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CLINICAL INVESTIGATION **Head and Neck**

PATTERNS OF FAILURE AFTER COMBINED-MODALITY APPROACHES INCORPORATING RADIOTHERAPY FOR SINONASAL UNDIFFERENTIATED CARCINOMA OF THE HEAD AND NECK

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Purpose: To report the clinical outcome of patients treated with combined-modality approaches for sinonasal undifferentiated carcinoma (SNUC) of the head and neck.

Methods and Materials: The records of 21 patients with SNUC treated with curative intent at the University of California, San Francisco between 1990 and 2004 were analyzed. Patient age ranged from 33 to 71 years (median, 47 years). Primary tumor sites included the nasal cavity (11 patients), maxillary sinus (5 patients), and ethmoid sinus (5 patients). All patients had T3 (4 patients) or T4 (17 patients) tumors. Local–regional treatment included surgery followed by postoperative radiotherapy (PORT) with or without adjuvant chemotherapy for 17 patients; neoadjuvant chemoradiotherapy followed by surgery for 2 patients; and definitive chemoradiotherapy for 2 patients. Median follow-up among surviving patients was 58 months (range, 12–70 months).

Results: The 2- and 5-year estimates of local control were 60% and 56%, respectively. There was no difference in local control according to initial treatment approach, but among the 19 patients who underwent surgery the 5-year local control rate was 74% for those with gross tumor resection, compared with 24% for those with subtotal tumor resection ($p = 0.001$). The 5-year rates of overall and distant metastasis-free survival were 43% and 64%, respectively. Late complications included cataracts (2 patients), lacrimal stenosis (1 patient), and sino-cutaneous fistula (1 patient).

Conclusion: The suboptimal outcomes suggest a need for more effective therapies. Gross total resection should be the goal of all treatments whenever possible.

Sinonasal, Undifferentiated carcinoma, Radiotherapy, Head and neck.

INTRODUCTION

Initially described by Frierson *et al.* in 1986 (1), sinonasal undifferentiated carcinoma (SNUC) is a neoplasm of the head and neck that has only recently been recognized as a distinct histologic entity. Given its aggressive biologic behavior and propensity to arise in close proximity to critical normal tissue structures, such as the anterior skull base, central nervous system, and optic pathways, SNUC poses a unique therapeutic challenge for clinicians. Management decisions are further complicated by the lack of consensus regarding the optimal treatment strategy due to the limited amount of data existing in the literature reporting on clinical outcomes for patients presenting with this relatively uncommon malignancy. On the basis of earlier reports demonstrating a dismal prognosis for those treated by single-modality therapy, typically by surgery alone, combined-modality approaches incorporating radiotherapy with or without chemotherapy have been widely adopted in an attempt to improve disease control (2–5). Indeed, currently accepted local–regional treatment options include surgery followed by postoperative radiotherapy (PORT), neoadjuvant radiotherapy followed by surgery, and definitive radiotherapy with concurrent chemotherapy. The purpose of this study was to review a single-institutional experience with the management of SNUC, focusing on patterns of recurrence in an attempt to identify clinical and pathologic parameters correlating with outcome.

METHODS AND MATERIALS

Patients

This study was approved by the University of California, San Francisco (UCSF) committee on human research before collection of all patient material. The medical records of 28 consecutively

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treated patients with a histologic diagnosis of SNUC between January 1990 and December 2004 at the Department of Radiation Oncology at UCSF were retrospectively reviewed. Pathologic specimens were retrieved from archival tissue banks and reviewed in cases in which there was uncertainty regarding the histologic diagnosis or in cases in which immunohistochemical staining was not originally performed. Two patients, both of whom were initially diagnosed with SNUC, were reclassified as esthesioneuroblastoma and small-cell neuroendocrine carcinoma, respectively, and were not included in this series. The remaining 26 patients had tumors that shared histopathologic features of SNUC on light microscopy (high mitotic rates, significant cellular pleomorphism, high nuclear to cytoplasmic ratios, necrosis, and vascular invasion) and stained positive for neuron-specific enolase and chromogranin and were negative for S-100 and vimentin. Testing for Epstein-Barr virus was not routinely performed. Five patients with distant metastatic disease at initial presentation were excluded from this analysis, and the 21 remaining patients with SNUC localized to the head and neck constituted the primary population of this analysis. The median age of the patients identified was 47 years (range, 33–71 years). Fourteen men and 7 women were included.

All patients underwent history and physical examination with direct nasopharyngolaryngoscopy. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head and neck were performed for all patients before treatment. Tumors involving more than one anatomic area or in which uncertainty existed regarding the epicenter were assigned to the location with the greatest volume of cancer according to clinical and radiographic studies while considering symptoms and potential pathways of disease spread. The primary involved sites were as follows: 11 nasal cavity; 5 maxillary sinus, and 5 ethmoid sinus. Patients were retrospectively staged in accordance with the 2002 American Joint Committee on Cancer (AJCC) staging classification (6). All had locally advanced cancers, with 17 patients (81%) having T4 tumors and the remaining 4 patients (19%) having T3 tumors. Distribution of T stage was as follows: 19% T3; 43% T4a; 38% T4b. Orbital invasion by tumor was present in 6 patients (29%). Four patients (19%) had documented cranial nerve involvement according to either physical examination or imaging. Four patients (19%) had evidence of intracranial disease with involvement of the dura, but none had evidence of parenchymal brain invasion at initial presentation. Two patients (10%) presented with clinical or radiographic evidence of cervical lymphadenopathy.

Treatment

All of the patients in this series completed a full course of external beam radiotherapy. Seventeen patients (81%) were treated with PORT after initial surgery, with 9 of these patients also receiving adjuvant chemotherapy either concurrently with (5 patients) or subsequent to (4 patients) radiotherapy. The remaining 4 patients (19%) were treated with initial radiotherapy, all of whom also received concurrent chemotherapy. Among these 4 patients treated initially with a nonsurgical approach, 2 patients subsequently underwent gross total resection, with pathology revealing residual disease measuring 2 and 5 cm in greatest dimension, respectively, consistent with a partial pathologic response to neoadjuvant therapy. Overall, 13 patients (62%) received systemic therapy with chemotherapy regimens varying according to the discretion of the treating physicians. There was no definite policy regarding the type and dosage of chemotherapy used during the time frame of this study. Chemotherapy regimens included cyclophosphamide, doxorubicin, and vincristine in 5 patients; cisplatin and etoposide in 4 patients; cisplatin and 5-fluoruracil in 2 patients; carboplatin and etoposide in 1 patient; and cisplatin alone in 1 patient.

The type of surgery for the 19 patients who underwent definitive resection, either up front or after neoadjuvant treatment, depended mainly on the primary site and the extent of disease. Criteria for operability were established at the discretion of the surgeon. In general, an attempt was made to maximize local control with preservation of cosmetic and functional outcome. Surgical approaches included transcranial resection (6 patients), transfacial resection (5 patients), combined transfacial and transcranial resection (7 patients), and unknown (1 patient). Gross total resection was attained in 12 of the 19 patients (63%) who underwent surgery. Among these 12 patients, surgical margins were microscopically positive in 7 and negative in 5. Orbital exenteration was performed in 4 patients.

Radiotherapy technique varied depending on the site of disease, the time period of treatment, and the discretion of the radiation oncologist. All patients were treated with megavoltage equipment using photons or mixed photons and electrons. The clinical target volume was designed to cover the primary tumor site as defined by CT and/or MRI, considering physical examination findings, pathologic findings, and the potential for microscopic extension. Margins were added to generate a planning target volume based on the location of the primary tumor relative to avoidance structures and were generally 0.5 to 1 cm but as close as 1 mm in areas of close proximity to critical organs. This typically included both halves of the nasal cavity and ipsilateral maxillary sinus extending to the medial wall of the orbit. In general, care was taken to delineate the location of the optic apparatus, brain stem, spinal cord, and parotid glands with respect to the primary tumor site for planning purposes. None of the patients received interstitial or intraoperative radiotherapy. Patients were treated with conventional fractionation, most commonly 2 Gy per fraction. Median dose for those treated with PORT and primary radiotherapy was 57 Gy (range, 50–70 Gy) and 60 Gy (range, 60–71 Gy), respectively. Treatment was by continuous-course radiation with once-a-day treatment. Radiation portals were based on plain X-ray films and/or CT taken at the time of simulation and designed at the discretion of the treating radiation oncologist, with the most common being three-field isocentric treatments (11 patients) and parallel–opposed lateral fields prescribed to midplane (5 patients). A shrinking field technique was used in the majority of patients. Wedges or tissue compensators were used to maintain dose homogeneity within 10% of the prescribed dose. Three-dimensional radiotherapy (3D-RT) using CT planning with non-coplanar beam arrangements was used in 7 patients. Serial CT scan slices, 3 mm thick, from the head down though the clavicles were obtained for delineation of tumor volumes in these cases. Intensity-modulated radiotherapy (IMRT) was implemented at UCSF in 1997, and an additional 5 patients were treated with this technique. Details regarding our institution's experience with IMRT for malignancies of the paranasal sinuses and nasal cavity have previously been described (7).

Treatment of the neck depended on multiple factors. The 2 patients who presented with palpable cervical lymphadenopathy (upper jugular) underwent a neck dissection followed by postoperative radiation to the primary site and bilateral necks. Surgical dissection of the clinically negative neck was generally not performed during the period of this study. Elective neck irradiation (ENI) was administered at the discretion of the treating radiation oncologist with consideration given to the extensiveness and lymphatic drainage of the primary tumor. Overall, 15 of 19 patients (79%) with clinically N0 necks received ENI to a median dose of 50 Gy (range, 45–59 Gy).

After completion of treatment, patients were evaluated every 1 to 2 months for the first 6 months, then every 3 months for the next 6–12 months, every 4–6 months from 18 months through 3 years, and annually thereafter. Follow-up consisted of routine physical examination and review of systems, focusing particularly on the presence or absence of head-and-neck as well as neurologic symptoms. A baseline posttreatment MRI scan of the head and neck was obtained within 2–6 months after completion of treatment and then yearly or when clinically indicated. Patient follow-up was reported to the date last seen in clinic or to the date of expiration.

Statistical analysis

The endpoints analyzed were overall survival, local control, and distant metastasis-free survival. All events were measured from the first day of treatment. Local control was judged to have been attained if there was no evidence of tumor growth at the primary site according to clinical and radiographic findings at follow-up. Median follow-up was 36 months (range, 6–86 months) for the entire patient population and 58 months among surviving patients (range, 9–86 months). Actuarial estimates of overall survival, local control, and distant metastases-free survival were calculated using the Kaplan-Meier method, with comparisons among groups performed with two-sided log–rank tests (8). All tests were two-tailed, with a probability value of <0.05 considered statistically significant.

RESULTS

Local control

After treatment, 2 patients, both of whom were treated initially with subtotal resection and PORT, continued to have persistent disease, and both progressed at the primary site with follow-up. An additional 5 patients experienced a local recurrence, three of which were isolated first events, at a median of 9 months (range, 3–27 months) from the first day of treatment. For the entire patient population, the 2- and 5-year estimates of local control were 60% and 56%, respectively. Notably, there was no difference in local control according to initial treatment approach. The 5-year local control rate was 59% among those treated by initial surgery, compared with 53% among those treated by initial chemoradiotherapy ($p = 0.54$). The only parameter that we identified that predicted for local control was gross total resection. Among the 19 patients who underwent surgery, the 5-year local control rate was 74% for those with gross tumor resection, compared with 24% for those with subtotal tumor resection ($p = 0.001$). Among the 12 patients with gross total resection, there was no difference in local control according to microscopic surgical margin status ($p = 0.71$). None of the other factors, including T stage, age, dural involvement, orbital invasion, cranial nerve involvement, radiation dose, radiation technique (conventional vs. 3D-RT/IMRT), and use of chemotherapy, predicted for local control ($p > 0.05$ for all). Figure 1 illustrates local control for the entire patient population.

Overall survival

As illustrated in Fig. 2, the 2- and 5-year estimates of overall survival for the entire patient population were 65% and 43%, respectively. Nine patients were alive at the time of this analysis, all of whom were treated with surgery followed by PORT. Seven of these patients were without clinical evidence of disease. The cause of death among the 12 patients who died during the evaluation period was recurrence or persistence of local–regional tumor in 5 patients, metastatic disease in 4 patients, and was indeterminable in the remaining 3 patients. There was no difference in overall survival according to initial treatment approach. The 5-year estimates of overall survival for those treated by surgery followed by PORT was 47%, compared with 41% for those treated by initial radiotherapy ($p = 0.21$). None of the other parameters analyzed, including clinical T stage, age, primary site (nasal cavity vs. paranasal sinus), dural involvement, orbital invasion, cranial nerve involvement, radiation dose, radiation technique (conventional vs. 3D-RT/IMRT), and use of chemotherapy, predicted for overall survival ($p > 0.05$ for all). Among the 19 patients who underwent surgery, there was

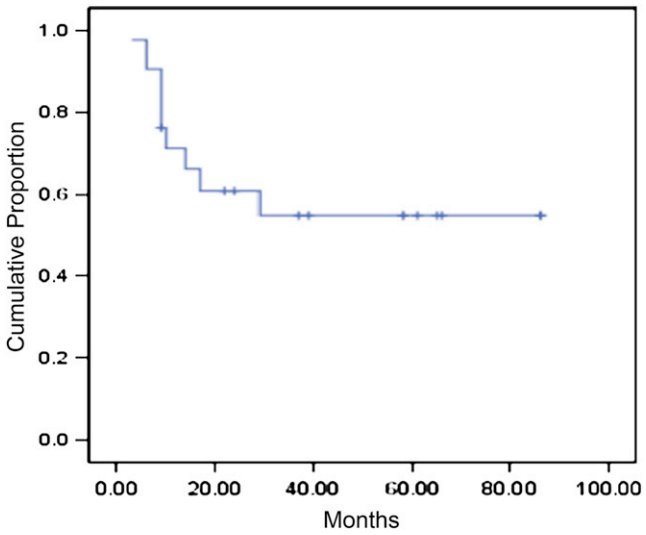

Fig. 1. Local control for the entire patient population.

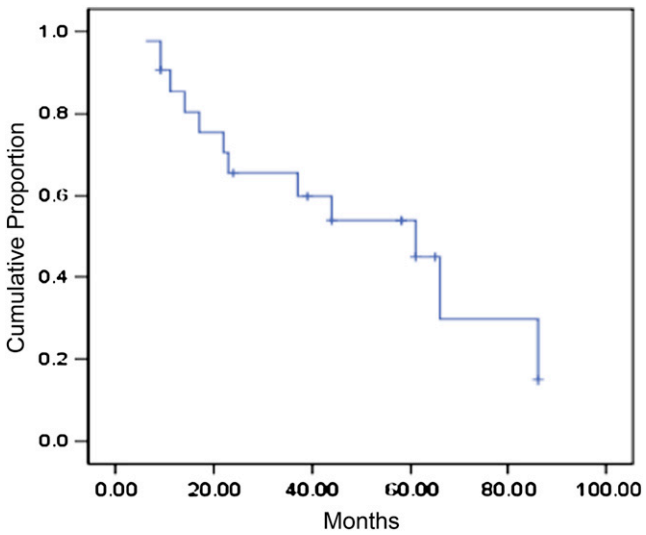

Fig. 2. Overall survival for the entire patient population.

no difference in overall survival according to the extent of resection. The 5-year overall survival rate for those with gross total resection was 50%, compared with 40% for those with subtotal resection ($p = 0.18$). Among the 12 patients with gross total resection, there was no difference in overall survival among those with negative and positive surgical margins ($p = 0.31$).

Distant metastasis-free survival

Seven patients, including both the patients with evidence of cervical lymphadenopathy at diagnosis, developed distant metastasis at a median time of 20 months (range, 7–37 months) from the initial date of treatment. Distant metastasis was an isolated first event in 4 patients and developed concurrently with local recurrence in 2 patients and subsequent to local recurrence in an additional 1 patient. As illustrated in Fig. 3, the 2- and 5-year estimates of distant metastasis-free survival were 71% and 64%, respectively. There was no difference in distant metastasis-free survival according to initial treatment modality (surgical vs. nonsurgical, $p = 0.75$). Among those treated surgically, neither the extent of surgical resection (gross vs. subtotal) nor margin status (negative vs. positive) predicted for distant metastasis-free survival ($p = 0.27$ and $p = 0.40$, respectively). None of the other factors, including T stage, age, dural involvement, orbital invasion, cranial nerve involvement, radiation dose, radiation technique (conventional vs. 3D-RT/IMRT), and use of chemotherapy, predicted for distant metastasis-free survival ($p > 0.05$ for all).

Sites of failure

All local recurrences occurred in the high-dose radiation field. There were no marginal or out-of-field local failures. Sites of distant failure were as follows: 4 lung (71%), 2 central nervous system (29%), and 1 bone (14%). Both of the central nervous system relapses occurred at geographically separate locations from the primary tumor site (1 brain parenchyma, 1 intramedullary brain stem). There were no isolated regional failures in the neck. Two patients experienced regional failures, both of which recurred subsequent to the development of distant metastasis. Both of these 2 patients initially presented with clinically N0 necks, with 1 receiving ENI as a component of definitive therapy.

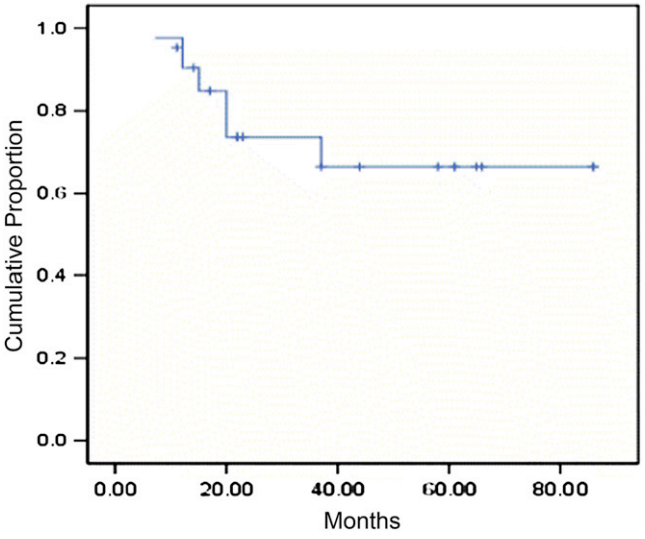

Fig. 3. Distant metastasis-free survival for the entire patient population.

Late complications

Information related to treatment-related toxicity, including visual acuity, was available for 16 of the 21 patients treated. Other than for patients who underwent orbital exenteration, no patient experienced a complete loss of either monocular or binocular vision. Two patients were diagnosed with cataracts at a median of 33 months after completion of treatment. An additional patient developed lacrimal stenosis, which was managed conservatively with artificial tears, at approximately 20 months after surgery and postoperative radiotherapy. Last, 1 patient presented with a sinocutaneous fistula requiring graft revision at approximately 7 months after surgery and postoperative radiotherapy. There were no documented cases of cerebral necrosis or osteoradionecrosis.

DISCUSSION

The results of the present series, representing one of the largest to date reporting on outcomes after the combined-modality management of SNUC, highlights the critical role of surgery for patients presenting with this relatively uncommon disease. Although we acknowledge the potential of selection bias in confounding our results, it is nevertheless notable that the only factor that was demonstrated to be predictive of improved prognosis was gross total tumor resection. We thus contend that aggressive surgical resection with en bloc removal of all macroscopic tumor, either up front or after neoadjuvant therapy, should be the goal of treatment for patients with SNUC who do not have evidence of metastatic disease.

Although comparisons between series are hampered by small patient sizes and heterogeneity with respect to both clinical characteristics and treatment modalities, the most consistently identified factor predictive of improved outcome has been gross total tumor resection (9–13). Jeng *et al.* (10) reviewed a series of 36 patients with SNUC treated at the National Taiwan University Hospital by a variety of methods. Although the 47% of patients who underwent surgery as the initial means of local–regional control had less advanced disease and better performance status, the investigators suggested that this group had an improved prognosis compared with those treated nonsurgically, particularly because all 5 of the long-term survivors in their series were surgically treated patients. Kim *et al.* (11) from the University of California, Los Angeles similarly reported that 5 of 5 patients treated surgically for SNUC were alive with a mean

follow-up of 23 months, whereas only 1 of 3 treated with a nonsurgical approach were alive.

Some investigators, however, have suggested that nonsurgical approaches may be a feasible alternative in the management of SNUC. A recent study from the Peter MacCallum Cancer Center in Australia demonstrated promising results among 7 patients treated with three cycles of platinum-based chemotherapy with 5-fluorouracil followed by definitive radiotherapy administered concurrently with either cisplatin or carboplatin (12). Further evidence supporting the effectiveness of chemoradiotherapy as definitive treatment without surgery is supported by data from the University of Virginia showing that 30% (3 of 10) of patients who subsequently underwent surgery after neoadjuvant chemoradiotherapy had no viable tumor in their pathological specimens (13).

Differences in selection and therapeutic strategies likely account for the discrepancies in outcome observed among those treated with various approaches across institutions. Most notably, criteria for operability differ drastically across institutions, and often a patient who is a surgical candidate at one institution may not be one at another. Additionally, it is likely that advances in surgical and reconstructive techniques with respect to skull base surgery have not only improved clinical outcomes for patients with tumors of the paranasal sinuses and nasal cavity but have also contributed to evolving changes in criteria for operability (14–16). Furthermore, the use of chemotherapy and the choice of agents have not been consistent among groups reporting their experiences with SNUC, which has contributed to the uncertainty of whether neoadjuvant or adjuvant treatment is superior.

Variability with respect to radiotherapy technique must also be considered when analyzing outcomes across series. Even within the present study, the dose of radiation used varied widely, from 50 to 71 Gy. Although it is quite possible that a dose–relationship exists for SNUC, as others have suggested, we were unable to demonstrate this, most likely owing to the small size and heterogeneity of our patient population (11). For similar reasons, it is still unclear whether the ability of IMRT to dose-escalate with significant precision and accuracy may lead to improved outcomes with respect to disease control (17, 18). Last, it must be recognized that a high percentage (79%) of patients received ENI for clinically N0 necks, although owing to the limited patient size we were unable to make specific recommendations regarding radiation treatment volume. The low rate of regional failure observed in our study (2 of 21), however, is consistent with those reported for squamous cell carcinomas of the paranasal sinuses and suggests that occult nodal involvement is either rare at the time of diagnosis or is sensitive to prophylactic radiation (19–21).

The comparison of results across series is further complicated by inconsistencies related to clinical staging and pathologic classification. Although some studies, including the present one, have used the AJCC staging system for the purposes of data reporting, others have favored the Kadish system, which was initially proposed for the staging of esthesioneuroblastoma, thus making comparisons exceedingly difficult (22–24). Moreover, it must be recognized that distinguishing between SNUC and other neuroendocrine tumors of the sinonasal region including esthesioneuroblastoma, small-cell carcinoma, and classic neuroendocrine carcinoma can be a dilemma, even when immunohistochemistry is routinely performed. This is important in view of a recent study published from the M. D. Anderson Cancer Center outlining differences in the natural history and prognosis of these cancers (25). Thus it is possible that the favorable and poorer outcomes reported by others for SNUC may have resulted from the inadvertent inclusion of small-cell histology and esthesioneuroblastoma, respectively.

The patterns of failure observed in the present series are consistent with those from other series reporting on SNUC. In the only other series in which pathologic confirmation was performed using immunohistochemical techniques, Rosenthal *et al*. (25) similarly showed that local recurrence was the most common site of disease failure among 16 patients with SNUC treated at the M. D. Anderson Cancer Center. Although in the present series we observed a more favorable prognosis among patients in which gross total tumor resection was achieved, outcomes for patients with SNUC remain suboptimal. The fact that we were unable to discern any significant difference in outcome among those with or without invasion of the dura, orbital contents, or cranial nerves on univariate analysis can largely be attributed to the poor prognosis of the entire patient population as a whole, because all of the patients had locally advanced tumors, with 81% having T4 disease. However, the effectiveness of surgical selection criteria in identifying those patients in whom gross total resection can be achieved even in the presence of these characteristics cannot be ignored. The critical role of radiotherapy in potentially eradicating subclinical deposits of disease in the setting of dura, orbital, or neural involvement must also be recognized, although the limited patient numbers did not allow us to assess the efficacy of PORT in improving outcome.

Despite the inherent selection bias in favor of surgically treated patients, our data are in accord with previous reports suggesting that gross total tumor resection is an integral component in the definitive treatment strategy for patients with SNUC. These results are particularly relevant given that a randomized study for this rare disease will unlikely be performed in the future. On the basis of our experience, our current policy is to perform surgical resection whenever possible, either up front or after neoadjuvant chemotherapy in those who present with initially unresectable tumors, followed by PORT for all patients. Given the relatively poor prognosis of patients with SNUC, the North American Skull Base Society is currently investigating the role of high-dose radiotherapy and concurrent cisplatin chemotherapy with or without surgery for advanced paranasal sinus cancer, including SNUC, using IMRT (26).

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