Incidence and Survival Patterns of Sinonasal Undifferentiated Carcinoma in the United States

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J Neurol Surg B 2015;76:94–100.

Abstract

Keywords

- ▶ sinonasal undifferentiated carcinoma
- ▶ SNUC
- ▶ survival
- ▶ multimodal treatment
- ▶ neuroendocrine tumors

Objective To determine trends in sinonasal undifferentiated carcinoma (SNUC) survival patterns in the United States.

Design Retrospective review of national database.

Participants All cases of SNUC in the National Cancer Institute's Surveillance Epidemiology and End Results program from 1973 to 2010 were examined.

Main Outcome Measures Age-adjusted incidence and survival rates were calculated and stratified by demographic information and treatment modality. Cohort analysis was performed to analyze survival patterns over time.

Results A total of 318 SNUC cases were identified. Age-adjusted incidence rate (IR) was 0.02 per 100,000. Incidence was greater in males (IR: 0.03) than females (IR: 0.01; $p = 0.03$). Overall 5- and 10-year relative survival rate was 34.9% and 31.3%, respectively. Overall median survival was 22.1 months. Median survival following surgery combined with radiation was 41.9 months. Five-year relative survival rate following surgery, radiation, or surgery combined with radiation was 38.7%, 36.0%, and 39.1%, respectively. Median survival from 1973–1986 and 1987–2010 was 14.5 and 23.5 months, respectively.

Conclusions This study provides new data regarding survival patterns of SNUC in the United States, confirming survival benefit with surgery and radiation as well as identifying a trend toward improved survival in recent decades.

Introduction

Sinonasal undifferentiated carcinoma (SNUC) is a rare and aggressive malignancy, often recalcitrant to treatment attempts.^{1,2} SNUC is often clinically silent until advanced in stage with extensive local invasion of surrounding structures³ and with cervical lymph node involvement in ~ 10 to 30% of patients at presentation.^{4–7}

The presenting symptoms of SNUC frequently appear benign, such as nasal obstruction, epistaxis, headache, and

facial pain, but they may also include visual impairment, periorbital swelling, proptosis, and cranial nerve palsies.⁸ With a predilection for males, SNUC demonstrates a 3:1 male-to-female ratio. Although the age of presentation is typically in the fifth decade of life, patients have ranged from 8 to 85 years at the time of diagnosis.⁸ A diagnosis of SNUC typically implies a rapid clinical progression and an overall poor prognosis.^{9,10} Conclusive epidemiological characterization, however, has been limited likely due to the low incidence of SNUC. The reported 5-year survival

received

May 5, 2014

accepted

June 14, 2014

published online

September 29, 2014

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Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0034-1390016>.
ISSN 2193-6331.

rate varies widely throughout the literature from 6.25 to 74%.^{8,11–15}

The differential diagnosis for sinonasal malignancies encompasses squamous cell carcinoma, esthesioneuroblastoma (olfactory neuroblastoma), neuroendocrine carcinoma, lymphoma, melanoma, rhabdomyosarcoma, lymphoepithelioma, as well as SNUC.¹ Imaging cannot reliably distinguish SNUC from these other entities, and thus the diagnosis of SNUC relies on histopathologic evaluation including immunohistochemical assessment.¹⁶ Thought to arise from specialized mucosal epithelium lining the sinonasal tract, SNUC demonstrates pathologic features of medium-size cells in nests or sheets with high rates of mitoses, tumor necrosis, and vascular permeation.¹⁷ The immunohistochemical profile is cytokeratin positive, S-100 protein negative, and variably positive for epithelial membrane antigen or neuron-specific enolase.¹

The current SNUC literature, which includes small to medium cases series and two meta-analyses each with < 170 patients, offers a limited ability to characterize overall incidence and survival patterns.^{3,4,8,11,15} To better understand the epidemiological patterns of SNUC, we evaluated 318 cases of SNUC between 1973 and 2010 from the Surveillance Epidemiology and End Results (SEER) program database. For the purpose of this study, the SEER database draws from multiple institutions and regions to offer the benefit of a much larger sample size than previously reported.

Methods

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), which covers ~28% of the US population, was accessed and searched for all cases of SNUC between 1973 and 2010 (SEER 18). Patient age, sex, race, treatment modality, and survival data were extracted for each SNUC case. Patient race was divided into white, black, Asian/Pacific Islander, and Alaskan/Native American based on the SEER categorization of race. Limited information was available as to the extent of surgical resection or surgical modality in each case; therefore, both total and subtotal resections are grouped together for inclusion in the surgical group. All modalities of radiation therapy were grouped together for the purposes of analysis. Information regarding chemotherapeutic treatment was not available.

The diagnosis of SNUC was based on microscopic confirmation according to the World Health Organization's *International Classification of Diseases for Oncology, Version Three* (ICD-O-3) morphology codes for SNUC (8020/3). Age-adjusted incidence was calculated based on the 2000 US Census Standard using SEER*Stat 8.1.2, a public use program provided by NCI. Relative survival and relative standard error were also calculated using SEER*Stat 8.1.2. The survival in months reported in the SEER database is overall relative survival not disease-specific survival. To obtain relative survival, expected survival was calculated using the Ederer II method based on the *U.S. Expected Survival Table 1970–2006 by Individual Year and Race*. Statistical significance was set at $p < 0.05$ for all analyses. The confidence interval was set at 95%.

Table 1 Demographics and treatment characteristics

	No.	%
Age group, y		
< 19	4	1.3
20–29	11	3.5
30–39	38	11.9
40–49	40	12.6
50–59	65	20.4
60–69	78	24.5
70–79	49	15.4
80+	33	10.4
Unknown	0	0.0
Sex		
Female	121	38.0
Male	197	62.0
Race		
White	263	82.7
Black	27	8.5
Asian/Pacific Islander	26	8.2
Native American/Alaskan	2	0.6
Unknown	0	0.0
Surgery		
Yes	175	55.0
No	143	45.0
Unknown	0	0.0
Radiation		
Yes	253	79.6
No	54	17.0
Unknown	11	3.5
Radiation and surgery		
Yes	142	44.7
No	175	55.0
Unknown	1	0.3
Cohort year		
1973–1986	62	19.5
1987–2010	256	80.5

Additional survival probabilities were estimated with the Kaplan-Meier method in SPSS v.21 software (IBM Corp., Armonk, New York, United States). The Cox regression model was used to estimate hazard rates and their ratios. In general, a hazard rate is the rate of events per person-time follow-up. In this study, the event of interest is mortality, and the hazard rate is thus the mortality rate. A hazard ratio (HR) > 1 indicates the prognostic factor is associated with an increase in the rate of mortality compared with the reference group, whereas an HR < 1 indicates the prognostic factor is

associated with a decrease in the rate of mortality compared with the reference group. The reference group is assigned an HR of 1, and an HR of 1 indicates that the prognostic factor is associated with neither an increase nor a decrease in the rate of mortality compared with the reference group.

Results

Incidence

A total of 318 cases of SNUC were identified. Age-adjusted incidence rate (IR) was 0.02 per 100,000. ►Table 1 shows the patient demographics and treatment characteristics. There were 197 male patients (62%) and 121 female patients (38%). Incidence was greater in males (IR: 0.026) than in females (IR: 0.012; *p* value = 0.03). Mean age of diagnosis was 57.8 years, and the patients were fairly evenly distributed among the age groupings between 20 and 80 years. The majority (82.7%) of patients were identified as white, 8.5% as black, 8.2% as Asian/Pacific Islander, and 0.6% as Native American/Alaskan. Most of the patients (79.6%) were treated with radiation, 55.0% were treated with surgery, and 44.7% received both surgery and radiation.

Survival

Median survival of all patients was 22.1 months. Overall 3-, 5-, and 10-year relative survival for SNUC was 44.3%, 34.9%, and 31.3%, respectively. ►Table 2 illustrates the median, 3-year, and 5-year survival for each prognostic factor variable for SNUC including gender, age, and treatment modality.

►Table 3 illustrates the predictors of mortality for SNUC. Males and females had similar 3-year (44.8% versus 42.5%)

and 5-year (34.7% versus 34.7%) survival probabilities with neither significantly associated with mortality (female HR: 0.95, *p* = 0.71; ►Fig. 1). Patients diagnosed with SNUC after age 60 generally had worse 3-year and 5-year survival than all other age groups (►Table 3). We chose the average age group of diagnosis (age 50–59 years) as the reference group for analysis of the HR. ►Table 3 demonstrates the successive increase in rate of mortality with increasing age. Compared with the reference group, patients 70 to 79 years of age had a 2.73 times greater rate of mortality (*p* < 0.01) and patients >80 years had a 2.67 times greater rate of mortality (*p* < 0.01). Patients 20 to 59 years of age had no difference in mortality rate compared with the reference group (HR: 0.67–1.13; *p* = 0.19–0.87). ►Fig. 2 demonstrates a Kaplan-Meier graph of each age group.

Radiation treatment was associated with significant improvement in survival at 3 years (49.2% versus 27.6%) and 5 years (38.7% versus 23.9%). Patients who had radiation had a 53% decreased mortality rate over those with no radiation (HR: 0.471 *p* < 0.01; ►Fig. 3). For patients who underwent surgery, there was also a trend toward improvement in survival at 3 years (45.1% versus 28.3%) and 5 years (34.1% versus 27.3%) versus no surgery. Patients who had surgery had a 27% decreased mortality versus those with no surgery (HR: 0.73; *p* = 0.06; ►Fig. 4). Surgery in combination with radiation therapy also demonstrated improvement in survival, with a 42% decreased mortality rate when compared with patients who received single modality therapy or no treatment (HR: 0.52; *p* < 0.01; ►Fig. 5). Median survival for surgery combined with radiation was 41.9 months.

Table 2 Survival in sinonasal undifferentiated carcinoma

	Median, mo	3 years, %	SE, % ^a	5 years, %	SE, % ^a
Male	26.8	44.8	4.3	34.7	4.3
Female	18.0	42.5	5.3	34.5.3	5.4
00–19 y	15.0	50.1	25.0	50.1	25.0
20–29 y	28.1	41.0	15.6	20.6	12.9
30–39 y	45.5	60.3	8.6	40.3	9.4
40–49 y	46.1	54.2	8.7	48.0	8.8
50–59 y	30.6	44.0	7.5	35.0	7.9
60–69 y	18.8	42.0	6.5	37.3	6.4
70–79 y	13.6	33.5	8.7	17.5	8.0
80+ y	12.0	12.4	10.9	12.4	10.9
Surgery ^b	23.5	45.1	6.6	34.1	6.3
No surgery ^b	11.8	28.3	7.6	27.4	8.0
Radiation	30.3	49.2	3.8	38.7	3.9
No radiation	9.1	27.6	7.9	23.9	38.1
Surgery and radiation	41.9	57.9	4.5	39.1	5.7
1973–1985	14.5	36.6	7.0	30.5	7.0
1986–2010	23.5	43.9	4.4	34.9	4.3

^aRelative standard error (SE) calculated based on SEER® Stat Database: Survival – Kaplan-Meier Method with Ederer II for expected survival and age-standardized to International Survival Standard 1 for age 15+.

^bIncludes data from 1983 to 2010 only.

Table 3 Predictors of mortality in sinonasal undifferentiated carcinoma

Predictor		HR	HR lower CL	HR upper CL	p value
Sex	Male	1.00			
	Female	0.95	0.71	1.26	0.71
Race	White	1.00			
	Black	0.94	0.57	1.55	0.82
	Asian/Pacific Islander	0.39	0.20	0.74	0.01
	Native American/Alaskan	0.49	0.00	17.2	0.38
Age, y	< 19	1.13	0.27	4.71	0.87
	20–29	1.26	0.55	2.85	0.59
	30–39	0.91	0.53	1.60	0.74
	40–49	0.67	0.39	1.21	0.19
	50–59	1.00	–	–	–
	60–69	1.13	0.72	1.76	0.61
	70–79	2.73	1.65	4.21	<0.01
	80+	2.66	1.58	4.48	<0.01
Surgery	No	1.00	–	–	–
	Yes	0.73	0.52	1.02	0.06
Radiation	No	1.00	–	–	–
	Yes	0.47	0.33	0.67	<0.01
Surgery and radiation	No	1.00	–	–	–
	Yes	0.58	0.44	0.78	<0.01
Cohort year	1975–1986	1.44	1.06	1.97	0.21
	1987–2010	1.00	–	–	–

Abbreviations: CL, confidence limit; HR, hazard ratio.

Survival for SNUC was also seen to improve over time. Median survival from 1973 to 1986 and 1987 to 2010 was 14.5 months and 23.5 months, respectively. A Kaplan-Meier graph illustrating survival difference between cohorts is shown in ►Fig. 6.

Discussion

Overall incidence of SNUC remains low at 0.02 per 100,000 persons, making it a challenging disease process to study.

Fig. 1 Survival functions by sex.

Fig. 2 Survival functions by age.

Fig. 3 Survival functions by treatment with radiation.

The NCI's SEER database used in this study combines data from multiple individual cancer registries, covering ~28% of the US population (SEER 18). To our knowledge, this study provides the largest series of SNUC cases to date and offers new information regarding survival patterns of SNUC in the United States. A drawback of the SEER database is that it does not differentiate between overall and disease-specific survival because cause of death is often unknown. Additionally, the SEER database contains only limited information regarding tumor size, locoregional recurrence, distant metastases, and comorbidities.

Overall 5-year survival for SNUC was found to be 35%, which falls within the wide range of 5-year survival rates from 6.25 to 74% identified in previous studies.^{8,11–15} This survival rate is less favorable than that of other neuroendocrine sinonasal tumors such as esthesioneuroblastoma, neuroendocrine carcinoma, and small cell carcinoma.¹³ In the present study, survival was found to decline with increased age at diagnosis. Compared with a reference group of patient

Fig. 5 Survival functions by treatment with surgery combined with radiation.

50 to 59 years of age (corresponding to the average age of diagnosis), patients had successively worse survival when presenting with SNUC after age 60. Patients diagnosed at ≥ 70 years had a 2.5 times worse mortality rate.

In previous studies, poor prognosis was associated with neck metastases, distant metastases, high-grade tumors with poor differentiation, and positive resection margins.^{12,18} Kadish staging, originally developed for esthesioneuroblastoma,¹⁹ has also been applied to SNUC with lower survival associated with Kadish stage C disease (defined as invasion beyond the nasal cavity and paranasal sinuses into the orbit, skull base, or brain).^{3,5,20} Of note, in the context of aggressive surgical management and multimodality therapy, patients who died of their disease did so within 20 months of treatment, suggesting improved survival for patients with SNUC who reach the 20th month mark.²¹ Survival may also be improved in patients with tumors positive for human papillomavirus (HPV) or that demonstrate p16 expression, as one recent series demonstrated.¹⁵

Fig. 4 Survival functions by treatment with surgery.

Fig. 6 Survival functions by cohort year.

Further study into the role of HPV as a positive prognostic factor is warranted.

Much of the previous SNUC literature comprises small- to medium-size case series that are weakened by heterogeneity in terms of the disease severities combined, the treatment paradigms used, and the outcomes measured.^{3,8} In recent years two meta-analyses have compiled these smaller studies to assess pooled survival outcomes.^{3,8} Combining data from 140 reported cases and 20 cases from their own institution, Xu and colleagues found 1-, 3-, and 5-year survival estimates of 51.2%, 19.4%, and 6.25%, respectively, with both median overall survival and median disease-free survival of 12.7 months. Potentially contributing to the very poor 5-year survival rate observed, the vast majority of the patients included in Xu and colleagues' analysis were diagnosed with advanced disease (87.6% stage IV), and only 39% of cases were treated with both surgery and at least one other mode of treatment (i.e., surgery combined with radiation or surgery combined with chemoradiation).⁸

These two meta-analyses champion multimodality treatment, confirming what was suggested by numerous preceding smaller studies that had been underpowered to reach statistical significance.^{4,22} In Xu and colleagues' meta-analysis, Cox regression analysis demonstrated an overall survival advantage with multimodality treatment ($p = 0.015$).⁸ Reiersen and colleagues (2012) combined data from 167 reported cases to offer further support for multimodality therapy. Patients who underwent surgery as well as radiation and/or chemotherapy experienced a 260% increased chance of survival relative to patients who underwent surgery alone (odds ratio: 2.6; 95% CI, 0.82–7.87).³ The benefit of multimodality therapy appears to be driven by improved outcomes in more advanced disease because patients with Kadish stage C experienced statistically significant improvement in overall survival with trimodal therapy (i.e., surgery, chemotherapy, and radiation) when compared with each as a single modality therapy ($p = 0.015$, <0.01 , and <0.01 , respectively).³

Consistent with previous reports,^{3,8,23} surgery alone had a favorable effect on survival in the present study with an HR of 0.73 (95% CI, 0.52–1.02). One limitation of this study, however, is the inability to distinguish gross total resection from subtotal or partial resection, which could also affect long-term survival rates. Radiation therapy alone also provided a relative overall survival benefit in the present study with an HR of 0.47 (95% CI, 0.33–0.67).

Although the preceding findings demonstrate a survival advantage of single-modality treatment over no treatment, multimodality treatment involving a combination of surgery, radiation, and chemotherapy has become the standard for patients with SNUC.^{3,11} Patients with SNUC receiving surgery combined with radiation had a median overall survival of 41.9 months in this study with an overall survival benefit when compared with single modality or no treatment (HR: 0.58; 95% CI, 0.44–0.78).

Although chemotherapy treatment was not assessed in the present study, SNUC is thought to be sensitive to both induction and concurrent chemotherapy regimens.⁷ Induction chemotherapy usually consists of both platinum

(e.g., cisplatin) and either 5-FU (i.e., fluorouracil) or etoposide, whereas chemotherapy concurrent with radiation may be restricted to platinum alone (e.g., cisplatin) out of concern for tissue toxicity.^{7,11,20} Undifferentiated tumors such as SNUC may not be subject to such rapid deleterious cell repopulation that more differentiated tumors may experience following chemotherapy, and thus they may have an improved response to such treatment.^{7,24} Of further possible benefit, induction chemotherapy may reduce SNUC tumor bulk in areas near vital radiation dose-limiting structures (e.g., optic chiasm) and thus may optimize outcomes achievable with radiation treatment.⁷ Specific chemotherapeutic agents and the distinction between induction and concurrent chemotherapy were not evaluated in the present study because information about their use is not available in the SEER database.

Given the often poor prognosis of SNUC despite aggressive application of currently available treatments, numerous novel therapies have been tried with limited success including neoadjuvant selective intra-arterial cisplatin, autologous bone marrow transplant, and boron neutron capture therapy.⁸ The advent of whole-genome analysis has provided an opportunity to begin to understand abnormalities in the tumor DNA code, which may offer targets for future cancer therapies. Although the recently identified expression of the tyrosine kinase receptor c-KIT was not found to be due to activating mutations or gene amplification, it is possible that tyrosine-kinase inhibitors targeting c-KIT (e.g., imatinib) could play a role in SNUC treatment in the future.²⁵

In evaluating the change in survival patterns over time, this study demonstrates improved survival for patients with SNUC over the past 4 decades. Median survival has increased from 14.5 months in 1973 to 1987 to 23.5 months in 1987 to 2010. Improved surgical techniques, including advances in craniofacial resection²¹ as well as endoscopic approaches to the skull base,²⁶ might play a role in this promising trend. Additionally, the improvement in radiation targeting and safer delivery of higher doses to the skull base may play a role in the observed improvement in survival, particularly for patients where gross total resection was not achieved.¹¹

SNUC continues to provide significant treatment challenges. The advanced stage at presentation, the difficulty achieving tumor resection with negative margins, and the high recurrence rates for SNUC require continued evaluation of our current treatment methods and protocols to improve outcomes. Advancement in surgical techniques, along with a multidisciplinary approach regarding multimodal therapy, should be the foundation of treatment for these complex tumors.

Conclusion

This study provides new data regarding survival patterns of sinonasal undifferentiated carcinoma in the United States, confirming a survival benefit from surgery combined with radiation therapy and identifying a trend toward improved survival in recent decades.

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