Sinonasal Neuroendocrine Carcinoma: A Population-Based Analysis of Incidence and Survival

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ABSTRACT

Introduction: Sinonasal neuroendocrine carcinoma (SNEC) is a rare, aggressive tumor usually associated with a poor prognosis. This study analyzes the clinicopathological characteristics and survival outcomes of SNEC using population-based data.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database (1973-2011) was queried for SNEC cases. Data analyzed included patient demographics, incidence, treatment modality, and survival.

Results: 201 cases of SNEC were identified. Mean age at diagnosis was 55.8 years (±15.7 years). Overall 5-year disease-specific survival (DSS) rate for SNEC was 50.8%. Five-year survival analysis for SNEC by site revealed DSS of 80.7%, 59.2%, 34.5%, and 33.0% for the sphenoid sinus, nasal cavity, maxillary sinus, and ethmoid sinus respectively (p = 0.0014). Cox proportional hazard analysis revealed greater hazard of death for the maxillary (HR 2.14, 95% CI 1.21 – 3.71, p = 0.0094) and ethmoid sinuses (HR 1.83, 95% CI 1.05 – 3.16, p = 0.0345) when compared to the nasal cavity. Advanced stage disease (stages III-IV, 5-year DSS 40.5%, p = 0.0008) was associated with poor survival outcomes. Survival was better among those treated with surgery (with [59.4%] or without [69.0%] radiotherapy) than those treated with primary radiotherapy alone (39.9%) (p < 0.0001).

Conclusions: SNEC commonly presents at an advanced-stage with poor survival outcomes. Negative prognostic factors include primary tumor site and advanced stage disease. SNEC is a highly aggressive tumor necessitating surgery and/or surgery with adjuvant radiotherapy as the treatment of choice.

INTRODUCTION

Within the head and neck region, neuroendocrine carcinoma (NEC) is most commonly found in the larynx, followed by the salivary glands.1 It is rare in the nasal cavity and the paranasal sinuses, accounting for approximately 5% of malignancies at these sites.2,3 The World Health Organization (WHO) classifies NEC into three sub-types: typical carcinoid, atypical carcinoid, and small cell carcinoma, neuroendocrine type.4 NECs have a varied histopathologic spectrum and some authors have suggested sub-classification of these tumors into well-differentiated (typical carcinoid), moderately differentiated (atypical carcinoid) and poorly differentiated neuroendocrine carcinomas. The last category is further subdivided into small cell and large cell variants.1,5 Well-differentiated (typical) and moderately differentiated (atypical) neuroendocrine carcinomas are exceedingly rare in the sinonasal tract, possibly because they are underreported or have been grouped into non-descriptive categories, such as "neuroendocrine carcinoma, NOS." These tumors are otherwise similar to neuroendocrine tumors at other sites.4

Patients with sinonasal NEC (SNEC) typically present with nasal obstruction, epistaxis, nasal drainage and/or facial pain.3 These symptoms overlap with other benign sinonasal diseases such as rhinosinusitis, often delaying diagnosis and appropriate treatment. Well-differentiated and moderately differentiated SNECs are locally aggressive, whereas poorly differentiated SNECs have a tendency to metastasize to cervical lymph nodes, lung, liver, bone marrow and vertebrae.3,4,6 Locally aggressive tumors may invade the skull base, orbit, or brain.4

Since SNEC is a rare entity, the literature is limited to case reports and small retrospective case series.3,5,7-14 The largest SNEC case series reported in the literature to date analyzed only 28 cases.3 Furthermore, some of the SNEC case series published to date had overlapping patient populations.3,5,10 For these reasons, a comprehensive analysis of a large patient population is potentially valuable. To better understand the current epidemiological trends of SNEC, we queried the Surveillance, Epidemiology, and End Results (SEER) database and identified 201 cases of SNEC. In this analysis, we present the incidence of SNEC, organized by patient demographics, treatment modalities, and long-term survival trends.

MATERIALS AND METHODS

Frequency and survival data were obtained from the SEER 18 dataset for years 1973 to 2011, whereas incidence data were obtained from the SEER 9 dataset for years 1986 to 2011. Institutional Review Board approval was not required, as SEER does not report sensitive patient information. We queried the SEER database for sinonasal tract malignancies using International Statistical Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography codes. The codes included were those for structures comprising the sinonasal tract, namely the nasal cavity (C30.0) and paranasal sinuses (C31.0, C31.1, C31.2, C31.3, C31.8 and C31.9). Subsequently, we filtered the results based on ICD-O-3 histology/behavior codes corresponding to typical carcinoid (8240/3), atypical carcinoid (8249/3), small cell neuroendocrine carcinoma (8041/3), large cell neuroendocrine carcinoma (8013/3) and neuroendocrine carcinoma, NOS (8246/3).

Frequency data were stratified and analyzed by age, gender, race, histologic grade, American Joint Committee on Cancer (AJCC) stage, and treatment modality. Incidence data were adjusted to the standard 2000 U.S. population as per Census Current Population Reports and reported per 100,000 people for cases diagnosed between 1986 and 2011. Five-year survival rates were calculated via Kaplan-Meier analysis, yielding disease-specific survival (DSS) rates. Relative survival (RS) for this time interval was represented using the ratio between the observed survival rate and the expected age-adjusted survival rate for a similar segment of the population.

SEER data were extracted using SEER*Stat 8.1.5 (National Cancer Institute, Bethesda, MD) software. Incidence data were analyzed via weighted least squares for annual percent change (APC) using one-year end-points in SEER*Stat 8.1.5 software. Joinpoint Regression Program 4.1.1.1 (National Cancer Institute, Bethesda, MD) was used to calculate annual percentage change in incidence and assess the statistical significance of the trends observed. Survival data from SEER*Stat 8.1.5 were reorganized and reclassified in Microsoft Excel 2013 and then imported into JMP Statistical Discovery 11 (SAS Institute, Cary, NC) for log-rank analysis to generate Kaplan-Meier curves and DSS rates. Cox proportional hazards model was used to calculate hazards ratios at 5-year intervalusing DSS. SEER*Stat 8.1.5 was also used to extract RS data. Probability values (p-value) < 0.05 were considered statistically significant for all tests. For direct pairwise comparisons in data involving three and four groups, significance was set at p < 0.017 and p < 0.0125 respectively using a Bonferroni correction

RESULTS

Analysis of Demographic and Clinicopathologic Factors

A total of 201 cases of SNEC were reported in the SEER database between 1973 and 2011 (**Table 1**). The mean age at diagnosis was 55.8 years with a standard deviation of 15.7 years. Males accounted for 59.2% of cases, while females accounted for 40.8% of cases resulting in a male-to-female ratio of 1.45:1. Whites made up the vast majority of the cases (83.6%), followed by blacks (8.0%) and "others" (8.0%).

The most common location for SNEC was the nasal cavity (40.8%). The ethmoid sinus was the second most common site (20.4%), followed by the maxillary sinus (18.4%) and the sphenoid sinus (12.9%). Only 2.0% of cases were found in the frontal sinus. Cases were also analyzed based on histologic grade into well-differentiated (grade I), moderately differentiated (grade II), poorly differentiated (grade III) and undifferentiated, anaplastic (grade IV) types. The majority of cases (62.7%) belonged to the high histologic grades (grades III and IV). Only 6.5% of the cases were of low histologic grades (grades I and II). Histologic grade information was not available for 30.8% of the cases (**Table 1**).

AJCC staging information was available for 75 (37.3%) out of 201 cases. The majority of cases (53/75 cases, 70.7%) for which staging information was available exhibited advanced stage IV disease at diagnosis. The most common treatment modality was surgical resection with radiotherapy (45.3%), followed by radiotherapy (19.4%) and surgery (14.9%).

Incidence analysis

The overall incidence of SNEC was 0.012 cases per 100,000 population in 1986, and 0.0077 cases per 100,000 population at risk in 2011. Joinpoint regression analysis revealed an increasing incidence of SNEC with the annual percent change (APC) being 1.02%. However, this trend was not statistically significant (p = 0.3931).

Survival analysis

The SEER18 data set was queried for survival data, and 201 cases were identified. Net survival was estimated by calculating both DSS and RS. DSS considers only deaths caused by the cancer of interest. RS is obtained by dividing the overall survival by the expected survival of a comparative segment of the population. RS is the standard measure of net survival in population-based cancer studies.

Kaplan-Meier survival analysis was conducted. Overall 5-year DSS for patients with SNEC was 50.8% (**Table 2**). DSS analysis by gender and race failed to show a statistically significant difference. DSS and RS were calculated for four of the most common primary sites for SNEC, namely the nasal cavity, ethmoid, maxillary and sphenoid sinuses. The sphenoid sinus had a much higher DSS at 5 years (80.7%) compared to any other site. Nasal cavity had a 5-year DSS rate of 59.2%, followed by maxillary (34.5%) and ethmoid (33.0%) sinuses. The log-rank test showed these differences to be statistically significant (p = 0.0014). Kaplan-Meier survival curves are shown in **Figure 1** for these sites. RS was also highest for the sphenoid sinus, with 5-year RS of 71.7%, followed by the nasal cavity (61.8%).

Hazard ratios (HRs) were also generated using DSS and the Cox proportional hazard regression model. Relative to the nasal cavity, involvement of the maxillary (HR 2.14, 95% CI 1.21-3.71, p = 0.0094) and ethmoid (HR 1.83, 95% CI 1.05-3.16, p = 0.0345) sinuses were significantly poor prognostic indicators (**Table 3**). Frontal sinus HR was not calculated due to the small sample size for this site.

Survival was also analyzed by histologic grade, AJCC stage and treatment modality (**Table 4**). Five-year DSS was the highest (92.3%) for low grade SNECs (grades I and II). Grade IV or undifferentiated histologic subtype showed the worst 5-year DSS rate (37.0%). This difference was statistically significant (p = 0.0368). Kaplan-Meier survival curves are shown in **Figure 2** for these histologic grades. Five-year DSS rate for the combined AJCC stages I and II (94.1%) was found to be significantly higher than that for the combined AJCC stages III and IV (40.5%, p = 0.0008) (**Figure 3**). Finally, the 5-year DSS for patients treated with surgery without radiotherapy was 69.0%, whereas that for patients treated with radiotherapy without surgery was 39.9%. Patients treated with both surgery and radiotherapy had a 5-year DSS of 59.4%. Patients that did not undergo surgery or radiotherapy had the poorest survival outcomes (5-year DSS 25.1%). These differences were statistically significant (p < 0.0001) (**Figure 4**).

In other to adjust for multiple comparisons, Bonferroni correction analyses were performed. The Kaplan-Meier survival analyses retained significance for primary sites, AJCC stage, and treatment modality. The statistical significance noted for survival in terms of histologic grades failed to maintain significance after Bonferroni correction.

Because this analysis encompasses almost 40 years and there have been advances in diagnostic and therapeutic modalities, a time-based 5-year survival analysis was performed. This analysis revealed a trend toward increasing survival rate from 1973 to 2011 for SNEC (**Figure 5**). However, this trend was not statistically significant (p = 0.2034).

Table 1 Demographic and clinicopathologic characteristics of sinonasal neuroendocrine carcinoma (SNEC) (1973–2011)

	n	%
Total	**201**	**100**
Mean age at diagnosis, years (± SD)	55.8 (15.7)	
Age groups		
0-19 years	2	1.0%
20-29 years	8	4.0%
30-39 years	23	11.4%
40-49 years	41	20.4%
50-59 years	40	19.9%
60-69 years	50	24.9%
70-79 years	25	12.4%
80+ years	12	6.0%
Gender		
Male	119	59.2%
Female	82	40.8%
Race*		
White	168	83.6%
Black	16	8.0%
Other	16	8.0%
Location		
Nasal cavity	82	40.8%
Ethmoid sinus	41	20.4%
Maxillary sinus	37	18.4%
Sphenoid sinus	26	12.9%
Frontal sinus	4	2.0%
Accessory sinus, NOS	6	3.0%
Overlapping lesion of accessory sinuses	5	2.5%
Histologic grade		
Well differentiated, Grade I	2	1.0%
Moderately differentiated, Grade II	11	5.5%
Poorly differentiated, Grade III	52	25.9%
Undifferentiated, anaplastic, Grade IV	74	36.8%
Unknown	62	30.8%
AJCC Stage†		
I	12	6.0%
II	5	2.5%
III	5	2.5%
IV	53	26.4%
Treatment		
Surgery	30	14.9%
Radiotherapy	39	19.4%
Surgery and radiotherapy	91	45.3%
No surgery or radiotherapy	28	13.9%
Unknown	13	6.5%

* Race was unknown for 1 case
† AJCC Staging information was available for 75/201 cases

Table 2 5-year survival analysis for SNEC by site

Site	n	DSS	p-value	RS
Total	201	50.8%		49.5%
Nasal Cavity	82	59.2%	0.0014*	61.8%
Ethmoid	41	33.0%		31.5%
Maxillary	37	34.5%		29.2%
Sphenoid	26	80.7%		71.7%

*p-value using log-rank test to compare DSS for 4 listed sites is significant
DSS = Disease-specific survival, RS = Relative survival
SNEC = Sinonasal neuroendocrine carcinoma

Table 3 Cox proportion hazards regression of SNEC by site

Site	HR	95% CI	p-value
Nasal Cavity	Ref		
Maxillary	2.14	1.21-3.71	0.0094*
Ethmoid	1.83	1.05-3.16	0.0345*
Sphenoid	0.45	0.13-1.13	0.0950

CI = confidence interval, HR = hazard ratio
SNEC = sinonasal neuroendocrine carcinoma

Table 4 5-year survival analysis for SNEC stratified by histologic grade, AJCC stage and treatment modality

	n	DSS	p-value
Histologic grade			0.0368*
Grades I and II	13	92.3%	
Grade III	52	48.0%	
Grade IV	74	37.0%	
AJCC Stage			0.0008*
I-II	17	94.1%	
III-IV	58	40.5%	
Treatment Modality			<0.0001*
Surgery	30	69.0%	
Radiotherapy	39	39.9%	
Surgery and radiotherapy	91	59.4%	
No surgery or radiotherapy	28	25.1%	

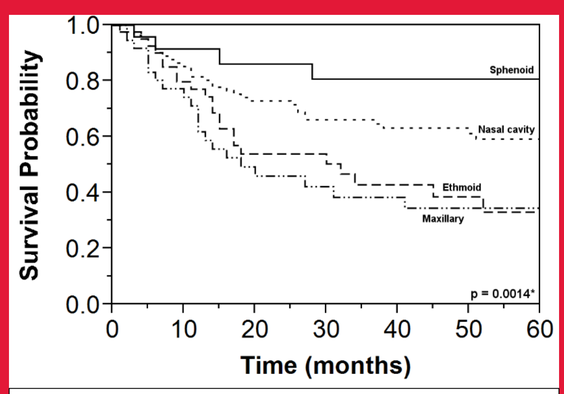

Figure 1. Kaplan-Meier analysis of 5-year disease-specific survival (DSS) for SNEC grouped by **primary site**.

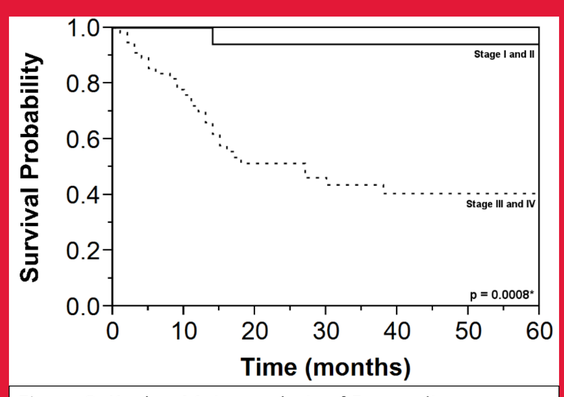

Figure 3. Kaplan-Meier analysis of 5-year disease-specific survival (DSS) for SNEC grouped by **AJCC stage**.

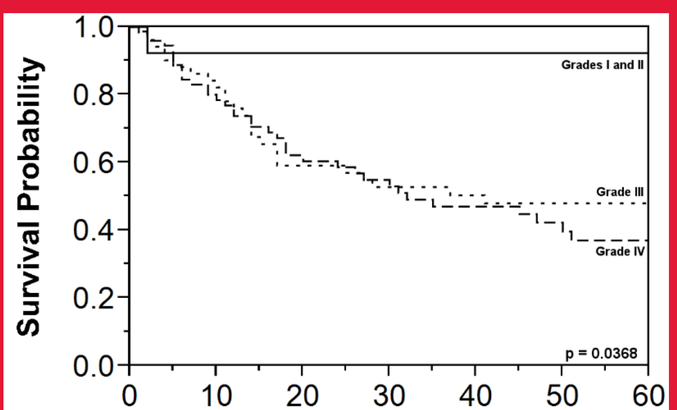

Figure 2. Kaplan-Meier analysis of 5-year disease-specific survival (DSS) for SNEC grouped by **histologic grade**.

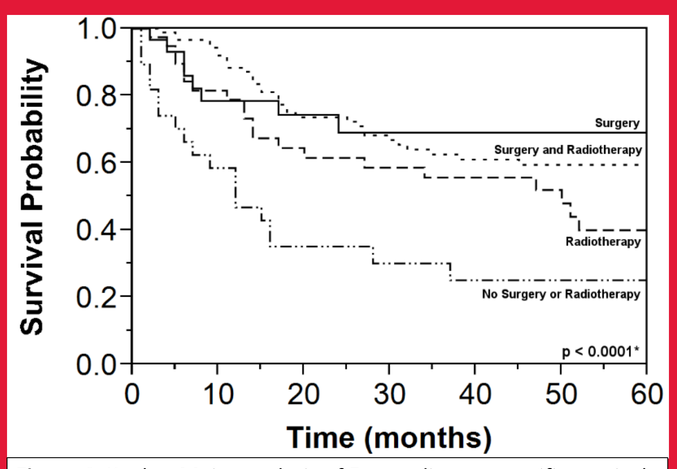

Figure 4. Kaplan-Meier analysis of 5-year disease-specific survival (DSS) for SNEC grouped by **treatment modality**.

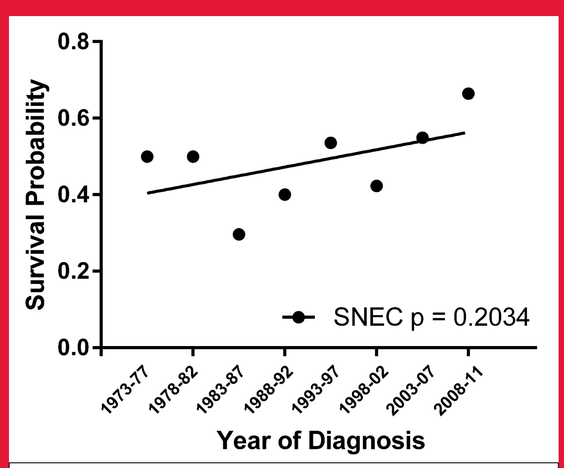

Figure 5. Five-year disease-specific survival by **year of diagnosis** for SNEC. SNEC = Sinonasal neuroendocrine carcinoma.

CONCLUSIONS

SNEC is an exceedingly rare tumor that commonly presents at an advanced-stage and exhibits poor survival outcomes. Poor prognostic factors affecting survival include tumor site (ethmoid and maxillary involvement), advanced AJCC disease stage (stages III and IV) and radiotherapy without surgical resection. We conclude that these tumors are highly aggressive and surgery alone or with radiotherapy should be considered.

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