Sinonasal Undifferentiated Carcinoma with Intracranial Extension

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ABSTRACT

Aim: To report our experience in the management of sinonasal undifferentiated carcinoma (SNUC) over a period of 15 years. **Study design:** A retrospective case review of 13 patients with SNUC treated at the University of California, Davis, Medical Center (UCDMC) Center for Skull Base Surgery, over the past 15 years. **Results:** Most tumors arose in the ethmoid sinuses. All but 1 patient had a combined intracranial-extracranial resection through the anterior fossa-transcranial route and postoperative irradiation. The 13th patient had a transfacial subcranial approach. There are 6 who have survived free of disease at 14 years' to 8 months' follow-up. The average follow-up was 6 years, 3 months. One patient died of a pulmonary embolism in the first postoperative week, a second died of a bowel infarction 3 months postoperatively. Three patients died of their disease at 20, 18, and 8 months postoperatively: 1 with local recurrence and distant metastasis and the other 2 with local control but distant disease. The 6 survivors are at 8, 20, 28, 62, 84, and 105 months. **Conclusion:** SNUC is a rare malignancy of the paranasal sinuses with a poor prognosis. Radical surgery and adjunctive therapy can achieve good survival in a significant proportion of patients who would hitherto have seemed incurable.

KEYWORDS: Sinonasal undifferentiated carcinoma, malignancy, skull base surgery

Sinonasal undifferentiated carcinoma (SNUC) is an aggressive malignancy originating in the mucosa lining the walls of the nasal cavity and paranasal sinuses. It is a rare tumor that usually presents in an advanced stage, is highly invasive, and is traditionally reputed to be refractory to even the most radical therapy with an attendant poor

prognosis. This is particularly true when it transgresses the cranial base. We present a personal series of 13 consecutive cases of SNUC with transgression of the skull base seen at the University of California Center for Skull Base Surgery, all of which were treated with curative intent by skull base surgery.

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METHODS AND MATERIALS

A review of the prospectively compiled database of the UCDMC Center for Skull Base Surgery collected between 1977 and 2004 revealed 13 cases of SNUC that invaded the cranial base. Patients were followed from the time of surgery until August 31, 2004, or until their time of death. All patients had intraoperative evidence of invasion through the cranial base into the intracranial compartment.

After the initial clinical work-up, a computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed in an attempt to as clearly as possible define the limits of the tumor and determine operability. In the more recent cases, a positron emission tomography scan was done in any patient in whom distant metastasis was suspected. The patients were then presented to the multidisciplinary skull base surgery conference and a therapeutic strategy was formulated. All patients were operated upon utilizing the standard transcranial/transfacial approach described elsewhere.¹⁻³ A team utilizing the coordinated efforts of a neurosurgeon and an otolaryngologist resected the tumor attempting to achieve tumor-free margins in all cases. In those patients who had not been previously irradiated, whenever possible a full course of radiation therapy was given 4 to 6 weeks following surgery. In a few, adjunctive chemotherapy was administered as well.

In the current series, patients were studied for demographics; presence of dural, orbital, and brain invasion; status of margins; presence of neck metastasis; death; cause of death; use of adjunctive therapy; and 2- and 5-year survival rates.

RESULTS

There were 10 males and 3 females in the group. The average age was 51 years with the eldest being 77 and the youngest 26 years old. None presented with neck metastasis. Table 1 gives the

tissues involved with tumor, which therefore required resection. Dura was invaded in 10 of 13 (76.9%) but brain was invaded in only 3 of 13 (20.1%). Most patients, 10 of 13, had orbital invasion requiring orbital exenteration (76.9%). All patients except 2 had negative surgical margins on both frozen and permanent histology. Both of these patients had microscopically positive margins at the optic chiasm and refused further resection at this site because of the inevitability of blindness in both eyes. These patients are both alive at this time following focused irradiation to the chiasm, one at 9 months and the other at 16 months postoperatively. The short-term survivor appears disease-free at this time but the other has MRI changes suggestive of brain metastasis. Although no patients presented with cervical lymph nodal metastasis, 1 patient had been treated elsewhere by wide local excision and radical neck dissection for metastatic neck disease. At the time of surgery to the primary tumor, he had a positive margin. Postoperative irradiation was employed but the primary tumor persisted. Following referral to the UCDMC Center for Skull Base Surgery, a complete resection was attempted. However, despite negative surgical margins the patient died of locally recurrent and distant metastatic disease 7 months postoperatively. All of the other patients in this series had a full course of postoperative irradiation.

The length of follow-up and the survival outcome of the patients are also seen in Table 1. The longest follow-up was 105 months and the shortest 1 month (this patient died of pulmonary embolism). The average follow-up was 21.4 months. The average follow-up of survivors was 49.3 months. The shortest disease-free survivor is 8 months postoperative and the longest 105 months. Three patients have been survivors for greater than 5 years. The average time from time of treatment to death from disease was 15 months. The shortest time from treatment to death from disease was 8 months and the longest survival until death from tumor was 20 months. Two additional patients died free of disease but of other causes: 1 of a pulmonary embolism 1 month postoperatively and the other

Table 1 Tissues Involved

Patient	Sex	Age	Orbital	Dura	Brain	Follow-up in Months	Outcome
1	M	69	+	+	-	8	DOD
2	M	53	+	-	-	10	DOD
3	M	42	-	+	-	20	A&W
4	M	59	-	+	+	62	A&W
5	M	45	+	+	-	7	DOD
6	M	40	+	+	+	8	A&W
7	M	44	+	+	-	20	DOD
8	F	77	+	+	-	3	DOC
9	F	60	+	+	+	84	A&W
10	M	26	+	+	-	20	DOD
11	M	56	+	+	+	1	DOC
12	M	53	+	+	-	28	A&W
13	F	40	+	-	-	105	A&W

DOD, dead of disease; A&W, alive and well; DOC, dead of other causes; A&W, alive with disease.

Table 2 Six of Thirteen Survivors

F/U in Months	Orbit	Dura	Brain
105	+	-	+
84	+	+	-
8	+	+	+
62	-	+	+
20	-	+	-
28	+	+	+

from a bowel infarction secondary to a mesenteric artery occlusion 3 months postoperatively.

Table 2 shows the survivors, the length of follow-up, and the tissues invaded by tumor. Survivorship in this small cohort of patients appears to be unrelated to invasion of the dura, brain, or orbit.

CASE REPORTS

Case 1

A 58-year-old man presented with a 3-year history of nasal obstruction, purulent nasal drainage from the right side of his nose, and intermittent blood

staining of his rhinorrhea. Over the 7 months prior to his admission he had the gradual onset of progressive forgetfulness, disorientation, and behavior characteristic of dementia. An MRI revealed a massive intracranial tumor that produced marked deformation of the right frontal lobe and third ventricle (Fig. 1). There was a small extracranial component in the ethmoidal sinuses that represented ~10% of the total tumor volume. Biopsy of the mass in the nose revealed the diagnosis of SNUC.

A low craniotomy was done. Extensive invasion of the frontal lobe dura was seen that at some sites invaded the underlying arachnoid. At the points where brain was invaded, it was removed with a 5-mm margin of grossly healthy tissue. Adequacy of removal was monitored by frozen section. Tumor was dissected from the optic chiasm, the diaphragma sellae, the interhemispheric fissure, and the hypothalamus. The subcranial portion was removed with little difficulty through an anterior subcranial approach, as described by Raveh and colleagues.⁴

The patient made a full recovery but didn't begin postoperative irradiation until 2 months postoperatively. He is 62 months postoperative with no signs of disease or metastasis.

Figure 1 Case 1. (A) Coronal and (B) axial MR scan illustrating deformation of the lateral ventricle from massive intracranial portion of a large SNUC. MR, magnetic resonance; SNUC, sinonasal undifferentiated carcinoma.

Case 2

A 60-year-old woman presented with a 3-month history of right-sided nasal obstruction, purulent rhinorrhea without epistaxis, and facial numbness over the second division of the trigeminal nerve. She began to experience diplopia and epiphora 19 days before presentation. Severe pain in the eye began 9 days prior to her first visit. On examination she had an incomplete ptosis of the right upper eyelid and an eye that was frozen in all aspects of gaze except laterally. A large mass was visible completely obstructing the left nasal cavity. A CT scan revealed a large mass originating in the right ethmoid sinuses and eroding into the anterior cranial fossa with suspicion of involvement of dura and overlying brain (Fig. 2).

The patient underwent a complete resection of the tumor using the lateral rhinotomy/anterior maxillary osteotomy/medial maxillectomy approach combined with a low anterior craniotomy. A complete ethmoidectomy, superior maxillectomy, and sphenoidotomy were performed. An orbital exenteration was necessary because of extensive orbital invasion. A tumor-free margin of resection of the optic nerve was carried close to the chiasm. A resection of frontal lobe dura, the falx cerebri, the olfactory bulb, and overlying frontal lobe was necessary to clear the tumor. She had tumor-free

margins and underwent postoperative radiation therapy and concomitant chemotherapy 3 weeks after her surgery that was completed 7 weeks later.

Approximately 18 months postoperatively the patient had the installation of Branemark intraosseous implants in the orbital rims in order for her to more easily wear a prosthesis. A year later she had the second stage placed and had the

Figure 2 Case 2. Axial CT scan of a SNUC invading the ethmoid sinuses, orbit, frontal dura, and frontal lobe of the brain. CT, computed tomography; SNUC, sinonasal undifferentiated carcinoma.

Figure 3 Case 2. Three years postoperatively. (A) With Branemark implants in place in orbit. (B) With ocular prosthesis applied. Photos printed with permission.

construction of an ocular prosthesis (Fig. 3). She is now 84 months postoperative and free of disease.

DISCUSSION

SNUC is a very aggressive, highly malignant tumor of the mucosal lining of the nose and paranasal sinuses first described as a distinct and separate entity by Frierson et al in 1986.⁵ The prognosis is described as being very poor with these patients having a high frequency of local recurrence and distant metastasis.

Difficulty still exists in histological differentiation of this tumor from poorly differentiated squamous or adenocarcinoma, esthesioneuroblastoma, melanoma, and neuroendocrine carcinoma. Tumors are comprised of nests, trabeculae, and sheets of mainly medium-sized cells, showing a high degree of mitotic activity and often showing

areas of necrosis. The cells have poorly defined cytoplasm and round hyperchromatic nuclei.^{5,6} There is a high nuclear to cytoplasmic ratio and vascular invasion is not uncommon.⁷

Franchi et al⁸ have discovered a characteristic cytokeratin (CK) expression that may help in establishing the diagnosis of SNUC. CK8 was present on immune histochemistry in 100% of their cases of SNUC. In addition, CK7 was expressed in 50% of cases and CK19 in 50% of SNUC, providing a unique pattern of CK expression compared with poorly and well-differentiated squamous cell carcinoma as well as schneiderian carcinoma. The relationship to the Epstein-Barr virus (EBV) is somewhat controversial. Although two studies, one by Lopategui and associates⁹ and another by Gallo and coworkers,¹⁰ have suggested such a relationship; two further studies by Jeng and colleagues¹¹ and Cerilli et al,¹² using in situ hybridization, found no positivity for EBV in their patients with SNUC.

Several series have been published, necessarily containing small numbers of patients due to the rarity of the disease, showing a dismal prognosis. Typical is a small series of patients published by Gorelick and coworkers¹³ describing their four cases of SNUC treated by interdisciplinary skull base surgery and postoperative adjunctive radiation and chemotherapy. Three of the patients died of their disease at an average of 15 months after surgery and the remaining patient is alive at 24 months with cerebral metastasis. In 1996 Righi and associates¹⁴ reported a series of seven cases of SNUC treated, with only one exception, using multimodality therapy over a 10-year period. Only three of the seven survived and the mean survival for the failures was 11.5 months. All died with recurrence of local disease. The three survivors were disease-free but their follow-up was short. A more recent report¹⁵ from the same institution published 4 years later included 14 patients with SNUC, 7 of whom were treated primarily by craniofacial resection. Radiation or a combination of chemoradiation was used as adjunctive therapy in 5 of these 7 patients. Two patients were free of disease, one with a long-term follow-up of 195 months and one with a short one of 18 months. Four patients died of disease at an average of 11 months and 1 died of other causes disease-free at 34 months.

Kim and colleagues¹⁶ reported a 10-year experience at UCLA. There were eight consecutive patients in the series seen between 1995 and 2002. Surgery was the primary modality of treatment in five patients and of these only one had surgery alone. Radiation therapy was used in 4/5 of these patients and combined with adjuvant chemotherapy in two patients. Combined radiation and chemotherapy without surgical resection was used in the remaining two. Unfortunately, only two of the total of eight patients were still alive and disease-free at an average of 12.3 months of follow-up. Two of the patients had died and four were alive with disease.

A more optimistic report by Musy et al¹⁷ analyzed a series of 25 patients with SNUC, of whom 10 were treated by up-front chemotherapy and irradiation which was followed by craniofacial

resection. There were 5 out of these 10 who were disease-free at follow-up times of 4, 36, 49, and 164 months. Since most patients recur within the first year after treatment for this deadly disease, the survivorship of these 4 patients is quite significant. However, the selection criteria limited the numbers who were operated on, as surgery was reserved for only those with minimal intraorbital and limited intracranial spread.

The current report is the first to describe a series of patients all of whom had invasion of the skull base, most of whom had extensive intracranial and extracranial spread. None had distant or cervical metastatic disease at the time of presentation. The majority of patients were treated using a classical lateral rhinotomy, anterior maxillary osteotomy, medial maxillectomy approach, combined with a low anterior craniotomy.¹ The degree of planned surgical exposure was based in part on the preoperative CT and MRI scans. Orbital exenteration was done only on those patients who had invasion of the intraconal fat, ocular muscles, sclera, or orbital apex. Dural resection was extended to include a 5- to 10-mm margin whenever possible. Margins of healthy brain of 5 to 7 mm were done to encompass any brain involvement. Posterior maxillectomy, wide sphenoidotomy, and total ethmoidectomy were usually needed to safely resect all tumor. Two patients had positive margins which were discovered at the time of surgery, but no further resection was done because this would have caused blindness in both eyes. There was no gross tumor left in these patients, only microscopic residua. Both were treated with focused irradiation to this site. One is alive with probable brain metastasis at 16 months and another is disease-free at 9 months. All patients who died of disease did so within 20 months of treatment. Two-year and better survival rates are probably significant. Discounting the two patients that died of other causes within a short time interval from their surgery, the 2-year and better crude disease-free survival rate was 4 of 7 or 57%.

The analysis of this series and the others in the current literature all suffer from the drawback of small numbers as well as the many different

treatment protocols used to manage this tumor. Our patients were exposed to a fairly consistent scheme of treatment. All had intracranial/extracranial surgery and postoperative irradiation. The only exceptions were the patient who had already been treated at another institution with a combination of chemotherapy and irradiation and the patient who died postoperatively of a pulmonary embolism.

In the series by Miyamoto and associates,¹⁵ one of their patients with SNUC with a Kadish IV classification survived more than 5 years, which coincides with our experience that dura, brain, and orbital involvement had no influence on survival (Table 2). In our experience, two long-term survivors had brain involvement, were treated by cerebral resection and postoperative irradiation, and are both alive over 5 years since their surgery. One of the other two patients with brain involvement died of a pulmonary embolism and the other is alive at 8 months but had a positive margin at the optic chiasm. The latter patient is thus far tumor-free.

CONCLUSIONS

Skull base surgery with a radicality that will ensure microscopically negative margins combined with postoperative irradiation therapy gives patients with even extensive intracranial invasion by SNUC a reasonable chance for long-term tumor-free survival.

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