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Prognostic Factors in Paranasal Sinus Squamous Cell Carcinoma and Adenocarcinoma: A SEER Database Analysis

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Abstract

Background Outcome studies on sinonasal malignancy are limited to retrospective case series, often with inclusion of diverse histology and short follow-up. The objective of this study was to identify key predictive variables that independently impact survival for paranasal sinus squamous cell carcinoma (SCC) and adenocarcinoma (AC) and to compare these variables in the context of these two distinct clinicopathologic entities.

Methods: Analysis was conducted using the Surveillance, Epidemiology, and End Results database from 1973 to 2012 to identify key variables that impact survival for SCC and AC.

Results A total of 3,714 cases were included. There were 2,895 SCC cases and 819 AC cases. The mean age at diagnosis was 64.1 years. The male to female ratio for SCC and AC was 1.85 and 1.04, respectively. Patients with SCC and AC were most often diagnosed with stage IV disease in 61.8 and 63.4% of cases, respectively. The majority of patients received combined surgery and radiation (52% for SCC and 43.1% for AC). For SCC, increased age ($p < 0.001$) and stage ($p < 0.001$) were negative predictors, and surgery improved survival ($p < 0.001$) on multivariate analysis. For AC, prognostic factors associated with worse survival include increased age ($p < 0.001$) and grade ($p < 0.001$) on multivariate analysis. Overall survival was significantly higher in AC compared with SCC at 5 years ($p = 0.001$).

Conclusion SCC and AC of the paranasal sinuses are both aggressive malignancies with poor survival. For both histological subtypes, increased age predicts worse survival and grade also closely links to survival in AC. These data have important potential implications for treatment planning and pretreatment counseling.

Keywords
- sinonasal
- carcinoma
- squamous cell carcinoma
- adenocarcinoma
- outcomes
- prognostic factors

Introduction

Malignancies of the paranasal sinuses are uncommon, with an incidence of 0.556 cases per 100,000, comprising 3 to 5% of primary cancers originating within the head and neck.[1,2] Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the most common histologic subtypes, together accounting for 60 to 70% of primary sinonasal malignancies.[2,3] The maxillary

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and ethmoid sinuses are the most commonly involved primary sites, whereas the frontal and sphenoid locations are observed much less frequently.[2,3] The clinical presentation of paranasal sinus malignancy is often nonspecific, with symptoms such as nasal obstruction, localizing facial pain and pressure, epistaxis, nasal discharge, or epiphora.[4,5] Furthermore, many sinonasal malignancies may remain asymptomatic for a prolonged duration, contributing to advanced disease at initial diagnosis.[6] Their proximity to critical structures, such as the orbit, carotid artery, and brain, and challenges to surgical access within the confines of the relatively small sinonasal tract, further add to the management dilemma.[7,8]

As paranasal sinus malignancies are extremely rare, much of the literature to date is limited to retrospective case series with small sample sizes, often with inclusion of diverse histology with short follow-up. Moreover, many of the studies are performed at a single institution and often present, at best, an anecdotal or biased experience. Indeed, there is a paucity of robust studies reporting treatment options and oncologic outcomes given the rarity of the disease. The objective of this current analysis is to identify key predictive factors that independently impact survival for the two most common paranasal sinus malignancies, SCC and AC, and to compare differences in survival, utilizing the Surveillance, Epidemiology, and End Result (SEER) database. This investigation will evaluate demographics, tumor stage, grade, primary site, and treatment strategy to detect important prognosticators. Accrual of institution-independent data has the potential to guide clinicians in formalizing treatment protocols and counseling patients.

Methods

All available cases of SCC and AC of the paranasal sinus were identified between 1973 and 2012 using all 18 registries of the SEER database. The SEER database, which is maintained and updated annually by the National Cancer Institute (NCI), represents ~28% of the U.S. population, and it contains medical information for more than 8 million cases of cancer diagnosed since 1973.[9] Permission was received from the NCI SEER program for use of the database. The study utilized deidentified population-based data and was exempted from Institutional Review Board approval.

Data collected in this study were standardized using the second and third edition schema for the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).[10,11] The primary sites were restricted to the four major sinus cavities (maxillary sinus [C31.0], ethmoid sinus [C31.1], frontal sinus [C31.2], and sphenoid sinus [C31.3]). Subsequent information was stratified for patient characteristics by age, sex, and race (Caucasian, African American, and other). Tumor characteristics were stratified by histologic grade (I—well differentiated, II—moderately differentiated, III—poorly differentiated, and IV—undifferentiated), American Joint Commission on Cancer, 7th edition tumor stage (I–IV), and primary site (maxillary, ethmoid, frontal, and sphenoid). Tumor-directed treatment was grouped into four categories, including surgery alone, radiation alone, surgery plus radiation, and neither surgery nor radiation.

Statistical Analysis

Data were extracted from the SEER database and organized in Microsoft Excel 2013 (Redmond, Washington, United States). Patients included in the analysis were assigned standard Kaplan–Meier binary assignment, with "1" denoting overall survival (OS) or death from any cause at the time of follow-up, or "0" for disease-specific survival (DSS) or death specifically from malignancy within the follow-up period. Data were analyzed using SEER*Stat software (NCI, Bethesda, Maryland, United States) and SPSS version 17.0 software (SPSS, Inc., Chicago, Illinois, United States). Kaplan–Meier survival analysis was completed using the log-rank test (univariate) and Cox proportional hazards regression analysis (multivariate) with significance level set at $p < 0.05$.

Results

Patient Characteristics

A total of 3,714 cases were identified and included in the study. A breakdown of baseline characteristics is depicted in ►**Table 1**. Histopathologic breakdown comprised 2,895 (77.9%) cases of SCC and 819 (22.1%) cases of AC. The mean age of the entire patient cohort was 64.1 years. Mean age at diagnosis was 65.4 and 59.6 years for SCC and AC patients, respectively. The male to female ratio for SCC and AC groups was 1.82 and 1.06, respectively. SCC affected Caucasians in 75.2%, followed by African Americans in 12.9% of cases. Similarly, AC affected Caucasians in 76.2%, followed by African Americans in 13.2% of patients. For both SCC and AC, the most common site of involvement was the maxillary sinus in 81.2 and 66.3%, respectively. The most common modality of treatment for both SCC and AC was combination of surgery and radiation in 41.3 and 50.1%, respectively. Both SCC and AC were typically found most commonly to be at grade 3 and stage 4 diseases at presentation. OS was 58.6% for SCC and 67.4% for AC at 5 years. At 10 years, OS was 34.7 and 42.0% for SCC and AC, respectively. DSS was 39.1% for SCC and 57.5% for AC at 5 years. At 10 years, DSS was 33.5 and 42.2% for SCC and AC, respectively. ►**Figs. 1** and **2** depict the Kaplan–Meier curves for overall and DSS for both histologic groups.

Statistical and Survival Analysis

Both univariate and multivariate analyses were performed and reported in ►**Tables 2–4**. Multivariate analysis for SCC revealed lower DSS with increasing age and higher stage ($p < 0.001$). Patients who had surgery had improved DSS overall ($p < 0.001$). No racial differences were seen in DSS ($p = 0.09$) on multivariate analysis. For AC, increased age ($p < 0.001$) and higher grade ($p < 0.015$) were associated with worse DSS on multivariate analysis. Location ($p = 0.1$) and stage ($p = 0.2$) were not significant variables. Surgery performed approached significance ($p = 0.058$) on multivariate analysis.

Discussion

This study analyzes a vast population with paranasal sinus SCC and AC using the SEER database gathering data for both malignancies between 1973 and 2012. For patients with SCC, prognostic factors associated with worse DSS include

Table 1 Baseline characteristics for squamous cell carcinoma and adenocarcinoma

Parameter	No. (%)	No. (%)
Race		
White	2,176 (75.2%)	624 (79.2%)
Black	374 (12.9%)	108 (13.2%)
Other	345 (11.9%)	87 (10.6%)
Gender		
Female	1,026 (35.4%)	398 (48.6%)
Male	1,869 (64.6%)	421 (51.4%)
Age		
≤ 40	129 (4.5%)	109 (13.3%)
41–50	281 (9.7%)	134 (16.4%)
51–60	633 (21.9%)	177 (21.6%)
61–70	733 (25.3%)	175 (21.4%)
71–80	702 (24.2%)	140 (17.1%)
≥ 81	417 (14.4%)	84 (10.3%)
Grade		
1	296 (10.2%)	66 (8.1%)
2	898 (31.0%)	111 (13.6%)
3	986 (34.1%)	139 (17.9%)
4	69 (2.4%)	71 (2.1%)
Unknown	646 (22.3%)	432 (52.7%)
Stage		
1	90 (3.1%)	30 (3.7%)
2	64 (2.2%)	25 (3.1%)
3	212 (7.3%)	48 (5.9%)
4	635 (21.9%)	167 (20.4%)
Unknown	1,894 (65.4%)	549 (67.0%)
Site		
Ethmoid	336 (11.6%)	191 (23.3%)
Frontal	68 (2.3%)	17 (2.1%)
Maxillary	2,352 (81.2%)	543 (66.3%)
Sphenoid	139 (4.8%)	68 (8.3%)
Treatment		
Both	1,196 (41.3%)	410 (50.0%)
Neither	303 (10.5%)	66 (8.1%)
Radiation	800 (27.6%)	130 (15.9%)
Surgery	475 (16.4%)	182 (22.2%)
Unknown	121 (4.2%)	31 (3.8%)

increasing age and higher stage, whereas surgery improved outcome. For AC factors that negatively affected DSS were increasing age and grade.

A majority of patients diagnosed with SCC or AC were Caucasian (76.6 and 75.3%). The age of diagnosis for SCC was significantly higher at 65.35 compared with AC at 59.63 ($p < 0.001$). Males were affected more than females for both SCC and AC (1.85:1 and 1.04:1). These finding correlated well with those found in the current literature.[2,4,8,12,13] Other studies have independently examined cancer based on the four major sinuses: frontal, maxillary, ethmoid, and sphenoid. The most common type of cancer of these sites was SCC similar to findings in our study.[14–19]

Previous studies have had a limited scope in characterizing features of paranasal SCC and AC. To our knowledge, no prior study has performed a direct comparison between SCC and AC utilizing multivariate analysis. Ansa et al used the SEER database to gather data for SCC between 1973 and 2009. They noted that the proportion of patients with advanced disease decreased over the past several decades, but survival trends remained unchanged.[12] They also observed that mortality among African American patients also increased after adjusting for age, sex, disease stage, tumor site, and treatment. In contrast, racial disparities in OS and DSS were not observed on the multivariate analysis in this study.

In 2015, Unsal et al used the SEER database to identify 1,180 cases of nasal cavity SCC between 2004 and 2012.[9] Stage I presentation was the most common (53.4%). Most cases had no nodal (90.8%) or distant (1.9%) metastases at presentation.[9] Nonetheless, both regional and distant involvement were deemed poor prognostic factors. Five-year DSS was 69.5% overall, 39.6% in cases with neck involvement, and 0.0% for metastatic cases. Similarly, Michel et al evaluated sinonasal SCC in 33 retrospective cases and found that patients with T1 and T2 diseases had significantly better OS compared with T3 or T4 stage.[20] This study further corroborates these previous observations. Multivariate analysis demonstrated that advanced stage adversely impacted DSS for SCC.

This study also demonstrates that surgery was found to portend higher OS compared with other treatment modalities for paranasal SCC. Current treatment options for paranasal malignancy are a controversial topic.[21] Given proximity to several important structures including the orbit and brain, radiotherapy has not been considered effective as a standalone treatment option.[21] Craniofacial resection, on the contrary, is associated with high morbidity and may require repeat future surgery to correct surgical defects.[21] In select candidates, endoscopic resection of sinonasal SCC has proven to be an effective surgical option with comparable survival to conventional craniofacial resection and reduced complication rate.[22] Several prior studies have shown that surgery or a combination of surgery and radiation has higher OS then radiation alone.[9,14,23] There is currently no randomized trial that has compared the different treatment modalities for paranasal SCC outcomes.

Contrary to SCC, grade was found to be a significant prognostic factor associated with worse DSS in AC. This may be due to the heterogeneity of AC. Sinonasal AC has been divided into multiple subtypes broadly grouped into salivary and nonsalivary type ACs, the latter of which is further subdivided into intestinal type and nonintestinal type ACs.[24] Nonintestinal type AC has been closely linked to grade in which high-grade variants are associated with worse prognosis.[25] As the SEER database does not provide subtype differentiation of AC, the reported effect of grade is possibly due to the inclusion of nonintestinal type AC. This

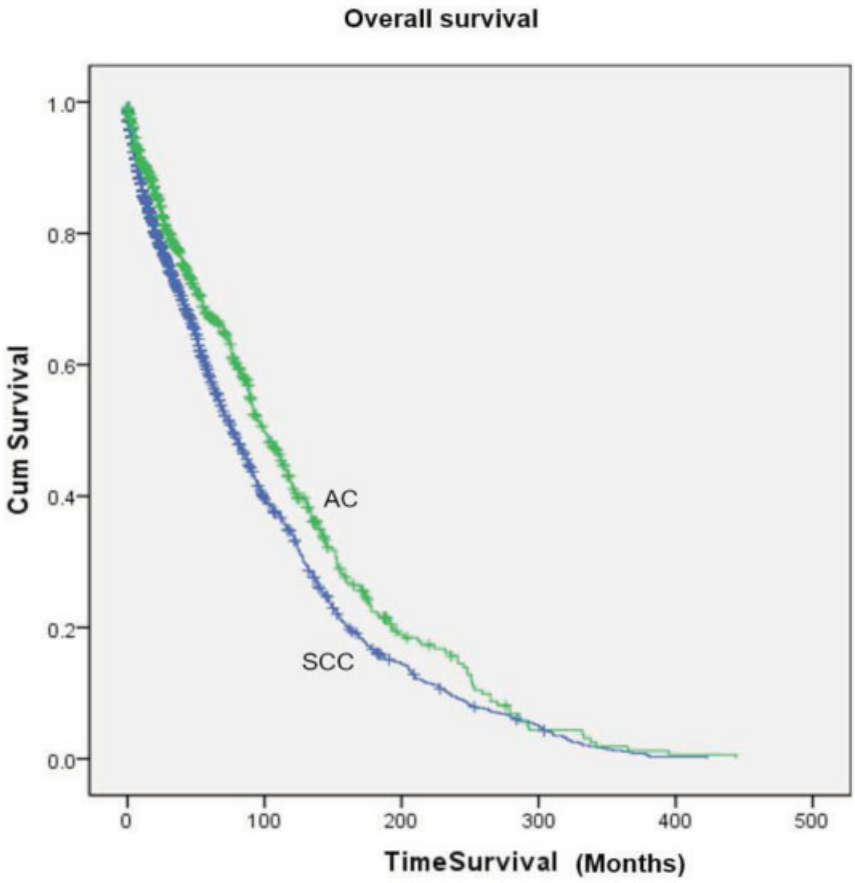

Fig. 1 Overall survival for squamous cell carcinoma (SCC) and adenocarcinoma (AC).

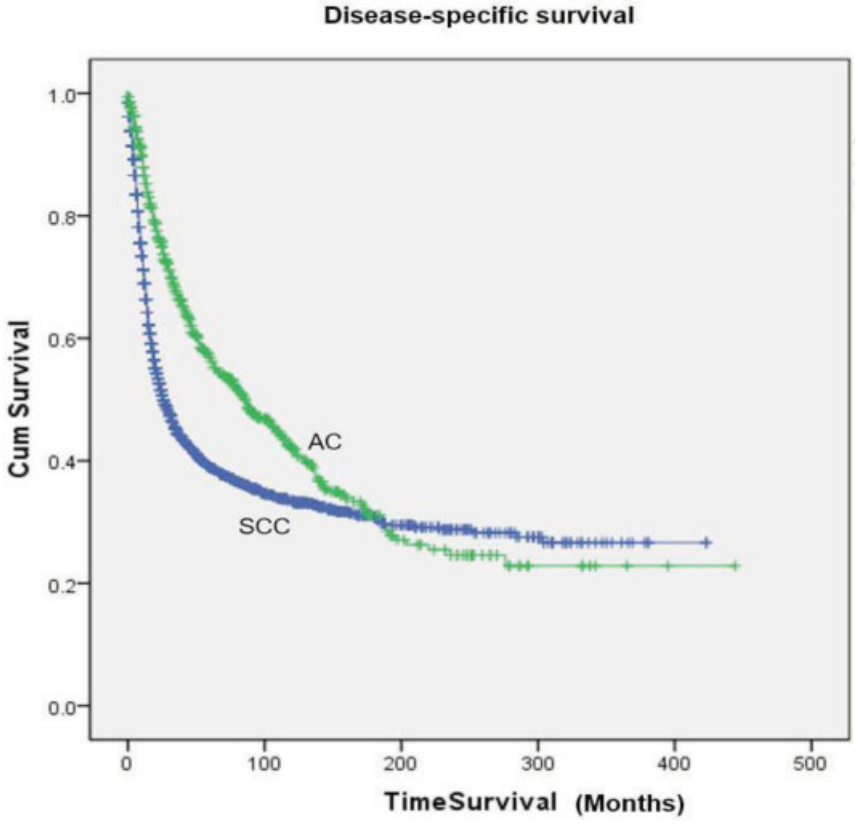

Fig. 2 Disease-specific survival for squamous cell carcinoma (SCC) and adenocarcinoma (AC).

Table 2 Univariate OS and DSS for SCC and AC

Characteristic	OS (log-rank *p*)		DSS (log-rank *p*)	
	SCC	AC	SCC	AC
Age	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Sex	0.863	0.720	0.792	0.652
Race	**0.012**	0.505	**<0.001**	0.298
Surgery	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Radiation therapy	0.686	0.058	0.576	0.173
Surgery and radiation	**0.004**	**0.001**	**<0.001**	**0.041**
Stage	**0.038**	0.263	**<0.001**	**0.021**
Primary site	0.329	0.096	0.708	**0.047**
Grade	**0.002**	0.103	0.289	**<0.001**

Abbreviations: AC, adenocarcinoma; DSS, disease-specific survival; OS, overall survival; SCC, squamous cell carcinoma.
Note: Bold denotes values of statistical significant difference.

may not explain the full effect; however, as nonintestinal type AC compromises ~13% of sinonasal AC, the effect of grade may be also factor in the remaining subtypes.[26]

Examination of prognostic factors revealed that for both paranasal AC and SCC, advanced age was associated with worse DSS. Ansa et al posit that elderly patients with cancer are often undertreated compared with younger patients.[12] This can partially be due to the higher prevalence of comorbidities in this population, but other factors that can contribute include patient preference, lack of regimen-specific data on efficacy, or tendency for clinicians to treat according to chronological rather than physiological age.[12]

To our knowledge, this is the first large-sized population study that examines prognostic factors associated with paranasal SCC and AC using multivariate analysis. Previously, Ganly et al examined prognostic factors for DSS in patients with paranasal sinus cancer as a whole. Similar to our study, their article shows that gender does not portend worse outcomes. Unlike our study, they did not find any significant difference in 5-year DSS in patients younger than and older than 50 years. Our study differs in this regard, which is likely secondary to the multivariate analysis performed on this variable and this study increased stratification of age.[27] The SEER database has more than 8 million cases and incorporates ~28% of the U.S. population. This database provides well-validated data that contains clinical relevant information regarding malignancies. However, there are few inherent limitations to use of this database. One limitation includes the lack of data regarding chemotherapy use or specifics about the radiation protocol. The staging information used in this article was performed using the American Joint Commission on Cancer, 7th edition tumor stage developed in 2010. As a result, staging information from patients in the database is unavailable from 1973 to 2009 (~65.4 and 67% for SCC and AC, respectively). The SEER database also does not contain information regarding socioeconomic status or health insurance, which determines health care access and in turn affects OS. In addition, management and technological advancements have changed substantially

Table 3 Multivariate OS and DSS for SCC

Characteristic	OS	*p*-Value	DSS	*p*-Value
	HR (95% CI)		HR (95% CI)	
Overall ($n = 15{,}832$)				
Age	1.008 (0.99–1.02)	0.068	**1.017 (1.01–1.03)**	**<0.001**
Race	0.953 (0.81–1.12)	0.553	1.015 (0.86–1.19)	0.858
Surgery performed	**0.778 (0.61–0.99)**	**0.049**	**0.539 (0.42–0.69)**	**<0.001**
Stage	1.059 (0.94–1.19)	0.340	**1.321 (1.13–1.54)**	**<0.001**
Grade	1.010 (0.88–1.16)	0.887	1.137 (0.97–1.33)	0.107

Abbreviations: CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival.
Note: Bold denotes values of statistical significant difference.

Table 4 Multivariate OS and DSS for adenocarcinoma

Characteristic	OS	*p*-Value	DSS	*p*-Value
	HR (95% CI)		HR (95% CI)	
Overall ($n = 15{,}832$)				
Age	1.006 (0.99–1.02)	0.399	**1.039 (1.01–1.07)**	**0.004**
Primary site	0.758 (0.47–1.22)	0.251	0.974 (0.41–2.29)	0.951
Surgery performed	1.145 (0.63–2.08)	0.655	0.465 (0.21–1.03)	0.058
Stage	0.907 (0.74–1.11)	0.907	1.364 (0.86–2.17)	0.188
Grade	**1.284 (1.02–1.62)**	**0.034**	**1.650 (1.10–2.47)**	**0.015**

Abbreviations: CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival.

throughout the past 39 years. The SEER database does not specify the type of surgical intervention utilized and includes noncurative biopsies, open surgery, and endoscopic minimally invasive approaches. In addition, several known factors including margin status, orbital involvement, and intracranial involvement are not available in the SEER database. These variables have previously been shown to be predictors for 5-year DDS.[27] Furthermore, several factors play a role in a surgeon's decision on whether to operate on a sinonasal tumor, which are not available in the SEER database. Therefore, the decision to operate should be based on the clinical context and the surgeon's expertise. Nonetheless, the study serves to provide a high-level overview of the key clinical characteristics for SCC and AC and factors impacting OS and DSS. As such, it should provide clinicians with salient data to guide clinical decision making and patient counseling in the care of these patients.

Conclusion

SCC and AC of the paranasal sinuses are both aggressive malignancies with poor survival. For both histological subtypes, increased age predicts worsened survival, while gender and race did not impact survival. Further, advanced stage and higher grade were closely linked to survival in SCC and AC, respectively. These data have important potential implications for patient treatment plan.

Note

This study was presented as a poster presentation at the ARS 61st Annual Meeting, September 25–26, 2015, in Dallas, Texas, United States.

Conflict of Interest

Dr. Batra reports grants from Medtronics, consultant from Acclarent, and royalties from Springer. All the other authors report no conflict of interest.

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