Sinonasal Carcinomas
Epidemiology, Pathology, and Management

Stephan K. Haerle, MD[a],
Patrick J. Gullane, CM, MB, FRCSC[a,*],
Ian J. Witterick, MD, MSc, FRCSC[a], Christian Zweifel, MD[b],
Fred Gentili, MD, MSc, FRCSC[b]

KEYWORDS

• Sinonasal carcinoma • Skull base • Epidemiology • Pathology • Management

KEY POINTS

- Sinonasal malignancies are uncommon neoplasms, and in most cases present in an advanced stage of disease.
- Exact staging necessitates a clinical and endoscopic examination with biopsy and imaging.
- Tumor resection using an open or endoscopic approach is usually considered as the first treatment option.
- In general, sinonasal carcinomas are radiosensitive and, therefore, adjuvant or neoadjuvant radiation treatment may be indicated in advanced disease.
- Multidisciplinary surgical and medical oncologic approaches, which include ablation and reconstruction, have enhanced the survival outcome over the past few decades.

INTRODUCTION

Sinonasal carcinomas are uncommon neoplasms that account for approximately 3% to 5% of all upper respiratory tract malignancies. Sinonasal malignancies in most cases do not cause early symptoms and present in an advanced stage of disease. In general, sinonasal carcinomas are radiosensitive; therefore, adjuvant or neoadjuvant radiation treatment may be indicated in advanced disease. Multidisciplinary surgical and medical oncologic approaches, which include ablation and reconstruction, have enhanced the survival outcome over the past few decades.

Epidemiology

Sinonasal carcinomas are uncommon malignancies, with an estimated incidence in the United States of 0.556 cases per 100,000 population.[1] This figure represents approximately 0.2% of all cancers and 3% to 5% of cancers in the upper aerodigestive tract.[2–4] The majority of published reports have identified the maxillary sinus to be the most common primary site.[4–8] Other studies have reported this to be the nasal cavity.[1,9] Because sinonasal malignancies often present in an advanced stage, the true identification of the site of origin may be difficult. Primary malignancy of the frontal sinus is uncommon, and those arising in the sphenoid sinus are rare.[10,11]

[a] Department of Otolaryngology – Head and Neck Surgery, Toronto General Hospital, University Health Network, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada; [b] Division of Neurosurgery, Toronto General Hospital, University Health Network, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada
* Corresponding author. Department of Otolaryngology – Head and Neck Surgery, University of Toronto, University Health Network/Toronto General Hospital, 200 Elizabeth Street, Room 8N-877, Toronto, Ontario M5G 2C4, Canada.
E-mail address: Patrick.gullane@uhn.ca

Neurosurg Clin N Am 24 (2013) 39–49
http://dx.doi.org/10.1016/j.nec.2012.08.004
1042-3680/13/$ – see front matter

Sinonasal carcinomas arise most often during the sixth decade of life with a male to female ratio of approximately 2:1. A recent study of population-based data (Surveillance, Epidemiology, and End Results [SEER]) included more than 6000 patients, and reported a decrease in the incidence of sinonasal cancer in men while remaining stable among women.[1] These findings reflect changing demographics and the socioeconomic developments seen also in other head and neck cancers.[12]

Risk Factors

Several occupational risk factors have been reported. Adenocarcinomas have been associated with hardwood dust exposure, chrome pigment, clothing, and leather, whereas squamous cell carcinoma (SCC) has been linked with nickel, soft wood dust, radium, mustard gas, and asbestos.[13–15] Occupational exposures such as those involving the use of formaldehyde have been shown to increase the risk of both adenocarcinoma and SCC.[15] Unlike other head and neck cancers, cigarette smoking and alcohol have less impact on the development of sinonasal carcinoma.

More recently, human papilloma virus (HPV) has also been associated with the malignant transformation of inverted papilloma and SCC.[16,17] Similar to HPV-associated SCC of the oropharynx, tumors in the sinonasal region that are HPV positive have a better treatment outcome.[18]

PATHOLOGY

Anatomy

The nasal cavity and the paranasal sinuses are in close proximity to many vital structures that can be involved by the contiguous spread of tumor. In addition, the paranasal sinuses have lymphatic and venous drainage pathways, which provide additional routes of spread intracranially. The skull base forms the floor of the cranial cavity and separates the brain from a variety of other important facial structures. The bony architecture of the skull base consists of the ethmoid, sphenoid, occipital, paired frontal, and parietal bones. Three regions can be differentiated: the anterior, middle, and posterior cranial fossae. In the case of sinonasal malignancy, the anterior skull base is the most commonly affected region. Thus, exact anatomic knowledge of the paranasal sinuses and anterior skull base is important for the treatment of sinonasal malignancies.

Staging

Because of late presentation, the diagnosis of malignant sinonasal tumors in patients often occurs in the later stages, so it is difficult to determine the exact site of tumor origin. The first staging system was described by Ohngren, and was based on resectability criteria established by the extension of the tumor with respect to Ohngren's line (connecting the angle of the mandible with the medial canthus).[19] Since then, a variety of classification systems have been published, including the seventh TNM classification system by the American Joint Committee on Cancer (AJCC).[20] There is a recognized correlation between tumor extension and treatment outcome. A review by the International Collaborative Group demonstrated that the histology, grade, intracranial extent, and status of surgical margins were independent predictors of treatment outcome.[21] The different staging systems for olfactory neuroblastoma are separately described in the relevant section of this article.

HISTOLOGIC SUBTYPES

Sinonasal carcinomas present with a variation of histologic heterogeneity in tumor type. The sinonasal tract and skull base is a region with the greatest histologic diversity in the body, and this

Box 1
Malignant sinonasal tumors

- Epithelial
  - Squamous cell carcinoma
  - Adenocarcinoma
  - Salivary-gland type tumors
    - Adenoid cystic carcinoma
    - Mucoepidermoid carcinoma
    - Acinic cell carcinoma
  - Sinonasal undifferentiated carcinoma
- Neuroectodermal
  - Melanoma
  - Olfactory neuroblastoma
- Neuroendocrine
  - Sinonasal neuroendocrine carcinoma
- Soft-tissue tumors
- Borderline and low malignant potential tumors of soft tissue
- Malignant tumors of bone and cartilage
- Hematolymphoid tumors
- Neuroectodermal tumors
- Germ cell tumors
- Secondary tumors

is reflected in the extensive disorder classification list compiled by the World Health Organization (WHO).[22,23] The major malignant subtypes are presented in **Box 1**. This article reviews the more common epithelial, neuroectodermal, and neuroendocrine type tumors. There are other more rare malignancies (eg, bone or soft-tissue tumors) that may also occur.

Squamous Cell Carcinoma

The most commonly encountered malignant neoplasms of the sinonasal tract are the keratinizing and nonkeratinizing types of SCC.[24] In 1% to 7% of all cases, SCC is seen in association with inverted papilloma.[25,26] SCC of the nasal cavity arises in the paranasal sinuses more frequently than in the nasal cavity.[27] The majority of SCC of the paranasal sinuses are keratinizing and nonkeratinizing lesions, with the undifferentiated type being less frequent. The latter subtype shows a more rapid course of growth. Similar to other locations in the head and neck, the basaloid variant of SCC has a more aggressive biological behavior.[28]

Early-stage disease (T1/T2) arising from the nasal cavity can be effectively managed by single-modality treatment (surgery or radiotherapy), whereas advanced-stage disease (T3/T4) requires a combined approach. SCC of the paranasal sinuses is often diagnosed at a late stage, and regional spread to the lymph nodes may be present.[29,30] Therefore elective treatment of the neck may be considered, especially when the SCC of the paranasal sinuses has invaded the overlaying soft tissue or adjacent bony structures.[31] The 5-year survival rates reported for SCC of the paranasal sinuses and the nasal cavity range from 40% to 70%.[6,32]

Adenocarcinoma

Adenocarcinoma represents the third most common malignancy in the sinonasal tract, after SCC and adenoid cystic carcinoma. It accounts for approximately 15% of all sinonasal cancers and is associated with certain risk factors.[2] Adenocarcinoma is male dominant and presents most frequently in the ethmoid sinuses. This malignancy is divided into a salivary-gland and non–salivary-gland type.[33,34] The latter is further separated into intestinal and nonintestinal types. Subclassifications of the intestinal type include papillary, colonic, solid, mucinous, or mixed, and the nonintestinal types are classified as either low or high grade. Intestinal-type carcinomas are generally aggressive with a local recurrence rate of up to 50%, lymphatic spread in 10%, and a distant metastasis rate of 20%. Low-grade nonintestinal adenocarcinomas most frequently occur in the ethmoid cells, and the 5-year survival rate is up to 85%. The high-grade nonintestinal adenocarcinomas are more commonly found in the maxillary sinus and have a very poor prognosis (3-year survival approximately 20%).[2] The majority of the adenocarcinomas arise from the mucoserous glands while the remainder originates in the respiratory epithelium.[35]

Many patients with adenocarcinomas are effectively treated with radiotherapy. However, surgical excision followed by radiotherapy is favored in many centers throughout the world. An open radical craniofacial resection is often warranted, and in many cases adjuvant radiotherapy needs to be scheduled because the disease is usually recognized in an advanced stage.[36] In carefully selected patients, a curative endoscopic approach may be considered. Another method of treatment involves surgical debulking via an endoscopic or open approach in combination with repeated topical chemotherapy (5-fluorouracil). Radiotherapy in this case is only given in cases of local recurrence.[37] Ten-year survival rates are reported to exceed 70%.[36,37]

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is the second most common tumor of the nasal cavity and paranasal sinuses, and accounts for approximately 10% of all non-SCC in the head and neck region and 15% of all salivary-gland cancers.[38–40] It arises more frequently in minor salivary glands than in all major salivary glands combined. Histologically, ACC exhibits 3 different subtypes based on the tumor architecture: cribriform, tubular, and solid. The cribriform pattern with its familiar stromal architecture is the most common. The tubular pattern, with a more typical glandular formation, has the best prognosis, and the less common solid pattern has the worst outcome. ACC in general is a slow-growing neoplasm, and recurrences often develop 10 to 20 years after initial treatment. ACC has a propensity for perineural spread and intracranial extension, reflecting the challenges of treating ACC and high morbidity. The most frequently involved nerves are the maxillary, mandibular, and vidian nerves. Because negative surgical resection margins may be difficult to achieve, ACC of the sinonasal tract has a poor prognosis.[39,41] Lymphatic spread to regional lymph nodes is uncommon and accounts for 10% to 30% of patients, whereas distant hematogenous spread is more frequent, with an average incidence of 40%.[42,43] The propensity for distant spread correlates with the stage at presentation,

and the most commonly affected distant sites are the lungs and long bones.

Surgical treatment with negative surgical margins is the gold standard for treating ACC. Postoperative radiation is used to achieve better local control, although the association with increasing survival remains controversial.[44,45] The role of systemic therapy is yet to be defined, although it has been shown to benefit some patients with recurrent, metastatic, and/or unresectable disease. Systemic therapy mainly consists of cisplatin alone or in combination with other agents (eg, doxorubicin, 5-fluorouracil), and the reported response rates to chemotherapy have been inconsistent and remain less than 20%.[46]

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) of the sinonasal tract is the second most common sinonasal salivary-gland type of malignancy after ACC. Differential diagnoses include adenosquamous carcinoma, adenocarcinoma, and necrotizing sialometaplasia. Overall, MEC accounts for fewer than 0.1% of all malignant sinonasal tract neoplasms, with no gender difference in disease prevalence.[47] MEC are histologically graded as low, intermediate, or high grade, with the latter having the worst prognosis. Clinical symptoms are nonspecific and usually present over a period of months. Invasive growth in MEC is common and recurrence is seen in approximately one-third of patients, usually within 2 years.[47] Surgery with the achievement of clear margins is the treatment of choice. Adjuvant radiotherapy in cases of positive margins is suggested to improve survival to the same level as that in patients with negative surgical margins. In cases of a high-grade tumor with negative resection margins, adjuvant radiotherapy is usually considered because of the aggressiveness of these tumors. Loh and colleagues[48] reported that disease-free survival for MEC in the nasal cavity was poorer than that for MEC in the oral cavity. MEC was associated with a greater tendency for local recurrences, which may be due to the incomplete tumor resection resulting from anatomic limitations.[48]

Acinic Cell Carcinoma

Acinic cell carcinoma is a low-grade malignant epithelial salivary-gland malignancy presenting very rarely in the sinonasal tract. Acinic cell carcinomas are most commonly found in the fifth and sixth decades of life, but are also reported in children.[49,50] There is no gender preference in the occurrence of these sinonasal tumors. Acinic cell carcinoma is believed to arise from the intercalated duct reserve cells.[49] Different grading systems and prognosis-related factors are described, but these studies are limited by small sample sizes and mainly concern major salivary glands outside the sinonasal tract. Laskawi and colleagues[51] found that histologically well-differentiated tumors in the parotid gland correlate with better prognosis than do poorly differentiated acinic cell carcinomas. There is a very low chance of nodal spread when the tumor originates in the sinonasal tract. The treatment of choice is surgical excision with adjuvant radiotherapy in patients with positive resection margins, perineural invasion, and/or lymphovascular invasion.[49] Similarly to ACC, patients with acinic cell carcinoma should be followed for long periods of time because metastases may occur many years after treatment.

Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinoma (SNUC) was first described by Frierson and colleagues[52] in 1986. SNUC is a very rare and aggressive malignancy that is hypothesized to be part of the spectrum of neuroendocrine carcinomas that include olfactory neuroblastoma, neuroendocrine carcinoma, and small cell carcinoma.[53] Usually it incorporates extensive tissue destruction and involvement of the orbit and anterior cranial fossa.[54] In general, light microscopy can differentiate between SNUC and other differential diagnoses such as olfactory neuroblastoma, lymphoma, rhabdomyosarcoma, and melanoma. In some cases, immunohistochemistry or electron microscopy is required to confirm the diagnosis. Differentiation between SNUC and olfactory neuroblastoma is important because the clinical behavior, prognosis, and treatment differ: olfactory neuroblastoma is generally slow growing with a better prognosis, whereas SNUC progresses more rapidly with a poor prognosis.[55] SNUC has been associated with Epstein-Barr virus; however, its role has not yet been confirmed.[55] The best treatment strategy for these tumors has yet to be defined. Some physicians have described preoperative chemotherapy followed by radiotherapy. In cases with no extensive intracranial involvement and without the presence of distant disease, a definitive surgical resection can be performed.[56] A recent meta-analysis of treatment outcomes for SNUC reported that treatment should include surgery, with radiation and/or chemotherapy as adjunctive treatments.[57] The role of induction chemotherapy in limiting the extent of surgery remains to be established.

Melanoma

Melanoma of the sinonasal tract is rare and accounts for only 1% of all melanomas.[58] The nasal

cavity is the most commonly affected site, followed by the maxillary antrum and the ethmoid sinuses, and it usually occurs between the fifth and eighth decades of life.[59] Clinical examination can be challenging when the melanoma is amelanotic because the typical heavily pigmented polypoid or fleshy mass is absent. Several histologic subtypes are described: amelanotic small blue cell, pleomorphic, epithelioid, spindle cell, and myxoid. All of these subtypes show a high mitotic rate, vascular invasion, regression, and absence of tumor-infiltrating lymphocytes.[60] Usually the presence of melanin helps to confirm the diagnosis. However, in the absence of melanin, specific stains are used to differentiate mucosal melanoma from other diagnoses such as anaplastic carcinoma, lymphoma, and olfactory neuroblastoma. In general, the prognosis of patients diagnosed with sinonasal mucosal melanoma is poor, with an average 5-year actuarial survival rate of less than 15%.[59,61] Patients with lesions that present on the nasal septum tend to do better than those with lesions at other sites within the sinonasal tract.[62] Primary treatment is surgery, either endoscopically or via an open resection. Radiotherapy may help to improve locoregional control; however, it does not affect overall survival.[63,64] There is limited evidence suggesting that prolonged survival is realized with the addition of chemotherapy, such as dacarbazine, platinum analogues, nitrosoureas, microtubular toxins, or taxols.[65,66] Further prospective, randomized clinical trials are necessary to confirm any definitive outcome effect.

Olfactory Neuroblastoma

Olfactory neuroblastoma is an uncommon malignancy hypothesized to arise from the olfactory epithelium. Its uncertain origin has resulted in different names; however, the most common terms used in the literature are olfactory neuroblastoma and esthesioneuroblastoma. This neoplasm accounts for approximately 7% to 10% of all sinonasal malignancies, and occurs with a bimodal peak in the second and sixth decades of life.[67,68] Impairment or a loss of the sense of smell, as one might expect, is not a common presentation because the contralateral part of the olfactory system is often still preserved. The initial stage of the disease is highly correlated with survival outcome. Several clinical staging systems have evolved over the past decades: the Kadish staging system,[69] described in 1976, is the first and most commonly used staging system incorporating 3 groups: group A contains tumors confined to the nasal cavity, group B tumors involving the paranasal sinuses, and group C tumors that extend beyond the sinonasal cavity. This system was modified by Foote and colleagues[70] with the addition of stage D, which includes cervical or distant metastasis. A third system, based on the TNM classification system, has been described by Dulguerov and Calcaterra (**Box 2**).[71] In addition, a histologic grading system reported by Hyams[72] describes 4 different grades, from Grade I (well differentiated) to Grade IV (undifferentiated). The grading is based on growth, architecture, mitotic activity, necrosis, nuclear polymorphism, rosette formation, and fibrillary stroma. There is a lack of consensus of whether this grading system is predictive of outcome. The most frequently used approach for treating olfactory neuroblastoma is a combined approach with radiotherapy given either before or after surgical resection.[73–75] Patients diagnosed with Kadish stage A or stage T1 lesions may not require adjuvant radiotherapy if clear surgical margins are achieved. To obtain adequate surgical margins, the cribriform plate is resected en bloc.[76] The classic combined anterior craniofacial resections have been replaced by expanded endoscopic approaches in selected cases, without impact on the 5-year control rate.[77–79] The 5-year disease-specific survival is reported to range from 52% to 90%.[71,75] Although olfactory neuroblastoma is not generally believed to be chemosensitive, some centers have advocated adjunctive chemotherapy to the treatment for Kadish B or C lesions. However, this combined-therapy approach has not been widely accepted.

Box 2
TNM-staging system according to Dulguerov and Calcaterra[71] for olfactory neuroblastoma

Stage	Characteristics
T1	Tumor involving nasal cavity and/or paranasal sinuses (excluding sphenoid sinus) sparing the most superior ethmoid cells
T2	Tumor involving nasal cavity and/or paranasal sinuses (including sphenoid sinus) with extension to or erosion of the cribriform plate
T3	Tumor extending into the orbit or protruding into anterior cranial fossa, without dural involvement
T4	Tumor involving the brain
N0	No cervical lymph node involvement
N1	Any form of cervical lymph node metastases
M0	No distant metastases
M1	Any distant metastases

Sinonasal Neuroendocrine Carcinoma

Sinonasal neuroendocrine carcinoma (SNEC) is rare and accounts for fewer than 5% of malignancies of the sinonasal tract.[80] The exact histologic diagnosis of this tumor can be challenging, owing to the difficulty of differentiating SNEC from olfactory neuroblastoma, sinonasal undifferentiated carcinoma, melanoma, and other small cell tumors of the sinonasal tract. The most common sites of origin are the ethmoid sinuses and the nasal cavity, with presenting symptoms that mimic those of rhinosinusitis and other benign sinonasal disorders, frequently resulting in a delayed diagnosis.[80,81] Accordingly, involvement of the skull base (bone or orbit) negatively affects survival. In general, SNEC shows epithelial differentiation with specific histologic and immunohistochemical features, such as a high mitotic rate and positivity for keratin and synaptophysin.[82,83] SNEC is associated with a high rate of locoregional recurrence and distant metastasis.[84,85] In a published series of 28 patients, Mitchell and colleagues[80] report a 25% recurrence of tumor in the neck and conclude that elective neck dissection should be considered in all patients considered for surgery. The ideal treatment strategy has yet to be determined. In addition to surgery and radiotherapy, systemic treatment may play a future role in the individualized management of this disease.

MANAGEMENT

In general, sinonasal malignancies do not cause symptoms until they have reached a certain size and expansion. Thus a high degree of suspicion is required to avoid delay in diagnosis. A thorough endoscopic examination with biopsy and radiographic imaging are the first steps when a suspicious lesion is present. Both computed tomography (CT) and magnetic resonance imaging (MRI) are now established as the optimum imaging assessment of

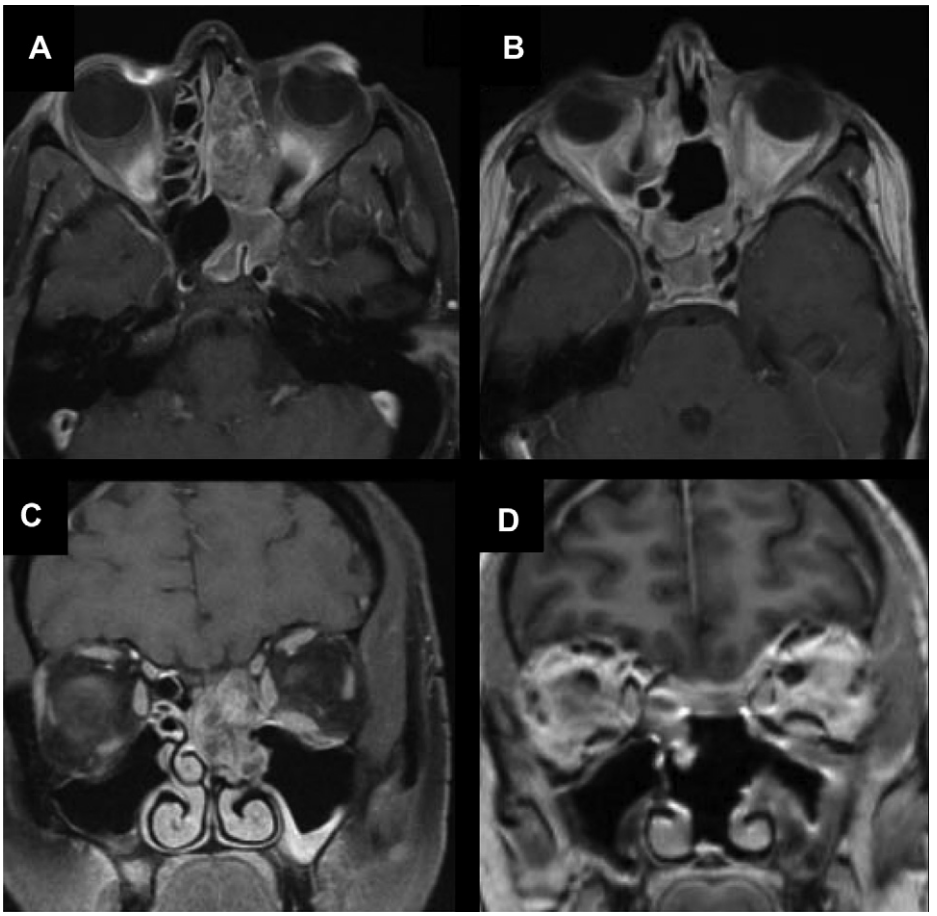

Fig. 1. (*A*) Axial and (*C*) coronal preoperative postcontrast-enhanced T1-weighted magnetic resonance images of a 40-year-old female patient with a seromucinous adenocarcinoma. Before surgery, the patient was radiated. (*B*) Axial and (*D*) coronal postoperative magnetic resonance images after an expanded endoscopic endonasal approach with nasoseptal flap showed complete removal of the tumor. All surgical margins were tumor negative.

sinonasal malignancy.[86] Haerle and colleagues[87] suggested that the radiologic evaluation in cases of sinonasal melanoma is best performed by metabolic imaging, such as ^{18}F-fluorodeoxyglucose positron emission tomography (PET), PET/CT, or PET/MRI if available. In general, metabolic imaging can be considered for initial exclusion of distant disease because the presence of such will alter the treatment plan significantly. MRI generally offers better tumor and tissue differentiation, whereas a CT scan is required to assess potential bone erosion.[88] During follow-up, MRI is considered to be the imaging modality of choice (**Fig. 1**).[89]

When exact staging is complete, a multidisciplinary oncologic discussion should take place. The optimal treatment for patients suffering from sinonasal malignancies remains to be defined, but open or endoscopic craniofacial resection followed by postoperative radiotherapy is currently considered for the vast majority of patients with locally advanced disease.

The Role of Radiotherapy

It is widely accepted that most sinonasal carcinomas are radiosensitive; however, radiosensitivity largely depends on the histology and growth rate of the tumor.[6] In the case of localized disease, radiation, either as a single-modality treatment or with combination treatment, offers a limited survival advantage.[1] Blanch and colleagues[8] reported no survival benefit with the addition of radiotherapy to surgery for early-stage disease Therefore, the primary treatment of choice for most sinonasal carcinomas is complete surgical tumor resection with adjuvant radiotherapy with or without systemic therapy.[6,90] There have been some published reports regarding intraoperative high-dose brachytherapy.[91] However, these studies are limited by small sample sizes and concern only patients with locally advanced or recurrent disease.

The Role of Chemotherapy

There are some preliminary reports on concurrent chemoradiation in sinonasal carcinomas, albeit limited to advanced SCC and SNUC.[92,93] Other literature describes the use of systemic treatments for specific histology subtypes of sinonasal carcinomas dependent on location and number of metastases. There is a role described in the literature for local chemotherapy using 5-fluorouracil in the treatment of adenocarcinoma, or as an adjuvant after minimal invasive surgical clearance.[94,95]

In the future, substantial improvements in prognosis will likely depend on the development and utilization of histology-specific and personally-directed systemic treatments.

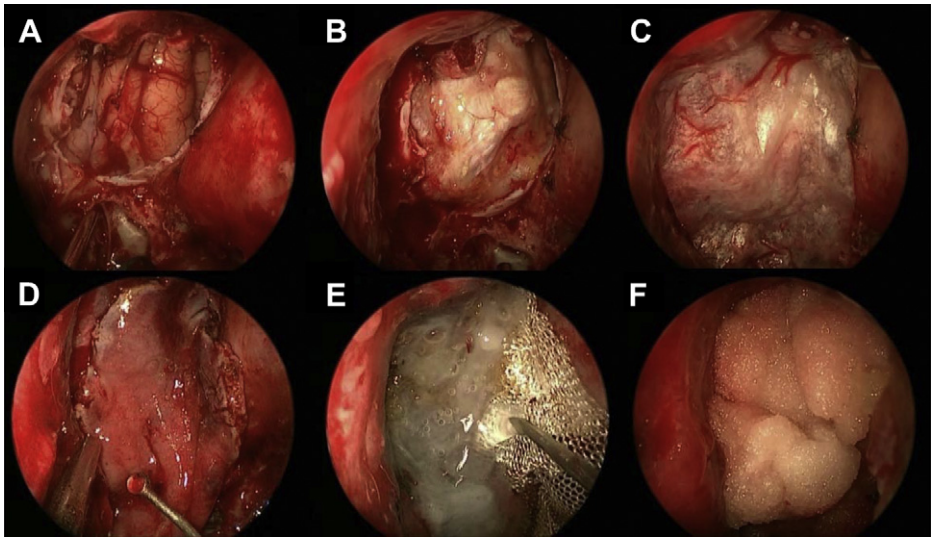

Fig. 2. Intraoperative view of an endoscopic endonasal approach to the anterior cranial fossa for resection and reconstruction of the 40-year-old woman in **Fig. 1** with a seromucinous adenocarcinoma. (*A*) View of the anterior cranial base after resection of the tumor, septum, cribriform plate, and dura. Olfactory bulb on the left side was resected. (*B*) Fascia lata was harvested and was put between the brain and dural edges. As second layer (*C*), artificial dura substitute was layered above the fascia lata graft and dural edges. The vascularized nasoseptal flap (*D*) was placed as a third layer over the artificial dura. The graft was further overlaid with Surgicel (*E*) and sealed with fibrin glue. Loose pieces of Gelfoam were placed over the reconstruction site. At the end of the procedure (*F*), a 24F Foley catheter balloon was placed and inflated to keep the grafts in place.

The Role of Surgery

There is a general consensus that the outcome of any alternative method of treatment should be compared with anterior craniofacial resection.[96,97] A surgical paradigm shift was initiated in the late 1990s with the introduction of endoscopic surgery as an exclusive approach or in combination with a frontal craniotomy.[98–100] Since then, endoscopic procedures have been compared with open approaches with regard to oncologic safety, outcome, and morbidity. According to Nicolai and colleagues,[77] the difficulty of exposing tumor margins does not impede a complete endoscopic resection. Only smaller lesions may be resected en bloc, whereas larger lesions are resected in a stepwise technique without compromising the oncologic safety. Hanna and colleagues[101] concluded that with appropriate use of adjuvant therapy, endoscopic resection of sinonasal cancer results in acceptable oncologic outcomes. For successful outcomes, endoscopic resection warrants the correct selection of cases, and should be performed by surgeons with experience in endoscopic techniques and oncologic principles. In an international collaborative study, there was an overall mortality rate of 4.7% and an overall postoperative complication rate of 36.3% using an open approach.[102] Quality-of-life measures were mainly addressed for open, craniofacial procedures, and the specific benefit of endoscopic techniques remains to be established.

An important goal of reconstruction in both open and endoscopic procedures is the separation of the sinonasal tract from cranial cavity to prevent ascending infections, cerebrospinal fluid (CSF) leaks, and pneumocephalus (**Fig. 2**). Different types of potential closures have been described, and innovative procedures such as vascularized pedicled or free flaps after an endoscopic or open approach, respectively, have reduced the postoperative complication rate. In the authors' experience, the use of vascularized free tissue transfer has substantially reduced the incidence of meningitis, CSF leaks, and pneumocephalus.[103]

SUMMARY

Over the last 40 years, improved prognosis in patients with sinonasal carcinoma has occurred as a result of advances in techniques of both evaluation and treatment. Despite these improvements, sinonasal carcinomas remain a challenging disease with high morbidity, low regional and distant disease control, and poor survival. However, future advancements to improve patient outcomes and survival include early detection, identification of tumor biological markers, and surgical innovations to provide superior access and minimize morbidity.

REFERENCES

1. Turner JH, Reh DD. Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data. Head Neck 2012;34(6): 877–85.
2. Lund VJ, Stammberger H, Nicolai P, et al. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. Rhinol Suppl 2010;1:1–143.
3. Myers LL, Nussenbaum B, Bradford CR, et al. Paranasal sinus malignancies: an 18-year single institution experience. Laryngoscope 2002;112: 1964–9.
4. Waldron J, Witterick I. Paranasal sinus cancer: caveats and controversies. World J Surg 2003;27: 849–55.
5. Khademi B, Moradi A, Hoseini S, et al. Malignant neoplasms of the sinonasal tract: report of 71 patients and literature review and analysis. Oral Maxillofac Surg 2009;13:191–9.
6. 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;92:3012–29.
7. Hoppe BS, Stegman LD, Zelefsky MJ, et al. Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting: the MSKCC experience. Int J Radiat Oncol Biol Phys 2007;67:691–702.
8. Blanch JL, Ruiz AM, Alos L, et al. Treatment of 125 sinonasal tumors: prognostic factors, outcome, and follow-up. Otolaryngol Head Neck Surg 2004; 131:973–6.
9. Grau C, Jakobsen MH, Harbo G, et al. Sino-nasal cancer in Denmark 1982-1991: a nationwide survey. Acta Oncol 2001;40:19–23.
10. Osguthorpe JD, Richardson M. Frontal sinus malignancies. Otolaryngol Clin North Am 2001;34: 269–81.
11. DeMonte F, Ginsberg LE, Clayman GL. Primary malignant tumors of the sphenoid sinus. Neurosurgery 2000;46:1084–91.
12. Sikora AG, Toniolo P, DeLacure MD. The changing demographics of head and neck squamous cell carcinoma in the United States. Laryngoscope 2004;114:1915–23.
13. Lund VJ. Malignancy of the nose and sinuses: epidemiological and aetiological considerations. Rhinology 1991;29:57–68.
14. Roush GC. Epidemiology of cancer of the nose and paranasal sinuses, current concepts. Head Neck Surg 1979;2:3–11.

15. Luce D, Leclerc A, Begin D, et al. Sinonasal cancer and occupational exposures: a pooled data analysis of 12 case-control studies. Cancer Causes Control 2002;13:147–57.
16. McKay SP, Gregoire L, Lonardo F, et al. Human papillomavirus (HPV) transcripts in malignant inverted papilloma are from integrated HPV DNA. Laryngoscope 2005;115:1428–31.
17. Syrjaenen KJ. HPV infections in benign and malignant sinonasal lesions. J Clin Pathol 2003; 56:174–81.
18. 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;115:2701–9.
19. Ohngren LG. Malignant tumours of the maxilloethmoidal region. Acta Otolaryngol 1993;19:101–6.
20. Edge SB, Byrd DR, Compton CC, et al, editors. AJCC cancer staging manual. 7th edition. New York: Springer; 2010.
21. Patel SG, Singh B, Polluri A, et al. Craniofacial surgery for malignant skull base surgery. Cancer 2003;98:1170–87.
22. Harvey RJ, Gallagher RM, Sacks R. Extended endoscopic techniques for sinonasal resections. Otolaryngol Clin North Am 2010;43:6113–638.
23. Barnes L, Everson JW, Reichart P, et al. Pathology and genetics of head and neck tumors. Lyon (France): IARC Press; 2005.
24. Wenig BM. Undifferentiated malignant neoplasms of the sinonasal tract. Arch Pathol Lab Med 2009; 133:699–712.
25. Woodson GE, Robbins T, Michaels L. Inverted papilloma. Consideration in treatment. Arch Otolaryngol 1985;11:806–11.
26. Tanvetyanon T, Qin D, Padhya T, et al. Survival outcomes of squamous cell carcinoma arising from sinonasal inverted papilloma: report of 6 cases with systematic review and pooled analysis. Am J Otolaryngol 2009;30:38–43.
27. Tufano RP, Mokadam NA, Montone KT, et al. Malignant tumors of the nose and paranasal sinuses: hospital of the University of Pennsylvania experience 1990-1997. Am J Rhinol 1999;13:117–23.
28. Wienecke JA, Thompson LD, Wenig BM. Basaloid squamous cell carcinoma of the sinonasal tract. Cancer 1999;85:841–54.
29. Hayashi T, Nonaka S, Bandoh N, et al. Treatment outcome of maxillary sinus squamous cell carcinoma. Cancer 2001;92:1495–503.
30. Tiwari R, Hardillo JA, Mehta D, et al. Squamous cell carcinoma of maxillary sinus. Head Neck 2000;22: 164–9.
31. Kim GE, Chung EJ, Lim JJ, et al. Clinical significance of neck node metastasis in squamous cell carcinoma of the maxillary antrum. Am J Otolaryngol 1999;20:383–90.
32. Kida A, Endo S, Iida H, et al. Clinical assessment of squamous cell carcinoma of the nasal cavity proper. Auris Nasus Larynx 1995;22:172–7.
33. Kleinsasser O, Schroeder HG. Adenocarcinomas of the inner nose after exposure to wood dust. Morphological findings and relationships between histopathology and clinical behaviour in 79 cases. Arch Otorhinolaryngol 1988;245:1–5.
34. Barnes L. Intestinal-type adenocarcinoma of the nasal cavity and the paranasal sinuses. Am J Surg Pathol 1986;10:192–202.
35. Gnepp DR, Heffner DK. Mucosal origin of sinonasal tract adenomatous neoplasms. Mod Pathol 1989;2: 365–71.
36. Stoll D, Bebar JB, Truilhe Y, et al. Ethmoid adenocarcinomas: retrospective study of 76 patients. Rev Laryngol Otol Rhinol 2002;122:21–9.
37. Knegt PP, Ah-See KW, van de Velden LA, et al. Adenocarcinoma of the ethmoid sinus complex: surgical debulking and topical fluorouracil may be the optimal treatment. Arch Otolaryngol Head Neck Surg 2001;127:141–6.
38. Perzin KH, Gullane P, Clairmont AC. Adenoid cystic carcinomas arising in salivary glands: a correlation of histologic features and clinical course. Cancer 1978;42:265–82.
39. Khan AJ, DiGiovanna MP, Ross DA, et al. Adenoid cystic carcinoma: a retrospective clinical review. Int J Cancer 2001;96:149–58.
40. Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary origin: a clinicopathologic study of 242 cases. Am J Surg 1974;128: 512–20.
41. Kim GE, Park HC, Keum KC, et al. Adenoid cystic carcinoma of the maxillary antrum. Am J Otolaryngol 1999;20:77–84.
42. Jones AS, Hamilton JW, Rowley H, et al. Adenoid cystic carcinoma of the head and neck. Clin Otolaryngol Allied Sci 1997;22:434–43.
43. Spiro RH. Distant metastasis in adenoid cystic carcinoma of salivary origin. Am J Surg 1997;174: 495–8.
44. Naficy S, Disher MJ, Esclamado RM. Adenoid cystic carcinoma of the paranasal sinuses. Am J Rhinol 1999;13:311–4.
45. Pitman KT, Prokopakis EP, Aydogan B, et al. The role of skull base surgery for the treatment of adenoid cystic carcinoma of the sinonasal tract. Head Neck 1999;21:402–7.
46. Airoldi M, Pedani F, Succo G, et al. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. Cancer 2001;91: 541–7.
47. Wolfish EB, Nelson BL, Thompson LDR. Sinonasal tract mucoepidermoid carcinoma: a clinicopathologic and immunophenotypic study of 19 cases

combined with a comprehensive review of the literature. Head Neck Pathol 2012;6(2):191–207.
48. Loh KS, Barker E, Bruch G, et al. Prognostic factors in malignancy of the minor salivary glands. Head Neck 2009;31:58–63.
49. Neto AG, Pineda-Daboin K, Spencer ML, et al. Sinonasal acinic cell carcinoma: a clinicopathologic study of four cases. Head Neck 2005;27:603–7.
50. Luna MA. Sialoblastoma and epithelial tumors in children, their morphologic spectrum and distribution by age. Adv Anat Pathol 1999;6:287–92.
51. Laskawi R, Rodel R, Zirk A, et al. Retrospective analysis of 35 patients with acinic cell carcinoma of the parotid gland. J Oral Maxillofac Surg 1998; 56:440–3.
52. Frierson HF Jr, Mills SE, Fechner RE, et al. Sinonasal undifferentiated carcinoma: an aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. Am J Surg Pathol 1986;10:771–9.
53. Tanzler ED, Morris CG, Orlando CA, et al. Management of sinonasal undifferentiated carcinoma. Head Neck 2008;30:595–9.
54. Gorelick J, Ross D, Marentette L, et al. Sinonasal undifferentiated carcinoma: case series and review of the literature. Neurosurgery 2000;47:750–4.
55. Cerilli LA, Holst VA, Brandwein MS, et al. Sinonasal undifferentiated carcinoma: immunohistochemical profile and lack of EBV association. Am J Surg Pathol 2001;25:156–63.
56. Deutsch BD, Levine PA, Stewart FM, et al. Sinonasal undifferentiated carcinoma: a ray of hope. Otolaryngol Head Neck Surg 1993;108:697–700.
57. Reiersen DA, Pahilan ME, Devaiah AK. Meta-analysis of treatment outcomes for sinonasal undifferentiated carcinoma. Otolaryngol Head Neck Surg 2012;147(1):7–14.
58. Ganly I, Patel SG, Singh B, et al. Craniofacial resection for malignant melanoma of the skull base. Arch Otolaryngol Head Neck Surg 2006; 132:73–8.
59. Batsakis JG, Suarez P, El-Naggar AK. Mucosal melanomas of the head and neck. Ann Otol Rhinol Laryngol 1998;107:626–30.
60. Regauer S, Anderhuber W, Richtig E, et al. Primary mucosal melanomas of the nasal cavity and paranasal sinuses. A clinicopathological analysis of 14 cases. APMIS 1998;106:403–10.
61. Lund VJ, Howard DJ, Harding L, et al. Management options and survival in malignant melanoma of the sinonasal mucosa. Laryngoscope 1999; 109:208–11.
62. Dauer EH, Lewis JE, Rohlinger AL, et al. Sinonasal melanoma: a clinicopathologic review of 61 cases. Otolaryngol Head Neck Surg 2008;138:347–52.
63. Lund VJ, Chisholm EJ, Howard DJ, et al. Sinonasal malignant melanoma: an analysis of 115 cases assessing outcomes of surgery, postoperative radiotherapy and endoscopic resection. Rhinology 2012;50:203–10.
64. Thomson LD, Wieneke JA, Miettinen M. Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115 cases with a proposed staging system. Am J Surg Pathol 2003;27: 594–611.
65. Lengyel E, Glide K, Remenar E, et al. Malignant mucosal melanoma of the head and neck. Pathol Oncol Res 2003;9:7–12.
66. Wang J, Murakami T, Hakamata Y, et al. Gene gun-mediated oral mucosal transfer of interleukin 12 cDNA coupled with an irradiated melanoma vaccine in a hamster model: successful treatment of oral melanoma and distant skin lesion. Cancer Gene Ther 2001;8:705–12.
67. Morita A, Ebersold MJ, Olsen KD, et al. Esthesioneuroblastoma: prognosis and management. Neurosurgery 1993;32:706–15.
68. Spiro JD, Soo KC, Spiro RH. Nonsquamous cell malignant neoplasms of the nasal cavities and paranasal sinuses. Head Neck 1995;17:114–8.
69. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer 1976;37:1571–6.
70. Foote RL, Morita A, Ebersold MJ, et al. Esthesioneuroblastoma: the role of radiation therapy. Int J Radiat Oncol Biol Phys 1993;27:835–42.
71. Dulguerov P, Calcaterra T. Esthesioneuroblastoma: the UCLA experience 1970-1990. Laryngoscope 1992;102:843–9.
72. Hyams VJ. Olfactory neuroblastoma. In: Hyams V, Batsakis Michaels L, editors. Tumours of the upper respiratory tract and ear. Washington, DC: Armed Forces Institute of Pathology; 1998. p. 240–8.
73. Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta- analysis and review. Lancet Oncol 2001;2:683–90.
74. Rastogi M, Bhatt M, Chufal K, et al. Esthesioneuroblastoma treated with non-craniofacial resection surgery followed by combined chemotherapy and radiotherapy: an alternative approach in limited resources. Jpn J Clin Oncol 2006;36:613–9.
75. Bachar G, Goldstein DP, Shah M, et al. Esthesioneuroblastoma: the Princess Margaret Hospital experience. Head Neck 2008;30:1607–14.
76. Girod D, Hanna E, Marentette L. Esthesioneuroblastoma. Head Neck 2001;23:500–5.
77. 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;22:308–16.
78. Folbe A, Herzallah I, Duvvuri U, et al. Endoscopic endonasal resection of esthesioneuroblastoma: a multicenter study. Am J Rhinol Allergy 2009;23: 91–4.

79. Villaret AB, Yakirevitch A, Bizzoni A, et al. Endoscopic transnasal craniectomy in the management of selected sinonasal malignancies. Am J Rhinol Allergy 2010;24:60–5.
80. Mitchell EH, Diaz A, Yilmaz T, et al. Multimodality treatment for sinonasal neuroendocrine carcinoma. Head Neck 2011. [Epub ahead of print].
81. Smith SR, Som P, Fahmy A, et al. A clinicopathological study of sinonasal neuroendocrine carcinoma and sinonasal undifferentiated carcinoma. Laryngoscope 2000;110:1617–22.
82. Cordes B, Williams MD, Tirado Y, et al. Molecular and phenotypic analysis of poorly differentiated sinonasal neoplasms: an integrated approach for early diagnosis and classification. Hum Pathol 2009;40:283–92.
83. Iezzoni JC, Mills SE. "Undifferentiated" small round cell tumors of the sinonasal tract. Differential diagnosis update. Am J Clin Pathol 2005;124: 110–21.
84. Rosenthal DI, Barker JL Jr, El-Naggar AK, et al. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. Cancer 2004;101:2567–73.
85. Perez-Ordonez B, Caruana SM, Huvos AG, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. Hum Pathol 1998; 29:826–32.
86. Lloyd G, Lund VJ, Howard D, et al. Optimum imaging for sinonasal malignancy. J Laryngol Otol 2000;114:557–62.
87. Haerle SK, Soyka MB, Fischer DR, et al. The value of ^{18}F-FDG-PET/CT imaging for sinonasal malignant melanoma. Eur Arch Otorhinolaryngol 2012; 269:127–33.
88. Lund VJ, Howard DJ, Lloyd GA. CT evaluation of paranasal sinus tumours for cranio-facial resection. Br J Radiol 1989;11:439–46.
89. Lund VJ, Howard DJ, Lloyd GA, et al. Magnetic resonance imaging of paranasal sinus tumours for craniofacial resection. Head Neck 1989;11: 279–83.
90. Jansen EP, Keus RB, Hilgers FJ, et al. Does the combination of radiotherapy and debulking surgery favor survival in paranasal carcinoma? Int J Radiat Oncol Biol Phys 2000;48:27–35.
91. Nag S, Tippin D, Grecula J, et al. Intraoperative high-dose-rate brachytherapy for paranasal sinus tumors. Int J Radiat Oncol Biol Phys 2004;58: 155–60.
92. Nishimura G, Tsukuda M, Mikami Y, et al. The efficacy and safety of concurrent chemoradiotherapy for maxillary sinus squamous cell carcinoma. Auris, Nasus, Larynx 2009;36:547–54.
93. Enepekides DJ. Sinonasal undifferentiated carcinoma: an update. Curr Opin Otolaryngol Head Neck Surg 2005;13:222–5.
94. Sato Y, Morita M, Takahashi HO, et al. Combined surgery, radiotherapy, and regional chemotherapy in carcinoma of the paranasal sinuses. Cancer 1970;25:571–9.
95. Knegt PP, deJong PC, van Ander JG, et al. Carcinoma of the paranasal sinuses. Results of a prospective pilot study. Cancer 1985;56:57–62.
96. Lund VJ, Howard DJ, Wei W. Endoscopic resection of malignant tumors of the nose and sinuses. Am J Rhinol 2007;21:89–94.
97. Batra PS, Citardi MJ, Worley S, et al. Resection of anterior skull base tumors: comparison of combined traditional endoscopic techniques. Am J Rhinol 2005;19:521–8.
98. Stammberger H, Anderhuber W, Wlach C, et al. Possibilities and limitations of endoscopic management of nasal and paranasal sinus malignancies. Acta Otorhinolaryngol Belg 1999;53:199–205.
99. Yuen AP, Fung CF, Hung KN. Endoscopic cranionasal resection of anterior skull base tumor. Am J Otolaryngol 1997;118:431–3.
100. Thaler ER, Kotapka M, Lanza DC, et al. Endoscopically assisted anterior cranial skull base resection of sinonasal tumors. Am J Rhinol 1999;13:303–10.
101. Hanna E, DeMonte F, Ibrahim S, et al. Endoscopic resection of sinonasal cancers with and without craniotomy: oncologic results. Arch Otolaryngol Head Neck Surg 2009;1135:1219–24.
102. Ganly I, Patel SG, Singh B. Complications of craniofacial resection for malignant tumors of the skull base: report of an International Collaborative Study. Head Neck 2005;27:445–51.
103. Neligan P, Mulholland S, Gullane P. Flap selection in cranial base surgery. Plast Reconstr Surg 1996;98:1159–66.