Treatment modalities in sinonasal undifferentiated carcinoma: an analysis from the national cancer database

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Background: Sinonasal undifferentiated carcinoma (SNUC) is a rare, aggressive malignancy of unknown etiology with a poor overall prognosis. Its relative rarity has made it difficult to determine the impact of different treatment modalities on survival.

Methods: Retrospective study of cases in the National Cancer Data Base (NCDB). NCDB cases that were diagnosed as having SNUC between January 1, 2004, and December 31, 2013 were included in the analysis. Outcomes of patients treated with surgery followed adjuvant chemoradiotherapy were compared with definitive chemoradiotherapy.

Results: A 5-year survival rate of 42.2% was observed in the 460 patients in the analysis. American Joint Committee on Cancer (AJCC) clinical staging data were available for 304 patients. Of these patients, 60.2% had advanced tumors (AJCC stage 3 or 4). Surgery followed by adjuvant chemoradiotherapy was associated with better survival than definitive chemoradiotherapy (55.8% vs 42.6%, $p = 0.007$) in the study population. However, in late-stage tumors, there was no difference in survival between the 2 treatment groups ($p = 0.22$). For late-stage tumors, the time to initiation of adjuvant therapy was 49.2 ± 5.1 days for the surgery plus adjuvant therapy group as compared with 25.9 ± 2.6 days in the definitive chemoradiotherapy group ($p < 0.0001$), yet this did not appear to affect outcomes. No differences in age, gender, race, Charlson-Deyo score, facility type (academic vs nonacademic), or radiation dose were found between the 2 treatment groups ($p > 0.05$). Margin status played a critical role in the success of surgical resection, as no patients with positive margin status receiving adjuvant therapy survived to 5 years.

Conclusion: Surgery may play a role in a multimodality approach to treatment of late-stage SNUC if the tumor is amenable to surgical resection and negative margins can be reliably obtained. However, in cases where there may be difficulty obtaining negative margins, or this is considered unlikely preoperatively, surgical resection does not appear to provide any additional survival benefit.

Key Words:
carcinoma; paranasal sinuses; paranasal sinus diseases; paranasal sinus neoplasms; sinonasal undifferentiated carcinoma

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Undifferentiated neoplasms of the sinonasal tract are a group of nonsquamous, epithelial and nonepithelial malignancies with differing histologic characteristics.[1]

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Sinonasal undifferentiated carcinoma (SNUC) was first described in 1986 by Frierson et al. as an aggressive undifferentiated tumor of the paranasal sinuses and nasal cavity that may have been described previously in the literature as anaplastic or undifferentiated carcinoma.[2,3] SNUC usually presents as a rapidly enlarging mass that involves many areas of the sinonasal cavity and commonly erodes into adjacent structures.[4] SNUC has the ability to exhibit aggressive local destruction, regional spread, and distant metastases.[5–7] Patients often present with nonspecific symptoms, such as epistaxis and nasal obstruction.[5,6,8] This leads to a delay in diagnosis, with many patients diagnosed with advanced disease. Currently, this diagnosis carries a poor prognosis and many centers advocate for aggressive surgical resection in those deemed to be resectable,

utilizing chemotherapy and radiation. However, a consensus on timing of therapy and appropriate sequence of treatment modalities does not exist. Earlier studies have advocated for chemoradiotherapy alone, neoadjuvant therapy with subsequent craniofacial resection, and upfront surgical resection with adjuvant therapy.[9–11] Despite the diverse methods used to treat this disease, overall survival remains poor, with several reports showing 5-year survival rates of <60%.[10–12]

SNUC comprises <1% of malignancies and, given its aggressive nature and lack of large numbers of cases at one institution, developing a uniform treatment protocol or conducting prospective analysis of treatment has been difficult.[13,14] In this analysis we aimed to capture a large group of patients with this rare malignancy and characterize the 2 most popular treatment protocols currently used for this disease.

Patients and methods

Data source

The National Cancer Data Base (NCDB) is a national hospital-based cancer registry sponsored by the American College of Surgeon's Commission on Cancer and the American Cancer Society. The NCDB includes approximately 70% of newly diagnosed cancer cases in the United States from over 1500 accredited cancer care programs. The database provides information on demographics, staging information and extent of disease, treatment strategies, as well as survival data.

Patient population

Patients diagnosed as having SNUC of the nasal cavity and paranasal sinuses between January 1, 2004 and December 31, 2010 were identified using the International Classification of Diseases for Oncology, Third Edition (ICDO-3), topography code 8020/3 for carcinoma, undifferentiated type. Patients with multiple malignant primary tumors and follow-up of <1 month were excluded from the analysis. Overall survival and 5-year survival were investigated as outcomes.

Prognostic variables

Patients' demographics (age, race, sex, facility type), disease characteristics (primary site of tumor origin, metastatic disease), and treatment variables (type of treatment, surgical margins) were investigated for association with overall survival. Patients were grouped as follows according to age: <45 years; 46 to 55 years; 56 to 65 years; and ≥75 years. Race was separated into white, black, and other. Facility type was separated into academic and nonacademic centers (combination of community cancer programs, comprehensive community cancer programs, and other programs). Patients' insurance was divided into according to private or government (Medicare and Medicaid) insurance.

Treatment regimens were separated into the 2 most common treatment modalities: surgery with adjuvant concurrent chemoradiation therapy and definitive chemoradiation. Positive margins (combination of microscopic residual tumor, macroscopic residual tumor, or residual tumor not otherwise specified) and negative margins (no residual tumor with negative margins) were identified. Residual tumor, or a positive margin, was defined by the NCDB as within 5 mm.

The Charlson Comorbidity Index was analyzed with descriptive statistics, but not for association with survival.

Statistical analysis

Statistical analyses were performed using statistical software (SAS, version 9.3 for Windows; SAS Institute, Cary, NC). Patients' demographics, tumor characteristics, treatment factors, and outcomes were compiled using standard summary statistics. Kaplan-Meier analysis and the log rank test were performed to determine the unadjusted association between overall survival and age, sex, insurance status (as a measure of socioeconomic status), metastatic disease, treatment, and margin status among the entire cohort, including all treatment modalities, as well as subanalyses by specific treatment modalities. Pearson chi-square tests were used to determine the association between categorical variables and different treatment groups. Multivariate analysis was conducted by Cox logistic regression. Survival effects of covariates were reported as hazard ratios. $p < 0.05$ was considered statistically significant in all comparisons.

Results

Four hundred sixty patients were found to have varying stages of SNUC in the NCDB. There were 292 male and 168 female patients. Of these, 216 were between 46 and 65 years of age at the time of diagnosis, with 50 patients <45 years and 52 patients >75 years of age. Two hundred sixty-nine patients were treated at an academic center, whereas 126 were treated at a nonacademic facility. The predominant race affected was white, with 375 patients identifying as white. The majority of patients, 403, had a score of 0 on the Charlson-Deyo scale, indicating no recorded comorbidities for these patients (Table 1).

Twenty-seven patients were found to have early-stage disease, defined as stage I/II, whereas 277 had late-stage tumors, defined as stage III/IV. One hundred fifty-six patients did not have complete staging data and were not included in this subanalysis. The 2 most frequently used treatment modalities in the overall population were surgery with adjuvant chemoradiotherapy and definitive chemoradiation. One hundred sixty-nine patients were treated with surgery with adjuvant chemoradiotherapy, whereas 146 were treated with definitive chemoradiation, giving a total of 315 patients. The remaining 145 patients had a variety of treatment modalities, ranging from surgery alone to palliative treatment.

TABLE 1. Patients' demographics

	Number [N = 460]	Number in late stage (>3) [N = 277]
Gender		
Male	292	173
Female	168	104
Age (years)		
<45	115	69
46 to 55	120	80
56 to 65	96	54
66 to 75	77	43
>75	52	31
Average	56.1 ± 15.4	55.8 ± 15.3
Race		
White	375	229
Black	49	27
Other	36	21
Facility		
Academic/research	269	157
Nonacademic	126	82
Unknown	65	38
Charlson Comorbidity Index score		
0	403	240
1	45	29
2	12	8
Treatment		
Surgery plus chemoradiotherapy	169	96
Chemoradiation	146	102

TABLE 2. Patients' outcomes

Overall patients			
	Number of patients	5-year survival	*p* value
Treatment modality			
Surgery plus chemoradiotherapy	169	55.80%	<0.05
Chemoradiotherapy	146	42.60%	
	Mean days to treatment		
Insurance type			
Government	28.75	30.00%	<0.05
Private	19.71	48.40%	
	Number of patients		
Metastatic disease			
Positive	45	18.60%	<0.05
Negative	415	45.60%	
Late-stage disease			
	Number of patients	5-year survival	*p* value
Treatment modality			
Surgery plus chemoradiotherapy	96	58.90%	0.22
Chemoradiotherapy	102	51.80%	
Margin status			
Surgery plus chemoradiotherapy with negative margins	31	75.28%	<0.05
Chemoradiotherapy	84	49.75%	

When analyzing the overall 315 patients for differences in outcome, surgery with adjuvant concurrent chemoradiotherapy was found to have greater overall 5-year survival than definitive chemoradiation (55.8% vs 42.6%, $p = 0.0071$) in the total population. Of the 277 patients diagnosed with late-stage disease, after removing 13 patients with distant metastases at the time of diagnosis, 102 received definitive chemoradiation and 96 underwent surgery with adjuvant chemoradiotherapy. There was no difference in survival between the 2 treatment groups when specifically analyzing patients with late-stage disease ($p = 0.22$). Patients with late-stage disease receiving surgery with adjuvant chemoradiation had a 5-year survival rate of 58.9%, whereas patients receiving definitive chemoradiation had a 5-year survival of 51.8%. A further analysis of late-stage tumors revealed that, in the group with surgery and adjuvant chemoradiotherapy, time to initiation of adjuvant therapy was 49.2 ± 5.1 days, as compared with 25.9 ± 2.6 days in the definitive chemoradiotherapy group ($p < 0.0001$) (Table 2).

A separate analysis was also conducted to determine the effect of metastatic disease at the time of diagnosis and the effect this has on outcome. Of the 460 patients, 45 were defined as having metastatic disease at the time of diagnosis, whereas 405 patients did not. Patients with metastatic disease at the time of diagnosis had a 5-year survival of 18.6%, whereas those who did not had a survival rate of 45.6% ($p < 0.0001$). No differences in age, gender, race, Charlson-Deyo score, facility type (academic vs nonacademic), or radiation dose were found between the 2 treatment groups ($p > 0.05$).

Insurance status was also compared in the late-stage cohort. Patients with private insurance were more likely to be treated with surgery and adjuvant chemoradiotherapy when compared with patients with government insurance (61.1% vs 58.3%; $p = 0.04$). Patients with private insurance were also found to have significantly greater 5-year survival compared with patients using government insurance (48.4% vs 30.0%; $p < 0.0001$).

Radiation dose for both treatment arms was statistically similar, with patients undergoing definitive chemoradiotherapy receiving a mean radiation dose of 60.6 Gy and those receiving adjuvant chemoradiation after surgery receiving a mean radiation dose of 63.9 Gy.

Margin status was reported in 59 of the patients with late-stage disease undergoing surgery with adjuvant chemoradiation. Of these 59 patients, 37 were able to be resected to negative margins. However, 22 of them were reported as having positive margins. Patients undergoing surgery to negative margins with adjuvant chemoradiotherapy were found to have statistically significantly better 5-year survival than those undergoing definitive chemoradiation (75.3% vs 49.8%, respectively; $p = 0.008$) (Table 2).

Discussion

Despite multiple types of aggressive therapy, including a mixture of induction chemotherapy, definitive chemotherapy, radiation, and craniofacial resection, the prognosis for patients afflicted with SNUC tends to be poor. In a large series of >300 patients with SNUC, Chambers et al. found an overall 5-year relative survival rate of 34.9% and an overall median survival of 22.1 months.[15] Gorelick et al. reported a poor prognosis in their small series of 4 patients, even with an aggressive treatment regimen that included chemotherapy, radiotherapy (60 to 65 Gy), and aggressive craniofacial resection.[16] Three of the 4 patients were dead of disease at an average of 15 months and the 1 remaining patient was alive at 24 months, although with metastatic intracranial disease. Our study has shown that, in the overall population of patients, despite stage at diagnosis, the group receiving surgery with adjuvant chemoradiotherapy had slightly better 5-year survival than the group receiving definitive chemoradiotherapy (55.8% vs 42.6%; $p = 0.0071$). However, overall, both groups exhibited poor 5-year survival with only 2 patients still alive at 10 years.

Tumor stage at time of diagnosis has also been shown to influence survival and possible treatment options. Kuan et al., in their large retrospective series, found that Kadish stage and tumor size were associated with worse overall and disease-specific survival.[17] Rischin et al. reported on their experience with 10 patients with SNUC.[10] One patient who was reported to have a T1N0M0 SNUC confined to the nasal cavity underwent a 50-Gy treatment and exhibited a complete response and was alive and disease-free at 62 months. However, the remaining 9 patients all were diagnosed with T4 tumors, 6 with intracranial extension. Seven of these patients were treated with definitive concurrent chemoradiation therapy; local-regional control was achieved in 4 of the 7. Two of the 7 patients died with disease, 1 patient was alive with disease, and 4 patients were alive and disease-free at 8, 10, 28, and 62 months, respectively, after treatment. For the 7 definitive chemoradiation patients, the 2-year progression-free survival rate was 43% and the 2-year overall survival rate was 64%. In our analysis we found that patients with late-stage disease displayed no difference in survival between the 2 treatment groups, surgery with adjuvant chemoradiotherapy or definitive chemoradiation (58.9% vs 51.8%, respectively; $p = 0.22$).

Extended time to initiation of treatment has been correlated with poor outcomes in head and neck cancer. Murphy et al., in 2 separate studies, found significantly worse prognosis when time to initiation of treatment was delayed beyond 52 days.[18,19] Our analysis of late-stage tumors has revealed that, in the group with surgery and adjuvant therapy, time to initiation of adjuvant therapy was 49.2 ± 5.1 days as compared with 25.9 ± 2.6 days in the definitive chemoradiotherapy group ($p < 0.0001$). However, survival between cohorts was not significantly different. This may have been due to the overall poor prognosis in this patient population.

Patients' insurance status and its role in the diagnosis and treatment of head and neck cancers has been examined in earlier studies and has shown a later diagnosis and a significant treatment gap between patients with private insurance and those with government insurance.[20,21] Our data indicate patients with private insurance were more likely to be treated with surgery and adjuvant chemoradiotherapy compared with patients with government insurance (61.1% vs 58.3%, respectively; $p = 0.04$). Patients with private insurance were also found to have significantly greater 5-year survival compared with those with government insurance (48.4% vs 30.0%, respectively; $p < 0.0001$). A separate analysis comparing time to initiation of treatment for patients in these 2 cohorts showed that patients with private insurance started treatment at a mean of 19.7 days, a significantly shorter time frame than for patients with government insurance, who started treatment at a mean of 28.7 days after diagnosis ($p = 0.01$). These results are most likely attributable to the increased health care utilization of physician services by patients with private medical insurance.[22] Patients without health insurance were also more likely to present with advanced-stage disease.[23]

It is widely recognized that distant metastasis at the time of diagnosis portends a poor prognosis. Studies have demonstrated poor outcomes in patients with metastatic disease.[24,25] Our data indicate metastatic disease at the time of diagnosis is a very poor prognostic indicator, with a 5-year survival of 18.6%, whereas those without metastatic disease had a survival rate of 45.6% ($p < 0.0001$).

Margin status has been reported to play a critical role in outcomes of patients diagnosed with SNUC. Musy et al.

reported on 20 patients treated over a 15-year period, 10 of whom were treated with neoadjuvant chemoradiation followed by craniofacial resection.[7] Of these 10 patients, 8 were Kadish stage C and 2 were Kadish stage B. Interestingly, 8 of the 10 patients treated with craniofacial resection had either positive or close margins, defined as ≤5 mm. Overall, only 1 patient was reported as having no evidence of disease after 5 years of follow-up and 1 patient died of disease after surviving for >5 years. One patient treated with definitive concurrent chemoradiation (65 Gy), consisting of cyclophosphamide/doxorubicin/vincristine, was alive with disease at 114 months. Our data also indicate difficulty obtaining negative margins in these patients, with 37.3% of patients undergoing surgery with adjuvant treatment reported as having positive margins. However, when comparing patients with negative margins with adjuvant concurrent chemoradiotherapy and those receiving definitive chemoradiotherapy, the group treated with surgical resection first had better 5-year survival (75.3% vs 49.8%, respectively; $p = 0.008$). More importantly, of the 22 patients with late-stage disease who underwent surgery with positive margins, none survived to 5 years.

In their meta-analysis examining 140 patients from the literature, along with 20 patients treated at their institution, Xu et al. found that, although multimodality treatment did benefit patients diagnosed with late-stage disease, there appeared to be significant difference in outcome when incorporating surgery.[26] Our findings advocate for use of definitive chemoradiotherapy in patients with advanced disease when the ability to obtain negative margins is questionable preoperatively. At the very least it should necessitate a discussion examining extent of disease and confidence in obtaining negative margins in patients with advanced disease.

The use of induction therapy has been advocated for in the treatment of SNUC. Kramer et al. described their experience with 4 patients diagnosed with advanced SNUC, as evidenced by skull-base involvement in 1 patient and brain involvement in the other 3 patients.[27] The 3 patients with brain involvement were treated with induction chemotherapy, which consisted of 5-flourouracil or etoposide followed by radiotherapy of 50 Gy over 5 weeks. All 3 were alive and disease-free at 27, 41, and 66 weeks, respectively. Van der Laan et al. advocated for an aggressive multimodality approach incorporating neoadjuvant chemoradiotherapy, radical surgery, and elective treatment of the neck in cases of sinonasal carcinoma with neuroendocrine differentiation. Our analysis did not include patients undergoing neoadjuvant treatment, as this represented a very small portion of patients in the data set, with markedly heterogeneous treatment regimens.

Given the sponsorship of the NCDB by the American College of Surgeon's Commission on Cancer and the American Cancer Society, patient data are available from >1500 accredited cancer care programs. Furthermore, compared with other databases, the NCDB provides extensive information on patients' demographics, extent of disease, treatment regimens, as well as long-term overall survival. However, limitations of the database include an inability to verify the fidelity of the data input, which may affect data output and conclusions made. There is an inherent surgical selection bias associated with conducting research using data such as that contained in the NCDB. Furthermore, patients were selected into the study by using ICDO-3 morphologic and topographic codes. Unfortunately, we relied on proper coding and accurate diagnosis of cases to generate our cohort, and we could not fully verify the data. There was a large subset of patients with incomplete data as well, and thus they could not be included in the subanalyses. Also, the NCDB is a hospital-based database, not population-based database, which limits extrapolation of data for epidemiologic information.

Conclusion

SNUC represents a rare, highly aggressive, and clinicopathologically distinctive carcinoma of uncertain histogenesis.[1] Given the rarity of the disease and the tendency for patients to present at an advanced stage, data supporting a universal strategy for treatment of SNUC do not currently exist. Multimodality treatment, including surgery, has been advocated for advanced disease; however, the impact of surgery on survival outcomes in this population appears to be minimal, and outcomes in cases with positive margins have been poor. Our analysis indicates surgery may play a role in the multimodality management of SNUC if negative margins can be reliably obtained. However, in cases where there may be difficulty in obtaining negative margins or this is not feasible, proceeding with surgical resection does not appear to provide any survival benefit. It is imperative that surgical oncologists make an unbiased and honest assessment of their ability to reliably obtain negative margins when considering surgical resection for patients with sinonasal undifferentiated carcinoma.

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