Sinonasal Undifferentiated Carcinoma: Case Series and Literature Review

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Purpose: The purpose of this study was to understand the natural history and progression of sinonasal undifferentiated carcinoma (SNUC) to establish optimal management guidelines.

Methods and Materials: We analyzed 8 consecutively treated patients diagnosed with SNUC between 1995 and 2002 at UCLA Medical Center. Staging was classified by the Kadish System with 7 patients presenting at stage C and 1 patient with stage B disease. Five patients received surgery. Four of these 5 patients received adjuvant radiotherapy, with 2 patients receiving it concurrently with chemotherapy (cisplatinum/5-fluorouracil). One patient received surgery alone as definitive management. Of the remaining 3 patients who did not receive surgical treatment, concurrent chemotherapy and radiation was used.

Results: At last follow-up, 6 of the 8 patients were still alive (overall survival 75%) with mean survival time of 20.6 months. However, only 2 of the 6 were alive and free of disease (disease-free survival 25%) with a mean disease-free survival time of 12.3 months. Locoregional recurrence occurred in 5 of the 8 patients (63%). Time to recurrence ranged from 3 to 30 months. Distant metastasis presented in 4 of the 8 patients (50%), all with disease spread to bone. Two of the 4 patients with distant metastasis were found to have locoregional disease recurrence at the same time. Time to metastasis ranged from 2 to 30 months. Results also show that the 5 patients who received surgery are still alive with a mean survival time of 23 months at last follow-up. Meanwhile, 1 of the 3 patients who received no surgical therapy is alive, with a mean survival time of 16.7 months in this group.

Conclusions: SNUC has proven to have a poor prognosis. Although limited by small numbers, this study along with reported series in the past appear to suggest longer survival results with aggressive multimodality therapy, especially with the incorporation of complete surgical resection.

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Originally described in 1986 by Frierson et al,[1] sinonasal undifferentiated carcinoma (SNUC) is a rare and aggressive malignancy arising in the nasal cavity or paranasal sinuses that carries a poor prognosis despite a multimodality treatment approach. Men are usually affected more than women (70%-93% of reported cases) with mean age at diagnosis being 51 to 58 years.[2-6] The pathogenesis of SNUC remains unclear.[2]

Histologically, SNUC does not have a tendency to express neuroendocrine markers (chromogranin, synaptophysin, S100) unlike esthesioneuroblastoma.[4] However, nearly all SNUCs are positive for cytokeratin and epithelial membrane antigen.[4] With advances in immunohistochemistry studies, SNUC has been gradually accepted as a distinct entity from other similar tumors such as an advanced stage, high-grade esthesioneuroblastoma.

Clinically, many patients present with locally advanced disease with spread to the orbit or anterior cranial fossa. The disease not only carries a high rate of locoregional recurrence after treatment (36%-50%)[3,4] but also carries a high incidence of distant metastasis (17%-75%)[3-5] in reported series. Here, we report our experience and review the literature to better evaluate the outcomes for SNUC to establish more optimal management guidelines.

METHODS AND MATERIALS

We analyzed 8 consecutively treated patients diagnosed with SNUC between 1995 and 2002 at

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TABLE 1. Kadish Staging System

Stage	Tumor Extension
A	Tumor limited to nasal cavity
B	Tumor involving nasal cavity and paranasal sinuses
C	Tumor extending beyond the nasal cavity and paranasal sinuses

UCLA Medical Center (Los Angeles, CA). Information was obtained by retrospective chart review from the Department of Radiation Oncology. The mean age at time of diagnosis was 48 years. There were 6 men and 2 women. Staging was classified by the Kadish System (Table 1) with 7 patients presenting at stage C and 1 patient with stage B disease.

Five patients received surgery, 3 undergoing a craniofacial resection (CFR) and 2 patients undergoing a partial maxillectomy and ethmoidectomy. Four of these 5 patients received adjuvant radiotherapy, with 2 patients receiving it concurrently with chemotherapy (cisplatinum/5-fluorouracil). One patient received a CFR alone as definitive management. No patient received neoadjuvant therapy.

Of the 4 patients treated with surgery and radiation, doses ranged from 5,040 in 180 cGy fraction to 5,400 in 200 cGy fractions. Regional lymph nodes were treated in only 1 of the 4 patients.

Of the remaining 3 patients who did not receive surgical treatment, concurrent chemotherapy and radiation was used. Gross tumor was carried to a dose ranging from 6,000 to 6,840 cGy. Regional lymphatics were treated to a dose of 5,000 cGy in 2 of the 3 patients. All patients received current cisplatinum/5-fluorouracil as their chemotherapy regimen.

RESULTS

Table 2 lists complete details regarding patient information and clinical management. At last follow-up, 6 of the 8 patients were still alive (overall survival 75%) with mean survival time of 20.6 months at last follow-up; however, only 2 of the 6 were alive and free of disease (disease-free survival 25%) with a mean disease-free survival time of 12.3 months.

Locoregional recurrence occurred in 5 of the 8 patients (63%). Two of these patients recurred at the original site of disease and 3 with regional spread (1 with a tracheal metastasis and 2 with cervical lymph node metastasis). In the 2 patients with recurrence at the original site of disease, 1 was originally treated by CFR alone with the other receiving a CFR and adjuvant chemotherapy and radiation. They were salvaged with palliative laser ablation and surgery, respectively, and are alive with disease. In patients presenting with regional spread after therapy, 2 of the patients had received a CFR with adjuvant radiation to the tumor bed alone without treatment of cervical lymph nodes. The other patient received chemoradiation alone; however, the regional lymph nodes were not treated by radiation. Time to recurrence ranged from 3 to 30 months.

Distant metastasis presented in 4 of the 8 patients (50%). Two of the 4 patients were found to have locoregional disease recurrence at the same time. All 4 patients presented with bone metastasis and were treated with palliative radiation to sites that were clinically symptomatic. Time-to-distant metastasis ranged from 2 months to 30 months.

Further analysis shows that the 5 patients who received surgery as part of their therapy are still alive with a mean survival time of 23 months at last follow-up. Meanwhile, one of the 3 patients who received no surgical ther-

TABLE 2. Patient Characteristics and Clinical Features

Patient	Age	Sex	Stage	Surgery	Radiation	Chemotherapy	Local or Regional Recurrence	Distant Metastasis	Survival
1	65	M	C	CFR	None	None	Yes-ethmoid (4 mo)	No	AWD (12 mo)
2	38	M	C	CFR	5400 cGy locally	None	Yes-trachea (30 mo)	Yes-bone (30 mo)	AWD (37 mo)
3	65	M	C	CFR	5040 cGy locally	None	Yes-neck nodes (3 mo)	Yes-bone (3 mo)	AWD (15 mo)
4	27	M	C	MM/ETH	5400 cGy localregionally	Yes-cis/5FU	Yes-nasal cavity (25 mo)	No	AWD (36 mo)
5	45	M	C	No	6840 cGy locally and 5000 cGy regionally	Yes-cis/5FU	No	No	NED (14 mo)
6	68	F	B	MM/ETH	5400 cGy locally	Yes-cis/5FU	No	No	NED (15 mo)
7	40	M	C	No	6300 cGy locally	Yes-cis/5FU	Yes-neck nodes (5 mo)	Yes-bone (24 mo)	DOD (32 mo)
8	36	F	C	No	6000 cGy locally and 5000 cGy regionally	Yes-cis/5FU	No	Yes-bone (2 mo)	DOD (4 mo)

Abbreviations: M, male; F, female; CFR, craniofacial resection; MM, medial maxillectomy; ETH, ethmoidectomy; cGy, centigray; cis, cisplatinum; 5FU, 5-fluorouracil; AWD, alive with disease; NED, no evidence of disease; DOD, dead of disease.

apy is alive, with a mean survival time of 16.7 months in this group. Also, in 3 of the 8 patients who had their nodal regions treated with radiation, their areas of recurrence were either at the original site of disease or distant; none recurred in the lymphatics.

DISCUSSION

SNUC is a highly lethal neoplasm that grows aggressively both locoregionally and distantly. Successful treatment of this neoplasm has been rare, and no optimal management guidelines have been developed to guide physicians in treating this fatal disease.

In a recently reported series from the University of Virginia,[6] the authors suggested a 2-year overall survival rate of 64% with neoadjuvant chemoradiation therapy (vincristine/doxorubicin/cyclophosphamide for 3 cycles and radiation to 50 Gy) followed by a CFR. Of the 10 patients who underwent this procedure, only 2 were free of disease with an equal number of local, regional, and distant recurrences. The authors suggested that a nonsurgical approach to this disease would be suboptimal based on a variety of reason. One, chemoradiation leaves viable tumor in a majority of the patients undergoing surgery. Also, they point to their 2-year survival of 64% in the group treated with CFR and 25% in the group treated with chemotherapy and/or radiation, although as the authors state, selection bias have a role in these survival rates.

Gorelick et al[5] reported on 4 patients considered to have advanced-stage disease either because of intracranial spread or metastatic disease. All were treated with aggressively surgical resection followed by chemotherapy and radiation to 60 to 65 Gy. Three of the 4 patients died of disease an average of 15 months after the diagnosis. Distant metastatic sites included bone, liver, and lung. Local recurrence occurred in 1 of the patients. Based on their series, the authors advocated radical resection as part of the initial combined therapy for patients presenting with nonmetastatic disease.

Smith et al[4] reported on 6 patients with SNUC treated with surgical resection followed by radiation therapy only. Three of the 6 patients presented with cervical lymphadenopathy. One patient died of disease (disease sites not specified), 2 were alive with no evidence of disease, 1 developed widespread bone metastasis, and the other 2 patients were noted to have persistent locoregional disease.

Finally, in a series reported by Jeng et al[2] consisting of 36 patients, 17% of patients presented with cervical node metastasis and 31% with distant metastasis. Median survival was 10 months. Only 5 patients were disease free at last follow-up, all having received surgical resection as part of their treatment modality.

Although all of these reported series are small, some conclusions can be drawn. First, whether used as part of a neoadjuvant plan or upfront therapy, complete surgical resection should be offered in patients with good performance status as better overall survival rates and long-term survival has been noted with the implementation of aggressive surgery as part of the treatment modality.[2,5,6] Our institutional series also support this trend because all 5 patients who received surgery as part of their therapy are still alive with a mean survival time of 23 months at last follow-up. Meanwhile, one of the 3 patients who received no surgical therapy is alive, with a mean survival time of 16.7 months in this group.

Furthermore, all patients should be offered adjuvant radiation and chemotherapy because of the aggressive nature of this disease to recur locally and spread distantly. From the radiation standpoint, the question is whether one should consider the head and neck lymphatics as a target along with the gross tumor/tumor bed. No series thus far has described their fields of treatment; however, we know from these reports that 17% to 50%[2,4] of patients can present with cervical lymphadenopathy at presentation. Furthermore, according to the University of Virginia experience,[6] an equal number of local, regional, and distant occurrences were observed. Our series also raises the idea of considering treatment of regional lymph nodes. In the 3 patients presenting with regional metastasis after therapy (1 with a tracheal met and 2 patients with cervical nodal spread), none had their lymphatics treated with radiation. In 3 patients who had their nodal regions treated with

radiation, their areas of recurrence were either at the original site of disease or distant; none recurred regionally. Of note, all patients who received radiation to the lymphatics also received concurrently cisplatinum and 5-fluorouracil, whereas only two of the 4 patients who did not receive radiation regionally received concurrent chemotherapy.

However, as seen in patients with advanced head and neck malignancies, undergoing radiation therapy to regional lymphatics can carry a higher morbidity rate when combined concurrently with chemotherapy.[7] Implementing such a radiation strategy may actually be disadvantageous in that toxicities may cause unwanted treatment breaks or compromise the need to deliver the proper radiation dose to the postsurgical bed or gross tumor if inoperable

Furthermore, one could argue that radiation should not address the regional lymph nodes in those presenting with node-negative disease and that a more aggressive chemotherapeutic approach be investigated to treat the micrometastatic disease because SNUC has a high predilection for metastasis after treatment. Also, with such a poor prognosis, one may not want to significantly deteriorate the quality of life in these patients by treating regional lymphatics, especially concurrently with chemotherapy.[8] Considering all these issues, it is difficult to ignore treatment of the lymphatics in analyzing the natural history of the disease to present and recur in regional lymph nodes.

As for the radiation dose, we recommend 70 Gy to the gross tumor if possible and in the postoperative setting, attempting to give 60 Gy. In our series, of the 5 patients who received surgical resection, 4 of them received postoperative radiation therapy, 1 of whom who recurred locally at the original site of disease after receiving 5,400 cGy with concurrent chemotherapy. In the series reported by Gorelick et al,[5] only 1 out of 4 patients recurred locally after being given 60 to 65 Gy postoperatively and that patient presented with advanced disease involving the left frontal lobe, the site of disease progression after therapy. If a neoadjuvant strategy is to be pursued, we would rely on the University of Virginia experience in giving 50 Gy.[6]

All patients with SNUC have a propensity to spread distantly, approximately 17% to 75%.[3-5] These patients should obviously have close follow-up and be monitored for bone symptoms because SNUC appears to have a predilection to spread to bone. Our series reports 4 patients with distant metastasis, all to bone. Although it is difficult to gauge the impact of chemotherapy, it seems intuitive that better systemic therapy would impact survival rates. Also, success in treating micrometastatic disease would likely translate to increased success in treating gross tumor in conjunction with radiotherapy in those unable to receive resection or those undergoing neoadjuvant therapy. Perhaps better chemotherapeutic regimens tested through a prospective, randomized trial may allow for more optimistic cure rates in the future.

CONCLUSIONS

Although limited by small numbers, this study along with reported series in the past, appear to suggest longer survival results with aggressive multimodality therapy, especially with the incorporation of complete surgical resection. Radiation plays a critical role in local control with questions still to be answered on the benefits of lymphatic radiation. Furthermore, finding the most beneficial chemotherapy regimen in controlling micrometastatic disease will be an important investigational topic. Performance status and presenting disease stage will be confounding factors in selecting those who would optimally benefit from this aggressively approach.

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