Sinonasal Undifferentiated Carcinoma: Case Series and Review of the Literature

Judith Gorelick, M.D., Donald Ross, M.D., Lawrence Marentette, M.D., Mila Blaivas, M.D., Ph.D.

Section of Neurosurgery (JG, DR, LM) and Departments of Otolaryngology (DR, LM) and Pathology (MB), University of Michigan Medical Center, Ann Arbor, Michigan

OBJECTIVE AND IMPORTANCE: We report on four cases of sinonasal undifferentiated carcinoma (SNUC), a relatively newly described clinicopathological entity of the nasal cavity and paranasal sinuses. SNUC tends to present with advanced-stage disease, often with intracranial invasion, and requires an aggressive treatment approach that includes surgical resection. A review of the literature identified several reports of SNUC in pathology and otolaryngology journals since its initial description in 1986, but no report has yet appeared in the neurosurgery literature.

CLINICAL PRESENTATION: Four patients presented with various symptoms related to the nose and/or orbit, including one or more of the following: obstruction, epistaxis, decreased visual acuity, diplopia, and pain. All patients were noted to have masses in the nasal cavity or paranasal sinuses, with or without intracranial extension.

INTERVENTION: All four patients underwent multimodal treatment with chemotherapy, radiotherapy (60–65 Gy), and aggressive surgical resection via a combined bifrontal craniotomy and a subcranial approach to the anterior cranial fossa. Three of four patients died as a result of their disease, an average of 15 months after diagnosis. Only one patient remains alive, although with metastatic intracranial disease, at 24 months after diagnosis.

CONCLUSION: SNUC is a rare neoplasm with a poor prognosis despite an aggressive multimodal approach to treatment. On the basis of our experience, we advocate radical resection as part of the initial combined therapy for patients who present with locally advanced, nonmetastatic disease but we suggest reserving surgery for patients with early brain invasion until there has been a radiographically proven central nervous system response to adjuvant therapy. (Neurosurgery 47:750–755, 2000)

Key words: Nasal cavity, Paranasal sinus, Sinonasal undifferentiated carcinoma, Subcranial resection

Sinonasal undifferentiated carcinoma (SNUC) is an uncommon aggressive malignancy of the nasal cavity and paranasal sinuses that was first described in 1986 by Frierson et al. (3). Since that time, several reports and small case series of SNUC have been published, primarily in otolaryngology journals, but no report has been published in the neurosurgery literature. Since the initial recognition of SNUC as a distinct clinicopathological entity, treatment regimens have evolved to include the current recommendation of combined radical resection, radiotherapy, and chemotherapy. Despite this aggressive therapy, outcomes have remained dismal, with the mean survival time still being less than 1 year after diagnosis. Many patients present with locally advanced disease with a tendency for the tumor to spread from the paranasal sinuses to the orbit and anterior cranial fossa. Because of this tendency for SNUC to invade the intracranial compartment, initial surgical intervention typically requires a team approach, including an otolaryngologist, neurosurgeon, ophthalmologist, and plastic surgeon. The goal of this article is to familiarize neurosurgeons with this relatively rare and recently described pathological entity, by presenting our own series of four cases of SNUC treated at the University of Michigan as well as a review of the current literature.

CASE REPORTS

Patient 1

A 51-year-old man with a 30-pack-year history of tobacco use presented with a 2-week history of toothache and decreased vision in the left eye (*Table 1*).

Examination results

The physical examination revealed ptosis of the left eye and reduced visual acuity to 20/800, with normal vision on the right side. The neurological examination results were otherwise unremarkable. Computed tomographic (CT) imaging revealed a left nasal cavity mass with extension to the left ethmoid and sphenoid sinuses, as well as into the left orbit. CT scans of the chest, abdomen, and pelvis yielded negative results at the time of diagnosis.

Clinical course

The patient underwent a biopsy of the mass, which was interpreted as SNUC. Light microscopy revealed a small blue cell tumor. During immunohistochemical inspection, the tumor cells exhibited positive labeling for pan-cytokeratin and CAM5.2 and negative labeling for HMB45, S-100, and LCA. The patient subsequently underwent a transglabellar subcranial resection (1) of the mass, with left orbital exenteration and a left medial maxillectomy. At the time of surgery, the left optic nerve was frankly

TABLE 1. Case Series Summary[a]

Patient No.	Age (yr)/Sex	Brain Invasion at Diagnosis	Metastasis at Diagnosis	Postoperative Radiotherapy (Gy)	Postoperative Chemotherapy	Surgery	Follow-up Results
1	51/M	No	No	63	Etoposide/carboplatin	Subcranial resection	DOD, 2 yr
2	33/F	Dural enhancement	No	64	Etoposide/cisplatin	Subcranial resection	DOD, 5 mo
3	19/M	Yes, frontal lobe	No	60	Etoposide/cisplatin	Subcranial resection	DOD, 15 mo
4	39/M	Yes, frontal lobe	Yes, lung	64	Cisplatin	Subcranial resection	AWD, 27 mo

[a] **DOD, dead as a result of disease; AWD, alive with disease.**

invaded by neoplasm at the orbital apex. Frozen sections of all surgical margins were tumor-negative. Postoperatively, the patient received adjuvant chemotherapy with etoposide and carboplatin and concurrent radiotherapy to a total dose of 63 Gy. Several months later, the patient developed multiple skin satellite lesions on the face and scalp, which progressed despite further radiotherapy and the use of multiple sequential chemotherapeutic regimens, including cyclophosphamide/doxorubicin/vincristine, methotrexate/5-fluorouracil, taxol/carboplatin, and navelbine/ifosfamide/mesna. Despite aggressive treatment, 23 months after the original diagnosis the patient developed systemic metastases to the liver and pelvis, as well as progressive scalp and orbital lesions. The patient died approximately 2 years after diagnosis.

Patient 2

A 33-year-old woman with a remote 10-year history of tobacco use (ending 10 years before presentation) presented with a 2-month history of nasal obstruction, left eye swelling with diplopia, and left otalgia (*Table 1*).

Examination results

In the physical examination, the patient was noted to have proptosis of the left eye, with reduced up-gaze and lateral gaze on the left. The rest of the neurological examination results were normal. CT imaging of the sinuses revealed a mass lesion filling the left nasal cavity, with extension to the left maxillary and frontal sinuses, the left orbit, and the floor of the anterior cranial fossa. Dural enhancement was noted.

Clinical course

The patient underwent a bifrontal craniotomy, a total left maxillectomy, left orbital exenteration, a left ethmoidectomy and sphenoidectomy, resection of the frontal floor dura and the inferior aspect of the left frontal lobe (with reconstruction of the anterior cranial fossa floor with a living pericranial flap), and a tracheostomy. Surgical margins were tumor-positive, as were biopsies taken from the left frontal lobe and dura. Pathological analysis revealed an aggressive appearing, pleomorphic, round cell neoplasm with areas of necrosis. In immunohistochemical analysis, tumor cells were noted to be cytokeratin-positive and LCA-, S-100-, synaptophysin-, and HMB45-negative, consistent with a diagnosis of SNUC. The patient received concurrent adjuvant treatment with 64-Gy radiotherapy to the tumor bed and four cycles of cisplatin/etoposide therapy, which were complicated by an episode of sepsis as well as the development of a large left parietal subdural hematoma that required surgical evacuation. The patient was noted to have been severely coagulopathic and thrombocytopenic at the time. Five months after the original diagnosis, the patient presented with mental status changes; head CT scans revealed progressive disease in the left frontal lobe, without recurrence of the subdural hematoma. One month later, the patient developed refractory seizures and died.

Patient 3

A 19-year-old man, who was a nonsmoker with a history of a right auricular neurofibroma that had been resected at 5 years of age, presented with a several-month history of bilateral nasal cavity obstruction and epistaxis and was noted to have an ethmoid sinus region mass lesion, which was biopsied at another institution. The results of the pathological examination at that time were thought to be consistent with a diagnosis of esthesioneuroblastoma (*Table 1*).

Examination results

During the month after the biopsy, the patient noted extensive growth of the tumor. By the time the patient was treated at our institution, the mass had nearly doubled in size and was observed to be obstructing the left nasal vestibule and extending medial to the inferior turbinate, along the middle to anterior one-third of the nasal septum, on the right. Magnetic resonance imaging performed at that time revealed extension of the mass into the anterior cranial fossa and bilateral orbits, with possible involvement of the frontal lobe brain parenchyma.

Clinical course

The patient underwent another biopsy at our institution, which revealed a mass consistent with a diagnosis of SNUC. The patient subsequently underwent gross total resection, consisting of a bifrontal craniotomy with subcranial resection of the mass and the dura of the anterior cranial fossa, bilateral resection of the medial orbits, and resection of the involved portions of the frontal and nasal bones, which were primarily reconstructed. The pathological analysis revealed SNUC, with a predominance of cells strongly expressing cytokeratin and rare cells with S-100 reactivity. Staining assays for synaptophysin, LCA, and HMB45 yielded negative results. Postoperatively, the patient received 60-Gy radiotherapy and concurrent chemotherapy with cisplatin and etoposide. He remained free of disease until 9 months after the initial diagnosis, when routine surveillance chest x-rays revealed bilateral hilar adenopathy, which a biopsy demonstrated to be metastatic disease. The patient was subsequently treated us-

ing multiple sequential chemotherapeutic regimens, including cyclophosphamide/doxorubicin/vincristine, high-dose cyclophosphamide, etoposide, carboplatin, ifosfamide, and mesna, but his disease progressed despite this treatment, with new lesions in the mediastinum and liver. The patient died 15 months after the original diagnosis.

Patient 4

A 39-year-old nonsmoking man presented with progressive nasal congestion, pain in the right maxillary region, and right-sided epistaxis and headache (*Table 1*).

Examination results

In the physical examination, the patient appeared well. The neurological examination results were unremarkable. All cranial nerves tested normal. Visual acuity was 20/20 bilaterally with corrective lenses. An endoscopic examination revealed a right posterior nasal mass extending to the roof of the nose. There were no neck masses. CT scans revealed a destructive right nasal mass extending into the right ethmoid, maxillary, and sphenoid sinuses and through the cribiform plate to the base of the right frontal lobe. A biopsy of the mass, performed at an outside institution, indicated SNUC. CT scans of the chest that were obtained during the initial staging revealed a 3-mm right lower lobe lung nodule, indicating metastatic disease.

Clinical course

The patient underwent a bifrontal craniotomy, via an anterior subcranial approach, for gross total resection of the tumor mass. This was complicated postoperatively by tension pneumocephalus. The patient recovered well. Pathological analysis of the surgical specimen revealed a round cell tumor, with the majority of cells exhibiting positive staining for cytokeratin and synaptophysin and negative staining for chromogranin, LCA, S-100, and HMB45. A focal region of the specimen demonstrated atypical columnar epithelium. The final diagnosis was SNUC with a focal segment of adenocarcinoma, intestinal type, at the olfactory bulb. The patient received postoperative cisplatin chemotherapy and concurrent radiotherapy. One year after the initial diagnosis, the patient developed two intracranial lesions, one in the anterior falx and one in the right temporal lobe dura, which were treated with radiosurgery. One year later, subsequent surveillance magnetic resonance imaging demonstrated growth of the temporal dural mass, with no change in the appearance of the falx lesion and no recurrence at the primary site. The chest lesion has remained stable on serial CT scans. The patient is scheduled to undergo a second craniotomy for resection of the temporal lobe lesion.

DISCUSSION

Pathological features

SNUC is a distinct histopathological entity that was initially described in 1986 by Frierson et al. (3). Before that report, it is likely that cases of SNUC were confused with other, well-known, medium-sized tumors of the nasal cavity and paranasal sinuses. The tumor is assumed to be derived from schneiderian epithelium or nasal ectoderm of the paranasal sinuses (6). Clinically, the tumors are very aggressive and are often advanced at the time of diagnosis. Prognoses are poor, with survival times generally being less than 1 year after diagnosis.

The histological differential diagnosis includes lymphoma, esthesioneuroblastoma, melanoma, rhabdomyosarcoma, lymphoepithelioma, poorly differentiated adenoid cystic carcinoma, and neuroendocrine carcinoma (9, 13). Radiographically, the differential diagnosis additionally includes tumors that extend to the superior nasal cavity from the anterior and central cranial base, such as chordoma, chondrosarcoma, plasmacytoma, and metastases (12). An accurate diagnosis can usually be made on the basis of light microscopic findings alone, where several distinguishing features of SNUC allow its identification.

At the light microscopic level (*Fig. 1*), SNUC consists of small to medium-sized polygonal cells, which tend to form nests, sheets, and trabeculae (11). The cells have high nucleus/cytoplasm ratios and numerous mitoses. The nuclei are moderately pleomorphic, hyperchromatic, and round to oval in shape. The cytoplasm is eosinophilic. Tumor permeation of blood vessels, with tumor filling and distending the vascular lumina, is extensive and often a distinguishing feature of SNUC (3). There is also extensive necrosis. Absent from SNUC are Homer-Wright rosettes, which are often observed in olfactory neuroblastoma, intercellular fibrils, argyrophilic granules, and squamous or glandular differentiation (3).

FIGURE 1. Histological features of SNUC (Patient 4). This typical area demonstrates sheets of malignant cells with round to oval vesicular nuclei, prominent nucleoli infiltrating the vascular walls, and frequent mitoses (hematoxylin and eosin; original magnification, ×330).

Immunohistochemically, virtually all SNUCs are positive for cytokeratin, epithelial membrane antigen, and may stain for both epithelial markers. Approximately one-half of the tumors are positive for neuron-specific enolase, most have S-100 immunoreactivity, and all are negative for vimentin (3, 6, 11, 15).

Clinical features

The most common initial symptoms are epistaxis, facial pain, and nasal obstruction (9, 13, 15). More than one-half of all patients exhibit symptoms referable to the eye, e.g., proptosis, cranial nerve palsies, diplopia, or decreased visual acuity (1, 3). Because many of the early symptoms are similar to those of benign sinus disease, patients often delay seeking treatment and ultimately present with advanced-stage disease (13).

Radiological features

SNUCs have no characteristic features that allow differentiation from other pathological entities of this region. They tend to be large, expansile, and aggressive, with areas of bone destruction and invasion of adjacent structures.

including the anterior cranial fossa, adjacent paranasal sinuses, and orbits (11, 12). On CT scans, the tumors are noncalcified, with variable contrast enhancement. On magnetic resonance imaging scans (*Fig.* 2), the lesions are typically isointense to muscle on T1-weighted scans and iso- to hyperintense to muscle on proton density-weighted and T2-weighted scans. Enhancement with gadolinium is heterogeneous (12).

Pathogenesis

The pathogenesis of SNUC remains unknown. Frierson et al. (3), noting that a significant number of their patients with SNUC were smokers, considered whether this factor or other environmental carcinogens could play a role in the development of SNUC. However, they concluded that, because patients came from a broad geographic area and had diverse occupations, an environmental cause was unlikely (3).

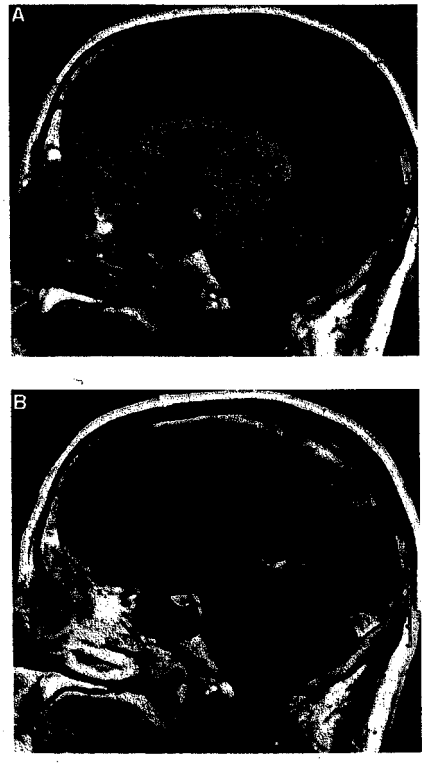

FIGURE 2. Precontrast (*A*) and postcontrast (*B*) sagittal, T1-weighted, brain magnetic resonance imaging scans for a 19-year-old man (Patient 3), showing an extensive, enhancing, soft-tissue mass filling the nasal cavity and extending through the anterior cranial fossa floor to involve the dura and possibly the parenchyma of the frontal lobe of the brain.

Several reports in the literature described SNUC arising in patients who survived retinoblastoma. It is well known that patients with the hereditary form of retinoblastoma carry a germline mutation at one of the two *RB1* gene loci in all cells and have an increased risk for nonocular tumors later in life. In 1989, Frierson et al. (4) reported on two patients who developed small cell sinonasal neoplasms 22 and 37 years after radiotherapy for bilateral retinoblastoma. Other reports of similar patients have been published and raise the question of whether the secondary tumor is initiated by radiotherapy itself or perhaps is the result of a spontaneous mutation in the *RB1* gene located on Chromosome 13. Greger et al. (6), using molecular probes for the *RB1* gene, detected a deletion at the *RB1* locus in metastatic SNUC cells that was not present in normal tissue. Although those authors could not definitively rule out the possibility that the mutation observed was not induced by radiation, their findings suggested that somatic mutations at the *RB1* locus may be involved in the formation or progression of ectodermal tumors (6).

Finally, Epstein-Barr virus has been implicated as a potential pathogen in the development of SNUC. Previous associations of Epstein-Barr virus with undifferentiated carcinomas of the nasopharynx, parotid gland, and thymus form the basis for this theory (5). Two separate studies, using in situ hybridization techniques with paraffin-embedded sections, demonstrated the presence of Epstein-Barr virus ribonucleic acid in 30 to 60% of SNUC samples, although in one of these studies this finding was present only in Asian patients (5, 10).

Treatment

In the initial 1986 report of eight cases of SNUC, each patient received radiotherapy (in varying doses) to the sinonasal region, with some patients also undergoing surgical resection or chemotherapy. Despite treatment, the prognoses were grave, with a median survival time of 4 months (3). In 1987, the same group presented a retrospective study of 11 patients (including some of the patients included in the initial report), all of whom received radiotherapy (usual dose, 50–60 Gy) and 7 of whom also received chemotherapy, i.e., either mitomycin C/5-fluorouracil with the institution of radiotherapy or cyclophosphamide/vincristine/doxorubicin before radiotherapy. One patient underwent craniofacial resection. Similar to their initial report, survival rates were poor, with death occurring an average of 12.4 months after the initial presentation; only three patients were alive at the time the report was submitted. Of those patients, only one was free of disease 10 months after diagnosis (9).

More recently, Deutsch et al. (2) reported improved survival benefits for patients with locally advanced disease, using an aggressive multimodal approach involving a standard regimen of chemotherapy (cyclophosphamide, doxorubicin, and vincristine) followed by radiotherapy (50–55 Gy) before definitive surgical resection. As noted in their 1993 report (2), three patients treated in this way exhibited no evidence of disease an average of 53.6 months after diagnosis. These findings compared favorably with results for a similar group of three patients, who were originally reported on by the same authors in 1987, who were treated nonsurgically, with radiotherapy alone or in combination with chemotherapy, and remained free of disease an average of 36 months after diagnosis (9). On the basis of their results, those authors recommended preoperative cyclophosphamide/doxorubicin/vincristine chemotherapy and radiotherapy (50 Gy) for patients without distant metastases and without extensive intracranial involvement (2).

Other authors subsequently concurred that a multimodal approach is indicated for the treatment of SNUC (7, 8, 15). Righi et al. (15) emphasized that control of local disease remains the central issue. However, most authors agree that the optimal treatment for this aggressive neoplasm has not yet been determined (14).

All of the patients in our series were considered to have advanced-stage disease, because of either intracranial extension or metastatic disease at the time of diagnosis or initial surgery. However, all patients were treated using an aggressive multimodal approach that included sur-

gery. Three of our four patients died as a result of disease, an average of 15 months after diagnosis. One patient remains alive at 2 years, although with metastatic intracranial and possibly pulmonary disease.

On the basis of our observation that patients who present with brain parenchymal invasion at the time of diagnosis have exceptionally poor prognoses, it is currently our opinion that surgical resection for these patients should be reserved until the intracranial disease demonstrates a response to adjuvant treatment. Even in cases with significant tumor shrinkage, however, we recommend that the entire pretherapy extent of tumor be resected. Other authors have advocated a similar approach, avoiding potential surgical morbidity among this patient population. Dural invasion should not contraindicate surgical resection, because the dura can be resected *en bloc* with the tumor. Because of the potential for deleterious effects on wound healing, we do not advocate the use of preoperative radiotherapy and chemotherapy for all patients with SNUC. It is our opinion that the negative effects of preoperative radiotherapy, for example, would mandate the use of a free-tissue transfer, whereas in our patient population subcranial resection was accomplished using living pericranial flap reconstruction of the anterior fossa floor.

CONCLUSION

SNUC is a rare aggressive neoplasm of the nasal cavity and paranasal sinuses that is associated with a poor prognosis. Its treatment requires an aggressive approach, including chemotherapy, radiotherapy, and surgical resection, especially for patients with locally advanced disease at the time of diagnosis.

ACKNOWLEDGMENT

We thank Kristin Switz, P.A.-C, M.P.H., for assistance in caring for the patients included in this report and for proofreading of the manuscript.

Received, December 7, 1999.
Accepted, May 10, 2000.
Reprint requests: Judith L. Gorelick, M.D., Section of Neurosurgery, Department of Surgery, 2128/0338 Taubman, The University of Michigan Medical Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0338. Email: jgorelic@umich.edu

REFERENCES

1. Ascaso FJ, Adiego MI, Garcia J, Royo J, Valles H, Palomar A, Ramón y Cajal S: Sinonasal undifferentiated carcinoma invading the orbit. **Eur J Ophthalmol** 4:234–236, 1994.
2. Deutsch BD, Levine PA, Stewart FM, Frierson HF Jr, Cantrell RW: Sinonasal undifferentiated carcinoma: A ray of hope. **Otolaryngol Head Neck Surg** 108:697–700, 1993.
3. Frierson HF Jr, Mills SE, Fechner RE, Taxy JB, Levine PA: Sinonasal undifferentiated carcinoma: An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. **Am J Surg Pathol** 10:771–779, 1986.
4. Frierson HF Jr, Ross GW, Stewart FM, Newman SA, Kelly MD: Unusual sinonasal small-cell neoplasms following radiotherapy for bilateral retinoblastomas. **Am J Surg Pathol** 13:947–954, 1989.
5. Gallo O, Di Lollo S, Graziani P, Gallina E, Baroni G: Detection of Epstein-Barr virus genome in sinonasal undifferentiated carcinoma by use of in situ hybridization. **Otolaryngol Head Neck Surg** 112:659–664, 1995.
6. Greger V, Schirmacher P, Bohl J, Bornemann A, Hurter T, Passarge E, Horsthemke B: Possible involvement of the retinoblastoma gene in undifferentiated sinonasal carcinoma. **Cancer** 66: 1954–1959, 1990.
7. Houston GD: Sinonasal undifferentiated carcinoma: Report of two cases and review of the literature. **Oral Surg Oral Med Oral Pathol Oral Radiol Endod** 85:185–188, 1998.
8. Kerrebijn JD, Tietze L, Mock D, Freeman JL: Sinonasal undifferentiated carcinoma. **J Otolaryngol** 27:40–42, 1998.
9. Levine PA, Frierson HF Jr, Stewart FM, Mills E, Fechner RE, Cantrell RW: Sinonasal undifferentiated carcinoma: A distinctive and highly aggressive neoplasm. **Laryngoscope** 97:905–908, 1987.
10. Lopategui JR, Gaffey MJ, Frierson HF Jr, Chan JK, Mills SE, Chang KL, Chen YY, Weiss LM: Detection of Epstein-Barr viral RNA in sinonasal undifferentiated carcinoma from Western and Asian patients. **Am J Surg Pathol** 18:391–398, 1994.
11. Mills SE, Fechner RE: "Undifferentiated" neoplasms of the sinonasal region: Differential diagnosis based on clinical, light microscopic, immunohistochemical, and ultrastructural features. **Semin Diagn Pathol** 6:316–328, 1989.
12. Phillips CD, Futterer SF, Lipper MH, Levine PA: Sinonasal undifferentiated carcinoma: CT and MR imaging of an uncommon neoplasm of the nasal cavity. **Radiology** 202:477–480, 1997.
13. Pitman KT, Lassen LF: Pathologic Quiz Case 2: Sinonasal undifferentiated carcinoma (SNUC). **Arch Otolaryngol Head Neck Surg** 121:1201, 1203, 1995.
14. Pitman K, Costantino P, Lassen L: Sinonasal undifferentiated carcinoma: Current trends in treatment. **Skull Base Surg** 5:269–272, 1995.
15. Righi PD, Francis F, Aron BS, Weitzner S, Wilson KM, Gluckman J: Sinonasal undifferentiated carcinoma: A 10-year experience. **Am J Otolaryngol.** 17:167–171, 1996.
16. Ross D, Marentette L, Moore C, Switz K: Craniofacial resection: Decreased complication rate with a modified subcranial approach. **Skull Base Surg** 9:95–100, 1999.

COMMENTS

This article presents four cases of sinonasal undifferentiated carcinoma (SNUC) with extension into the cranial cavity treated with cranial facial resection, irradiation, and chemotherapy. Two patients experienced significant complications after surgery, and three patients died, with an average survival of 15 months. The fourth patient is alive with metastatic disease at 27 months. This report serves two purposes. The first is to alert the neurosurgical community to the existence of this rare and highly aggressive tumor. This is an important point, because of the frequent extension of SNUC into the cranial cavity. The second purpose of this report is to initiate discussion on the proper management of this tumor. Specifically, the authors suggest that, given the exceptionally poor prognosis of patients who present with brain invasion, surgical resection should be attempted in these patients only after the intracranial disease demonstrates response to adjuvant therapy. This seems to be a reasonable suggestion in light of the significant morbidity associated with resection.

A major unanswered question is the effectiveness of adjuvant therapy in the treatment of SNUC. Some series (2) suggest that radiation and chemotherapy are of little use in treatment of this neoplasm. Some more recent studies, however, suggest that at least some patients may benefit from adjuvant therapy. Are there clinical characteristics that would identify patients most likely to benefit from adjuvant therapy? This is an issue that deserves clarification.

Deborah L. Comm
Neuropathologist
Los Angeles, Califor

1. Deutsch BD, Levine PA, Stewart FM, Frierson HF Jr, Cantrell RW: Sinonasal undifferentiated carcinoma: A ray of hope. **Otolaryngol Head Neck Surg** 108:697–700, 1993.
2. Frierson HF Jr, Mills SE, Fechner RE, Taxy JB, Levine PA: Sinonasal undifferentiated carcinoma: An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. **Am J Surg Pathol** 10:771–779, 1986.

The authors bring to our attention a very aggressive clinicopathological entity, which may present as an anterior cranial base tumor. The prognosis for

cases of SNUC is dismal. From the authors' report, it seems clear that multimodality management with chemotherapy and radiation before an attempt at definitive surgical resection yields the most hope for these patients. In the cases of intracranial extension at presentation, it seems that an aggressive surgical resection is probably unwarranted because of the poor prognosis.

This pathological entity and other aggressive pathologies lend support to the general strategy of obtaining a transnasal biopsy of such lesions before treatment planning. This is the general strategy in our practice for the reasons presented in this case series. Some pathologies that we, as neurosurgeons, may encounter require adjuvant therapy before surgical intervention, and this is a fact of which neurosurgeons should be aware.

J. Diaz Day
Los Angeles, California

In this article, the cranial base surgery group at the University of Michigan describes four cases of SNUC treated with craniofacial resection, radiation, and chemotherapy. Two patients sustained serious complications of surgery. Median and mean survival after treatment were expected to be approximately 18 months. The authors conclude from this experience and from a review of the literature that brain invasion is a contraindication to surgery, unless there is first a response to adjuvant therapy.

SNUC is a recently described tumor of the anterior cranial base with a poor prognosis. Its location and radiographic appearance raise the differential of esthesioneuroblastoma, neuroendocrine carcinoma, adenoid cystic carcinoma, and chordoma, as well as lymphoma, melanoma, and metastases. Immunohistochemical staining for cytokeratin, but not for synaptophysin, chromogranin, HMB45, or S-100, helps determine the pathological diagnosis.

The poor prognosis of patients with these tumors reflects the combination of an inherently aggressive lesion, a tendency to present in an advanced stage, and a subfrontal location with easy access to the anterior cranial fossa. The authors' recommendation for aggressive multimodality therapy is reasonable, although the limited experience with this newly distinguished entity precludes definitive statements. Deutsch et al. (2) suggest a role for surgery in their report of a median duration of freedom from disease of 53.6 months in three patients who received surgery, radiation, and chemotherapy and 36 months in three patients receiving radiation and chemotherapy or radiation alone.

The authors argue that the particularly poor outcome of patients who present with parenchymal disease warrants withholding surgery until a response to adjuvant therapy is demonstrated. This is at odds with their own experience: of their two patients with brain invasion, one died of disease at 15 months, and the other is alive with disease at 27 months, compared with the two patients without brain invasion who died of disease at 5 and 24 months, respectively. Experience with esthesioneuroblastomas and neuroendocrine carcinomas of this region suggests a trial for SNUC involving neoadjuvant chemotherapy for all cases, followed by fractionated stereotactic radiosurgery and chemotherapy to responding tumors and surgery plus radiotherapy and chemotherapy for nonresponding tumors (1, 3, 4).

Griffith R. Harsh IV
Stanford, California

1. Bhattacharyya N, Thornton AF, Joseph MP, Goodman ML, Amrein PC: Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation: Results in 9 cases. Arch Otolaryngol Head Neck Surg 123:34–40, 1997.
2. Deutsch BD, Levine PA, Stewart FM, Frierson HF, Cantrell RW: Sinonasal undifferentiated carcinoma: A ray of hope. Otolaryngol Head Neck Surg 108:697–700, 1993.
3. Irish J, Dasgupta R, Freeman J, Gullane P, Gentili F, Brown D, Neligan P, O'Sullivan B: Outcome and analysis of the surgical management of esthesioneuroblastoma. J Otolaryngol 26:1–7, 1997.
4. Polin RS, Sheehan JP, Chenelle AG, Munoz E, Larner J, Phillips CD, Cantrell RW, Laws ER Jr, Newman SA, Levine PA, Jane JA: The role of preoperative adjuvant treatment in the management of esthesioneuroblastoma: The University of Virginia experience. Neurosurgery 42:1029–1397, 1998.

This report by Gorelick et al. details the natural history of a rare, aggressive neoplasm. SNUC was first differentiated from other sinonasal neoplasms by Frierson et al. (1) in 1986. All reports since then have highlighted its nearly universal fatal course. In its lethality, it seems to rank with undifferentiated thyroid carcinoma.

These authors recommend radical triple therapy in the absence of brain invasion and initial chemoradiation with brain invasion. These recommendations are similar to those of other authors. Although, for the moment, I agree with these recommendations, I also think that the final role of surgery remains to be determined. Evidence to date, intuitive thinking notwithstanding, shows scant support for a positive effect of resection. The final role of resection may be akin to its role in rhabdomyosarcoma, or it may be that only earlier detection will prove resection efficacious. This report provides the neurosurgery community with information concerning an important carcinoma that at present often requires neurosurgical assistance in the planning and execution of meaningful resection.

Dale H. Rice
Otolaryngologist
Los Angeles, California

1. Frierson HF Jr, Mills SE, Fechner RE, Taxy JB, Levine PA: Sinonasal undifferentiated carcinoma: An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. Am J Surg Pathol 10: 771–779, 1986.