Sinonasal undifferentiated carcinoma: an update

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Purpose of review

Sinonasal undifferentiated carcinoma is a rare and extremely malignant tumor of the paranasal sinuses. Historically, treatment outcomes have been poor. This review presents recent data on the management of sinonasal undifferentiated carcinoma and examines treatment trends that may result in improved locoregional control and survival.

Recent findings

Patients who receive aggressive multimodality treatments have improved outcomes. In particular, a chemoradiotherapy regimen including concurrent platinum-based chemotherapy given preoperatively or postoperatively to patients with resectable disease seems to result in better disease-free survival. Neoadjuvant chemotherapy, although strongly advocated by some, is currently not offered by many. Although surgery seems to be an important part of the treatment for sinonasal undifferentiated carcinoma, its ideal timing, either upfront or after radiotherapy, remains uncertain.

Summary

Overall, outcomes for sinonasal undifferentiated carcinoma are poor. An aggressive approach using surgery, platinum-based chemotherapy, and radiation seems to offer the greatest chance for significant locoregional control and survival.

Keywords

craniofacial resection, sinonasal carcinoma, skull base surgery

Curr Opin Otolaryngol Head Neck Surg 13:222–225. © 2005 Lippincott Williams & Wilkins.

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Current Opinion in Otolaryngology & Head and Neck Surgery 2005, 13:222–225

Abbreviations

CAV cyclophosphamide, doxorubicin, and vincristine
SNUC sinonasal undifferentiated carcinoma

1068-9508

Introduction

First described in 1986 by Frierson *et al*. [1], sinonasal undifferentiated carcinoma (SNUC) is a rare and extremely malignant neoplasm. It is characterized by rapid growth, a propensity for locoregional recurrence, distant metastases particularly to lung and bone, and poor prognosis. Since its original description, its optimal management has been debated. Consensus has been lacking, with most reports citing frustratingly poor outcomes regardless of treatment strategy. There is agreement, however, that an aggressive multimodality approach including surgery, radiation, and chemotherapy offers the best chance for locoregional control and cure.

Histopathology

Sinonasal undifferentiated carcinoma is believed to originate from schneiderian epithelium or from the nasal ectoderm of the paranasal sinuses [1]. It is a member of the neuroendocrine group of sinonasal malignancies that also includes esthesioneuroblastoma, neuroendocrine carcinoma, and small cell carcinoma. Conceptually, these malignancies may be divided into two groups, esthesioneuroblastoma and nonesthesioneuroblastoma neuroendocrine carcinomas. The distinction is based on the observation that significant locoregional and distant control of esthesioneuroblastoma may be achieved by local treatment alone. Unfortunately, the same cannot be said for its counterparts, including SNUC, which requires, according to most authors, aggressive multimodality therapy including chemotherapy [2]. These tumors share histopathologic features that may complicate diagnosis. SNUC is classically composed of small to medium-sized undifferentiated cells and is characterized by high mitotic rates, significant cellular pleomorphism, and high nuclear to cytoplasmic ratios, necrosis, and vascular invasion. In most cases, the diagnosis can be made on light microscopic features alone. Given the undifferentiated nature of this malignancy, however, immunohistochemical analysis is extremely helpful. In addition to often staining positive for neuron-specific enolase and chromogranin, SNUC may also express cytokeratin, particularly cytokeratins 7, 8, and 19. It is often nonreactive to S-100 and never expresses vimentin [3•]. Despite the use of immunohistochemical techniques, the differentiation between SNUC and esthesioneuroblastoma can be quite difficult. Given the difference in natural history, treatment, and prognosis between these two malignancies, correct diagnosis is essential.

Prognostic factors

Given the rarity of SNUC, strong prognostic data are lacking. Many patients receive nonoperative treatment,

further limiting the understanding of certain histologic criteria including margin status and grade. In an attempt to better understand such information, Suarez *et al.* [4••] examined prognostic factors for sinonasal tumors involving the anterior skull base. This retrospective review consisted of 100 cases representing many different malignancies. Obviously, extrapolating these data and applying them to a specific disease such as SNUC are difficult. In spite of these limitations, the study did reveal several important prognostic factors as they relate to craniofacial resection for malignant disease. Dural involvement has traditionally been associated with poor outcome and increased local failure. The authors of this series, however, did not find dural invasion to be a predictor of poor outcome. Margin status of the dura is more than likely the important prognostic variable [5]. In addition, the results of this series confirm that the orbit may safely be preserved, without compromising survival or local control, if orbital periosteum and fat are resected to negative margins. Unfortunately, orbital apex involvement portends a poor outcome even if the orbit is exenterated.

Miyamoto *et al.* [6] demonstrated that both histologic grading and surgical staging might predict prognosis for SNUC. The Kadish staging system (Table 1), initially proposed for esthesioneuroblastoma, was used to surgically stage SNUC. In addition, the authors applied the histologic grading system for esthesioneuroblastoma put forth by Hyams *et al.* [7] to SNUC. As expected, patients with Kadish stage C or Hyams grade 3 or 4 lesions had poorer prognosis.

Treatment

As is the case with most sinonasal malignancies, patients with SNUC often present with locally advanced disease. In a recent series published by Musy *et al.* [8], 50% of patients presented with dural invasion, 30% had invasion of the cavernous sinus, and the orbit was involved in another 30%. Bloody rhinorrhea was the presenting complaint in 53% of cases and 47% had visual acuity changes or diplopia. Unilateral nasal obstruction, headache, and facial pain were also frequent presenting complaints. Given the aggressive and destructive nature of SNUC and the intimate relation of the paranasal sinuses with the skull base, skull base erosion is a common finding at presentation. Not surprisingly, most patients with SNUC present with Kadish stage C lesions.

Table 1. Kadish staging system

Stage	Tumor extension
A	Tumor limited to the nasal cavity
B	Tumor involves nasal cavity and paranasal sinuses
C	Tumor extends beyond the nasal cavity and paranasal sinuses

The original report on SNUC by Frierson *et al.* [1] in 1986 painted a grim picture. The series consisted of eight patients. All received radiation therapy to varying total doses. In addition, some of the patients were treated with chemotherapy or underwent surgical resection. Median survival was only 4 months. In 1987, the same group reported an update that included 11 patients, some of whom were included in the original series [9]. Once again, all patients received radiation therapy. Seven also received chemotherapy and one patient had a craniofacial resection. The results were equally poor, with a median survival of 12.4 months. Three patients were alive at the end of the follow-up. Only one was free of disease, however. In 1993, Deutsch *et al.* [10] reported improved survival results for SNUC when treated with aggressive multimodality therapy as compared with radiation alone or in conjunction with either chemotherapy or surgery. The treatment regimen consisted of standardized neoadjuvant chemotherapy using a combination of cyclophosphamide, doxorubicin, and vincristine (CAV therapy), followed by radiotherapy (50–55 Gy), and finally, 1–2 months later, followed by craniofacial resection. With this aggressive approach, three patients remained free of disease an average of 53.6 months from the time of presentation. The three surviving patients had tumors that did not extend intracranially or involve the orbit. When compared with previous reports the results were encouraging, and it was recommended that patients without distant metastases or extensive intracranial disease receive preoperative CAV chemotherapy and radiotherapy.

In 2002, the same group, from the University of Virginia, reported on a series of 20 patients with SNUC treated between 1986 and 2000 [8]. As expected, the majority presented with Kadish stage C lesions. Dural, periorbital, and orbital involvement was documented at presentation in 53%, 40%, and 33% of patients, respectively (data available on 15 of 20 patients). Regional metastases were documented in two cases and none presented with distant disease. Radiotherapy was administered in all cases. Craniofacial resection was possible in only 11 of the patients. Sixteen patients also received chemotherapy, which consisted of the standard preoperative CAV regimen in 13 cases. At the termination of follow-up, four patients were alive and free of disease an average of 68 months after initial presentation. One of these patients had already been treated for two local recurrences, however. Three patients were alive with disease, with an average follow-up of 66 months, and the remaining 13 were dead of disease. Actuarial 2-year survival for the entire group was 47%.

The authors also assessed the response to neoadjuvant chemotherapy and preoperative radiotherapy in 10 patients who subsequently underwent craniofacial resection. Three of the patients had no viable tumor in the surgical

specimen. Of the remaining seven, two had clear margins, three had close margins, and the final two patients had either microscopically or grossly positive margins. Among the five patients with complete resection, three remained free of disease (mean follow-up of 36 months). In comparison, only one patient with positive margins remained free of disease at 164 months. Although not statistically significant, these results suggest that complete resection to negative margins offers a survival advantage. Furthermore, comparing outcomes among patients who did and patients who did not undergo craniofacial resection enabled assessment of the role of surgery. Although there is an obvious selection bias in the comparison, there was a clear survival advantage seen with surgical resection. Actuarial 2-year survival was 64% in the surgical group as compared with 25% in the nonsurgical group. The authors listed significant involvement of the infratemporal fossa, orbital apex, cavernous sinus, and extensive brain invasion as contraindications for surgery. Orbital exenteration was considered only when the tumor was otherwise resectable. In this series, aggressive resection of the periorbita and orbital fat enabled preservation of the orbit in all operative cases.

Jeng *et al.* [11] reviewed a very large series of 36 cases of SNUC. Treatment was variable, with surgery being the primary treatment in 47% of cases. Radiation therapy and high-dose chemotherapy were administered to 64% and 25% of patients, respectively. In this series, prognosis was very poor, with median survival being 10 months. Only five patients remained free of disease at the end of follow-up (median follow-up was 31 months). The authors highlighted the fact that surgery was included in the treatment of all five patients.

In 2004, Rischin *et al.* [12•] questioned the role of primary surgery in the management of SNUC. Although two of the 10 patients in this series had prior resection, the primary treatment modality was chemoradiotherapy. The treatment regimen consisted of three cycles of neoadjuvant cisplatin or carboplatin combined with infusional 5-fluorouracil. This was followed by full-course irradiation (median dose of 54 Gy) combined with two cycles of concurrent single-agent platinum chemotherapy administered in the first and last weeks of treatment. Three patients with cervical nodal metastases also received neck irradiation (50–54 Gy). The two patients who underwent resection of their tumors received postoperative radiation alone. Margin status was not reported but both patients had locoregional and distant recurrence. An additional patient had an early T1 N0 SNUC limited to the nasal cavity. She was treated with radiation alone and has remained free of disease for more than 5 years. Of the remaining seven patients (all T4), four cases remain disease free 8–51 months following presentation. Furthermore, none of the patients who were treated with 60 Gy to the primary tumor experienced a local recurrence. The 2-year progression-free survival was 43% and 2-year overall survival was 64%. The authors stated that no grade 3 or 4 late toxicity was observed. Based on these promising results, the authors concluded that neoadjuvant platinum and 5-fluorouracil chemotherapy followed by concurrent platinum-based chemoradiotherapy was an appropriate regimen for the treatment of locally advanced SNUC. Unlike the University of Virginia protocol that advocates routine craniofacial resection after chemoradiotherapy, salvage surgery was recommended only for patients with evidence of resectable residual disease.

Kim *et al.* [3•] presented a series of eight patients with SNUC. As expected, seven had Kadish stage C lesions and one had stage B disease. Five of the patients underwent craniofacial resection. Four of these operative cases also received adjuvant radiation therapy, with two also receiving concurrent chemotherapy (cisplatin and 5-fluorouracil). The final three patients were treated with concurrent chemoradiotherapy alone. Once again outcomes were poor. Although six of eight patients were still alive at the end of follow-up, only two were free of disease. The mean disease-free interval was only 12.3 months and locoregional recurrence was documented in five of eight patients. Half of the patients developed distant metastases, all to bone. All five patients who had received surgical treatment remained alive at the end of follow-up (mean survival time of 23 months). Three patients initially presented with cervical metastases and received radiation to the neck. None of these patients had in-field recurrences. Of the five remaining patients who did not receive neck irradiation, however, three developed regional metastases. Based on these findings, the authors drew several conclusions. First, it was recommended that patients without distant metastases and with acceptable performance status be offered complete surgical extirpation of resectable disease. In addition, all patients should be offered adjuvant chemoradiation therapy, given the propensity for SNUC to recur locally and metastasize systemically. Finally, the authors recommended consideration for prophylactic neck irradiation in cases of advanced disease.

In cases of metastatic or locally far advanced SNUC, most authors seem to advocate aggressive chemoradiation for palliation if performance status permits. These malignancies demonstrate short-lived but impressive responses to this treatment regimen and consequently such treatment may offer excellent palliation. When comorbidities prevent such aggressive therapy, however, radiation alone may be considered. Kouri *et al.* [13] reported good palliation of an unresectable locally recurrent SNUC using single-fraction boron neutron capture therapy. This complex treatment involves administration of boron-10 to the tumor using a carrier, in this case 4-dihydroxyboryl-L-phenylalanine, which is administered systemically. The tumor is then

treated with a single dose of neutron irradiation. When the boron-10 captures the low-energy neutron within the irradiation field, a nuclear capture reaction occurs that results in production of a high-energy α-particle. This treatment resulted in a near-complete response and effective palliation. In this case, the patient experienced mild to moderate toxicity including grade 3 vomiting and mucositis, alopecia, and fatigue. He was able to return to work for 5 months, however. He developed local recurrence 6 months after treatment. Historically, SNUC has responded very poorly to radiation alone. How newer techniques, including intensity-modulated radiation therapy, that can deliver more radiation to the target volume while sparing critical structures, such as the optic chiasm, compare with boron neutron capture therapy remains to be seen.

Conclusion

Sinonasal undifferentiated carcinoma remains a very aggressive sinonasal malignancy with poor prognosis. Recent data certainly demonstrate an improvement in both locoregional control and survival as compared with initial reports, but the gains have been modest. There is no doubt that multimodality approaches to the management of SNUC are necessary. The optimal sequence of treatments remains unresolved. Certainly, the University of Virginia experience makes the case for preoperative chemoradiotherapy. Postoperative complications, however, increase in frequency and complexity following skull base surgery in the patient who has undergone radiation treatment [14]. For this reason, many authors advocate postoperative chemoradiotherapy. Our treatment strategy at the University of California, Davis, is craniofacial resection for all resectable tumors followed by postoperative chemoradiotherapy. In cases of unresectable disease, patients are treated with platinum-based chemoradiotherapy and surgery is reserved when salvage is possible. Current data demonstrate an advantage when surgery is included in the management of SNUC. Although these findings are largely influenced by a strong selection bias to operate on the most resectable lesions, current treatment strategies for SNUC should include platinum-based chemoradiotherapy and, whenever possible, surgery.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Frierson HF, Mills S, Fechner R, *et al*. Sinonasal undifferentiated carcinoma: an aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. Am J Surg Pathol 1986; 10:771–779.

2 Rosenthal D, Barker J, El-Naggar A, *et al*. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. Cancer 2004; 101:2567–2573.

3 • Kim B, Vongtama R, Juillard G. Sinonasal undifferentiated carcinoma: case series and literature review. Am J Otolaryngol 2004; 25:162–166.
This retrospective review suggests that aggressive multimodality treatment including surgery offers the best chance for locoregional control and longer survival. In addition, the literature review is excellent.

4 •• Suarez C, Llorente J, De Leon R, *et al*. Prognostic factors in sinonasal tumors involving the anterior skull base. Head Neck 2004; 26:136–144.
This is an excellent review of prognostic factors in anterior skull base surgery for sinonasal malignancy. Although the case series is comprised of many different histopathologies, the analysis is thoughtful and the findings significant. In particular the study showed that involvement of the periorbita, dura, and frontal sinus have no impact on outcome. The results also demonstrated, however, that aggressive histopathology, brain invasion, sphenoid sinus involvement, orbital apex involvement, and previous treatment are all associated with poor outcome.

5 Gorelick J, Ross D, Marentette L, *et al*. Sinonasal undifferentiated carcinoma: case series and review of the literature. Neurosurgery 2000; 47:750–755.

6 Miyamoto C, Gleich L, Biddinger P, *et al*. Esthesioneuroblastoma and sinonasal undifferentiated carcinoma: impact of histological grading and clinical staging on survival and prognosis. Laryngoscope 2000; 110:1262–1265.

7 Hyams VJ, Batsakis JG, Michaels L. Olfactory neuroblastoma. In: Hyams VJ, Batsakis JG, Michaels L, editors. Tumors of the upper respiratory tract and ear. Fascicle 25, 2nd series. Washington, DC: Armed Forces Institute of Pathology; 1988. pp. 240–248.

8 Musy P, Reibel J, Levine P. Sinonasal undifferentiated carcinoma: the search for a better outcome. Laryngoscope 2002; 112:1450–1455.

9 Levine PA, Frierson HF, Stewart FM, *et al*. Sinonasal undifferentiated carcinoma: a distinctive and highly aggressive neoplasm. Laryngoscope 1987; 97:905–908.

10 Deutsch BD, Levine PA, Stewart FM, *et al*. Sinonasal undifferentiated carcinoma: a ray of hope. Otolaryngol Head Neck Surg 1993; 108:697–700.

11 Jeng Y, Sung M, Fang C, *et al*. Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma: two clinically, biologically, and histopathologically distinct entities. Am J Pathol 2002; 26:371–376.

12 • Rischin D, Porseddu S, Peters L, *et al*. Promising results with chemoradiation in patients with sinonasal undifferentiated carcinoma. Head Neck 2004; 26:435–441.
This is a good retrospective review of an institution's experience treating SNUC with primary chemoradiotherapy. Although the authors do not discount the utility of surgical salvage, this approach does not advocate routine postchemoradiotherapy craniofacial resection and results do not seem to be significantly different from most surgical series.

13 Kouri M, Kankaanranta L, Seppala T, *et al*. Undifferentiated sinonasal carcinoma may respond to single-fraction boron neutron capture. Radiat Oncol 2004; 72:83–85.

14 Enepekides DJ, Donald PJ. Long-term outcomes of anterior skull base surgery. Curr Opin Otolaryngol Head Neck Surg 2000; 8:130–136.