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Impact of Clinical Factors and Treatments on SMARCB1 (INI-1)-Deficient Sinonasal Carcinoma

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Abstract

The objective of this study was to report outcomes for 19 consecutive patients with SMARCB1 (INI-1)-deficient sinonasal carcinoma. Patients were treated from 2014 to 2021 and followed for a median of 22.3 months. The median overall survival (OS) and disease-free survival (DFS) were 31.8 and 9.9 months, respectively. Patients with nasal cavity or maxillary sinus tumors had 84% better disease-specific survival (DSS) (hazard ratio [HR], 0.136; 95% confidence interval [CI], 0.028-0.66; $p = .005$) and 71% better DFS (HR, 0.29; 95% CI, 0.097-0.84; $p = .041$) than patients with other sinonasal sites. Patients who received induction chemotherapy were 76% less likely to die of disease (DSS HR, 0.241; 95% CI, 0.058-1.00; $p = .047$). In the largest single-institution study of SMARCB1-deficient sinonasal carcinoma to date, OS and DFS approached 3 years and 1 year, respectively, but were better for nasal cavity and maxillary sinus tumors. Patients may benefit from induction chemotherapy.

Keywords

carcinoma, induction chemotherapy, INI-1, sinonasal, SMARCB1

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SMARCB1 (INI-1)-deficient sinonasal carcinoma was first described in 2014.[1,2] It is named after the loss of the *SMARCB1* tumor-suppressor gene on chromosome 22q11.2. Survival is generally poor, but with less than 200 cases reported worldwide, data on which factors affect prognosis are limited.[2-8] The optimal treatment for SMARCB1-deficient sinonasal carcinoma has not been defined. Recent studies have reported improved survival with induction chemotherapy for other high-grade sinonasal malignancies, but evaluations for SMARCB1-deficient sinonasal carcinoma are limited.[3,6,9,10]

The objective of this study was to report outcomes for a consecutive series of patients with SMARCB1-deficient sinonasal carcinoma treated at a single institution. We evaluated clinical factors and treatments associated with survival.

Methods

We identified all patients with immunohistochemistry-confirmed SMARCB1-deficient sinonasal carcinoma from January 1, 2014 to January 1, 2022 after MD Anderson Institutional Review Board approval (protocol RCR04-0636). Treatments were determined by the managing providers. After 2 cycles of platinum-based induction chemotherapy, responses were assessed clinically (symptoms and nasal endoscopy) and radiographically (response evaluation criteria in solid tumors [RECIST] and positron emission tomography).[11] Patients with poor responses were treated with endoscopic or open

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surgery followed by chemoradiation. The primary outcomes were overall survival (OS) and disease-specific survival (DSS). Secondary outcomes included disease-free survival (DFS) and factors associated with survival.

Data were analyzed using the univariable Cox proportional hazard model, Kaplan-Meier estimate, and log-rank test. Covariables included age at diagnosis, sex, race (white vs other), disease stage (T category and overall stage per the American Joint Committee on Cancer Staging Manual, 8th edition[12]), tumor site, and treatment. The covariates stage (II-IVa vs IVb-c; T4b vs other; N+ vs N−) and subsite (nasal cavity or maxillary sinus vs other) were dichotomized to sufficiently power the analysis. Confidence intervals (CIs) of 95% were utilized. Significance testing was performed using 2-sided tests with a type I error rate of 0.05 Statistical analyses were done using SAS version 9.4 (SAS Institute).

Results

A total of 19 patients with SMARCB1-deficient sinonasal carcinoma were treated between 2014 to 2021 with a median follow-up of 22.3 months (range, 6-62). Patient and tumor characteristics are found in Table 1. The median (±standard deviation) age was 47.2 ± 18.6 years (range, 19.3-75.6). The majority of patients were male (74%), white (68%), and never smokers (79%). Treatment included surgery with adjuvant chemoradiotherapy (47%) or definitive chemoradiotherapy (54%). Ten of these patients (54%) were also treated with induction chemotherapy.

Kaplan-Meier survival curves for OS and DFS are shown in Figure 1. The median OS and DSS were 31.8 months and 31.9 months, respectively. The median DFS was 9.9 months. Patients with nasal cavity or maxillary sinus tumors were 84% less likely to die of disease (DSS hazard ratio [HR], 0.136; 95% CI, 0.028-0.66; $p = .006$; Figure 2A) compared to patients with sphenoid, ethmoid, or frontal sinus tumors. Patients with nasal cavity or maxillary sinus tumors were also 71% less likely to have disease recurrence (DFS HR, 0.29; 95% CI, 0.097-0.84; $p = .041$). Age, sex, race, and stage were not associated with survival differences.

We then evaluated survival by treatment. Of the 10 patients who received induction chemotherapy, 7 (70%) had a clinical response, of which 3 met RECIST criteria for partial response (≥30% decrease in the sum of their longest diameter). One patient had a progression of the disease. Patients who received induction chemotherapy were 76% less likely to die of disease (DSS HR, 0.241; 95% CI, 0.058-1.00; $p = .047$; Figure 2B). The median DSS was not reached for patients who received induction chemotherapy and 6.0 months for patients who did not receive induction chemotherapy. Induction chemotherapy did not have a significant impact on DFS. There was no difference in DSS ($p = .88$) or DFS ($p = .79$) between patients who underwent definitive chemoradiotherapy versus surgery with adjuvant chemoradiotherapy.

Table 1. Patient and Tumor Characteristics

Characteristic	No. (%)
Age, y, median ± standard deviation	47.2 ± 18.6
Male gender	14 (73.7)
Race/ethnicity	
White	13 (68.4)
Black	1 (5.2)
Hispanic	3 (15.8)
Asian	1 (5.3)
Other	1 (5.3)
Tobacco	
Never	15 (78.9)
Current or former	4 (21.1)
Tumor site	
Sphenoethmoid sinuses	5 (26.2)
Nasal cavity	7 (36.8)
Frontal sinus	3 (15.8)
Maxillary sinus	4 (21.1)
T category	
T2	2 (10.5)
T3	2 (10.5)
T4a	10 (52.6)
T4b	5 (26.3)
N+	0 (0)
M+	1 (5.3)
Overall stage	
Stage II-III	4 (21.1)
Stage IVa	9 (47.4)
Stage IVb	5 (26.3)
Stage IVc	1 (5.3)
Treatment	
Chemoradiotherapy	10 (53.6)
Surgery + chemoradiotherapy	9 (47.4)
Induction chemotherapy	10 (53.6)

Discussion

This study represents the largest single-institution analysis of SMARCB1-deficient sinonasal carcinoma to date. Outcomes for SMARCB1-deficient sinonasal carcinoma appear to be worse than those for most other sinonasal cancers, including sinonasal undifferentiated carcinoma (SNUC) and poorly differentiated squamous cell carcinoma.[7,8,13-15] We found a median OS and DFS were 32 months and 10 months, respectively. A team from Hong Kong recently conducted a systematic review with 128 patients and found a comparable median OS of 39 months.[16]

Our study appears to be the first to suggest better outcomes based on anatomic subsites, specifically the nasal cavity and maxillary sinus. Although the aforementioned systematic review found worse survival with T4b disease, they did not evaluate the impact of a subsite on

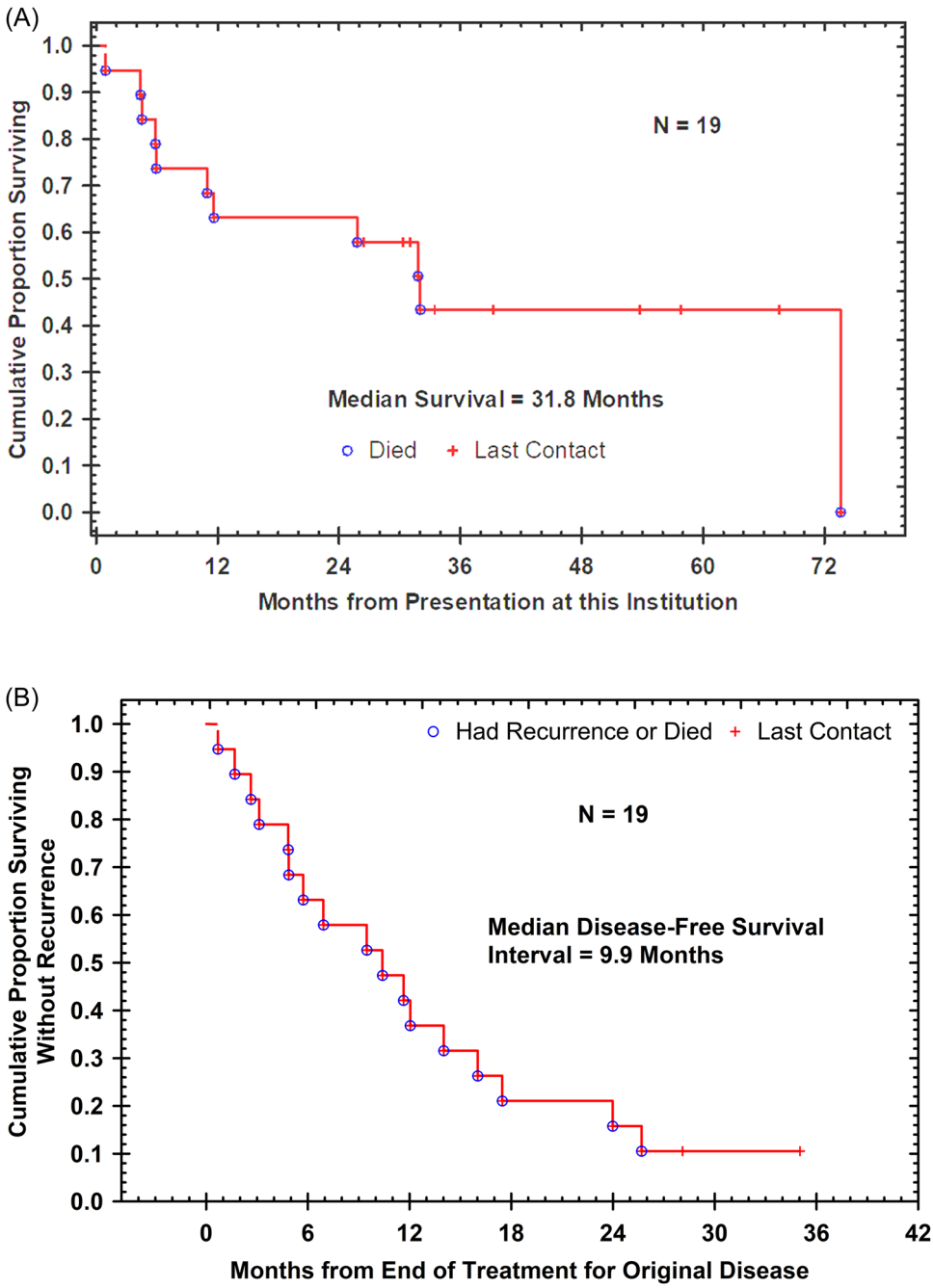

Figure 1. Kaplan-Meier curves for (A) overall survival and (B) disease-free survival for patients with SMARCB1-deficient sinonasal carcinoma.

outcomes due to limitations in composing studies.[16] Other sinonasal malignancies also have been associated with improved outcomes when localized to the nasal cavity.[17]

To our knowledge, no study to date has reported improved survival with induction chemotherapy for SMARCB1-deficient sinonasal carcinoma. Neoadjuvant chemotherapy has demonstrated benefits for some (eg, SNUC, squamous cell carcinoma), but not all, sinonasal malignancies.[9,18-20] However, treatments must be determined individually as our study was limited to a small, single-institutional retrospective series. Larger, prospective trials are currently ongoing to evaluate the use of neoadjuvant chemotherapy for sinonasal malignancies.[21-23] Targeted therapy is also being evaluated.[24,25]

Conclusions

In the largest single-institution report of SMARCB1 (INI-1)-deficient sinonasal carcinoma to date, OS was approximately 3 years and DFS was 1 year. DSS and DFS seem better for patients with tumors of the nasal cavity and maxillary sinus. Induction chemotherapy may potentially

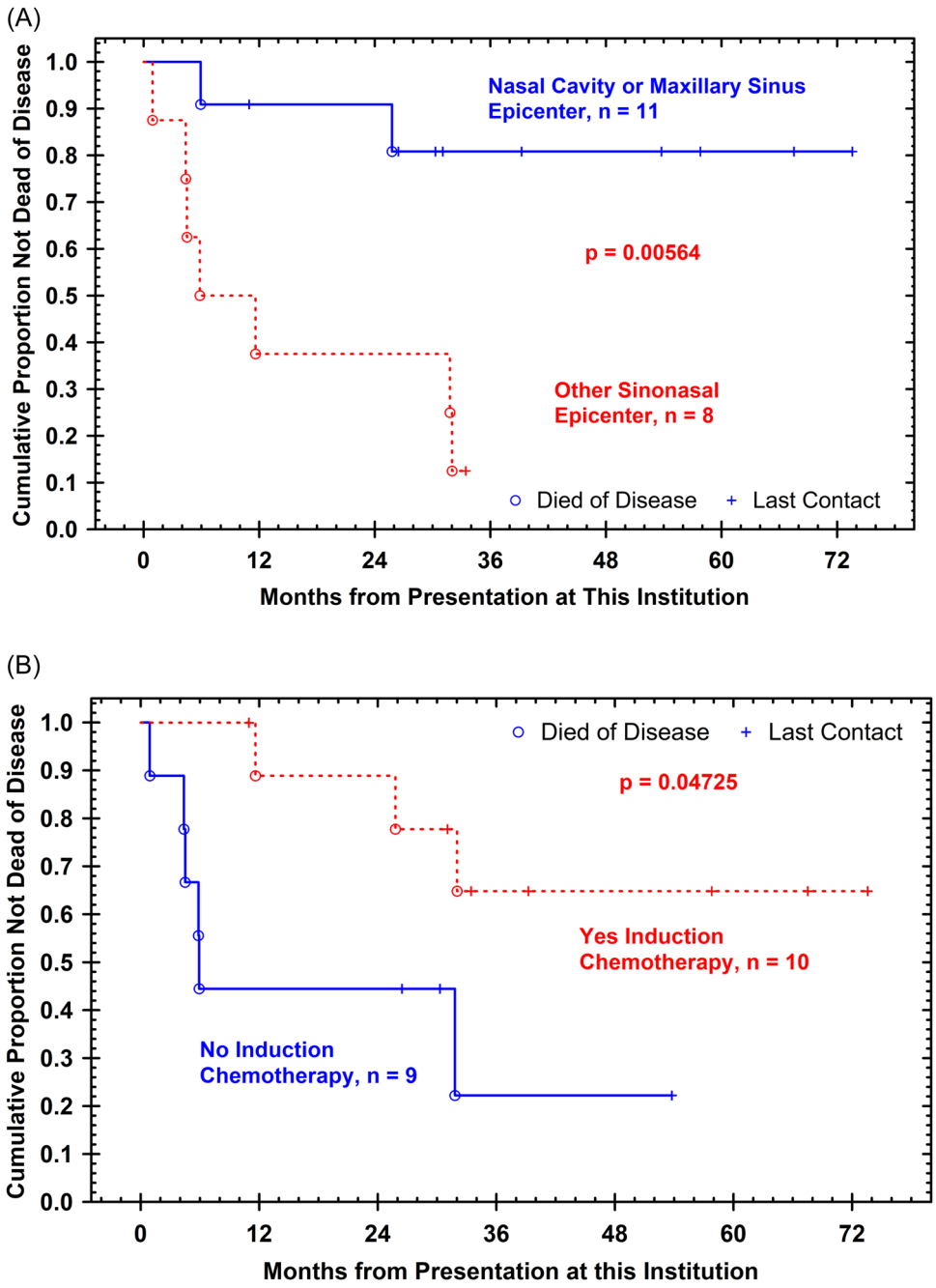

Figure 2. Kaplan-Meier curves for disease-specific survival for patients with SMARCB1-deficient sinonasal carcinoma by (A) disease site and (B) treatment with or without induction chemotherapy.

improve outcomes. Additional research is needed to determine optimal treatment strategies for SMARCB1-deficient sinonasal carcinoma.

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Author Contributions

Kevin J. Contrera, study design, data acquisition and interpretation, manuscript writing, review, and revisions; **Nasim Shakibai**, data acquisition and interpretation, manuscript review, and revisions; **Shirley Y. Su**, data interpretation, manuscript review, and revisions; **Maria K. Gule-Monroe**, data acquisition and interpretation, manuscript review, and revisions; **Dianna Roberts**, statistical analysis, manuscript review, and revisions; **Bledi Brahimaj**, data interpretation, manuscript review, and revisions; **Michelle D. Williams**, data interpretation, manuscript review, and revisions; **Renata Ferrarotto**, data interpretation, manuscript review, and revisions; **Jack Phan**, data interpretation, manuscript review, and revisions; **Brandon Gunn**, data interpretation, manuscript review, and revisions; **Shaan Raza**, data interpretation, manuscript review, and revisions; **Franco DeMonte**, data interpretation, manuscript

review, and revisions; **Ehab Y. Hanna**, study design, data interpretation, manuscript review, and revisions.

Disclosures

Competing interests: Michelle D. Williams has received consultation fees and participated in Scientific Advisory Boards for Bayer. Renata Ferraroto reports personal fees from Regeneron-Sanofi, Prelude Pharmaceuticals, Klus Pharma, Medscape, and Carevive; personal fees and other support from Ayala Pharmaceuticals and Bicara; and other institutional support from AstraZeneca, Merck, Genentech, and Pfizer. The remaining authors made no disclosures.

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Data Availability Statement

Data can be obtained on request. Requests should be directed toward the corresponding author. Because of restrictions based on privacy regulations, data cannot be made freely available in a public repository.

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