ORIGINAL ARTICLE

MANAGEMENT OF SINONASAL UNDIFFERENTIATED CARCINOMA

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Abstract: *Background.* Our aim was to report the outcomes of treatment for sinonasal undifferentiated carcinoma (SNUC).

Methods. Between September 1992 and October 2005, 15 patients were treated with curative intent with surgery ($n = 1$), surgery and adjuvant radiotherapy ($n = 9$), and definitive radiotherapy (RT) ($n = 5$). Follow-up ranged from 11 to 151 months (median, 30); follow-up on living patients ranged from 12 to 151 months (median, 22). No patient was lost to follow-up.

Results. Seven patients (47%) developed a recurrence from 3 to 50 months (median, 9) after treatment. The 3-year outcomes were: local control, 78%; locoregional control, 65%; distant metastasis–free survival, 82%; cause-specific survival, 77%, and survival, 67%. The local control rates versus treatment modality were: surgery, 0/1 (0%); surgery and postoperative RT, 7/7 (100%); preoperative RT and surgery, 2/2 (100%); and definitive RT, 2/5 (40%). One patient (7%) treated with surgery and postoperative RT sustained a fatal complication.

Conclusions. Combined surgery and adjuvant RT likely offer the best chance of cure compared with either modality alone. The impact of adjuvant chemotherapy is unclear. ©2008 Wiley Periodicals, Inc. *Head Neck* **30:** 595–599, 2008

Keywords: sinonasal undifferentiated carcinoma; radiotherapy; surgery

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Sinonasal undifferentiated carcinoma (SNUC) is a rare, aggressive malignancy that is thought to be part of the spectrum of neuroendocrine carcinomas that includes esthesioneuroblastoma, neuroendocrine carcinoma, and small cell carcinoma.[1,2] The prognosis for patients with SNUC is likely better than those with small cell carcinoma, similar to that observed with neuroendocrine carcinomas, and worse than for those with esthesioneuroblastomas.[1,2]

SNUC arises in the nasal cavity and is usually locally advanced when first appreciated; clinically positive regional nodes are present at diagnosis in 10% to 30% of patients.[3–6] Distant metastases often involve the lungs and bone and are uncommon at presentation. SNUC may rarely seed the cerebrospinal fluid and "drop metastases" may develop.[7]

The optimal management of patients with SNUC remains unclear.[1] Most series contain 10 to 20 patients or less and follow-up is sometimes short. A number of questions remain, including the role of craniofacial resection, altered fractionation, and adjuvant chemotherapy. Our aim was to present our experience with treatment of

Table 1. Patient population.

Stage	Surgery	RT	ENI	Chemotherapy	Follow-up
$T_{4A}N_0$	CF/OE	No	No	No	7 mo. – LR; 47mo. – DWD – P
$T_{4A}N_0$	CF	PORT64.2 Gy – BD	Yes	No	19 mo. – NED
$T_{4A}N_0$	CF/OE	PORT64.8 Gy – BD	Yes	Concomitant Cisplatin	12 mo. – NED
$T_{4A}N_0$	CF	PORT74.4 Gy – BD	No	No	4 mo. – NR 11 mo. – DWD – N
$T_{4B}N_0$	CF/OE	PORT74.4 Gy – BD	Yes	No	20 mo. – Dead – Complications
$T_{4A}N_0$	CF	PORT64.8 Gy – BD	No	Concomitant Cisplatin	14 mo. – NED
$T_{4A}N_0$	CF/OE	PORT62.4 – BD	No	No	128 mo. – NED
$T_{4A}N_0$	CF	PORT64.8 Gy – BD	Yes	No	47 mo. – DID
$T_{4B}N_0$	CF/OE	Pre-op RT60 Gy – BD	Yes	Concomitant Cisplatin	9 mo. – DM; 22 mo. – AWD – DM
$T_{4B}N_1$	CF/OE	Pre-op RT59.4 Gy – BD	–	Concomitant Cisplatin/5FU	12 mo. – NR; 21 mo. – DM; 38 mo. DWD – DM
$T_{4B}N_0$	No	70.2 Gy – QD	No	No	51 mo. – LR; 52 mo. – DWD – P
$T_{4B}N_0$	No	70 Gy - QD	No	Concomitant IA-Cisplatin	36 mo. – DID
$T_{4B}N_{2C}$	No	72 Gy – QD	–	Induction – Cis/ ETConcomitant Cisplatin	41 mo. – NED
$T_{4A}N_0$	No	70.8 Gy – BD	No	Concomitant Carboplatin/TAXOL	16 mo. – LR + NR; 18 mo. – DWD – P + N
$T_{4B}N_0$	Attempted CF	74.8 Gy – BD	Yes	No	10 mo. – Dural recurrence; 16 mo. – Dural recurrence; 84 mo. – NED

Abbreviations: CF, craniofacial resection; OE, orbital exenteration; mo., months; BD, twice-daily fractionation; QD, once-daily fractionation; 5FU, fluorouracil; IA, intra-arterial; CIS/ET, cisplatin and etoposide; LR, local recurrence; DWD, died with disease; P, primary site; NR, neck recurrence; NED, alive, no incidence of disease; N, neck; DID, dead, intercurrent disease; DM, distant metastasis.

patients with SNUC and to attempt to define the optimal treatment strategy.

MATERIALS AND METHODS

Between September 1992 and October 2005, 15 patients with previously untreated SNUC were treated with curative intent at the University of Florida College of Medicine and were included in this Institutional Review Board–approved outcomes study. No patients with this diagnosis were initially treated with palliative care during the study time period. Ten patients (67%) were men and 5 were women. Age ranged from 23 to 82 years (median, 57 years). Disease was staged according to the 2002 American Joint Committee on Cancer (AJCC) staging system.[8] Follow-up ranged from 11 to 151 months (median, 30 months); follow-up on living patients ranged from 12 to 151 months (median, 22 months). No patient was lost to follow-up.

All patients underwent CT and/or MRI, as well as a chest radiograph as part of the initial evaluation. The pathology on all patients was reviewed at our institution to confirm the diagnosis of SNUC. All patients had T_4 primary lesions; 2 patients (13%) were seen with clinically positive regional lymph nodes. No patient was seen with hematogenous dissemination.

The preferred treatment during the time period of the study was craniofacial resection followed by postoperative radiotherapy (RT). One patient who underwent craniofacial resection declined postoperative RT and was thus treated with surgery alone (Table 1). Orbital exenteration was combined with craniofacial resection in 6 patients. Seven patients underwent postoperative RT after surgery; 2 patients with marginally resectable T_{4B} cancers underwent preoperative RT followed by craniofacial resection. All patients who underwent resection had all gross tumor removed.

Definitive RT was used to treat 5 patients, including 1 patient who underwent attempted craniofacial resection followed by definitive RT after the procedure was aborted when the tumor was found to be incompletely resectable.

Despite the relatively high risk of subclinical disease in the cervical lymph nodes, the neck was not routinely electively irradiated in patients with a clinically N_0 neck. Of 13 patients with a clinically negative neck, 7 patients received elec-

tive neck irradiation and 6 patients did not receive elective treatment. Both patients with clinically positive nodes received RT and chemotherapy to the regional disease; no patient underwent a neck dissection.

Adjuvant chemotherapy was employed based on the inclinations of the attending physicians (Table 1). Six patients received concomitant chemotherapy; 1 patient received both induction and concomitant chemotherapy. One patient received concomitant intra-arterial cisplatin and RT according to the RADPLAT protocol[9]; the remaining patients received intravenous chemotherapy (Table 1). The irradiated volumes and dose-fractionation schedules for those patients who received adjuvant chemotherapy were similar to those employed for patients treated with RT alone.

The rates of local control, locoregional control, distant metastasis–free survival, cause-specific survival, and survival were calculated using the Kaplan-Meier product-limit method.[10]

RESULTS

Seven patients (47%) developed recurrent disease from 3 to 50 months (median, 9 months) after treatment.

The 3-year local control rate was 78% (see Figure 1). The local control rates according to treatment groups were: surgery alone, 0 of 1 (0%); surgery and postoperative RT, 7 of 7 (100%); preoperative RT and surgery, 2 of 2 (100%); RT alone, 2 of 5 (40%); and overall, 11 of 15 (73%). Local control was obtained in 6 of 7 patients (86%) who received adjuvant chemotherapy and 5 of 8 patients (63%) who received surgery and/or RT

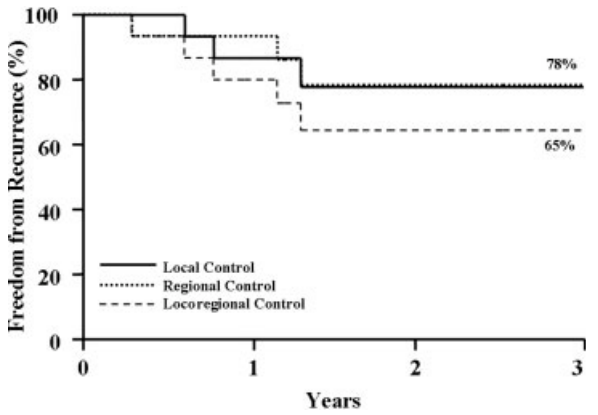

FIGURE 1. Local control, regional control, and locoregional control.

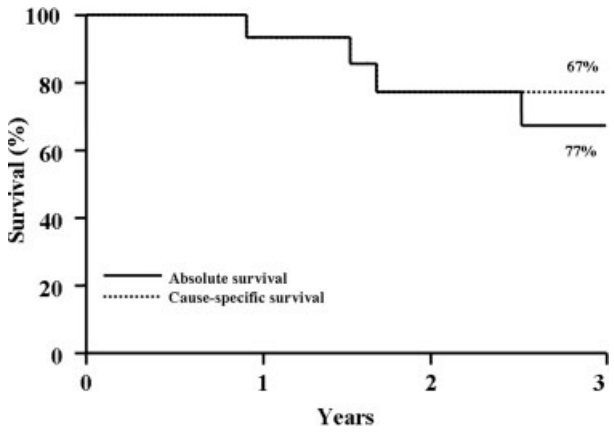

FIGURE 2. Cause-specific and absolute survival.

without adjuvant chemotherapy. The patient treated with surgery alone developed a local recurrence and was then treated with definitive RT and concomitant intra-arterial cisplatin with curative intent. The patient subsequently developed another local recurrence and died with local disease alone. One patient who underwent an attempted craniofacial resection and was subsequently treated with definitive RT developed a marginal dural recurrence 10 months after treatment and underwent palliative RT (30 Gy/12 fractions). A second marginal dural recurrence developed 16 months after definitive RT, and the patient was again treated with palliative RT (32.5 Gy/13 fractions). The dural recurrences resolved, and the patient remains disease-free 84 months after the initial course of RT.

Of the 13 patients with a clinically negative neck, the regional control rate was 7 of 7 patients (100%) who received elective neck irradiation versus 4 of 6 patients (66%) who did not receive elective neck irradiation (Table 1). One of the patients with recurrence in a clinically negative neck died with neck disease alone; the second patient died with disease in both the neck and primary site. One patient with a clinically positive neck had recurrence in the neck, underwent salvage treatment, and died with distant metastases alone. The second patient with a clinically positive neck is alive and disease free at 41 months (Table 1).

The 3-year locoregional control rate was 65%. The locoregional control rates versus treatment group were: surgery alone, 0/1 (0%); surgery and preoperative or postoperative RT, 7/9 (78%); RT alone, 2/5 (40%); and overall 9/15 (60%).

The 3-year distant metastasis–free survival rate was 82%. Two of 7 patients (29%) who received adjuvant chemotherapy developed hema-

Table 2. Treatment outcomes.

Outcome	Series				
	MDACC[2]	U. Cincinnati[4]	U. Virginia[5]	PMCC[3]	UF[†]
No. of patients	16	14	20	10	15
Percent treated surgically	63%	64%	55%	20%	67%
Local control	79% (5 y)*	–	–	–	78% (3 y)
Regional control	84% (5 y)*	–	–	–	78% (3 y)
Distant metastasis–free survival	75% (5 y)*	–	–	–	82% (3 y)
Alive, disease-free	–	36% (3–195 mo)	20% (24–164 mo)	50% (8–62 mo)	40% (12–128 mo.)
Alive with disease	–	0%	15%	10%	7%
Dead with disease	–	50%	65%	40%	46%[‡]
Dead, intercurrent disease	–	14% (24–34 mo)	0%	0%	7%
Overall survival	63% (5 y)*	36%	20%	50%	67% (3 y)

Abbreviations: MDACC, The University of Texas M. D. Anderson Cancer Center; PMCC, Peter MacCallum Cancer Centre.
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**Outcomes are expressed as crude percentages unless otherwise indicated. Follow-up intervals are indicated in parentheses. Five-year outcomes are calculated by Kaplan-Meier product-limit method.*
[†]University of Florida, present series.
[‡]Six dead with disease; 1 dead due to complications.

togenous metastases compared with 0 of 8 patients (0%) treated with surgery and/or RT alone.

The 3-year cause-specific and absolute survival rates were 77% and 67%, respectively (see Figure 2). Six patients are alive and disease-free, 2 patients died due to intercurrent disease without evidence of recurrence, 5 patients died with cancer, 1 patient is alive with distant metastases alone, and 1 patient died due to complications. The latter patient had an infected frontal bone flap and died due to a brain abscess and is coded as dead with disease in the analysis of cause-specific survival.

Three of 15 patients (20%) developed severe treatment-related complications. Two patients who underwent craniofacial resection and postoperative RT developed a brain abscess; 1 patient was treated successfully with resection and the remaining previously mentioned patient died due to the complication. One patient treated with salvage RADPLAT developed a frontal bone flap osteoradionecrosis that necessitated debridement.

DISCUSSION

The majority of patients with SNUC present with locally advanced disease that is amenable to craniofacial resection. Approximately one third of patients have incompletely resectable disease that is optimally treated with definitive RT. The likelihood of cure is roughly 50% (Table 2). It is unclear whether combined surgery and RT results in a higher likelihood of local control compared with definitive RT or whether any perceived improvement in outcome is due to selection bias. It is also unclear whether adjuvant chemotherapy improves the likelihood of cure. Given the rarity of SNUC, it is unlikely that there will be a clear answer to these questions in the near future.

Our current guidelines are to treat patients with apparently resectable tumor with a craniofacial resection and postoperative RT. One advantage associated with combined surgery and RT is that it may be possible to reduce the RT dose and thus reduce the risk of RT-induced optic neuropathy.[11] Hyperfractionated RT is employed to further reduce the risk of injury to the visual apparatus. Patients with apparently unresectable tumor are treated with definitive RT. Intensity modulated radiotherapy (IMRT) and/or proton beam therapy may be useful to produce a more conformal dose distribution to reduce the dose to normal tissues and, thus, late toxicity. The entire neck is electively irradiated in patients with an N_0 neck because of the high risk of subclinical regional disease. Patients are offered concomitant single agent cisplatin chemotherapy (30 mg/M^2/week) to hopefully improve outcome despite the lack of definitive evidence supporting its efficacy for this histology.[12]

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