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Adenocarcinoma of the Sinonasal Tract: A Review of the National Cancer Database

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Abstract

Background Sinonasal adenocarcinoma (SNAC) is a rare malignancy arising from mucus-secreting glandular tissue. Limited large-scale studies are available due to its rarity. We evaluated SNAC in the National Cancer Database (NCDB), a source that affords multi-institutional, population studies of rare cancers and their outcomes.

Methods The NCDB was queried for adenocarcinoma in the sinonasal tract. Multivariate analyses were performed to evaluate for factors contributing to overall survival (OS).

Results A total of 553 patients were identified. The cohort was composed of 59.3% males. The nasal cavity was the most common primary site, representing 44.1% of cases. About 5.7% of patients presented with nodal disease, while 3.3% had distant metastases. About 40.6% of cases presented with stage IV disease. About 73.5% of patients underwent surgery, 54.2% received radiation therapy, and 27.7% had chemotherapy. Median OS was 71.7 months, while OS at 1, 2, and 5 years was 82, 73.0, and 52%, respectively. On multivariate analysis, advanced age (hazard ratio [HR]: 1.04; 95% confidence interval [CI]: 1.02–1.05), Charlson–Deyo score of 1 (HR: 1.99; 95% CI: 1.20–3.30), advanced tumor grade (HR: 2.73; 95% CI: 1.39–5.34), and advanced tumor stage (HR: 2.71; 95% CI: 1.33–5.50) were associated with worse OS, whereas surgery (HR: 0.34; 95% CI: 0.20–0.60) and radiation therapy (HR: 0.55; 95% CI: 0.33–0.91), but not chemotherapy (HR: 1.16; 95% CI: 0.66–2.05), predicted improved OS.

Conclusions SNAC is a rare malignancy with 5-year survival approximating 50%. Surgery and radiation therapy, but not chemotherapy, are associated with improved survival, and likely play a critical role in the interdisciplinary management of SNAC.

Keywords

- National Cancer Database
- sinonasal adenocarcinoma
- skull base
- cranial base
- nose and paranasal sinuses
- outcomes/cost-effectiveness

Introduction

Sinonasal adenocarcinoma (SNAC) is a tumor arising from either the surface respiratory epithelium or underlying seromucinous glands in the nasal cavity and paranasal sinuses.[1] SNAC is broadly categorized into salivary-type and nonsalivary type, with the latter further defined as either intestinal-type or nonintestinal type.[2] Adenocarcinoma is the second most common primary malignant neoplasm of the sinonasal tract, accounting for 10 to 20% of cases.[3,4] Nevertheless, with an annual incidence of only 0.44 per million in the US population, SNAC represents a rare tumor, and, therefore, elucidating key determinants of patient survival is challenging.[2]

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When symptomatic, SNAC typically presents with vague and nonspecific symptoms, such as nasal obstruction, rhinorrhea, and facial pain, often leading to late-stage diagnosis.[5,6] Some studies have shown that SNAC has a predilection for the ethmoid sinuses compared with other anatomical subsites along the sinonasal tract.[7,8] Numerous case series have reported occupational exposures, including wood dust, varnishes, synthetic paints, and adhesives, as key risk factors for SNAC.[9,10] These reports have also demonstrated that males are more commonly affected, attributed to the male-dominated occupations with carcinogenic exposure.[7]

Although not formally tested in rigorous randomized controlled trials, the general consensus for the treatment of SNAC is primary surgical resection with postoperative radiotherapy.[11,12] SNAC 5-year overall survival (OS) rates vary widely among studies, ranging from 36 to 86%.[13] However, descriptive case series differ on exact combinations of treatment modalities. While case series such as these are important when investigating specific risk factors and single-institutional experiences, multicenter retrospective analyses of registry data afford greater generalizability and statistical power to observations of rare cancers such as SNAC.

Two studies have reported on SNAC cases documented in the U.S. National Cancer Institute Surveillance, Epidemiology, and End Result (SEER) database.[2,14] These reports represent the only large-scale analyses of the North American SNAC population. While D'Aguillo et al focused on demographic characterization of SNAC,[14] Kılıç et al also included clinicopathologic, and histological characteristics.[2] To date, no SNAC study has leveraged the National Cancer Database (NCDB) registry. An advantage of the NCDB over other registry data sources, such as SEER, is that it captures nearly 70% of all incident cancers in the United States and includes more complete patient information, such as chemotherapy status.[15] Moreover, to be accredited as a participating facility, the NCDB mandates 90% or greater annual follow-up among patients.[15] Given the untapped value in the NCDB as it relates to this rare neoplasm, we sought to query this database to further characterize SNAC and evaluate independent determinants important for patient OS.

Materials and Methods

Data Source

Data were obtained from the NCDB for patients with tumors of the head and neck diagnosed between 2004 and 2012. The NCDB was established in 1989 and is jointly sponsored by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB is a nationwide, facility-based, comprehensive clinical surveillance resource oncology dataset that includes more than 34 million records that represent ~70% of incident cancer cases in the United States, diagnosed at over 1500 CoC-accredited programs.[15] The use of this registry was deemed exempt from review by the institutional review board of the primary institution, as the database is publicly available and contains completely deidentified information. The American College of Surgeons and the CoC have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigative team.

Study Population

The NCDB was queried for cancers of the nasal cavity and paranasal sinuses (location codes: C300, C310, C311, C312, C313, C318, C319) with the histology code corresponding to adenocarcinoma (8200). Cases were excluded if no values were available for either follow-up or vital status, or if surgery was performed at a distant site to avoid confounding of surgical procedures other than at the primary site.

Variables Analyzed

Variables included in the Cox proportional hazard model for OS were age, insurance status, tumor grade, tumor stage, presence of metastasis, days from diagnosis to treatment, and treatment modality. The Charlson–Deyo comorbidity score was also included in the Cox proportional hazard model. The Charlson–Deyo comorbidity score is computed using an abbreviated version of the Charlson Comorbidity score drawn from weighted select secondary diagnosis codes from the International Classification of Disease—9th edition, Clinical Modification. Patients with none of the select secondary diagnosis codes receive a Charlson–Deyo score of 0. Patients with a Charlson comorbidity score of 1 or 2 receive a Charlson–Deyo score of 1 or 2, respectively, while patients with a Charlson comorbidity score of 3 or greater receive a Charlson–Deyo score of 3.

Statistical Analysis

The primary outcome measure was OS, defined as time from initial diagnosis to death of any cause. Kaplan–Meier survival functions were calculated and univariate analysis of covariates associated with OS was determined using the log-rank test. Multivariable analyses were conducted using Cox proportional hazard models and included those variables of clinical significance and those with $p < 0.25$ on univariate analysis.[16] The use of multivariate analysis allows for determination of independent prognosticators of OS. Statistical analysis was performed with R version 3.4.1 (https://cran.r-project.org) via RStudio version 1.1.23 (RStudio, Boston, Massachusetts, United States) and SPSS 21 (IBM Corporation, Armonk, New York, United States) software.

Results

Demographics

A total of 553 patients diagnosed with SNAC were identified in the NCDB. Demographic data for the final cohort are detailed in ►**Table 1**. Mean age at diagnosis was 61.8 years, and the cohort was 59.3% male, resulting in a 1.46:1.00 male-to-female ratio. The vast majority of SNAC occurred in whites (81%), with blacks representing the second most commonly affected race (15%). The most common primary site was the nasal cavity (44.1%) followed by the maxillary sinus (24.4%), and then ethmoid sinus (21.0%). Among the included patients, 48.1% received their care in an academic or research-affiliated

Table 1 Patient demographics

Mean (±SD) age	61.8 ± 16.6
Sex	
Female	40.7% (225)
Male	59.3% (328)
Race	
White	81.2% (441)
Black	15.3% (83)
Asian	3.1% (17)
Other	0.4% (2)
Primary site	
Nasal cavity	44.1% (244)
Maxillary sinus	24.4% (135)
Ethmoid sinus	21.0% (116)
Frontal sinus	0.9% (5)
Sphenoid sinus	2.9% (16)
Overlapping lesion of sinuses	1.3% (7)
Accessory sinus, NOS	5.4% (30)
Facility type	
Community	7.1% (35)
Comprehensive community	36.3% (179)
Academic/Research	48.1% (237)
Integrated system	8.5% (42)
Geography	
Northeast	20.6% (102)
South	31.7% (157)
Midwest	32.9% (163)
West	14.7% (73)
Insurance status	
Uninsured	5.8% (31)
Private insurance	45.2% (243)
Medicaid	5.6% (30)
Medicare	42.4% (228)
Other government	1.1% (6)
Median annual income	
< $30,000	14.2% (76)
$30,000–$35,000	17.4% (93)
$35,001–$50,000	28.7% (154)
> $50,000	39.7% (213)

Abbreviations: NOS, not otherwise specified; SD, standard deviation.

Table 2 Tumor characteristics

T	
1	27.2% (103)
2	18.7% (71)
3	17.2% (65)
4	36.9% (140)
N	
0	94.3% (346)
1	1.9% (7)
2	3.8% (14)
M	
0	96.7%% (462)
1	3.3% (16)
Stage	
I	25.4% (95)
II	17.4% (65)
III	16.6% (62)
IV	40.6% (152)
Grade	
Well differentiated	26.9% (119)
Moderately differentiated	30.7% (136)
Poorly differentiated	35.7% (158)
Undifferentiated	6.8% (30)
Lymphovascular Invasion	
Yes	11.4% (10)
No	88.6% (78)
Mean size (millimeters ± SD)	41.1 ± 21.3

Abbreviations: M, metastasis; N, node; SD, standard deviation; T, tumor.

medical center, located across a broad geography across the United States.

Tumor Characteristics

Tumor characteristics are listed in ►**Table 2**. TNM classification and tumor staging, defined by the American Joint Committee on Cancer (AJCC) 6th and 7th edition staging systems for head and neck cancers, were available for 374 patients. Cases in this cohort demonstrated a predominance of stage IV disease (40.6%); however, only 5.7% of patients presented with nodal disease, and 3.3% had evidence of distant metastases. In terms of grade, 26.9% of tumors were well differentiated, while, 30.7 and 35.7% were moderately or poorly differentiated, respectively.

Treatment Characteristics

As demonstrated in ►**Table 3**, the majority of patients (73.5%) underwent surgical resection as part of their primary management and a significant portion of patients required primary, neoadjuvant, or adjuvant radiation therapy (54.2%) or chemotherapy (27.7%). The most common treatment modality sequence was surgery with adjuvant radiation therapy (37.2%), while 12.3% of patients underwent surgery with adjuvant chemotherapy and 9.8% underwent surgery with adjuvant radiation and chemotherapy. Margin status was negative in 74.9% of cases. Mean duration of follow-up was 38.8 months with standard deviation 30.9.

Table 3 Disease and treatment characteristics

Mean ± SD Months of Follow-Up	38.8 ± 30.9
Charlson–Deyo Score	
0	80.3% (444)
1	16.3% (90)
2	3.4% (19)
Treatment	
Surgery	73.5% (403)
Radiation therapy	54.2% (291)
Chemotherapy	27.7% (134)
Combo treatment sequence	
XRT then surgery, no chemo	2.1% (11)
Surgery then XRT, no chemo	37.2% (198)
Chemo then surgery, no XRT	2.3% (10)
Surgery then chemo, no XRT	12.3% (53)
CXRT then surgery	0
Surgery then CXRT	9.8% (49)
Margins	
Positive	25.1% (74)
Negative	74.9% (221)
Mean days from diagnosis to treatment	28.5 ± 41.3
Mean days of postoperative LOS	6.6 ± 11.2
Mean (cGy) total radiation dose	5449 ± 1304

Abbreviations: Chemo, chemotherapy; CXRT, combined chemo- and radiation therapy; cGy, centigray; LOS, length of stay; XRT, radiation therapy.

Survival

The median OS in the entire cohort was 71.7 months, while OS at 1, 2, and 5 years was 82, 73.0, and 52%, respectively (►**Fig. 1**). On multivariable analysis, worse OS was associated with Charlson–Deyo score of 1 or greater ($p = 0.012$), advanced age ($p < 0.001$), and advanced tumor grade ($p = 0.015$) and stage ($p < 0.001$) (►**Table 4**).

All-cause mortality was greater for patients with Charlson–Deyo comorbidity score of 1 compared with 0 (HR: 1.99; 95% confidence interval [CI]: 1.20–3.30) but was not significantly different for patients with Charlson–Deyo score of 2 compared with 0. OS by tumor stage and grade is shown in ►**Fig. 2**. The multivariable model demonstrated that stage IV disease was associated with significantly worse OS compared with stage I (HR: 2.71; 95% CI: 1.33–5.50) and that poorly differentiated tumors were associated with significantly worse OS compared with well-differentiated tumors (HR:2.73; 95% CI: 1.39–5.34). Stage II and III did not reach significance on multivariate analysis when compared with stage 1, nor did moderately-differentiated and undifferentiated tumors when compared with well-differentiated tumors. Both surgery (HR: 0.34; 95% CI: 0.20–0.60) and radiation therapy (HR: 0.55; 95% CI: 0.33–0.91) were significantly associated with increased OS, but chemotherapy was not (HR: 1.16; 95% CI:0.66–2.05; $p = 0.635$) (►**Fig. 3**).

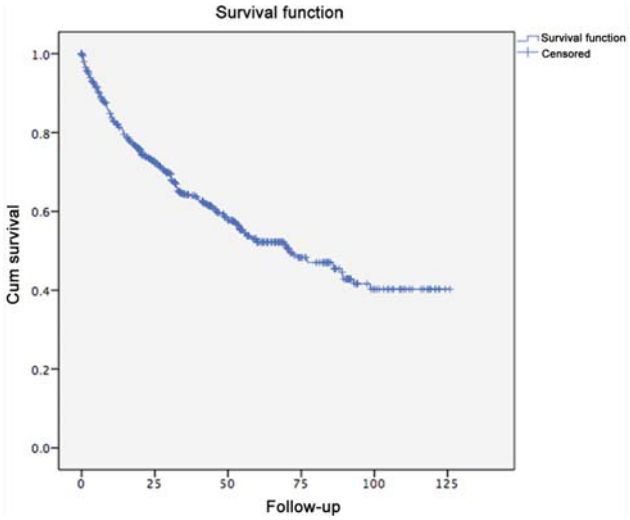

Fig. 1 Kaplan–Meier curve for overall survival of patients with sinonasal adenocarcinoma. Duration of follow-up is in months.

Table 4 Predictors of all-cause mortality

	OS	
Characteristic	**HR (95% CI)**	***p*-Value**
Advanced age	1.04 (1.02–1.05)	<0.001[a]
Insurance status		0.084
Charlson–Deyo score		0.012[a]
0	Reference	
1	1.99 (1.20–3.30)	0.008[a]
2		0.090
Grade		0.015[a]
Well-differentiated	Reference	
Moderately differentiated		0.257
Poorly differentiated	2.73 (1.39–5.34)	0.004[a]
Undifferentiated		0.349
Stage		<0.001[a]
I	Reference	
II		0.512
III		0.656
IV	2.71 (1.33–5.50)	0.006[a]
Days from diagnosis to treatment		0.892
Surgery	0.34 (0.20–0.60)	<0.001[a]
Radiation therapy	0.55 (0.33–0.91)	0.020[a]
Chemotherapy		0.635

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.
[a]Statistically significant.

Discussion

Prior studies of SNAC have aimed to determine factors that yield prognostic insight. However, the vast majority of the literature surrounding this rare malignancy describes case series, often in

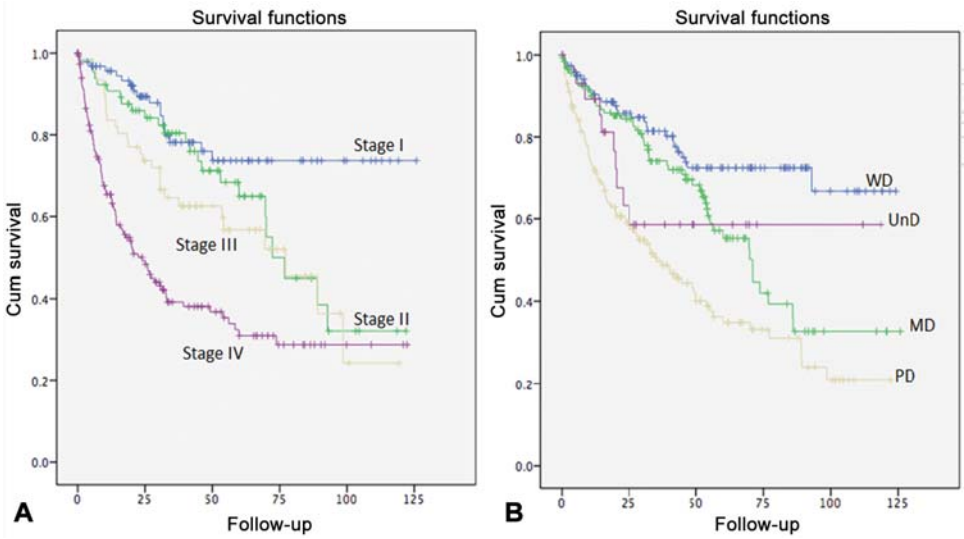

Fig. 2 Overall survival of patients with sinonasal adenocarcinoma by (**A**) tumor stage and (**B**) tumor grade. MD, moderately differentiated, PD, poorly differentiated; WD, well differentiated, UnD, undifferentiated.

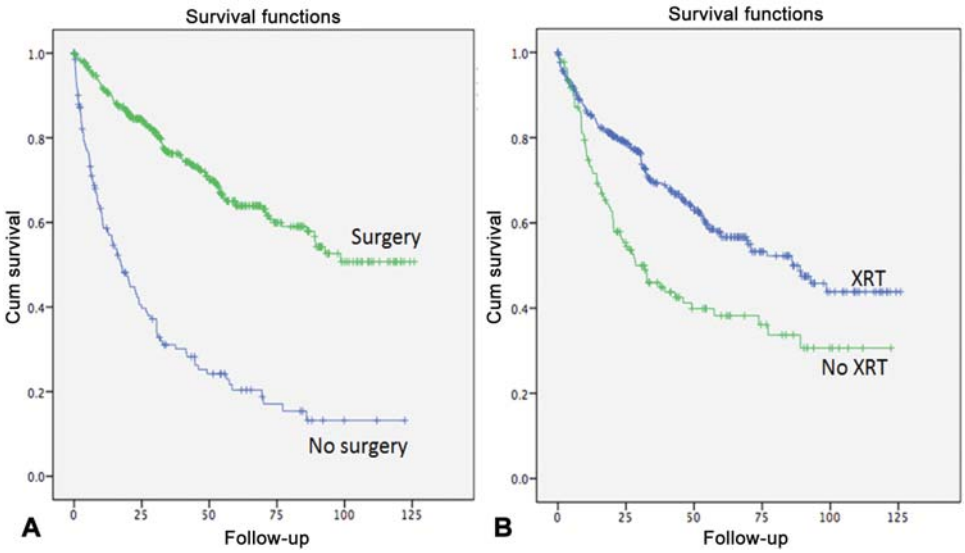

Fig. 3 Overall survival of patients with sinonasal adenocarcinoma by treatment modality. (**A**) Kaplan–Meier curves showing surgery versus no surgery. (**B**) Kaplan–Meier curves showing radiation therapy (XRT) versus no radiation therapy (No XRT). Duration of follow-up is in months.

European populations or from limited geographic regions in which a known exposure has occurred. Larger retrospective studies, such as those reporting on the SEER registry, describe a more heterogeneous patient population that affords greater generalizability. To our knowledge, the present study represents the first comprehensively large-scale retrospective analysis of the NCDB, which examines SNAC patient, tumor, and treatment factors and their relationship to OS.

SNAC classically has been described as a tumor disproportionately affecting males, with most studies reporting a 6:1 male-to-female ratio.[5–7] The present study found a 1.46:1 male-to-female ratio. This finding falls more in line with SEER database studies, which have reported a 1.06:1.00[14] and 1.39:1.00[2] male-to-female ratio. A possible explanation for this variation may be the fact that registry data minimizes selection bias. Therefore, spontaneous adenocarcinomas, which are not confounded by male-dominated occupational exposures, are comprehensively captured in registry databases, thus reducing geographical site-selection bias. Likewise, case series have traditionally reported a predilection of SNAC for the ethmoid sinuses.[7,8,17] In the NCDB, we found that the nasal cavity, followed by the maxillary sinuses, are the most common sites of SNAC. Given that ethmoidal SNAC has been linked to exposure-associated disease, we again can see how a more comprehensive study in the North American population can differ from prior literature.

Overall, primary sinonasal malignancies are rare pathologies, accounting for only 1 to 3% of all head and neck cancers.[18,19] Even among sinonasal cancers, SNAC is the second most common malignancy, and therefore represents a rare tumor overall. This necessitates an evidenced-based approach to more efficiently and effectively treat SNAC patients, with the

simultaneous challenge of generating adequately powered studies to understand what factors determine outcomes.

Five-year survival data for SNAC have been heterogeneous in prior reports, ranging from 36 to 86%.[13] Some investigators have made the argument that survival has improved in more recent decades, with reports ranging from 66 to 84%.[6,13] In support, Turner and Rey reported that SNAC 5-year survival has been improving over the past three decades.[20] However, other studies have failed to demonstrate this trend.[7,21] In the present NCDB analysis, we report a 5-year OS of 52%, which is within the range found in literature, but falls on the lower end of the spectrum. Our results also corroborate SEER analyses that report 5-year disease-specific survival of 65.2[14] and 63.8%[2] from 1973 to 2009.

To further evaluate which factors portend worse survival outcomes, we utilized a multivariate Cox proportional hazard model. We found that AJCC stage and tumor grade predict survival, which is consistent with the SEER analyses and other multicenter studies.[2,7,11,14] When considering the clinical management of SNAC, the gold standard—largely based on large-volume, institutional experiences—continues to be surgery with radiotherapy.[4,22] Data in the NCDB support that both surgery and radiotherapy significantly improve patient OS.

Interestingly, we found that chemotherapy was administered to a sizable minority of SNAC patients (27.7%); however, on multivariate analysis, the use of chemotherapy was not significantly related to an improvement in survival. Several reports in the literature describe the use of systemic[23–25] and even selective intra-arterial chemotherapies[26] to treat SNAC; nevertheless, none demonstrates overwhelming success. The question is further confounded by the lack of a universally selected chemotherapy agent.[4] Limited case reports have focused specifically on the use of chemotherapy on intestinal type adenocarcinoma; however, no standardized regimen has been adopted.[27–30] Further analysis on the use of chemotherapies in certain histopathologies of SNAC is certainly warranted. As additional studies elucidate SNAC pathogenesis, more targeted use of therapies may find a role in treatment.[29,31] In the meantime, the data in the present study do not necessarily support or refute the use of chemotherapy in the treatment paradigm of SNAC.

While analysis of the NCDB provides a robust set of SNAC patients from which we can draw insights to help guide clinical decision making, several limitations inherent to all population-based studies exist. For instance, confounding has been shown to be an issue due to the clinically relevant variables that may not be available for analysis in the NCDB.[32] It could be the case that extenuating circumstances, such as prior-treatment regimens or misdiagnoses, were correlated with particular metrics in the NCDB, but were not themselves uniformly recorded in the database. Another limitation of our study is the fact that the NCDB pools data from various centers, each with variable data collection standards. Beyond defined histologic diagnosis codes, there is no additional information provided in most databases regarding specific tumor subtypes and genetic mutations. In the NCDB, no information on disease-specific survival is available for review. These limitations are tradeoffs that must be considered in the effort to perform large population-based studies. The results of our analysis are meant to guide clinical decision-making and even springboard more nuanced investigation of SNAC.

Conclusion

SNAC is a rare primary malignancy with 5-year survival approximating 50%. A significant proportion of patients presents with advanced disease. Advanced tumor stage and grade predict worse outcomes. Surgery and radiation therapy, but not chemotherapy, are associated with improved survival, and likely play a critical role in the interdisciplinary management of this disease.

Funding and Conflicts of Interest
The authors have no funding, financial relationships, or conflicts of interest to disclose.

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