primary site and can include an open approach, an endoscopic approach, or a combination of the two. Traditional surgical approaches have been performed through external-access incisions (lateral rhinotomy, bicoronal flap, or a combination of the two), and such approaches can lead to local complications. Intraoral approaches to the maxillary sinus and palate are often adequate for infrastructure, nasal floor, and inferior septal tumors. Such resections are distinct from the resections of advanced tumors or those involving the superior nasal vault and skull base. Reconstruction of these areas was typically not performed, primarily to facilitate disease monitoring, and rehabilitation was instead left to prosthodontics and obturator placement. Unpredictable scarring of the midface structures would often occur and implants used to reconstruct the orbital floor were often extruded. Additionally, larger defects in the hard palate often led to chronic challenges with obturator retention, given the limited bone and soft-tissue support. The use of free tissue transfer has improved these outcomes because the defects are closed and the remaining structures (orbit, dura, etc) are well supported by the reconstruction. If bone is included in the free tissue transfer, such reconstruction can also replace the bony alveolar ridge to help facilitate dental restoration or prosthetic retention. When possible, free tissue transfer should be the default reconstructive option. Inferior maxillectomy defects, however, remain particularly amenable to obturator reconstruction for patients in whom free tissue transfer is either not appropriate or not

desired. These procedures remain important options, particularly in the case of recurrent disease, but these tumors are more frequently managed through minimally invasive endoscopic techniques.

Current minimally invasive surgical techniques with immediate reconstruction have altered the postoperative landscape for these patients. Open craniofacial resections, traditionally used for tumors involving the cribriform plate, have been reported to have rates of postoperative morbidity approaching 40% and mortality rates of approximately 5% [13,14]. Widespread adoption of endoscopic sinus surgery for benign disease led to the evolution of endoscopic resection of sinonasal tumors. A recent meta-analysis of 47 studies with 453 patients evaluated various surgical approaches including endonasal, cranionasal, and craniofacial resections [15]. The authors noted a selection bias for the surgeries performed, with a larger proportion of lower-grade smaller tumors being treated endoscopically. The local recurrence rates in the endoscopic, cranionasal, and craniofacial groups were 8%, 16.7%, and 22%, respectively. Similar experiences have been reported by others [16,17]. Current endoscopic techniques allow resection of all aspects of the paranasal sinuses and cranial base, including intracranial tumor resection, dural resection, and complex reconstruction to achieve negative margins while minimizing cerebrospinal fluid leak and other complications. Endoscopic skull base surgery for sinonasal cancers has gained increasing acceptance and is now practiced at many centers. Smaller tumors involving the maxillary infrastructure do not require such technical options and are appropriately managed through anterior or transoral "open" techniques with excellent results and minimal morbidity. Debilitating defects are no longer routine and soft-tissue coverage of the resected field and adjacent skull base has reduced the cosmetic consequences of adjuvant therapy (see Variant 1).

Even though the majority of patients present with locally advanced (T3-T4) disease, surgical resection must be considered as part of the initial management whenever possible. There is also interest in exploring the role of neoadjuvant chemotherapy to make the tumor more amenable to surgical resection. This topic is discussed below. Many retrospective series have compared the outcomes of patients treated with surgery followed by adjuvant RT versus RT alone. A selection bias towards comparatively lower-stage and less-invasive cancers may be present in patients who undergo initial surgery. Jansen et al [18] identified 6 parameters that were associated with higher likelihood to recommend RT alone: clinical T4 classification, radiological evidence of skull base invasion, age >65 years, radiological evidence of nasopharynx invasion, clinical suspicion of palate invasion, and radiological evidence of skin invasion. As skull base surgery has evolved, however, surgical resection of advanced tumors is more commonplace, including those previously defined as "unresectable" (see Variant 2 and Variant 3).

At the University of Florida between 1964 and 2005, 109 patients with nasal cavity and paranasal sinus cancers (excluding maxillary sinus) were treated with curative intent [19]. Fifty-six patients were treated with definitive RT and 53 with surgery and RT. Patients who received combined-modality therapy had a 5-year local control rate of 84%, compared to 43% in those treated with RT alone. Other reports, each with more 200 patients, from Dulguerov et al and Guntinas-Lichius et al also confirm the benefit of combining surgery and RT for locally advanced sinonasal cancers [9,11].

Due to the complex anatomy, proximity of critical normal tissues, and advanced stages at presentation, complete resection with negative margins may be difficult to achieve. Resto et al [20] evaluated the impact of extent of surgical resection in 102 patients with various histologies. Patients were characterized as having had a complete resection with negative margins (20%), partial resection with positive margins (49%), or biopsy only (31%). RT was delivered using a combination of protons and photons. Complete resection was found to be associated with better treatment outcomes. Although a higher radiation dose was delivered to patients with positive margins (75 Gy versus 68 Gy for those with negative margins), there was a strong trend toward improved local control with greater extent of surgery. A statistically significant improvement in disease-free survival (DFS) and overall survival (OS) was noted in patients who had undergone a complete resection. The 5-year DFS rates were 90%, 49%, and 39% for complete resection, partial resection, and biopsy-only patients, respectively (P=0.009). The 5-year OS rates were 90%, 53%, and 49% for complete resection, partial resection, and biopsy-only patients, respectively (P=0.02).

Radiation Therapy

After resection of the primary tumor, radiation is recommended in the adjuvant setting depending on pathologic risk factors. Indications for postoperative RT include positive or close surgical margins, high-grade tumor, perineural invasion, or concern regarding the surgical margins. RT is then used to target the tumor bed, resection cavity, any areas of residual disease, and areas at high risk of harboring microscopic disease. Blanco et al [21]

reported one of the largest series of patients treated for maxillary sinus and ethmoid tumors. The majority of the 206 patients were treated using conventional external-beam RT to a median dose of 60 Gy (range, 30–81 Gy). Radiation was delivered preoperatively (26.4%), postoperatively (38.7%), or as a single modality (28.3%). At a median follow-up of 60 months, 82% of the patients had died, 58% with recurrent or persistent primary tumor. This resulted in 5-year DFS and OS rates of 33% and 27%, respectively. An analysis of prognostic factors identified the presence of intracranial extension, high tumor grade, nodal involvement at diagnosis, and radiation alone as poor prognostic factors.

Primary RT alone or with concurrent chemotherapy is typically employed in patients with unresectable disease or those who refuse surgery.

Techniques and toxicity of RT: The techniques of RT have evolved over time. The proximity of critical organs and structures resulted in high rates of complications with 2-D techniques [5,7,21-24]. These complications included visual complications (chronic pain and visual loss), pituitary dysfunction, osteoradionecrosis, and frontal/temporal lobe necrosis. The development of 3-D techniques and intensity-modulated RT (IMRT) has led to a decline in the rate of these complications. Chen et al [25] reviewed their single-institutional experience with treating 127 patients with cancers of the maxillary sinus and naso-ethmoidal complex from April 1960 to December 2005. In this very interesting analysis, the authors noted that there was no improvement in local control or survival over the decades. However, a significant decrease in grade 3-4 toxicity was seen, with rates of 53%, 45%, 39%, 28%, and 16% for patients treated in the 1960s, '70s, '80s, '90s, and 2000s, respectively. This reflected improvement in RT delivery techniques. Thirty-two of 59 patients treated with conventional RT experienced grade 3-4 toxicity, compared to 10 out of 45 and 3 out of 23 patients experiencing the same when treated with 3-D and IMRT techniques, respectively.

However, another report addressing the same question noted an improvement in survival over a similar time period [9]. The authors compared their outcomes in 386 patients treated between 1975 and 1995 with 16,396 patients studied in 154 previously published reports. The most significant improvement was seen in squamous cell and glandular histology and for maxillary and ethmoid sinus location.

Investigators at the Ghent University Hospital treated 105 patients with sinonasal malignancies using IMRT and reported the outcomes on 84 patients with adenocarcinoma, squamous cell carcinoma, esthesioneuroblastoma, and adenoid cystic carcinoma [26]. CT- and MRI-based planning was used to deliver 70 Gy in 35 fractions of 2 Gy each. Seven noncoplanar beams were used to treat the planning target volume while restricting the dose to critical normal structures. The IMRT dose-volume constraints on the optic nerves and chiasms were set at 60 Gy to <5% of the volume. The retina was allowed to receive 55 Gy to <5% of the volume, and the dose to 50% of the lacrimal gland was kept below 30 Gy. With a median follow-up of 40 months, the 5-year local control and OS rates were 70.7% and 58.5%, respectively. One patient developed grade 3 radiation-induced visual impairment. Temporal lobe necrosis was noted in 3 patients on long-term follow-up.

The use of proton therapy has also been reported for unresectable nasal cavity and paranasal sinus cancers. Locally advanced sphenoid sinus cancers of various histologies were treated to a dose of 76 Gy equivalent (GyE) [27], with 2-year local control, DFS, and OS rates of 86%, 31%, and 53%, respectively. No grade 3-4 visual toxicities were noted. The nasal and auditory complications were also low. One patient died due to chronic cerebrospinal fluid leak and infectious meningitis. Two recent reports from Japan have demonstrated the ability to use protons in these patients. Zenda et al [28] treated 39 patients with unresectable paranasal sinus and nasal cavity cancers and noted a 5-year OS of 55%. Grade 3 to 5 late toxicities occurred in 13% of cases, with 1 death due to cerebrospinal fluid leak. Another report, however, did not note such high rates of survival with unresectable carcinomas. A median dose of 78 GyE was used in 17 patients, with the dose to optic chiasm and brainstem kept below 50 GyE [29]. The 5-year survival was 16% and the local control rate was 17.5%. Two patients experienced grade 3 or more toxicity (1 brain necrosis, 1 ipsilateral blindness).

Ethmoid sinus cancers: The largest reported series for ethmoid sinus cancers is a retrospective multicenter analysis from France including 418 patients with ethmoid sinus adenocarcinoma treated between 1976 and 2001 [30]. The T-stage was T3 or T4 in 269 patients (64%). A worse prognosis was noted for patients with disease involving the orbit, dura, brain, or sphenoid sinus. The majority of the patients (78%) underwent surgery followed by RT and this group was noted to have the best outcome. A total of 10 patients had lymph node involvement at presentation and elective nodal irradiation (ENI) was done in 11 patients. The rate of recurrence was 51% at a median of 28 months after treatment, with only 3 patients having lymph node metastases (see Variant 4).

Sphenoid sinus cancers: Sphenoid sinus cancers are very rare. The Groupe d'Etude des Tumeurs Tête Et Cou published a series on 23 patients with varied histologies treated over a 16-year period [31]. In this series, cranial neuropathy at presentation was associated with an inferior locoregional control and OS rate, and any surgical resection, including debulking procedures, resulted in better outcomes. The negative prognostic implications of cranial nerve involvement were also noted in another report of 27 patients [32].

The above-referenced series for locally advanced sphenoid sinus cancers reported by Truong et al had analyzed 20 patients treated over a 14-year period [27]. Oropharyngeal involvement and anterior cranial fossa invasion were predictive for poor DFS rate, and brain invasion was predictive for decreased OS.

All reports have included patients with diverse histologies, including squamous cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, chondrosarcoma, neuroendocrine carcinoma, lymphoma, etc. Also, treatments have included surgery with radiation, radiation alone, radiation with chemotherapy, surgery and chemotherapy, etc, determined on an individual case basis.

Nasal cavity cancers: Published literature on nasal cavity/septal cancers is predominantly in combination with paranasal sinus cancers. One of the very few reports that addressed nasal cavity cancers separately was published by Allen et al [7] based on a retrospective review of 68 patients treated between 1969 and 2000. These cancers were almost equally distributed between the nasal septum (46%) and the nasal floor/lateral wall (54%). The predominant histology was squamous cell carcinoma (66%), followed by adenoid cystic (18%) and adenocarcinoma (12%). Thirty-two patients received definitive RT and the rest were treated with surgery and radiation (3 preoperative RT, 33 postoperative RT). The authors noted better outcomes in these patients as compared to historically reported results when nasal cavity cancer outcomes were presented combined with other paranasal sinus outcomes. At 5 and 10 years, the local relapse-free survival was 86% and 76%, disease-specific survival was 86% and 78%, and OS was 82% and 62%, respectively. No difference was noted based on nasal septum versus nasal cavity origin of these cancers. At a median post-treatment interval of 16.8 months, neck failure was seen in 7% of cases even though none of the patients had received elective neck nodal irradiation.

Chemotherapy

Attempts have been made to improve upon primary RT by the addition of induction chemotherapy and concurrent chemotherapy with radiation. Cisplatin-based chemotherapy is often used based on extrapolation from the results of clinical trials in head and neck cancers of other subsites [33,34].

Induction: For patients with borderline resectable disease, preoperative chemotherapy followed by surgery and postoperative radiation, or chemoradiation followed by surgery, can be used. Induction treatment can decrease the size of the tumor and facilitate surgery, although the original margins should be maintained. This approach may increase the possibility of orbital preservation in select situations. Lee et al [35] reported on 19 patients treated at the University of Chicago with induction chemotherapy. They reported an 87% response rate to the chemotherapy, and in half of these patients, a complete pathologic response was noted at the time of surgery. Local control at 5 and 10 years was 76% each, DFS was 67% each, and OS was 73% and 54%, respectively. Induction chemotherapy followed by definitive concurrent chemoradiation for organ preservation is under investigation. Hanna et al [36] recently presented their institutional experience with 46 patients treated with induction chemotherapy. Thirty-one (67%) had partial response to the chemotherapy. Subsequently, 14 patients had definitive radiation; 5, chemoradiation; and 8, chemoradiation followed by planned surgery for any residual disease. The rest had surgery, usually followed by postoperative radiation. The reported 2-year OS for all patients was 67%. The 2-year OS for those with partial response to the induction chemotherapy was significantly better than those with progressive disease (77% versus 36%, P=0.05). Licitra et al had evaluated the role of induction chemotherapy using a combination of cisplatin, fluorouracil, and leucovorin in 49 patients with resectable paranasal sinus tumors [37]. They noted a pathologic complete response rate of 16% (8 of 49), with these 8 patients achieving 100% OS at 3 years. However, this regimen also resulted in significant toxicities, with 2 treatment-related deaths and 8 other patients with significant cardiac toxicities.

Concurrent: The role of concurrent radiation and chemotherapy in patients with unresectable stage IVB paranasal sinus and nasal cavity tumors was reported by Hoppe et al [38] in 39 patients (4 received radiation alone without chemotherapy due to comorbidities). The majority of these patients (n=32) received concurrent therapy of cisplatin and a median radiation dose of 70 Gy. Unfortunately, even with this aggressive treatment, 22 tumors recurred within the radiation field, resulting in a 5-year local progression-free survival of 21% and OS of 15%.

This highlights the limited efficacy of nonsurgical therapy in this patient group and the poor prognosis for patients with unresectable disease.

Radiation and concurrent chemotherapy are also often used for patients who are noted to have positive margins on pathology after a surgical resection. This is based on extrapolation of the results from 2 randomized trials and their combined analysis, which showed that patients with positive margins or extracapsular nodal extension of squamous cell cancer benefitted from the additional chemotherapy [33,34,39]. Although this extrapolation may be appropriate for squamous cell or adenocarcinomas of the paranasal sinuses and nasal cavity, the data are less robust for other histologies like adenoid cystic carcinoma. Concurrent chemotherapy with radiation in these cases must only be recommended after careful deliberation in a multidisciplinary setting.

Intra-arterial: Intra-arterial cisplatin has been employed in the treatment of head and neck cancers. However, a randomized trial did not demonstrate any benefit of intra-arterial chemotherapy as compared to standard intravenous chemotherapy in other (nonparanasal sinus) head and neck squamous cell cancers [40]. Its use in the paranasal sinuses and nasal cavity is limited. Samant et al [41] treated 19 patients (14 patients with T4 disease) with nasal cavity and paranasal sinus cancers using a regimen of preoperative RT to a dose of 50 Gy in 2 Gy per fraction with concurrent intra-arterial cisplatin (150 mg/m^2 per week) with systemic sodium thiosulfate neutralization. This was followed by planned surgery 8 weeks after completion of RT, and the 5-year OS noted in this group was 53%. A Japanese group, using a similar protocol, showed more promising results in 47 patients [42]. Radiation was delivered to a higher dose, 65 Gy to 70 Gy, using a conventional wedge-pair technique. Intra-arterial cisplatin, 100–120 mg/m^2 per week for 4 weeks, was given concurrently with radiation. Surgical resection was not performed in these patients and radiation and chemotherapy was used with a definitive intent. The 5-year local progression-free survival was 78% for all patients, 69% for patients with unresectable (T4b) disease, and 83% for those with resectable (<T4b) disease. Similarly, the 5-year OS rate was 69% for all patients and 61% and 71% for T4b and <T4b cases, respectively. Acute toxicity was conservatively managed and there were no treatment-related deaths. Late toxicities included osteonecrosis (n=7) and brain necrosis (n=2). Unfortunately, severe ocular/vision problems occurred in 16 of 38 patients followed for 2 years. The local control and OS results of this approach appear superior compared to other reported chemotherapy and radiation series, although the toxicities are more significant. Unfortunately, the technical expertise needed to administer this technique is not easily generalizable for the purposes of larger-scale trials.

Management of Cervical Lymph Nodes

Elective neck management in clinically N0 necks in nasal and paranasal sinus cancer has been controversial. There are conflicting reports regarding the risk of regional failures without elective neck irradiation and many surgical series do not include elective neck dissection. Dirix et al [43] reported only 4 of 122 (3%) originally N0 patients developed a regional failure in the neck. Others have reported higher incidences ranging from 10% to 30% [5,6]. In general, elective neck treatment is not necessary. A recent report from China used the superior soft-tissue imaging capabilities of MRI scans to study the incidence of cervical and retropharyngeal lymph node (RPLN) involvement in sinonasal cancers [44]. This study included a total of 59 patients with squamous cell carcinoma of the maxillary sinus (n=19) and naso-ethmoid region (n=40). Eighteen of the 59 patients had lymph node metastases at presentation, with 11 patients having RPLNs that were involved by radiologic criteria (shortest axial diameter ≥5 mm) but not pathologically. Three of these 11 were solely in the RPLNs and 8 were in combination with level Ib and II cervical lymph nodes. Pathologic confirmation was not, however, available. The rate of lymph node metastasis in primary adenocarcinoma of the ethmoid sinus appears to be very low. As described above for the series from France, only 3 patients out of >400 failed in the neck at time of recurrence [30]. These data demonstrate the heterogeneity inherent to this disease class, given the differing lymphatic drainage patterns of the sinuses and the differing metastatic rates of the separate histologies.

There are, however, circumstances in which elective nodal treatment is important. Reports have shown that in patients with stage T3-4 squamous cell and poorly differentiated carcinoma of the maxillary sinus, elective neck irradiation improves regional control, distant metastasis, and potentially OS [5,6,14]. Le et al [6] reported on 97 patients with maxillary sinus cancer and noted that the 5-year nodal recurrence was 20% for patients without elective neck irradiation and 0% for those who received neck irradiation. Patients with neck recurrence had a significantly higher risk for distant metastasis. The 5-year distant failure rate was 81% for patients with neck recurrence versus 29% for those with neck control (P=0.02). There was a trend for decreased survival with nodal failure. The 5-year OS was 37% for patients with neck control and 0% for patients with regional recurrence.

Jiang et al [5] had reviewed their experience of 73 patients with maxillary sinus cancer treated between 1969 and 1985. There were 49 patients with T3/4N0 and 36 patients with squamous cell and undifferentiated carcinoma. The overall regional recurrence rate for those without neck radiation was 33% for squamous cell and undifferentiated carcinoma. None of 16 patients who received elective neck irradiation recurred in the neck. Following this report, their institution changed its radiation techniques and began to deliver elective neck irradiation for patients with T2-T4 maxillary sinus squamous cell and undifferentiated carcinoma. Bristol et al [45] updated the experience and compared patients treated before and after this change. For patients with squamous cell and undifferentiated carcinoma, 13 of 36 patients (36%) without neck radiation developed regional recurrence, compared to 3 of 45 patients (7%) with elective neck irradiation ($P<0.001$). Those receiving elective neck irradiation had a significant reduction in distant metastasis as well, 3% versus 20% at 5 years ($P=0.045$). Although there was no difference between the groups in 5-year OS, there was a significant improvement in 5-year recurrence-free survival (67% in treated versus 45% in untreated patients, $P=0.025$).

In a Chinese study of patients with initial N0 disease, ENI was delivered to level Ib, II, and III cervical nodes at the discretion of the treating oncologist but not specifically to the RPLNs [44]. With a median follow-up of 28 months, there were no nodal failures seen in the 11 patients who received ENI. However, among those who did not receive ENI, 6 out of 33 patients (18.2%) recurred in level Ib and/or IIa. No nodal failures were noted in the RPLNs. The authors evaluated the RT plans and determined that the retropharyngeal space received a median dose of 43.3 Gy (range, 28.1–61.8 Gy) even though this area was not outlined as a clinical treatment volume. Based on these experiences, it appears that ENI should be considered in patients with T3-T4 disease. For patients with an N0 neck who did not receive elective neck irradiation, when they had nodal failure, most failed at the ipsilateral level II and level Ib. If the tumor is lateralized, ENI to the ipsilateral neck should be sufficient.

As surgical techniques have improved, both with resection and reconstruction, elective neck surgery has become more common to provide access for the vascular anastomosis required for free tissue transfer. It will be interesting to assess any changes in pattern of recurrence, survival, or metastasis resulting from elective surgical management of the neck.

Nasal Cavity Cancers—Unusual Pathologies

Esthesioneuroblastoma

Esthesioneuroblastoma (olfactory neuroblastoma) is encountered in the superior nasal cavity and anterior skull base. The exact site of its origin is unknown but is thought to arise from the basal neural cells of the olfactory epithelium. This is a rare pathology among the already rare nasal cavity carcinomas. Clinical presentation is similar to that described above for tumors of the naso-ethmoidal complex. One unique symptom noted is anosmia, which may precede the diagnosis by a few months. Diagnosis is established by imaging using CT or MRI scans followed by a biopsy obtained through nasal endoscopy.

Esthesioneuroblastomas are staged using the Kadish [46] staging system, which is divided into groups A (tumor limited to nasal cavity), B (tumor limited to nasal cavity and paranasal sinuses), and C (tumor extends beyond the nasal cavity and paranasal sinuses, including base of skull, intracranial compartment, orbit, and distant metastatic disease). An additional group D was proposed by Chao et al [47] to include patients with cervical lymph node metastases.

The management paradigms of this entity are similar to those described in the general principles above. Surgery plays a major role and most centers recommend initial surgical resection followed by external-beam RT. The surgical technique to be employed could be either endoscopic resection or open craniofacial resection. A meta-analysis of 361 patients treated over a 16-year period compared these approaches and concluded that endoscopic surgery for esthesioneuroblastomas is a viable treatment option with comparable survival when compared to open surgery [48]. A review article also examined this issue and the authors concluded that currently available evidence suggests that equivalent short-term outcomes are seen with either surgical approach as long as the resection is complete [49]. Some centers have described the use of preoperative RT [50] or RT with concurrent chemotherapy [51] with an aim to shrink the tumor and allow better or easier surgical resection. The advantages of preoperative RT are that it allows delivery of a lower dose of radiation (50 Gy in 25 fractions) to the tumor and surrounding critical optic pathway structures and that the brain can be spared the high doses that are required postoperatively (60–70 Gy), depending on pathologic margin status. Additionally, tumor edges are better visualized on the MR or CT scans (see Variant 5).

There are conflicting results on elective neck irradiation and the use of chemotherapy. One series of 77 patients had a nodal-only failure rate of 7% in the untreated N0 neck (local and nodal failure rate was noted in 11 of 68 patients with initially N0 neck) [52]; another report noted a decrease in nodal recurrence from 44% to 0% following ENI [53]. A review article by Zanation et al [54] examined this issue but no definite consensus could be reached about how to manage initial N0 disease. The role of chemotherapy is also not well defined, with a variety of agents reported. Cisplatin is often employed in combination with etoposide, vincristine, ifosfamide, or other agents [51,55].

Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinoma (SNUC) is a relatively recently described pathologic entity representing a rare cancer of uncertain origin [56]. A male predominance is noted with a wide range of ages at presentation, the median being in the sixth decade. Patients present with signs and symptoms similar to those for other sinonasal malignancies including nasal obstruction, epistaxis, proptosis, cranial nerve involvement, and facial pain [57], and these symptoms are usually of short duration. Radiographic evaluation frequently reveals a large, locally advanced malignancy invading into the orbits or intracranially. This is often a central nasal cavity tumor. The gross pathology, histology, and immunohistochemical profile have been described in a review by Ejaz and Wenig [57]. No staging system has been developed specifically for SNUC, but the Kadish system has been used in many publications. The prognostic factors for SNUC are not well understood as most reported series include small numbers of patients. Chen et al [58] evaluated multiple disease- and treatment-related parameters including clinical T-stage, age, primary site, dural involvement, orbit invasion, cranial nerve involvement, radiation dose and technique, and use of chemotherapy. None of these were found to be predictive for OS.

A meta-analysis was recently published with individual data on 167 patients from 30 previously published series [59]. The mean age of patients was 53 years (range, 12–84 years), with 73% being males. Sixty percent had disease extension beyond the paranasal sinuses. Approximately 8%–9% had cervical lymph node metastases at presentation, and 25% of Kadish group C patients had metastases at presentation. A majority of patients underwent surgical resection (53%) either alone or followed by adjuvant RT with or without chemotherapy. The most commonly employed chemotherapeutic agents were cyclophosphamide, doxorubicin, and vincristine. Radiation was part of the treatment in >80% of the patients. Surgical resection seemed to confer a survival advantage, and presence of disease in the neck nodes and Kadish group C were poor prognostic factors. Overall, trimodality therapy appeared to be the best treatment option. The role of ENI is also undefined in SNUC. In a report from the University of Florida 7 of 13 patients with clinically N0 neck at presentation received ENI and 6 did not. None of the irradiated 7 patients failed regionally, although 2 of the 6 patients who did not receive ENI failed in the neck [60]. In another series 15 of 19 patients received ENI and no neck nodal failures were noted on follow-up [58].

Summary of Recommendations

- Upfront surgery is the treatment of choice for all resectable lesions. Nasal endoscopic resection should be considered over open surgery in appropriate cases.
- Adjuvant RT with or without concurrent chemotherapy is advised based on the presence of adverse pathologic features. These adverse features are the same as those for squamous cell carcinomas of other head and neck sites.
- Intensity-modulated therapy, with photons or protons, reduces radiation-induced toxicity and should be preferentially considered over 3-D conformal RT.
- Cisplatin-based concurrent chemotherapy is often used in patients with unresectable disease, positive margins, or lymph nodes with extracapsular extension, based on extrapolation from randomized trials conducted for head and neck cancer of other subsites.
- The role of induction and intra-arterial chemotherapy is controversial.
- The benefit and role of elective neck node treatment is also undefined and controversial. Elective neck management is recommended for patients with T3-4 squamous cell carcinoma and poorly differentiated carcinoma of the maxillary sinus.

Summary of Evidence

Of the 60 references cited in the *ACR Appropriateness Criteria® Nasal Cavity and Paranasal Sinus Cancers* document, all of them are categorized as therapeutic references including 3 well designed studies, 37 good quality

studies, and 5 quality studies that may have design limitations. There are 11 references that may not be useful as primary evidence. There are 4 references that are meta-analysis studies.

The 60 references cited in the *ACR Appropriateness Criteria® Nasal Cavity and Paranasal Sinus Cancers* document were published from 1976-2013.

While there are references that report on studies with design limitations, 40 well designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

References

1. Muir CS, Nectoux J. Descriptive epidemiology of malignant neoplasms of nose, nasal cavities, middle ear and accessory sinuses. *Clin Otolaryngol Allied Sci.* 1980;5(3):195-211.
2. Roush GC. Epidemiology of cancer of the nose and paranasal sinuses: current concepts. *Head Neck Surg.* 1979;2(1):3-11.
3. Ansa B, Goodman M, Ward K, et al. Paranasal sinus squamous cell carcinoma incidence and survival based on Surveillance, Epidemiology, and End Results data, 1973 to 2009. *Cancer.* 2013;119(14):2602-2610.
4. Goldenberg D, Golz A, Fradis M, Martu D, Netzer A, Joachims HZ. Malignant tumors of the nose and paranasal sinuses: a retrospective review of 291 cases. *Ear Nose Throat J.* 2001;80(4):272-277.
5. Jiang GL, Ang KK, Peters LJ, Wendt CD, Oswald MJ, Goepfert H. Maxillary sinus carcinomas: natural history and results of postoperative radiotherapy. *Radiother Oncol.* 1991;21(3):193-200.
6. Le QT, Fu KK, Kaplan MJ, Terris DJ, Fee WE, Goffinet DR. Lymph node metastasis in maxillary sinus carcinoma. *Int J Radiat Oncol Biol Phys.* 2000;46(3):541-549.
7. Allen MW, Schwartz DL, Rana V, et al. Long-term radiotherapy outcomes for nasal cavity and septal cancers. *Int J Radiat Oncol Biol Phys.* 2008;71(2):401-406.
8. Ang KK, Jiang GL, Frankenthaler RA, et al. Carcinomas of the nasal cavity. *Radiother Oncol.* 1992;24(3):163-168.
9. Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer.* 2001;92(12):3012-3029.
10. Duprez F, Madani I, Morbee L, et al. IMRT for sinonasal tumors minimizes severe late ocular toxicity and preserves disease control and survival. *Int J Radiat Oncol Biol Phys.* 2012;83(1):252-259.
11. Guntinas-Lichius O, Kreppel MP, Stuetzer H, Semrau R, Eckel HE, Mueller RP. Single modality and multimodality treatment of nasal and paranasal sinuses cancer: a single institution experience of 229 patients. *Eur J Surg Oncol.* 2007;33(2):222-228.
12. Wiegner EA, Daly ME, Murphy JD, et al. Intensity-modulated radiotherapy for tumors of the nasal cavity and paranasal sinuses: clinical outcomes and patterns of failure. *Int J Radiat Oncol Biol Phys.* 2012;83(1):243-251.
13. Ganly I, Patel SG, Singh B, et al. Craniofacial resection for malignant paranasal sinus tumors: Report of an International Collaborative Study. *Head Neck.* 2005;27(7):575-584.
14. Kraus DH, Shah JP, Arbit E, Galicich JH, Strong EW. Complications of craniofacial resection for tumors involving the anterior skull base. *Head Neck.* 1994;16(4):307-312.
15. Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH. Endoscopic endonasal compared with anterior craniofacial and combined cranionasal resection of esthesioneuroblastomas. *World Neurosurg.* 2013;80(1-2):148-159.
16. Hanna E, DeMonte F, Ibrahim S, Roberts D, Levine N, Kupferman M. Endoscopic resection of sinonasal cancers with and without craniotomy: oncologic results. *Arch Otolaryngol Head Neck Surg.* 2009;135(12):1219-1224.
17. Nicolai P, Battaglia P, Bignami M, et al. Endoscopic surgery for malignant tumors of the sinonasal tract and adjacent skull base: a 10-year experience. *Am J Rhinol.* 2008;22(3):308-316.
18. Jansen EP, Keus RB, Hilgers FJ, Haas RL, Tan IB, Bartelink H. Does the combination of radiotherapy and debulking surgery favor survival in paranasal sinus carcinoma? *Int J Radiat Oncol Biol Phys.* 2000;48(1):27-35.

19. Mendenhall WM, Amdur RJ, Morris CG, et al. Carcinoma of the nasal cavity and paranasal sinuses. *Laryngoscope.* 2009;119(5):899-906.
20. Resto VA, Chan AW, Deschler DG, Lin DT. Extent of surgery in the management of locally advanced sinonasal malignancies. *Head Neck.* 2008;30(2):222-229.
21. Blanco AI, Chao KS, Ozyigit G, et al. Carcinoma of paranasal sinuses: long-term outcomes with radiotherapy. *Int J Radiat Oncol Biol Phys.* 2004;59(1):51-58.
22. Jiang GL, Morrison WH, Garden AS, et al. Ethmoid sinus carcinomas: natural history and treatment results. *Radiother Oncol.* 1998;49(1):21-27.
23. Karim AB, Kralendonk JH, Njo KH, Tabak JM, Elsenaar WH, van Balen AT. Ethmoid and upper nasal cavity carcinoma: treatment, results and complications. *Radiother Oncol.* 1990;19(2):109-120.
24. Katz TS, Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Villaret DB. Malignant tumors of the nasal cavity and paranasal sinuses. *Head Neck.* 2002;24(9):821-829.
25. Chen AM, Daly ME, Bucci MK, et al. Carcinomas of the paranasal sinuses and nasal cavity treated with radiotherapy at a single institution over five decades: are we making improvement? *Int J Radiat Oncol Biol Phys.* 2007;69(1):141-147.
26. Madani I, Bonte K, Vakaet L, Boterberg T, De Neve W. Intensity-modulated radiotherapy for sinonasal tumors: Ghent University Hospital update. *Int J Radiat Oncol Biol Phys.* 2009;73(2):424-432.
27. Truong MT, Kamat UR, Liebsch NJ, et al. Proton radiation therapy for primary sphenoid sinus malignancies: treatment outcome and prognostic factors. *Head Neck.* 2009;31(10):1297-1308.
28. Zenda S, Kohno R, Kawashima M, et al. Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses. *Int J Radiat Oncol Biol Phys.* 2011;81(5):1473-1478.
29. Fukumitsu N, Okumura T, Mizumoto M, et al. Outcome of T4 (International Union Against Cancer Staging System, 7th edition) or recurrent nasal cavity and paranasal sinus carcinoma treated with proton beam. *Int J Radiat Oncol Biol Phys.* 2012;83(2):704-711.
30. Choussy O, Ferron C, Vedrine PO, et al. Adenocarcinoma of Ethmoid: a GETTEC retrospective multicenter study of 418 cases. *Laryngoscope.* 2008;118(3):437-443.
31. Vedrine PO, Thariat J, Merrot O, et al. Primary cancer of the sphenoid sinus--a GETTEC study. *Head Neck.* 2009;31(3):388-397.
32. DeMonte F, Ginsberg LE, Clayman GL. Primary malignant tumors of the sphenoidal sinus. *Neurosurgery.* 2000;46(5):1084-1091; discussion 1091-1082.
33. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350(19):1945-1952.
34. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350(19):1937-1944.
35. Lee MM, Vokes EE, Rosen A, Witt ME, Weichselbaum RR, Haraf DJ. Multimodality therapy in advanced paranasal sinus carcinoma: superior long-term results. *Cancer J Sci Am.* 1999;5(4):219-223.
36. Hanna EY, Cardenas AD, DeMonte F, et al. Induction chemotherapy for advanced squamous cell carcinoma of the paranasal sinuses. *Arch Otolaryngol Head Neck Surg.* 2011;137(1):78-81.
37. Licitra L, Locati LD, Cavina R, et al. Primary chemotherapy followed by anterior craniofacial resection and radiotherapy for paranasal cancer. *Ann Oncol.* 2003;14(3):367-372.
38. Hoppe BS, Nelson CJ, Gomez DR, et al. Unresectable carcinoma of the paranasal sinuses: outcomes and toxicities. *Int J Radiat Oncol Biol Phys.* 2008;72(3):763-769.
39. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck.* 2005;27(10):843-850.
40. Rasch CR, Hauptmann M, Schornagel J, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. *Cancer.* 2010;116(9):2159-2165.
41. Samant S, Robbins KT, Vang M, Wan J, Robertson J. Intra-arterial cisplatin and concomitant radiation therapy followed by surgery for advanced paranasal sinus cancer. *Arch Otolaryngol Head Neck Surg.* 2004;130(8):948-955.
42. Homma A, Oridate N, Suzuki F, et al. Superselective high-dose cisplatin infusion with concomitant radiotherapy in patients with advanced cancer of the nasal cavity and paranasal sinuses: a single institution experience. *Cancer.* 2009;115(20):4705-4714.

43. Dirix P, Nuyts S, Geussens Y, et al. Malignancies of the nasal cavity and paranasal sinuses: long-term outcome with conventional or three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys.* 2007;69(4):1042-1050.
44. Guan X, Wang X, Liu Y, Hu C, Zhu G. Lymph node metastasis in sinonasal squamous cell carcinoma treated with IMRT/3D-CRT. *Oral Oncol.* 2013;49(1):60-65.
45. Bristol IJ, Ahamad A, Garden AS, et al. Postoperative radiotherapy for maxillary sinus cancer: long-term outcomes and toxicities of treatment. *Int J Radiat Oncol Biol Phys.* 2007;68(3):719-730.
46. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. *Cancer.* 1976;37(3):1571-1576.
47. Chao KS, Kaplan C, Simpson JR, et al. Esthesioneuroblastoma: the impact of treatment modality. *Head Neck.* 2001;23(9):749-757.
48. Devaiah AK, Andreoli MT. Treatment of esthesioneuroblastoma: a 16-year meta-analysis of 361 patients. *Laryngoscope.* 2009;119(7):1412-1416.
49. Soler ZM, Smith TL. Endoscopic versus open craniofacial resection of esthesioneuroblastoma: what is the evidence? *Laryngoscope.* 2012;122(2):244-245.
50. Polin RS, Sheehan JP, Chenelle AG, et al. The role of preoperative adjuvant treatment in the management of esthesioneuroblastoma: the University of Virginia experience. *Neurosurgery.* 1998;42(5):1029-1037.
51. Sohrabi S, Drabick JJ, Crist H, Goldenberg D, Sheehan JM, Mackley HB. Neoadjuvant concurrent chemoradiation for advanced esthesioneuroblastoma: a case series and review of the literature. *J Clin Oncol.* 2011;29(13):e358-361.
52. Ozsahin M, Gruber G, Olszyk O, et al. Outcome and prognostic factors in olfactory neuroblastoma: a rare cancer network study. *Int J Radiat Oncol Biol Phys.* 2010;78(4):992-997.
53. Monroe AT, Hinerman RW, Amdur RJ, Morris CG, Mendenhall WM. Radiation therapy for esthesioneuroblastoma: rationale for elective neck irradiation. *Head Neck.* 2003;25(7):529-534.
54. Zanation AM, Ferlito A, Rinaldo A, et al. When, how and why to treat the neck in patients with esthesioneuroblastoma: a review. *Eur Arch Otorhinolaryngol.* 2010;267(11):1667-1671.
55. Resto VA, Eisele DW, Forastiere A, Zahurak M, Lee DJ, Westra WH. Esthesioneuroblastoma: the Johns Hopkins experience. *Head Neck.* 2000;22(6):550-558.
56. Frierson HF, Jr., Mills SE, Fechner RE, Taxy JB, Levine PA. Sinonasal undifferentiated carcinoma. An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. *Am J Surg Pathol.* 1986;10(11):771-779.
57. Ejaz A, Wenig BM. Sinonasal undifferentiated carcinoma: clinical and pathologic features and a discussion on classification, cellular differentiation, and differential diagnosis. *Adv Anat Pathol.* 2005;12(3):134-143.
58. Chen AM, Daly ME, El-Sayed I, et al. Patterns of failure after combined-modality approaches incorporating radiotherapy for sinonasal undifferentiated carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys.* 2008;70(2):338-343.
59. Reiersen DA, Pahilan ME, Devaiah AK. Meta-analysis of treatment outcomes for sinonasal undifferentiated carcinoma. *Otolaryngol Head Neck Surg.* 2012;147(1):7-14.
60. Tanzler ED, Morris CG, Orlando CA, Werning JW, Mendenhall WM. Management of sinonasal undifferentiated carcinoma. *Head Neck.* 2008;30(5):595-599.

Clinical Condition: **Carcinoma of the Maxillary Sinus—Resectable Early Stage**

Variant 1: **cT1-T2N0M0 maxillary sinus squamous cell carcinoma.**

Treatment	Rating	Comments
Surgery		
Surgery should be performed	9	See references 19, 20, 21. Studies suggest better outcomes with the addition of surgery.
Inferior maxillectomy	8	
Ipsilateral selective neck dissection (I-III)	4	
Bilateral selective neck dissection (I-III)	2	
Radiation		
Definitive RT alone	5	See references 19, 20, 21. Studies suggest better outcomes with the addition of surgery.
Definitive RT and concurrent chemotherapy	4	
Adjuvant RT alone in the *absence* of negative pathologic features (eg, lymphovascular invasion, perineural invasion, positive margins)	3	
Adjuvant RT with concurrent chemotherapy in the *absence* of positive margins or extracapsular extension	2	
Preoperative RT followed by surgery	2	
If adjuvant RT is necessary based on surgical pathology review:		
Radiation Technique		
3-D conformal therapy	5	
Intensity-modulated therapy	9	Proton therapy may be considered in cases where normal tissue constraints to critical structures (eg, optic nerves, optic chiasm, spinal cord, brainstem, etc) are not achievable using standard IMRT techniques. See references 25, 26, 28, 29, 30.
Target Volume		
Primary tumor only	8	See references 5, 6, 43, 44 for risk of neck failure with or without ENI.
Primary tumor and ipsilateral neck	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Primary tumor and bilateral neck	2	
Adjuvant Radiation Dose		
60 Gy	8	
66 Gy	7	
70 Gy	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Carcinoma of the Maxillary Sinus—Resected Advanced Stage**

Variant 2: **pT3-T4aN0M0 maxillary sinus squamous cell initially treated with total maxillectomy, ipsilateral level I-III selective neck dissection, and a free-flap reconstruction. Pathologic margins negative.**

Treatment	Rating	Comments
Adjuvant RT	8	
Adjuvant RT with concurrent chemotherapy	3	If margins are positive, this should be considered. See references 33, 34 for other head and neck sites.
Induction chemotherapy prior to surgery	4	See references 35, 36, 37.
Radiation Technique		
3-D conformal therapy	5	
Intensity-modulated therapy	8	Proton therapy may be considered in cases where normal tissue constraints to critical structures (eg, optic nerves, optic chiasm, spinal cord, brainstem, etc) are not achievable using standard IMRT techniques. See references 25, 26, 28, 29, 30.
Target Volume		
Primary tumor only	7	
Primary tumor bed and ipsilateral neck	6	See references 5, 6, 43, 44 for risk of neck failure with or without ENI.
Primary tumor bed and bilateral neck	3	
Radiation Dose		
60 Gy	8	
66 Gy	5	
70 Gy	3	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Carcinoma of the Maxillary Sinus—Unresectable**

Variant 3: **cT4bN0M0 maxillary sinus squamous cell carcinoma invading the middle cranial fossa and orbital apex.**

Treatment	Rating	Comments
Surgery		
Surgery should be performed	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Nasal endoscopic resection	2	
Radiation		
Definitive RT alone	5	
Definitive RT and concurrent chemotherapy	8	See reference 38.
Preoperative RT followed by surgery	3	
Preoperative RT and concurrent chemotherapy followed by surgery	4	
Radiation Technique		
3-D conformal therapy	4	
Intensity-modulated therapy	9	Proton therapy may be considered in cases where normal tissue constraints to critical structures (eg, optic nerves, optic chiasm, spinal cord, brainstem, etc) are not achievable using standard IMRT techniques. See references 25, 26, 28, 29, 30.
Target Volume		
Primary tumor only	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Primary tumor and ipsilateral neck	8	See references 5, 6, 43, 44 for risk of neck failure with or without ENI.
Primary tumor and bilateral neck	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Definitive Radiation Dose		
60 Gy	3	
66 Gy	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
70 Gy	8	
Chemotherapy		
Chemotherapy alone	4	
Induction chemotherapy followed by RT	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. See references 36, 37.
Intra-arterial chemotherapy	3	See references 41, 42.
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Carcinoma of the Nasal Cavity and Ethmoid Sinuses**

Variant 4: **cT2N0M0 adenocarcinoma of the ethmoid sinuses and bilateral nasal cavity.**

Treatment	Rating	Comments
Surgery		
Surgery should be performed	9	See reference 30.
Craniofacial resection	5	
Nasal endoscopic resection	8	
Radiation		
Definitive RT alone	5	
Definitive RT and concurrent chemotherapy	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Adjuvant RT alone after surgical resection	6	
Adjuvant RT with concurrent chemotherapy after surgical resection	5	
Preoperative RT followed by surgery	3	
Preoperative RT and concurrent chemotherapy followed by surgery	3	
Radiation Technique		
3-D conformal therapy	5	
Intensity-modulated therapy	8	Proton therapy may be considered in cases where normal tissue constraints to critical structures (eg, optic nerves, optic chiasm, spinal cord, brainstem, etc) are not achievable using standard IMRT techniques. See references 25, 26, 28, 29, 30.
Target Volume		
Primary tumor only	8	
Primary tumor and ipsilateral neck	3	See reference 7 for risk of neck failure.
Primary tumor and bilateral neck	3	
Adjuvant Radiation Dose		
60 Gy	7	
66 Gy	6	
70 Gy	3	
Chemotherapy		
Chemotherapy alone	2	
Induction chemotherapy followed by RT	2	See references 36, 37.
Intra-arterial chemotherapy	2	See references 41, 42.

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Esthesioneuroblastoma**

Variant 5: **Kadish stage C esthesioneuroblastoma initially treated with surgical resection. All lymph nodes were clinically negative.**

Treatment	Rating	Comments
Radiation		
Adjuvant RT alone	8	See reference 48.
Adjuvant RT with concurrent chemotherapy	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Preoperative RT followed by surgery	5	See reference 50.
Preoperative RT and concurrent chemotherapy followed by surgery	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. See reference 51.
Radiation Technique		
3-D conformal therapy	5	
Intensity-modulated therapy	8	Proton therapy may be considered in cases where normal tissue constraints to critical structures (eg, optic nerves, optic chiasm, spinal cord, brainstem, etc) are not achievable using standard IMRT techniques. See references 25, 26, 28, 29, 30.
Target Volume		
Primary tumor only	7	
Primary tumor and ipsilateral neck	5	See references 52, 53, 54.
Primary tumor and bilateral neck	5	
Adjuvant Radiation Dose		
60 Gy	7	
66 Gy	7	
70 Gy	4	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**