AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
1–5

DOI: 10.1177/0194599816670146
http://otojournal.org
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Survival Outcomes for Combined Modality Therapy for Sinonasal Undifferentiated Carcinoma

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Received May 23, 2016; revised August 30, 2016; accepted August 30, 2016.

Abstract

Objective. Sinonasal undifferentiated carcinoma is a rare and aggressive malignancy of the nasal cavity and paranasal sinuses. Multi-institutional studies examining outcomes of combined modality treatment versus other treatment modalities have not been performed. The objective of our study was to present outcomes for multimodality therapy through use of the National Cancer Database.

Study Design. Retrospective cohort study.

Setting. National Cancer Database.

Methods. A total of 435 cases of SNUC diagnosed between 2004 and 2012 were identified. Kaplan-Meier analyses were performed to find 5-year cumulative survival rates. Multivariate Cox regression evaluated overall survival based on treatment when adjusting for other prognostic factors (age, primary site, sex, race, comorbidity, insurance, and TNM stage). Within the surgery + chemoradiotherapy group, survival analysis was also performed to compare outcomes for induction and adjuvant chemotherapy.

Results. The cumulative 5-year survival rate was 41.5%, and 36.1% of patients received surgery with chemoradiotherapy. In multivariate analysis, surgery + chemoradiotherapy was associated with significantly improved overall survival versus surgery + radiotherapy and radiotherapy but not significantly different from chemoradiotherapy. Within the surgery + chemoradiotherapy group, induction and adjuvant chemotherapy groups did not have associated differences in survival.

Conclusion. Combined modality therapy (chemoradiotherapy or surgery + chemoradiotherapy) is associated with improved survival outcomes versus other treatment modalities in patients with sinonasal undifferentiated carcinoma.

Keywords

sinonasal undifferentiated carcinoma, SNUC, survival outcomes, surgery, chemoradiation

Sinonasal undifferentiated carcinoma (SNUC) is a rare cancer of neuroendocrine origin that arises in the paranasal sinuses and nasal cavity. It was first described as a distinct clinicopathologic entity by Frierson et al in 1986.[1] These cancers are characterized by rapid progression, advanced locoregional disease, and overall poor prognosis. Due to their rarity, the available literature consists primarily of small single-institutional series.[2-10] Most authors have concluded that multimodality therapy with surgery and chemoradiotherapy (CRT) is the best treatment course given the aggressive nature of the malignancy.[3,4,7,9,11] However, there have not been larger multi-institutional studies, and previous population-based studies have not examined chemotherapy outcomes.[12-14] The objective of our study was to present outcomes for multimodality therapy through use of the National Cancer Database (NCDB).

Methods

Data Source

Data originated from the NCDB, a comprehensive clinical surveillance resource oncology data set that currently captures approximately 70% of all newly diagnosed malignancies in the United States annually. The nationwide facility-based database is sourced from hospital registry data from >1500 cancer programs to track clinical information at the tumor, patient, and facility levels. Begun in 1989, the NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. Data collection is carried out under a business associate agreement that includes a data use agreement

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between Commission on Cancer–accredited hospitals and the American College of Surgeons.

Exclusion Criteria

We identified cases of SNUC between 2004 and 2012 with the morphology code 8020 and *International Classification of Disease for Oncology, Third Edition* topography codes for the nasal cavity (C30.0), maxillary sinus (C31.0), ethmoid sinus (C31.1), frontal sinus (C31.2), sphenoid sinus (C31.3), or other accessory sinuses (C31.8, C31.9). Patients were excluded if they were <18 years old at the age of diagnosis or had unknown follow-up or treatment status.

Statistical Analysis

The primary outcome was all-cause mortality. In univariate analysis, Kaplan-Meier curves were compared by log-rank tests. Multivariate Cox regression was performed to evaluate the association between treatment modality and overall survival when adjusting for other demographic, clinical, and oncologic prognostic factors (age, primary site, sex, race, comorbidity, insurance, and TNM stage). Race was categorized into white, black, and other/known. Comorbidity was measured by the Charlson/Deyo score, with 0 corresponding to no comorbidity; 1 to cardiovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, or diabetes; and 2 to diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, or AIDS. Insurance was categorized into private, Medicare, Medicaid/other government, uninsured, and unknown. Patients were classified by T stage (T1, T2, T3, T4a, T4b, and TX), N stage (N0, N1, N2, N3, and NX), and M stage (M0, M1, and MX) according to seventh edition of the American Joint Committee on Cancer staging.[15]

Treatment modalities examined were surgery alone, surgery with radiotherapy (RT), surgery with CRT, RT alone, and CRT. Only treatments during the first course of therapy were included, which is defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. Patients were considered to have RT if they received either external beam radiation alone or external beam radiation in conjunction with other RT. Patients were considered to have received chemotherapy if they received any chemotherapy as part of their first course of therapy, regardless of the type or number of agents. Surgery with CRT was further split into adjuvant chemotherapy and induction chemotherapy groups, as well as adjuvant CRT and induction CRT groups. Induction chemotherapy was defined as chemotherapy administered from 6 months to 2 weeks before surgery, while adjuvant chemotherapy was administered up to 6 months after surgery. Induction CRT was defined as induction chemotherapy where RT was administered before surgery and within 30 days of the start of chemotherapy, while adjuvant CRT was defined as adjuvant chemotherapy where RT was administered after surgery and within 30 days of the start of chemotherapy.

Statistical significance was determined with 2-sided tests at the $P < .05$ level. Bonferroni correction was used for pairwise comparison. Data analysis was performed with SPSS 22.0 (IBM, Armonk, New York). This study was determined to be exempt from review by the institutional Human Investigation Committee.

Results

Frequency of Treatment Modalities

There were 435 eligible cases of SNUC in the NCDB. The demographic characteristics of the patients are described in **Table 1**. The majority of patients were Caucasian and male, and half of patients were <55 years old. The most common treatment modalities were surgery with CRT (36.1%), followed by CRT (27.6%). Overall, 325 (74.7%) patients received RT, 316 (72.6%) chemotherapy, and 240 (55.2%) surgery. Of patients receiving surgery for whom the surgical approach was known (n = 73), 20 (27.4%) had an endoscopic approach, 50 (68.5%) an open approach, and 3 (4.11%) an endoscopic approach that was converted to an open approach. Of patients receiving radiation (n = 325), 162 (49.8%) received intensity-modulated radiation therapy.

Univariate Survival Outcomes

The cumulative 5-year survival rate in all patients was 41.5%. In M0 patients, the cumulative 5-year survival was 43.7% overall and 46.8% in patients who received definitive treatment. The Kaplan-Meier curves for M0 patients receiving different treatment modalities are shown in **Figure 1**. In pairwise log-rank comparisons, surgery with CRT was associated with superior survival as compared with surgery ($P = .007$), surgery with RT ($P < .001$), and RT ($P = .009$) but not significantly better compared with CRT ($P = .101$). With Bonferroni correction, the log-rank tests would still be significant.

Multivariate Survival Outcomes

Multivariate Cox regression was performed on 251 M0 patients, with frontal and sphenoid cancers excluded given their small numbers. The significant prognostic factors were age ($P = .034$), insurance status ($P = .027$), T stage ($P < .001$), N stage ($P < .001$), and treatment modality ($P = .007$; **Table 2**). Uninsured patients were found to have significantly worse hazard ratio (HR) when compared with privately insured patients (HR = 2.75, 95% confidence interval [95% CI] = 1.21-6.23, $P = .016$).

Surgery with CRT was associated with improved overall survival versus all other treatment modalities. Relative to surgery with CRT, there were significantly worse HRs associated with surgery with RT (HR = 2.71, 95% CI = 1.43-5.15, $P = .002$), RT (HR = 3.01, 95% CI = 1.13-7.99, $P = .027$), and surgery (HR = 2.15, 95% CI = 1.12-4.14, $P = .021$). The only group where the HR was not significantly different was CRT, which, relative to surgery with CRT, had an HR of 1.24 (95% CI = 0.779-1.97, $P = .364$). When treatment modalities were compared with CRT as the

Table 1. Demographic Characteristics of Patients with Sinonasal Undifferentiated Carcinoma (N = 435).

Characteristic	n (%)	Characteristic	n (%)
Primary site		AJCC T	
Nasal cavity	165 (37.9)	T1	14 (3.2)
Maxillary sinus	65 (14.9)	T2	14 (3.2)
Ethmoid sinus	100 (23.0)	T3	45 (10.3)
Frontal sinus	5 (1.1)	T4a	87 (20.0)
Sphenoid sinus	21 (4.8)	T4b	108 (24.8)
Other sinuses	79 (18.2)	Unknown	167 (38.4)
Age, y		AJCC N	
18-54	200 (46.0)	N0	208 (47.8)
55-64	83 (19.1)	N1	20 (4.6)
65-74	76 (17.5)	N2	36 (8.3)
75-84	57 (13.1)	N3	3 (.7)
85+	19 (4.4)	Unknown	168 (38.6)
Sex		AJCC M	
Male	270 (62.1)	M0	294 (67.6)
Female	165 (37.9)	M1	25 (5.7)
Race/ethnicity		Unknown	116 (26.7)
White	358 (82.3)	Treatment	
Black	45 (10.3)	Surgery	37 (8.5)
Other/unknown	32 (7.4)	Surgery + RT	32 (7.4)
Charlson/Deyo Score		Surgery + CRT	157 (36.1)
0	374 (86.0)	Surgery + chemotherapy	14 (3.2)
1	51 (11.7)	RT	16 (3.7)
2	10 (2.3)	CRT	120 (27.6)
Insurance status		Chemotherapy	25 (5.7)
Private	224 (51.5)	None	34 (7.8)
Medicare	141 (32.4)		
Medicaid/other government	41 (9.4)		
Uninsured	21 (4.8)		
Unknown	8 (1.8)		

Abbreviations: AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; RT, radiotherapy.

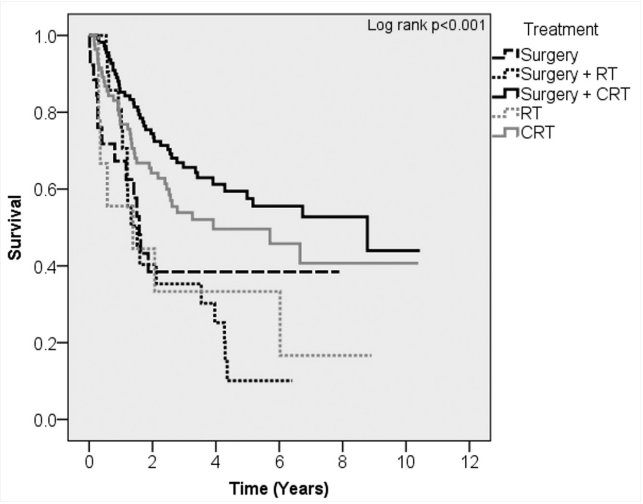

Figure 1. Kaplan-Meier curves for sinonasal undifferentiated carcinoma based on treatment modality. CRT, chemoradiotherapy; RT, radiotherapy.

reference variable, CRT was associated with significantly better survival than surgery with RT, but it did not have significant differences in survival when compared with surgery with CRT, surgery alone, or RT alone. Of the patients with known radiation therapy doses, 54.6% of patients received >60 Gy of radiation; when Cox regression was performed excluding patients who did not receive >60 Gy of radiation or whose radiation dose was unknown, surgery with CRT was still associated with significantly improved survival versus surgery alone and surgery with RT (n = 149).

Further subset analysis was performed with the TX and NX patients excluded (n = 200). In this subset, the HRs relative to surgery with CRT were 3.06 for surgery with RT (95% CI = 1.45-6.48, P = .003), 2.88 for surgery alone (1.27-6.54, P = .012), 2.65 for RT alone (95% CI = 0.905-7.74, P = .076), and 1.04 for CRT (95% CI = 0.619-1.742, P = .887).

Comparison of Induction and Adjuvant Therapy

For patients who had surgery with CRT, had known treatment sequences, and met the treatment definitions (n = 140), 31 patients received induction chemotherapy and 109 adjuvant chemotherapy. A log-rank test between induction and adjuvant chemotherapy was not significant (P = .427). In multivariate Cox regression, there was no significant difference for induction chemotherapy relative to adjuvant chemotherapy (HR = 0.559, 95% CI = 0.251-1.20, P = .136).

When the timing of radiation was considered within this group, 20 patients met treatment definitions for induction CRT and 84 for adjuvant CRT. A log-rank test between induction and adjuvant CRT was not significant (P = .304). In multivariate Cox regression, there was no significant difference for induction CRT relative to adjuvant CRT (HR = 0.437, 95% CI = 0.138-1.39, P = .160).

Discussion

SNUC is a challenging malignancy to treat for a number of reasons, including advanced stage at presentation, proximity to critical structures, and rarity. Its aggressive progression and high locoregional failure rates further contribute to a poor prognosis. In our analysis of a nationwide cancer database, the cumulative 5-year survival rate was 41.5%, which is consistent with other studies reporting <50% 5-year survival rates.[1,4,7,10,13] When comparing outcomes by treatment modality, we found that surgery with CRT and CRT were associated with the best survival outcomes in univariate and multivariate analyses.

The general consensus regarding treatment of these cancers is that aggressive multimodality therapy is recommended, but this conclusion has been limited by small sample sizes in the literature. There have many published single-institution series in the literature, the largest of which reported 36 patients.[2-10] Additionally, previous population-based studies with the Surveillance, Epidemiology, and End Results (SEER) database have been performed.[13,14] Chambers

Table 2. Multivariate Cox Regression (n = 251).

Characteristic	Hazard Ratio	95% CI	*P* Value
Age	1.02	1.00-1.04	.034
Primary site			
Nasal cavity	1	Reference	
Maxillary sinus	1.36	0.789-2.33	.269
Ethmoid sinus	1.21	0.772-1.88	.411
Sex			
Male	1	Reference	
Female	1.27	0.861-1.88	.227
Race/ethnicity			
White	1	Reference	
Black	1.26	0.671-2.37	.473
Other/unknown	0.592	0.241-1.45	.252
Charlson/Deyo score			
0	1	Reference	
1	0.880	0.489-1.59	.671
2	1.25	0.374-4.16	.719
Insurance status			
Private	1	Reference	
Medicare	1.84	1.09-3.09	.022
Medicaid/other government	1.71	0.863-3.40	.124
Uninsured	2.75	1.21-6.23	.016
Unknown	0.676	0.083-5.04	.676
AJCC T stage			
T1	1	Reference	
T2	0.367	0.095-1.41	.145
T3	0.765	0.261-2.24	.625
T4a	1.24	0.463-3.34	.667
T4b	1.10	0.394-3.05	.861
TX	0.092	0.023-0.378	.001
AJCC N stage			
N0	1	Reference	
N1	1.20	0.465-3.09	.706
N2	1.27	0.648-2.47	.490
N3	15.4	3.02-78.3	.001
NX	9.15	3.58-23.41	<.001
Treatment			
Surgery + CRT	1	Reference	
Surgery + RT	2.71	1.43-5.15	.002
Surgery	2.15	1.12-4.14	.021
RT	3.01	1.13-7.99	.027
CRT	1.24	0.779-1.97	.364

Abbreviations: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; RT, radiotherapy.

et al examined 318 cases from SEER and reported a 5-year survival rate of 34.9%. They found a survival benefit associated with combined surgery and RT, with an HR of 0.58.[13] Kuan et al analyzed 328 patients from SEER and similarly reported the best survival outcomes associated with surgery with RT.[14] However, one disadvantage of these SEER analyses is that the database does not report chemotherapy status.

The NCDB offers a valuable tool for investigation of rare cancers such as SNUC. While it is a more recent database than SEER, it represents about 70% of newly diagnosed malignances in the United States, compared with about 30% in SEER. The NCDB therefore allows analysis of sample sizes that are equivalent to or larger than those in SEER, although SEER is more suitable for analysis of temporal trends spanning decades. Another difference between these 2 cancer databases is that SEER offers information about cause-specific survival. A substantial advantage of the NCDB versus SEER is that it includes chemotherapy status, particularly for diseases that commonly receive chemotherapy, such as SNUC. To our knowledge, this is the largest cohort of patients of SNUC that has been described in the literature, enabling comparisons of survival outcomes among therapy modalities.

Limitations are inherent to a study that uses secondary source data from a large database. There are many centers and physicians represented in this data set, introducing variation in the administration of surgery, RT, and chemotherapy. In particular, we were not able to distinguish chemotherapy by the number of agents, types of agents, or duration of treatment. The only outcome available was overall survival and not cause-specific survival or locoregional failure rates, so patients may have succumbed to competing causes of mortality. Additionally, some cases were excluded from multivariate analysis because of missing data values. Of note, a substantial percentage of patients did not have known staging. The findings were largely unchanged in a subset analysis evaluating only patients with known staging, but it is unknown whether such subsets are representative and whether there was an effect of missing data on the results. Finally, although we adjusted for prognostic factors such as age, comorbidity, and stage, bias remains a concern with retrospective studies where there may be other unmeasured confounders. For example, there may be selection bias, as we did not assess the reasons why patients did not receive therapy, such as refusal, contraindications, or availability of neurosurgical resources to assist with surgery. A particular concern is that the group receiving surgery with CRT would not include unresectable tumors, which would be expected to have a poorer outcome.

Given these limitations, our results confirm the poor prognosis of SNUC and suggest a survival benefit with multimodality therapy (CRT or surgery with CRT) over other treatment options. SNUC is a challenging disease both to treat and to study, and in the absence of high-quality studies that adequately control for selection bias, we recommend a continued multidisciplinary approach.

Author Contributions

Phoebe Kuo, conception and design, analysis and interpretation, drafting manuscript, final approval; **R. Peter Manes**, conception and design, revising manuscript, final approval; **Zachary G. Schwam**, conception and design, revising manuscript, final approval; **Benjamin L. Judson**, conception and design, interpretation of data, revising manuscript, final approval.

Disclosures

Competing interests: R. Peter Manes—Medtronic, consultant; Intersect ENT, research funding (unrelated to manuscript).

Sponsorships: None.

Funding source: Yale School of Medicine Medical Student Research Fellowship.

References

1. Frierson HF Jr, Mills SE, Fechner RE, et al. Sinonasal undifferentiated carcinoma: an aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. *Am J Surg Pathol*. 1986;10:771-779.
2. Jeng YM, Sung MT, Fang CL, et al. Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma: two clinically, biologically, and histopathologically distinct entities. *Am J Surg Pathol*. 2002;26:371-376.
3. Kim BS, Vongtama R, Juillard G. Sinonasal undifferentiated carcinoma: case series and literature review. *Am J Otolaryngol*. 2004;25:162-166.
4. Lin EM, Sparano A, Spalding A, et al. Sinonasal undifferentiated carcinoma: a 13-year experience at a single institution. *Skull Base*. 2010;20:61-67.
5. Lopez F, Suarez V, Vivanco B, et al. Current management of sinonasal undifferentiated carcinoma. *Rhinology*. 2015;53:212-220.
6. Miyamoto RC, Gleich LL, Biddinger PW, et al. Esthesioneuroblastoma and sinonasal undifferentiated carcinoma: impact of histological grading and clinical staging on survival and prognosis. *Laryngoscope*. 2000;110:1262-1265.
7. Musy PY, Reibel JF, Levine PA.Sinonasal undifferentiated carcinoma: the search for a better outcome. *Laryngoscope*. 2002;112:1450-1455.
8. Rischin D, Coleman A. Sinonasal malignancies of neuroendocrine origin. *Hematol Oncol Clin North Am*. 2008;22:1297-1316.
9. Tanzler ED, Morris CG, Orlando CA, et al. Management of sinonasal undifferentiated carcinoma. *Head Neck*. 2008;30:595-599.
10. Xu CC, Dziegielewski PT, McGaw WT, et al. Sinonasal undifferentiated carcinoma (SNUC): the Alberta experience and literature review. *J Otolaryngol Head Neck Surg*. 2013;42:2.
11. Reiersen DA, Pahilan ME, Devaiah AK.Meta-analysis of treatment outcomes for sinonasal undifferentiated carcinoma. *Otolaryngol Head Neck Surg*. 2012;147:7-14.
12. Ahn PH, Mitra N, Alonso-Basanta M, et al. Nodal metastasis and elective nodal level treatment in sinonasal small-cell and sinonasal undifferentiated carcinoma: a surveillance, epidemiology and end results analysis. *Br J Radiol*. 2016;89:20150488.
13. Chambers KJ, Lehmann AE, Remenschneider A, et al. Incidence and survival patterns of sinonasal undifferentiated carcinoma in the United States. *J Neurol Surg B Skull Base*. 2015;76:94-100.
14. Kuan EC, Arshi A, Mallen-St Clair J, et al. Significance of tumor stage in sinonasal undifferentiated carcinoma survival: a population-based analysis. *Otolaryngol Head Neck Surg*. 2016;154:667-673.
15. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*. 7th ed.New York, NY: Springer; 2010.