Surgery in the Multimodality Treatment of Sinonasal Malignancies

Malignancies of the paranasal sinuses represent a rare and biologically heterogeneous group of cancers. Understanding of tumor biology continues to evolve and will likely facilitate the development of improved treatment strategies. For example, some sinonasal tumors may benefit from treatment through primarily nonsurgical approaches, whereas others are best addressed through resection. The results of clinical trials in head and neck cancer may not be generalizable to this heterogeneous group of lesions, which is defined anatomically rather than through histogenesis. Increasingly sophisticated pathologic assessments and the elucidation of molecular markers, such as the human papilloma virus (HPV), in sinonasal cancers have the potential to transform the clinical management of these malignant neoplasms. Published reports often suggest that treatment approaches that include surgery result in better local control and survival. However, many studies are marked by selection bias. The availability of effective reconstruction makes increasingly complex procedures possible, with improved functional outcomes. With advances in surgery and radiation, the multimodal treatment of paranasal sinus cancers is becoming safer. The use of chemotherapy remains a subject of active investigation.

Introduction

Sinonasal malignancies, a highly heterogeneous group of cancers, account for less than 1% of all cancers and less than 3% of all upper aerodigestive tract tumors. These lesions may originate from any of the histopathologic components of the sinonasal cavities, including Schneiderian mucosa, minor salivary glands, neural tissue, and lymphatics. Sixty percent of sinonasal tumors arise in the maxillary sinus, whereas approximately 20% arise in the nasal cavity, 5% in the ethmoid sinuses, and 3% in the sphenoid and frontal sinuses. Fifty-five percent of sinonasal malignancies are carcinomas. Squamous cell carcinomas are more common within the nasal cavity or maxillary sinus, whereas tumors of the

Curr Probl Cancer 2010;34:304-321.
0147-0272/$34.00 + 0
doi:10.1016/j.currproblcancer.2010.07.001

ethmoid sinus and superior nasal vault are usually adenocarcinomas. Mucosal melanoma frequently originates within the nasal cavity, particularly along the lateral nasal side wall and inferior turbinates. Although traditional risk factors for sinonasal cancers have included exposure to nickel, wood dust, and tobacco, no predisposing factors are identified in most patients. Recent reports suggest that HPV promotes the development of some sinonasal squamous cancers.[1]

Moreover, skull base involvement from neglected or progressive cutaneous malignancies is increasingly common. Nonmelanoma skin cancers are distinguished by extensive local spread along embryonic fusion planes in the facial "H zone," allowing tumors to invade deeply to the skull base. In addition, neural invasion is a recognized mechanism of spread in 2.5% of squamous cell carcinomas and 1% of basal cell carcinomas, providing access to the skull base by means of the maxillary (V2), mandibular (V3), or facial nerve. Immunosuppression secondary to organ transplantation, human immunodeficiency viral infection, lymphoproliferative disease, or advanced age is associated with heightened aggressiveness of some cutaneous malignancies.

Histology

The accurate histopathologic diagnosis of sinonasal malignancies can be more demanding than for tumors from other upper aerodigestive tract sites. Poorly differentiated and undifferentiated cancers are not uncommon at the skull base and require careful pathologic characterization. "Small blue cell" cancers in the sinonasal region encompass disparate entities, such as esthesioneuroblastoma, lymphoma, melanoma, and rhabdomyosarcoma, all of which benefit from different treatment approaches and are associated with different outcomes. Poorly differentiated subtypes of esthesioneuroblastomas, primarily "solid" adenoid cystic carcinomas, or squamous cell carcinomas may be distinguished using immunohistochemical stains (Table 1). Squamous carcinomas arising in the nasal cavity are more often keratinizing and well differentiated. Those from the paranasal sinuses are more often nonkeratinizing and moderately to poorly differentiated. Poorly differentiated squamous carcinomas that stem from a preexisting inverted papilloma are associated with a better prognosis. There is, however, no association between inverted papilloma and HPV (which causes exophytic papillomas). In a review of 60 sinonasal squamous cell carcinomas, 20% contained HPV 16 or 35 DNA and overexpressed p16 on immunohistochemistry. Most of these, but not all, were nonkeratinizing or basaloid. Of 12 carcinomas arising in an inverting papilloma, only one was HPV/p16-positive.[1] Several variants of

TABLE 1. Selective immunohistochemical reactivity of sinonasal malignancies[2]

	CK	NSE	CG	SYN	S100	HMB	LCA	CD56	CD99	VIM	DES	Myf-4
SCC	+	−	−	−	−	−	−	−	−	−	−	−
SNUC	+	v	−	−	−	−	−	−	−	−	−	−
Esth	−	+	v	v	+*	−	−	−	−	−	−	−
SCUNC	+	+	+	+	+	−	−	−	−	−	−	−
MMM	−	−	−	−	+	+	−	−	−	+		−
T/NK ML	−	−	−	−	−	−	−	+	−	v	−	−
RMS	−	−	−	−	−	−	−	−	−	+	+	+

Abbreviations: CD99, Ewing marker; CG, chromogranin; CK, cytokeratin; DES, desmin; Esth, esthesioneuroblastoma; HMB (includes HMB-45 and Melan-A), melanocytic marker; LCA, leukocyte common antigen; MMM, mucosal malignant melanoma; NSE, neuron-specific enolase; RMS, rhabdomyosarcoma; SCC, squamous cell carcinoma; SCUNC, small cell undifferentiated neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; SYN, synaptophysin; S100, S100 protein; T/NK ML, nasal-type natural killer/ T cell lymphoma; v, variably positive; VIM, vimentin; +, positive; −, negative.
*Positive in the peripherally situated sustentacular cells.

squamous cell carcinoma have been described, whereas sinonasal undifferentiated carcinoma (SNUC) and nasopharyngeal-type carcinomas or lymphoepitheliomas are considered distinct entities (Table 2).

Sinonasal Undifferentiated Carcinoma

SNUC, first described in 1986, involve extensive regions of the skull base, with frequent orbital invasion and intracranial extension on presentation. Although rare, it is diagnosed with increasing frequency. SNUCs are believed to arise from Schneiderian epithelium, the sinonasal ectoderm. Smoking and radiation have been posited as risk factors. Histologically, it is characterized by medium-sized polygonal cells with distinct borders, eosinophilic cytoplasm lacking syncytial quality, high mitotic index, and prominent necrosis. Neurotropism and lymphovascular invasion as well as direct soft tissue invasion are common. By definition, there is an absence of differentiated foci. Epithelial markers are positive. This entity must be differentiated from nasopharyngeal-type squamous cell carcinoma, high-grade adenocarcinoma, high-grade olfactory neuroblastoma, neuroendocrine carcinoma, and small cell carcinoma. Some undifferentiated carcinomas, particularly in young adults, have been found to harbor a balanced translocation t(15;19) resulting in BRD4-NUT oncogene. Such tumors may show abrupt squamous differentiation, are highly lethal, and are classified with undifferentiated carcinomas of the upper aerodigestive tract with NUT rearrangement.[2]

TABLE 2. Sinonasal carcinomas

Squamous cell carcinoma, conventional
• Keratinizing
• Nonkeratinizing (formerly cylindrical cell, transitional cell)
Variants of squamous cell carcinoma
• Acantholytic squamous cell carcinoma
• Adenosquamous carcinoma
• Basaloid squamous cell carcinoma
• Papillary squamous cell carcinoma
• Spindle cell squamous cell carcinoma
• Verrucous carcinoma
Nasopharyngeal-type carcinoma (lymphoepithelioma)
Sinonasal undifferentiated carcinoma (SNUC)
Adenocarcinoma, nonsalivary gland type
• Intestinal type
• Nonintestinal type
Carcinomas of minor salivary glands
• Acinic cell carcinoma
• Adenoid cystic carcinoma
• Adenocarcinoma, not otherwise specified (NOS)
• Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
• Clear cell adenocarcinoma
• Mucoepidermoid carcinoma
• Epithelial–myoepithelial carcinoma
• Myoepithelial carcinoma (malignant myoepithelioma)
• Oncocytic carcinoma
• Polymorphous low-grade adenocarcinoma
• Salivary duct carcinoma
• Other

From Carlson, et al. Protocol for the examination of specimens from patients with carcinomas of the nasal cavity and paranasal sinuses. College of American Pathologists Web site, January 2010, based on AJCC, ed 7.

Nasopharyngeal-Type Undifferentiated Carcinoma

Poorly differentiated nasopharyngeal carcinomas, frequently referred to as lymphoepitheliomas, are characterized by undifferentiated tumor cells accompanied by a prominent lymphoid infiltrate. In contrast to SNUC, cell borders are indistinct, creating a syncytial appearance, and necrosis is not seen. Primary sinonasal nasopharyngeal-type undifferentiated carcinomas are rare. Epstein–Barr virus (EBV) markers, by immunohistochemistry and in situ hybridization for EBV-encoded RNA, will typically be negative in SNUCs, even in Asian patients, and positive in poorly differentiated nonkeritanizing nasopharyngeal-type carcinomas.[2]

Neuroendocrine Carcinomas

Among poorly differentiated sinonasal malignancies, there may be variable neuroendocrine differentiation. The members of this group,

which includes esthesioneuroblastoma, SNUCs, neuroendocrine carcinoma, and small cell undifferentiated carcinoma, have distinct clinical characteristics warranting different treatments. Esthesioneuroblastomas, also known as olfactory neuroblastomas, are thought to arise from bipolar neurons of the olfactory membrane and typically present high in the upper nasal cavity. In some cases, a t(11:22) translocation is found. This translocation, also seen in primitive neuroectodermal tumors (PNETs) and Ewing's sarcoma, does not indicate a common lineage. Low-grade esthesioneuroblastomas are readily identified on the basis of architecture and the presence of neurofibrillary matrix, Homer-Wright rosettes, and/or Flexner–Wintersteiner rosettes. However, distinguishing between high-grade esthesioneuroblastomas and other neuroendocrine lesions may rest on immunohistochemical staining. Hyams and Taxy[3,4] have described the microscopic and immunohistochemical features of esthesioneuroblastomas and neuroendocrine carcinoma and argue that these entities represent a histopathologic spectrum. However, the clinical behaviors of these lesions differ markedly. In a review from the University of Texas, Rosenthal et al. described clinical outcomes of 72 patients with esthesioneuroblastoma, SNUC, neuroendocrine carcinoma, and small cell carcinoma. Those with esthesioneuroblastomas had prolonged local control and disease-free survival with local therapy alone. In contrast, SNUC, neuroendocrine carcinoma, and small cell carcinoma were linked with inferior survival and higher rates of systemic failure, particularly for small cell carcinoma. The survival outcomes from their cohort of patients with neuroendocrine carcinoma and SNUC seemed better than those previously reported by others, perhaps reflecting improved identification of small cell histologies.[5] Assessment of treatment outcomes depends on accurate histopathologic diagnosis of these poorly differentiated sinonasal malignancies.

Adenocarcinomas

Primary sinonasal adenocarcinomas can be grouped into salivary and nonsalivary types, the latter of which can be further classified into intestinal and nonintestinal variants (Table 2). Adenocarciomas arise either from the respiratory epithelium or the underlying seromucinous glands. Patients with exposure to hardwoods and leather manufacturing develop intestinal type adenocarcinomas in the ethmoid sinuses, which resemble colonic adenocarcinoma but may show mucinous or signet ring features. The incidence of ethmoid sinus adenocarcinoma appears to be higher in Europe, for reasons that are not entirely clear. The most common sinonasal salivary-type adenocarcinoma is adenoid cystic carci-

TABLE 3. Kadish staging system for esthesioneuroblastoma

Stage A: Lesion is confined to the nasal cavity
Stage B: Involvement of nasal cavity and one or more of the paranasal sinuses
Stage C: Involvement beyond the nasal cavity, including the orbit, skull base, intracranial cavity, cervical lymph nodes, or systemic metastases

noma, which may be further subclassified into tubular, cribriform, and solid types on histologic grounds. All forms are marked by neurotropism. Solid adenoid cystic carcinomas must be distinguished from basaloid squamous, neuroendocrine carcinomas, and SNUCs.

Staging

Many sinonasal malignancies present at an advanced stage, when they have grown to a large size and/or invaded sites beyond the bony confines of the sinus cavity. Innocuous symptoms, such as nasal airway obstruction, facial pain, pressure, and epistaxis, may be followed by proptosis, diplopia, nasal or facial mass, cerebrospinal fluid leak, loosening dentition, or epiphora, depending on the site and extent of the tumor. Ideal tumor staging not only reflects tumor extent and prognosis, but also facilitates treatment planning and enables comparisons of outcomes. Several prognostic systems have been devised for sinonasal malignancies. The Kadish staging system[6] roughly correlates with 5-year survival for esthesioneuroblastomas and divides patients into three groups based on the extent of disease (Table 3). This approach is sometimes inappropriately used to describe tumor extent for other tumor types.

For most sinonasal cancers, T and N classification, intracranial extension, dural invasion, orbital invasion, and tumor histology have been consistently found to affect local control and survival. In the staging of maxillary sinus cancers, local extension of cancer into the pterygoid and infratemporal fossa has prognostic value. Ohngren's line, representing an imaginary plane from the medial canthus of the eye to the angle of the mandible, separates the maxillary sinus into anterior inferior (infrastructure) and superior posterior (suprastructure) sites. Infrastructure carcinomas are associated with a good prognosis, whereas carcinomas of the suprastructure are associated with a poor prognosis because of ready spread of these tumors to the eye, skull base, pterygoids, and infratemporal fossa. In the American Joint Committee on Cancer (AJCC) staging system,[7] T4 maxillary sinus cancers are subdivided into T4a and T4b, based on current standards of resectability (Table 4). Brain invasion or involvement of the orbital apex, optic chiasm, cavernous sinus, and

TABLE 4. AJCC Staging: Sinonasal Carcinomas (ed 7)

Primary tumor: maxillary sinus	
TX	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the 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	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus
Primary tumor: nasal cavity and ethmoid sinus	
TX	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor restricted to any one subsite, with or without bone invasion
T2	Tumor invading 2 subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bone invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	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	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus

internal carotid artery are generally accepted to be contraindications to surgery and mark the cancer as surgically unresectable.

For patients with cutaneous squamous cell carcinomas, a number of high-risk factors have been recognized, including depth of invasion, neural invasion, and vascular invasion (Table 5). These risk factors have been included in the pathologic staging of cutaneous squamous cell carcinoma. Direct tumor invasion of maxilla, mandible, temporal bone, or orbit characterizes T3 lesions, whereas direct or neural involvement of the skull base characterizes T4 lesions (Table 6).

In cutaneous malignancies, nerve invasion has been associated with an increased risk of local recurrence, which may be reduced by approximately half with the addition of radiation.[8,9] However, it is important to make a distinction between incidentally identified pathologic involvement

TABLE 5. Cutaneous squamous cell carcinoma: high-risk pathologic features

Clinical: Primary site on ear or glabrous lip	
Histologic: ≥ 2 mm depth	
	Clark level IV/V
	Perineural invasion
	Lymph-vascular invasion
	Poor differentiation

From Rao et al. Protocol for the examination of specimens from patients with squamous cell carcinoma of the skin. College of American Pathologists Web site, February 2010, based on AJCC (ed 7).

TABLE 6. Pathologic staging: cutaneous squamous cell carcinoma: primary tumor

pTX:	Primary tumor cannot be assessed
pT0:	No evidence of primary tumor
pTis:	Carcinoma in situ
pT1:	Tumor 2 cm or less in greatest dimension with less than two high risk features
pT2:	Tumor greater than 2 cm in greatest dimension with or without 1 additional high risk feature, or any size with 2 or more high-risk features
pT3:	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
pT4:	Tumor with direct or perineural invasion of skull base or axial skeleton

Based on AJCC (ed 7).

of nerves and clinical involvement manifested by sensory changes or motor dysfunction because clinical involvement is associated with a greater risk of local recurrence. For skin cancers, pathologic involvement of nerves less than 0.1 mm in diameter does not have the same impact on prognosis[9] as the involvement of larger nerves. The decision to sacrifice an abnormally thickened but functional nerve identified at the time of surgery remains controversial and subject to individual surgeon judgment.

Neural invasion is also a property of certain sinonasal malignancies, including adenoid cystic carcinoma, SNUC, and select squamous cell carcinomas. Neural invasion in these sinonasal malignancies does not as clearly affect prognosis, which is usually explained by other factors, including histology and stage.[10]

Treatment Strategies

The physical proximity of sinonasal malignancies to critical structures (orbit, brain, and optic apparatus) complicates treatment, regardless of modality. Sinonasal cancers are frequently managed with resection, but treatment strategies are often modified based on tumor type and extent. Adjuvant radiation is usually recommended for high-grade tumors, advanced T classification, bone or neural invasion, intracranial extension, dural or brain involvement, or positive margins. Patients with neuroen-

docrine carcinomas, SNUCs, and high-grade sarcomas seem to benefit from the addition of chemotherapy. The type and sequence of multimodal treatment is typically modified by factors such as tumor extent, histology, and institutional bias. Regardless of treatment approach, most recurrences of paranasal sinus malignancies result from local failures.

Surgery in the Management of Sinonasal Cancer

Surgery for sinonasal malignancies has undergone considerable evolution. The development of craniofacial resection in the 1970s by Kecham and others for the management of esthesioneuroblastoma combined with radiotherapy doubled local control and survival. The approach enabled the resection of the olfactory system and dura as well as involved paranasal sinuses. Nonetheless, margins of resection are typically limited, and radiation treatment, found repeatedly to improve local control, is typically recommended even for early-stage disease.[11,12] It may be delivered either before or after resection. The use of minimally invasive and endoscopic surgical approaches has increased substantially over the last 10-20 years. Exclusively endoscopic resections of selected esthesioneuroblastomas have been reported. Generally, these reports contain small numbers of patients with relatively short follow-ups.[13] For esthesioneuroblastoma, local recurrences can develop 10 years or more after the completion of treatment, so prolonged follow-up is needed. With surgical techniques changing rapidly, craniofacial resection remains an important standard by which other treatments for esthesioneuroblastoma should be judged.

Craniofacial resections may also be used in the surgical treatment of other skull base malignancies involving the cribriform plate, fovea ethmoidalis, and anterior cranial base. The nature and extent of the surgical resection for sinonasal malignancies is determined by the tumor itself. Invasion of the orbit may necessitate exenteration. Hard palate and alveolar involvement necessitates an infrastructure maxillectomy. Microvascular soft tissue transfer may be required if there is a significant skin and soft tissue defect following resection and may reduce complications of aggressive resection of the skull base. Ideally, surgery of sinonasal cancers is performed by means of an en bloc resection. However, en bloc resection with clear margins is seldom feasible. Experience has shown that piecemeal resection is not incompatible with successful surgical excision. The goal of surgery, whether open or using endoscopic approaches, remains complete tumor removal with negative surgical margins.[14] When this is not possible, a resection of all gross tumor is preferable to "debulking."[15] Resection should be undertaken only if it is

anticipated that all gross tumor can be removed at the time of operation. However, this cannot always be determined before before the procedure.

Some tumor histologies, such as SNUCs, are less often amenable to primary surgery than other tumor types due to rapidly destructive growth patterns, prominent neurotropism, and vascular invasion. Approximately one-third of SNUCs are considered unresectable at the time of presentation.[16] Although not universally accepted, the presence of distant metastases, brain, optic chiasm, cavernous sinus, and internal carotid artery invasion are widely regarded as contraindications to surgery.

Management of the Orbit

In patients with sinonasal malignancies, the proximity of the orbit to the tumor places it at risk for invasion or treatment-related damage. The eye can often be preserved without compromising overall survival or local control. The recognized indications for orbital exenteration have evolved. Historically, tumor abutting the lamina was a sufficient reason for exenteration. More recent commonly accepted indications have included penetration through the periorbita into orbital fat and invasion of extraocular muscles, the optic nerve, or orbital apex. Proptosis or diplopia may be due to displacement of orbital contents; decreased visual acuity or the presence of an afferent pupillary defect usually indicates gross orbital invasion. CT scan or MRI is helpful in delineating the extent of disease. Tumor spread into the orbit may occur by means of direct extension or by neural spread along V1 and V2 through the superior or inferior orbital fissures. Orbital involvement by cancer and the need for orbital exenteration may not be accurately determined before the procedure. Patients undergoing surgical resection require appropriate counseling.

As in other aerodigestive tract sites, preservation of a structure is not always associated with preservation of function. Resection of the orbital floor or periorbital dissection may lead to postoperative problems, including enopthalmos, ectropion, canthal dystopia, epiphora, and diplopia. Postoperative radiation (which is invariably required in this setting) worsens these problems and may result in retinopathy and optic neuropathy. Validated measures of functional outcome and disease-specific quality of life for sinonasal cancer patients have not yet been systematically employed.

Skull Base Reconstruction

Surgical resection of extensive sinonasal cancers can lead to significant functional deficits and morbidity. Reconstruction of sinonasal defects to achieve cranionasal separation, eye and cheek support, or oronasal

separation is beneficial. In particular, creation of an initial watertight seal with separation of brain from the sinonasal cavity is critical in preventing a cerebrospinal fluid (CSF) leak, meningitis, and pneumocephalus. A vascularized pericranial flap is the most frequent expedient for this purpose. Fibrin glue and tissue adhesives do not compensate for poor surgical technique. A lumbar subarachnoid drain may be used for a few days. Endoscopic approaches have been associated with a higher rate of CSF leak due to limitations in effective cranial base reconstruction. The development of the Haddad-Bassagasteguy flap, or nasoseptal flap, a reliable vascularized local flap used in endoscopic approaches has lead decreasing rates of postoperative CSF leak, approaching those of open procedures. This flap, however, cannot be used if the mucosa or pedicle is involved with cancer. A tracheotomy is seldom needed.

Maxillectomy defects may be managed with palatal obturation or microvascular free flap reconstruction. Small defects in the palate are effectively treated with a palatal obturator. For extensive palatal defects (ie, greater than 50% of the palate and/or anterior resections including both canines), reconstruction with a free flap has been associated with better functional results in experienced hands. The use of a fibula flap for reconstruction of anterior defects results in restoration of the palatal arch and a stable occlusal plane.[17] Such reconstructions may be combined with reconstruction of the inferior orbital rim, which is less effectively managed with skin graft and palatal obturator. The use of well-vascularized soft tissue with bone grafts or titanium mesh may diminish resorption of bone grafts, infection, or extrusion of alloplastic materials and provide requisite durable support for the globe.

Complications

Skull base procedures have been associated with significant morbidity and risk of treatment-related death. In an international collaborative study of 334 patients who underwent a craniofacial resection, mortality of 4.5% was reported (15 patients) with a postoperative complication rate of 33%.[18] The development of microvascular free flap reconstruction has allowed patients not previously considered for operations to undergo otherwise extensive procedures. The use of free flaps has not been associated with an increased rate of surgical complications despite the increased length and complexity of these procedures.[19] In fact, the incidence of postoperative complications appears to be decreasing.[20]

Radiotherapy for sinonasal malignancy has changed over the last decade. The use of intensity modulated radiotherapy rather than three-dimensional conformal radiotherapy has been associated with diminished

acute, chronic toxicity, and improved disease-free survival.[21,22] It is now considered the standard treatment modality for sinonasal malignances. Proton radiotherapy remains under investigation. It seems that the surgical and radiotherapeutic treatment of sinonasal malignancies has become much safer over the last few decades.[15] In addition, improved survival following treatment has been observed by some[23] but not all institutions.[15]

Nonsurgical Management of Sinonasal Malignancies

Nasopharyngeal-type undifferentiated carcinomas or lymphoepitheliomas presenting as sinonasal malignancies may be effectively treated by nonsurgical means. Clinical experience and randomized trial results involving nasopharyngeal carcinoma may be reasonably generalized to patients with sinonasal lymphoepitheliomas.

In general, however, evidence to support the nonsurgical management for sinonasal malignancies remains relatively weak, and results of randomized clinical trials of squamous cancer of the head and neck do not readily apply to paranasal sinus cancers. Sinonasal malignancies are extremely rare, account for 2%-3% of upper aerodigestive tract malignancies, and are marked by far greater clinical and biological heterogeneity than nasopharyngeal carcinoma or other head and neck cancers (although pooling of patients in head and neck clinical trials may have obscured differences between upper aerodigestive tract sites).

Much of the literature on skull base malignancies is characterized by single-institution experiences with small numbers of patients, variable histologies and stages, aggregating several anatomic sites, in patients who have undergone a variety of treatments. Clinical outcomes from studies that include patients with esthesioneuroblastoma, SNUC, and sinonasal melanoma are difficult to interpret, given the different clinical behaviors of these lesions. Advances in surgery and radiation treatment further confound analysis because most series reflect decades of clinical experience.

Nevertheless, a variety of treatment schemes incorporating the use of chemotherapy and radiation have been explored. The results of radiation given definitively have been disappointing, and historically have been associated with high rates of ocular complications. Local control rates ranging from 14% to 53% have been reported.[24-29] However, many studies are marked by selection bias, and patients treated nonsurgically more often have locally advanced disease or are considered inoperable (Table 7).[23,28,30-33] The use of induction chemotherapy for sinonasal squamous cell carcinomas has not been associated with improved local

TABLE 7. Treatment outcomes for sinonasal cancers

Author (years)	N	Histology (% SCC)	T-stage	Surgery	Induction chemo	Concurrent chemo	Radiation dose	Local control*	Overall survival*
Lee[31] (1984-1996)	19	81%	100% T3-4 T4bNR	yes	yes	yes	45-74 Gy	76%	73%
Mendenhall[28] (1964-2005)	53	15%	T4 23%	yes	no	rare	65 Gy	84%	73%
	56	43%	T4 41%	no	no	rare	70 Gy	43%	38%
Porceddu[32] (1991-2000)	60	58%	78% T3-4 T4b 3%	usually	rare	rare	56 Gy	49%	40%
Thorup[23] (1995-2004)	96	55%	Stage III-IV 69%	yes	no	no	NR	64%	65%
	79			no	no	no	NR	34%	40%
Hoppe[30] (1990-2006)	39	38%	T4b 100%	no	yes	yes	70 Gy	20%	15%
Homma[33] (1999-2006)	47	76%	100% T3-4 T4b 38%	rare	no	yes RADPLAT	65-70 Gy	78%	69%

Abbreviations: N, number of patients; RADPLAT, intraarterial high-dose cisplatin.
*At 5 years.

control or a survival advantage.[34] Schemes using induction chemotherapy for organ (primarily ocular) preservation, based on pioneering work from Japan,[35-38] have been explored. At the University of Texas, induction chemotherapy with intraarterial cisplatin (RADPLAT) and intravenous paclitaxel and ifosfamide yielded a complete clinical response in 26% and complete pathologic response in 20%. However, the high rates of central nervous system toxicity led this group to abandon this treatment approach.[39] In a subsequent study from Hokkaido University, concurrent intraarterial treatment with high-dose cisplatin yielded impressive cancer outcomes and was associated with manageable toxicity and no treatment-related cerebrovascular accidents or mortality. Of 47 patients with paranasal sinus cancers, 35 (77%) had squamous cell carcinoma and 9 (19%) had undifferentiated carcinoma. Treatment with intraarterial cisplatin (100-120 mg/m^2 weekly) combined with conventional external beam radiation (65-70 Gy), yielded 5-year local progression-free survival of 78% overall, and 69% for patients with T4b cancers. Sixteen of 38 patients developed severe ocular problems.[33] Such impressive oncologic results have not as of yet been duplicated elsewhere.

Response to induction chemotherapy has been used to select patients with sinonasal squamous carcinomas for subsequent definitive treatment. Hanna et al. reviewed the experience of 46 patients initially treated with induction chemotherapy using a combination of taxane and platinum either alone or with a third agent, before definitive local therapy. Patients with T3 or T4 squamous cancers, requiring orbital exenteration or craniofacial resection, were eligible. Sixty-seven percent of patients achieved at least a partial response, whereas 24% progressed. Response to induction chemotherapy was highly predictive of survival. The 2-year survival was 77% in patients with stable disease compared with 36% for patients with progression. Surgical resection was performed in only 50%. Long-term outcomes and toxicity results are still pending.[13] Although chemosensitivity may identify patients with a better prognosis, it is unlikely that patients who progressed during chemotherapy benefited from the delay in definitive local treatment. The role of induction chemotherapy in the setting of paranasal sinus cancer remains under investigation.

Management of SNUC

Clinical outcomes for patients with SNUC have historically been dismal. SNUC is characterized by destructive rapid growth, a greater tendency to metastasize than squamous carcinomas, and frequent vascular and neural invasion. Some of these properties suggest that it may respond

more favorably to aggressive chemotherapeutic approaches. Results of small published series, however, have been inconsistent. Ten patients with sinonasal SNUCs were treated at the Peter MacCallum Cancer Centre between April 1990 and April 2002. Although 1 patient had a T1N0 tumor, the rest were classified T4 with intracranial and/or orbital invasion. Of these 9 patients, 2 had initial surgery followed by postoperative radiation to a dose of 54 Gy in 30 fractions, and both developed locoregional recurrence. The other 7 patients received induction chemotherapy with cisplatin (or carboplatin if cisplatin was contraindicated) with infusional 5-FU for 3 cycles followed by concurrent chemoradiation with cisplatin during the first and last weeks of radiation. One patient progressed while receiving induction chemotherapy and died 5 months after completing radiation. Six patients had stable disease or partial responses after induction chemotherapy, and 4 subsequently had complete responses after radiation, remaining free of disease 8-51 months after completing treatment. Two patients with incomplete responses progressed 11 months after completing treatment. Because patients who recurred received 50-54 Gy and those who remained free of disease received 60 Gy, the authors speculate that at least 60 Gy is needed to control this tumor type.[40] Although generally these results are better than those reported previously, follow-up of 2 of 4 patients rendered disease-free (of the 7 total in the cohort) was less than 1 year (8 and 10 months).

In a review of 15 patients with T4 SNUCs treated at the University of Florida between September 1992 and October 2005, patients underwent either postoperative radiation, preoperative radiation, or definitive radiation with or without concomitant chemotherapy. All patients received 60-75 Gy of radiation. Concurrent treatment with cisplatin was most commonly employed. Patients treated with surgery, either before radiation or following preoperative radiation, had better local control than patients treated with definitive radiation, despite the use of higher doses of radiation (70-75 Gy) in the nonsurgical group. One of 7 patients treated with surgery and postoperative radiation developed a neck recurrence in a nonirradiated neck 4 months after treatment, whereas the others remained free of disease for 12-128 months. Local control was also achieved in the 2 patients who had preoperative radiation. However, both patients experienced disease recurrence, 1 in the neck and the other at distant sites. Three of 5 patients treated with definitive radiation developed recurrences, 1 local and 2 locoregional. One of these with a marginal dural recurrence was successfully salvaged. Based on their results, Tanzer et al. conclude that combined surgery and adjuvant radiation likely offer the best chance of cure compared with either modality alone.[16] However, it is important to note that most patients

who underwent initial surgery were classified as T4a, whereas those who underwent definitive radiation were staged T4b. On the whole, however, it does seem likely that surgery, either before or after radiation, improves local control. Relapses for SNUCs and other sinonasal malignancies are usually marked by local failure and sometimes locoregional failure. The authors favor a combined approach using surgery followed by radiation to a lower dose for resectable disease, to diminish the risk of radiation-induced optic neuropathy.[41]

Conclusions

Given the complexity of sinonasal malignancies, a multidisciplinary approach for treatment and rehabilitation is advocated. Survival after treatment for advanced sinonasal carcinomas remains suboptimal. Nevertheless, there is evidence that incremental changes have resulted in a decrease in treatment-related complications. As technical and technological advances are incorporated into the surgical and radiotherapeutic management of sinonasal malignancies, more effective treatments will be offered to a larger variety of patients. Improved understanding of tumor biology and tumor markers will permit a more individualized treatment approach.

REFERENCES

1. Alos L, Moyano S, Nadal A, et al. Human papillomaviruses are identified in a subgroup of sinonasal squamous cell carcinomas with favorable outcome. Cancer 2009;115(12):2701-9.
2. Wenig BM. Undifferentiated malignant neoplasms of the sinonasal tract. Arch Pathol Lab Med 2009;133(5):699-712.
3. Hyams VJ, Batsakis JG, Michaels L, eds. Atlas of Tumor Pathology. Washington, D.C.: Armed Forces Institute of Pathology, 1988.
4. Taxy JB, Bharani NK, Mills SE, et al. The spectrum of olfactory neural tumors. A light-microscopic immunohistochemical and ultrastructural analysis. Am J Surg Pathol 1986;10(10):687-95.
5. Rosenthal DI, Barker JL Jr, El-Naggar AK, et al. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. Cancer 2004;101(11):2567-73.
6. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer 1976;37(3):1571-6.
7. American Joint Committee on Cancer. AJCC Cancer Staging Manual (ed 7). New York: Springer, 2010.
8. Mendenhall WM, Amdur RJ, Hinerman RW, et al. Radiotherapy for cutaneous squamous and basal cell carcinomas of the head and neck. Laryngoscope 2009;119(10):1994-9.
9. Ross AS, Whalen FM, Elenitsas R, et al. Diameter of involved nerves predicts outcomes in cutaneous squamous cell carcinoma with perineural invasion: an

investigator-blinded retrospective cohort study. Dermatol Surg 2009;35(12): 1859-66.
10. Gil Z, Carlson DL, Gupta A, et al. Patterns and incidence of neural invasion in patients with cancers of the paranasal sinuses. Arch Otolaryngol Head Neck Surg 2009;135(2):173-9.
11. Dulguerov P, Allal AS. Nasal and paranasal sinus carcinoma: how can we continue to make progress? Curr Opin Otolaryngol Head Neck Surg 2006;14(2):67-72.
12. Dulguerov P, Jacobsen MS, Allal AS, et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. Cancer 2001;92(12):3012-29.
13. Hanna EY, Kupferman M, Webber R, et al. Induction chemotherapy for advanced squamous cell carcinoma of the paranasal sinuses. Presented at the American Head and Neck Society Annual Meeting, Las Vegas, 2010.
14. Resto VA, Chan AW, Deschler DG, et al. Extent of surgery in the management of locally advanced sinonasal malignancies. Head Neck 2008;30(2):222-9.
15. 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):141-7.
16. Tanzler ED, Morris CG, Orlando CA, et al. Management of sinonasal undifferentiated carcinoma. Head Neck 2008;30(5):595-9.
17. Moreno MA, Skoracki RJ, Hanna EY, et al. Microvascular free flap reconstruction versus palatal obturation for maxillectomy defects. Head Neck 2010;32(7):860-8.
18. Ganly I, Patel SG, Singh B, et al. Complications of craniofacial resection for malignant tumors of the skull base: report of an International Collaborative Study. Head Neck 2005;27(6):445-51.
19. Califano J, Cordeiro PG, Disa JJ, et al. Anterior cranial base reconstruction using free tissue transfer: changing trends. Head Neck 2003;25(2):89-96.
20. Gil Z, Patel SG, Bilsky M, et al. Complications after craniofacial resection for malignant tumors: are complication trends changing? Otolaryngol Head Neck Surg 2009;140(2):218-23.
21. Hoppe BS, Wolden SL, Zelefsky MJ, et al. Postoperative intensity-modulated radiation therapy for cancers of the paranasal sinuses, nasal cavity, and lacrimal glands: technique, early outcomes, and toxicity. Head Neck 2008;30(7):925-32.
22. Dirix P, Vanstraelen B, Jorissen M, et al. Intensity-modulated radiotherapy for sinonasal cancer: improved outcome compared to conventional radiotherapy. Int J Radiat Oncol Biol Phys 2010, Epub ahead of print.
23. Thorup C, Sebbesen L, Dano H, et al. Carcinoma of the nasal cavity and paranasal sinuses in Denmark 1995-2004. Acta Oncol 2010;49(3):389-94.
24. Giri SP, Reddy EK, Gemer LS, et al. Management of advanced squamous cell carcinomas of the maxillary sinus. Cancer 1992;69(3):657-61.
25. Amendola BE, Eisert D, Hazra TA, et al. Carcinoma of the maxillary antrum: surgery of radiation therapy? Int J Radiat Oncol Biol Phys 1981;7(6):743-6.
26. Lee F, Ogura JH. Maxillary sinus carcinoma. Laryngoscope 1981;91(1):133-9.
27. Paulino AC, Marks JE, Bricker P, et al. Results of treatment of patients with maxillary sinus carcinoma. Cancer 1998;83(3):457-65.
28. Mendenhall WM, Amdur RJ, Morris CG, et al. Carcinoma of the nasal cavity and paranasal sinuses. Laryngoscope 2009;119(5):899-906.
29. Jang NY, Wu HG, Park CI, et al. Definitive radiotherapy with or without

chemotherapy for T3-4N0 squamous cell carcinoma of the maxillary sinus and nasal cavity. Jpn J Clin Oncol 2010;40(6):542-8.
30. 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):763-9.
31. Lee MM, Vokes EE, Rosen A, et al. Multimodality therapy in advanced paranasal sinus carcinoma: superior long-term results. Cancer J Sci Am 1999;5(4):219-23.
32. Porceddu S, Martin J, Shanker G, et al. Paranasal sinus tumors: Peter MacCallum Cancer Institute experience. Head Neck 2004;26(4):322-30.
33. 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): 4705-14.
34. Kim GE, Chang SK, Lee SW, et al. Neoadjuvant chemotherapy and radiation for inoperable carcinoma of the maxillary antrum: a matched-control study. Am J Clin Oncol 2000;23(3):301-8.
35. Shibuya H, Horiuchi J, Suzuki S, et al. Maxillary sinus carcinoma: result of radiation therapy. Int J Radiat Oncol Biol Phys 1984;10(7):1021-6.
36. Shibuya H, Hoshina M, Shagdarsuren M, et al. Squamous cell carcinoma of the maxillary sinus and the oral part of the upper jaw. Comparison of treatment results. Acta Oncol 1994;33(1):43-7.
37. Shibuya H, Suzuki S, Horiuchi J, et al. Reappraisal of trimodal combination therapy for maxillary sinus carcinoma. Cancer 1982;50(12):2790-4.
38. Shibuya H, Takagi M, Horiuchi J, et al. Clinicopathological study of maxillary sinus carcinoma. Int J Radiat Oncol Biol Phys 1985;11(9):1709-12.
39. Papadimitrakopoulou VA, Ginsberg LE, Garden AS, et al. Intraarterial cisplatin with intravenous paclitaxel and ifosfamide as an organ-preservation approach in patients with paranasal sinus carcinoma. Cancer 2003;98(10):2214-23.
40. Rischin D, Porceddu S, Peters L, et al. Promising results with chemoradiation in patients with sinonasal undifferentiated carcinoma. Head Neck 2004;26(5):435-41.
41. Bhandare N, Monroe AT, Morris CG, et al. Does altered fractionation influence the risk of radiation-induced optic neuropathy? Int J Radiat Oncol Biol Phys 2005; 62(4):1070-7.