Loss of *SMARCB1* Expression Confers Poor Prognosis to Sinonasal Undifferentiated Carcinoma

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Abstract

Background Due to the diverse histopathologic features and variable survival rates seen in sinonasal undifferentiated carcinoma (SNUC), it is likely that this diagnostic entity is comprised of a heterogonous group of morphologically undifferentiated tumors. As advancements in molecular testing have led to a better understanding of tumor biology, it has become increasingly evident that SNUC may actually encompass several tumor subtypes with different clinical behavior. As a result, it is also likely that all SNUC patients cannot be treated in the same fashion. Recent investigations have identified loss of the tumor suppressor *SMARCB1* (INI1) expression in a subset of undifferentiated sinonasal tumors and extrasinonasal tumors and, studies have suggested that this genetic aberration may be a poor prognostic marker. The objective of this study was to identify differential expression of *SMARCB1* in SNUC and to analyze and compare the survival outcomes in SNUC patients with and without *SMARCB1* expression.

Methods All cases of undifferentiated or poorly differentiated neoplasms of the sinonasal tract treated between 2007 and 2018 at a single tertiary care institution were selected. All cases of SNUC were tested for *SMARCB1* status by immunohistochemistry (IHC). Clinical parameters were analyzed using Student's *t*-test and Fischer's test. Kaplan–Meier methods were used to estimate survival durations, while comparison between both the subgroups was done using the log-rank test. Statistical analysis was performed with the use of SPSS software, Version 25 (IBM, New York, NY, United States).

Keywords
- *SMARCB1*
- INI-1
- undifferentiated
- sinonasal
- survival
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Results Fourteen cases of SNUC were identified. Approximately two-thirds (64%; $n = 9$) of patients were male and the majority (79%; $n = 11$) were between fifth to seventh decade. Skull base and orbital invasion were seen in 79% ($n = 11$) and 93% ($n = 13$) of cases, respectively. Fifty-seven percent of tumors ($n = 8$) retained *SMARCB1* expression by IHC (SR-SNUC), while the remaining 43% ($n = 6$) showed loss of *SMARCB1* expression and, thus, were considered as *SMARCB1*-deficient (SD-SNUC). Although clinicopathological features and treatment modalities were similar, SD-SNUC showed poorer (OS: $p = 0.07$; disease free survival [DFS]: $p = 0.02$) overall survival (OS) and DFS on Kaplan–Meier curves. Additionally, SD-SNUC showed higher recurrence (75 vs. 17%) and mortality (67 vs. 14%) (hazard rate = 8.562; $p = 0.05$) rates. Both OS (28.82 ± 31.15 vs. 53.24 ± 37.50) and DFS durations (10.62 ± 10.26 vs. 43.79 ± 40.97) were consistently worse for SD-SNUC. Five-year survival probabilities were lower for SD-SNUC (0.33 vs. 0.85).

Conclusion SNUC represents a heterogeneous group of undifferentiated sinonasal malignancies. Based on the status of *SMARCB1* expression, the two subgroups SD-SNUC and SR-SNUC appear to represent distinct clinical entities, with loss of *SMARCB1* expression conferring an overall worse prognosis.

Introduction

Sinonasal undifferentiated carcinoma (SNUC) is defined by the World Health Organization (WHO) as a highly aggressive carcinoma lacking squamous or glandular features.[1] Extension to extrasinonasal sites, such as the orbit and skull base, is common. Treatment generally involves multimodality therapy using both surgical and nonsurgical (chemotherapy and/or radiation) therapies.[2,3] Irrespective of treatment, however, SNUC has one of the worst prognoses among all sinonasal malignancies with a high risk of recurrence and extremely poor survival.[3–11]

Five-year survival rates of SNUC over the past decade reveal widely variable rates ranging from 6 to 75%.[10–12] This significant variability suggests that SNUC likely represent a heterogeneous group of tumors with distinct behavior and aggressiveness.

Loss of *SMARCB1* (INI-1, BAF47, or hSNF5), a tumor suppressor gene, is a genetic aberration that has been recently described in various undifferentiated sinonasal and extra sinonasal malignancies including rhabdoid tumors, epithelioid sarcomas, renal medullary carcinomas, etc.[13–18] Although *SMARCB1* gene loss appears to confer poor prognosis to these tumors,[19–21] there is paucity of data on the effect of this genetic aberration on survival in SNUC population. The objectives of this study were, first, to examine the differential expression of *SMARCB1* in the SNUC population and, second, to analyze whether this differential expression is associated with different survival outcomes.

Methodology

Institutional review board approval was obtained from Thomas Jefferson University Hospital.

Case Selection

All cases of malignant tumors occurring in the sinonasal tract which were diagnosed between 2007 and 2018 at a single tertiary care center were identified. Among these cases, patients with the following descriptions in their respective pathology reports were selected: "poorly differentiated", "undifferentiated", or "high grade, not otherwise specified." Fifty-eight cases were identified according to the aforementioned criteria. Of them, 14 cases were SNUC and had adequate tissue available for testing. Full details of case selection criteria are shown in ►**Fig. 1**.

Immunohistochemistry

Formalin-fixed, paraffin-embedded (FFPE) specimens were retrieved for selected cases and 4-µm-thick sections were cut from paraffin blocks using a fully automated system ("Benchmark XT System", Ventana Medical Systems Inc., Arizona, United States). These cut sections were then mounted on coated slides (Matsunami Glass Ind. Ltd, Japan), deparaffinized in xylene, and rehydrated in descending grades (100 and 70%) of ethanol. Immunohistochemistry (IHC) was performed using the *SMARCB1* (INI1) antibody (MRQ-27, 1:50, Zytomed).

Evaluation of the IHC staining results was performed as described.[22] Based on the IHC staining patterns, three staining grades were defined as follows: *intact* (strong nuclear staining in malignant cells), *deficient* (completely unstained nuclei in malignant cells), and *reduced* (very weak but still noticeable nuclear staining in malignant cells) in comparison to strong staining of normal background cells.[21,22] Strong homogeneous nuclear staining in the background (in inflammatory cells, stromal fibroblasts, vascular endothelial cells, and/or normal epithelial cells) served as an internal control and was considered a prerequisite for IHC interpretation. Only unequivocal staining of the nuclei in viable tumor tissue (away from necrotic areas) was analyzed. Cases with absent or very weak staining in

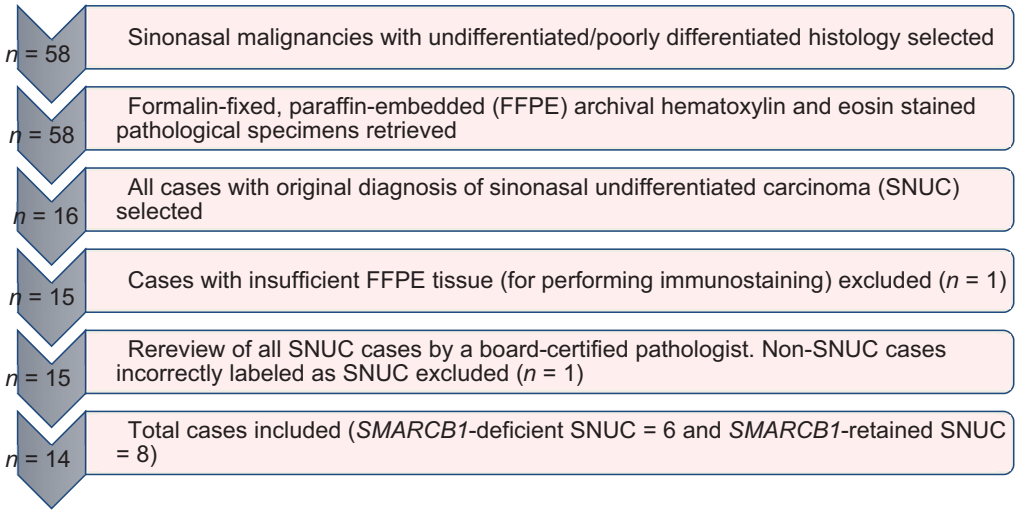

Fig. 1 Flowchart depicting selection of cases for the study.

the normal background cells ($n = 2$) underwent repeat IHC testing with subsequent interpretable results.

Cases were divided into two subgroups, *SMARCB1*-retained SNUC (SR-SNUC) and *SMARCB1*-deficient SNUC (SD-SNUC).

Statistical Analysis

Survival durations were calculated for only those patients who underwent treatment with curative intent ($n = 13$). Patients who underwent palliative treatment ($n = 1$) and those who did not complete treatment were excluded from analysis.

Results are presented as of July 11, 2018. Descriptive statistics (mean, median, standard deviation [SD], and confidence intervals [CI]) are provided wherever relevant to summarize patient characteristics and outcomes. Student's *t*-test (compare continuous variables) and Fisher's exact test or Chi-square test (compare categorical variables) were used as relevant. The Cox Proportional Hazard Model was used to quantify association between mortality and *SMARCB1* gene expression. Kaplan–Meier methods were used to estimate survival durations, while comparison between both the subgroups was done using the log-rank test. A two-tailed *p*-value of 0.05 was considered statistically significant and all limits reported are provided for 95% CI. Statistical analysis was performed with the use of SPSS software, Version 25 (IBM, New York, NY, United States).

Effect Size Calculation

Considering SNUC is a rare sinonasal malignancy,[1] the sample size for most studies is low. As a result, minor changes in sample size may significantly shift the *p*-value.[23,24] Therefore, effect size, which is independent of sample size, was calculated (using Cohen's "d") and results were expressed as small, medium, or large based on conventional guidelines.[25]

Results

A. *SMARCB1 nuclear expression by IHC:*

Fourteen patients were included in the study. Forty-three percent ($n = 6$) of SNUC cases showed complete loss of nuclear expression of *SMARCB1* in the tumor cells (►**Fig. 2**). None of the cases demonstrated a reduced or mixed pattern of IHC staining.

B. *Comparison of pretreatment and treatment related characteristics:*

Sixty-four percent ($n = 9$) of patients were male and 79% ($n = 11$) were within the fifth and seventh decade. Fifty percent ($n = 7$) of patients showed bilateral sinonasal tract involvement, 79% ($n = 11$) had skull base invasion and 93% ($n = 13$) had orbital invasion. More than two-thirds of patients (71%; $n = 10$) presented with TNM stage-IV disease.

Comparison of SR-SNUC and SD-SNUC on the basis of pretreatment- and treatment-related characteristics was performed. Pretreatment data (demographics, functional status, and comorbidity index) were found to be comparable between the groups (►**Table 1**). There were no statistically significant differences in growth pattern, cytomorphology, presence of necrosis, and mitotic rate between the SR-SNUC and SD-SNUC groups (►**Tables 2** and **3**). Site of origin, extent and stage of tumor were comparable between the two subgroups (►**Table 2**). Of note, the SD-SNUCs showed diverse cytomorphology (squamoid, basaloid, and plasmacytoid/rhabdoid, $n = 2$ each). On analyzing various treatment-related variables, it was noted that both SR-SNUC and SD-SNUC received comparable treatment (►**Table 4**).

C. *Comparison of posttreatment characteristics:*

Following completion of treatment, patients were under surveillance for a mean duration of 41.97 ± 35.61 months. Posttreatment variables analyzed included recurrence and mortality. Overall recurrence rate was 40% and overall mortality was 38%. On analyzing the sub group-specific data, it was noted that SD-SNUC had both higher recurrence (75 vs. 17%) and higher mortality rates (67 vs. 14%; hazard rate = 8.562; $p = 0.05$). The pattern of recurrent disease was distinct between both the groups. Patients with SR-SNUC developed local recurrence ($n = 1$), while patients with SD-SNUC developed all three patterns of recurrent disease–local ($n = 1$), regional ($n = 1$), and metastatic ($n = 1$). Metastatic disease was noted in adrenal, portocaval, and mediastinal

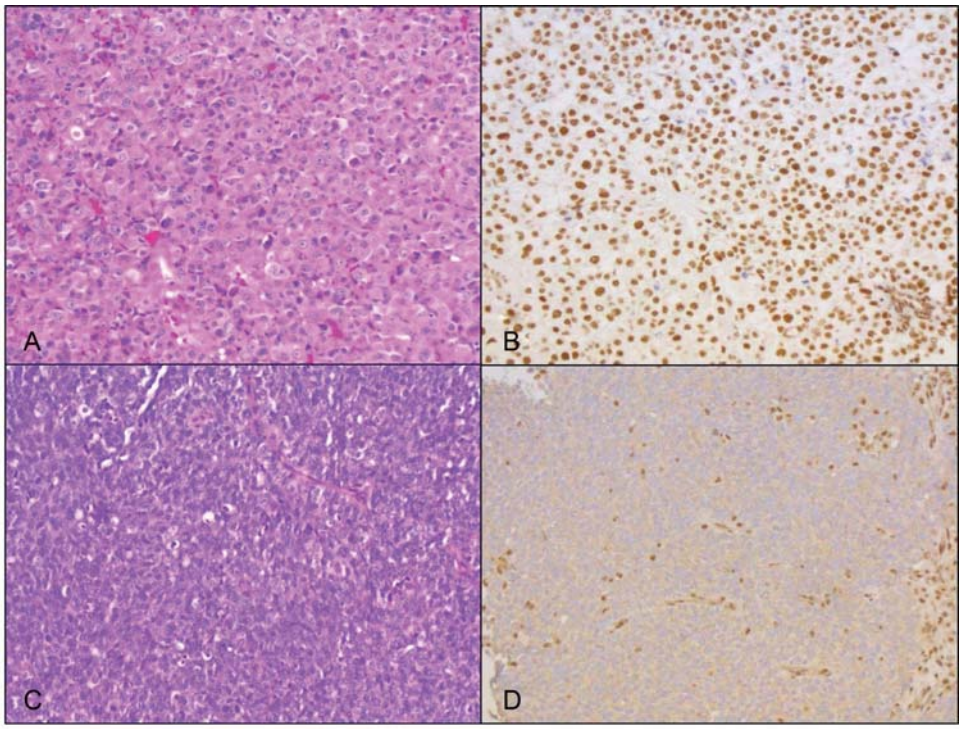

Fig. 2 Histology of one SR-SNUC case and one SD-SNUC case. Hematoxylin and eosin (H&E) stained section of the SR-SNUC case demonstrates squamoid morphology characterized by tumor cells with abundant eosinophilic cytoplasm and distinct cell borders (A, ×20); IHC for *SMARCB1* shows strong nuclear staining in the tumor cells (B, ×20). The SD-SNUC case shows basaloid morphology characterized by tumor cells with high nuclear to cytoplasmic ratio (C, H&E, ×20); *SMARCB1* nuclear expression is lost in the tumor cells and retained in the background nonneoplastic inflammatory and stromal cells (D, ×20). SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC.

lymph nodes. One of the SD-SNUC cases recurred twice, both times in the skull base region. Time to recurrence was shorter for SR-SNUC (7.3 months [$n = 1$] vs. 16.64 ± 11.54 months [mean: $n = 3$]). Overall, 62% of patients (86% of SR-SNUC and 33% of SD-SNUC) were alive at the time of completion of the study.

Comparison of Survival Outcomes

Kaplan–Meier survival curves showed that both overall survival (OS) and disease free survival (DFS) were consistently (OS: $p = 0.07$; DFS: $p = 0.02$) worse for SD-SNUC (►**Figs. 3** and **4**). Additionally, 5-year survival probabilities were lower for SD-SNUC (0.33 vs. 0.85; ►**Table 5**). The rest of the survival outcomes are shown below (►**Table 6**, ►**Figs. 5** and **6**).

Discussion

A pathologic diagnosis of exclusion, SNUC represents a diverse group of highly aggressive malignancies that frequently invade the skull base, dura or brain (62–64%).[26] Classically, SNUC presents as a rapidly growing mass in the sinonasal tract with aggressive clinical behavior. Males are more frequently affected and most commonly present in their sixth decade.[6,27] The typical histological appearance includes sheets and trabeculae of cytologically malignant tumor cells with frequent mitoses and necrosis (WHO). Both SR-SNUC and SD-SNUC in our study showed variable growth patterns (trabecular, sheet-like, and papillary) and cytomorphology (squamoid, rhabdoid, and basaloid). A recent study of 39 *SMARCB1*-deficient sinonasal carcinomas, which included 10 cases originally diagnosed as SNUC, likewise showed diverse histomorphologic findings in these tumors.[21]

Studies conducted in the past few years (2010–2018) have demonstrated that 5-year survival rates for SNUC vary significantly, ranging from 6 to 75%.[10–12] This variability demonstrates that SNUC is not a homogenous group of tumors and, therefore, these cases may not all respond equally to the same treatments. There is a clear need to subtype tumors in an effort to better stratify them by behavior and varying aggressiveness in order to individualize treatment. However, attempts to do so remain challenging and are limited by the fact that SNUC has significant variations with respect to histopathological and immunohistochemical features.

In this study, we propose a new classification system for all cases of SNUC based on the expression of *SMARCB1* by IHC. The *SMARCB1* gene is a tumor suppressor gene found on chromosome 22q11.2 and is a highly conserved core subunit of SWF/SNF complex responsible for regulation of cell differentiation, cell cycle control, and apoptosis.[28–30] Recent studies have identified loss of *SMARCB1* expression in poorly differentiated sinonasal malignancies and have suggested its potential to be a poor prognostic marker.[19,20,31] Of note, similar genetic aberrations have also been identified not only in sinonasal tumors[31–34] but also nonsinonasal[13–18] malignancies.

Furthermore, irrespective of the site of origin, genetic aberrations in *SMARCB1* expression appear to confer a poor prognosis with high-recurrence rates[19,20] and short-survival durations.[31] For example, *SMARCB1* deficient

Table 1 Comparison of demographic details and preoperative comorbidity status between SR-SNUC and SD-SNUC

Variable	SR-SNUC	SD-SNUC	*p*-Value
Age (in y)			
Mean	52.88	56.50	0.59
Standard deviation	10.60	14.52	
Gender			
Males	05	04	1.000
Females	03	02	
Race			
Caucasian	06	03	0.74
African American	01	02	
Asian	01	01	
Smoking history			
Ever	04	04	1.000
Never	02	02	0.58 (including UK)
UK	02	00	
Alcohol intake history			
Ever	03	03	1.000
Never	03	03	0.6 (including UK)
UK	02	00	
Preoperative Charlson's comorbidity index			
Score 2	06	05	0.99
Score 3	01	01	
Score 4	01	00	
Preoperative ECOG functional status			
0	01	00	0.99
1	03	03	0.86 (including UK)
2	00	01	
UK	04	02	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC; UK, unknown.

Table 2 Comparison of pathological characteristics between SR-SNUC and SD-SNUC

Variable	SR-SNUC	SD-SNUC	*p*-Value
Primary site			
PNS alone	04	06	0.08
Both nasal cavity and PNS	04	00	
Laterality			
Unilateral	03	04	0.59
Bilateral	05	02	

Table 2 (*Continued*)

Variable	SR-SNUC	SD-SNUC	*p*-Value
Orbital involvement			
Present	07	06	1.000
Absent	01	00	
Skull base involvement			
Present	05	06	0.2
Absent	03	00	
T stage			
T3	01	00	1.000
T4a	04	04	1.000 (including UK)
T4b	02	02	
UK	01	00	
N stage			
N_0	06	05	1.000
N_2	01	01	0.99 (Including UK)
Unknown	01	00	
M stage			
M_0	01	01	1.000
M_1	06	05	0.99 (Including UK)
UK	01	00	
Overall TNM stage			
Stage III	01	00	1.000
Stage IVA	03	03	1.000 (including UK)
Stage IVB	02	02	
UK	02	01	
Growth pattern			
Trabecular	05	04	0.74
Sheet-like	03	01	
Papillary	00	01	
Cytomorphology			
Basaloid	04	02	1.000
Squamoid	02	02	
Plasmacytoid/ rhabdoid	02	02	
Necrosis			
Absent	00	02	0.3
Focal	05	03	
Diffuse	03	01	
Mitotic count			
Mean	26.50	22.17	0.6
Standard deviation	16.87	11.67	

Abbreviations: PNS, paranasal sinus; SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC; TNM, tumor node metastasis; UK, unknown.

Table 3 Comparison of immunostaining characteristics between SR-SNUC and SD-SNUC

Variable	SR-SNUC	SD-SNUC	*p*-Value
Pancytokeratin			
Absent	01	01	0.99
Focal	01	00	
Diffuse	06	05	
P40			
Absent	01	01	0.19
Focal	00	03	
Diffuse	01	00	
Not available	06	02	
P63			
Absent	02	01	1.000
Focal	00	01	
Diffuse	00	01	
Not available	06	03	
Synaptophysin			
Absent	04	06	1.000
Focal	00	00	
Diffuse	00	00	
Not available	04	00	
Chromogranin			
Absent	05	06	1.000
Focal	00	00	
Diffuse	00	00	
Not available	03	00	
S-100			
Absent	05	06	1.000
Focal	00	00	
Diffuse	00	00	
Not available	03	00	
P16			
Absent	01	01	0.6
Focal	00	01	
Diffuse	02	00	
Not available	05	04	

Abbreviations: SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC.

Table 4 Comparison of treatment details between SR-SNUC and SD-SNUC[a]

Variable	SR-SNUC	SD-SNUC	*p*-Value
Treatment lag (from diagnosis to initiation of treatment), d			
Mean	48.50	52.67	0.46
Standard deviation	31.13	34.72	
Treatment modality			
Surgery ± adjuvant chemo radiation	06	02	0.1
Neoadjuvant chemotherapy + concurrent chemoradiation	01	04	
Surgical approach			
Endoscopic	05	01	0.46
Open	00	01	
Combined	01	00	
Oncological clearance following surgical treatment			
Total clearance	01	02	0.21
Microscopic disease present	04	00	
Gross disease present	01	00	
Type of radiation therapy			
VMAT	03	03	0.46 0.23 (including UK)
IMRT	03	00	
UK	01	03	
Radiation dose (in cGy)			
Mean	61.56	66.67	0.43
Standard deviation	06.88	05.77	
Interruption during radiation therapy (d)			
Mean	4.25	1.33	0.05
Standard deviation	2.50	0.58	

Abbreviations: cGy, centigray; IMRT, intensity-modulated radiation therapy; SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC; UK, unknown; VMAT, volumetric modulated arc therapy.
[a]excluding one case of palliative treatment in SR-SNUC which was treated with radiotherapy.

gastrointestinal carcinomas have a poorer prognosis when compared to those tumors that express *SMARCB1*, with 1-year mortality of over 80% in the *SMARCB1*-deficient subtype.[31] Similarly, the results of our study suggest that loss of *SMARCB1* expression may be associated with poor prognosis in SNUC. In the SD-SNUC group, 1-year mortality rate following treatment was over 50%, while it was 0% for the SR-SNUC group

This stark contrast in prognosis between the two subgroups based on *SMARCB1* expression is could be the basis for pathological subtyping of SNUC patients. In addition to subtyping, *SMARCB1* loss could potentially serve as a basis for a novel therapeutic model for SNUC. Newer treatment strategies for nonsinonasal *SMARCB1* deficient malignancies that are currently under clinical trials include targeted therapies using EZH2 inhibitors, histone deacetylase inhibitors, and CDK4 inhibitors.[35] Based on similar genetic aberration, it is possible that these agents may prove to be beneficial in treating *SMARCB1* deficient sinonasal malignancies including SD-SNUC.

The results of our study, including subgroup analysis, demonstrate that the poor prognosis observed in *SMARCB1* deficient SNUC is in accordance with shorter survival and frequent recurrences noted in nonsinonasal *SMARCB1* deficient tumors described in the current literature. All survival

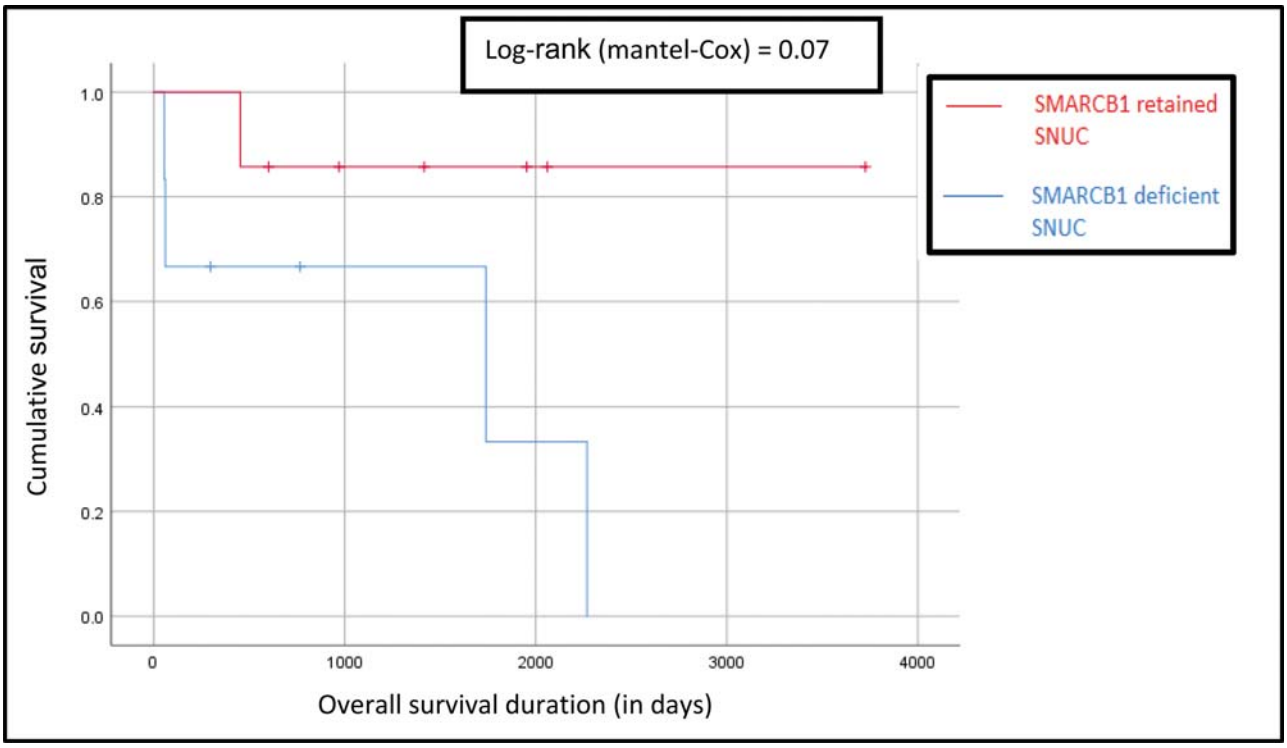

Fig. 3 Comparison of Kaplan–Meier survival curves for overall survival between SR-SNUC and SD-SNUC. X axis denotes the duration of survival (in days) and Y axis denoted the cumulative survival. Vertical lines on each of the curves denote censored patients. SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC.

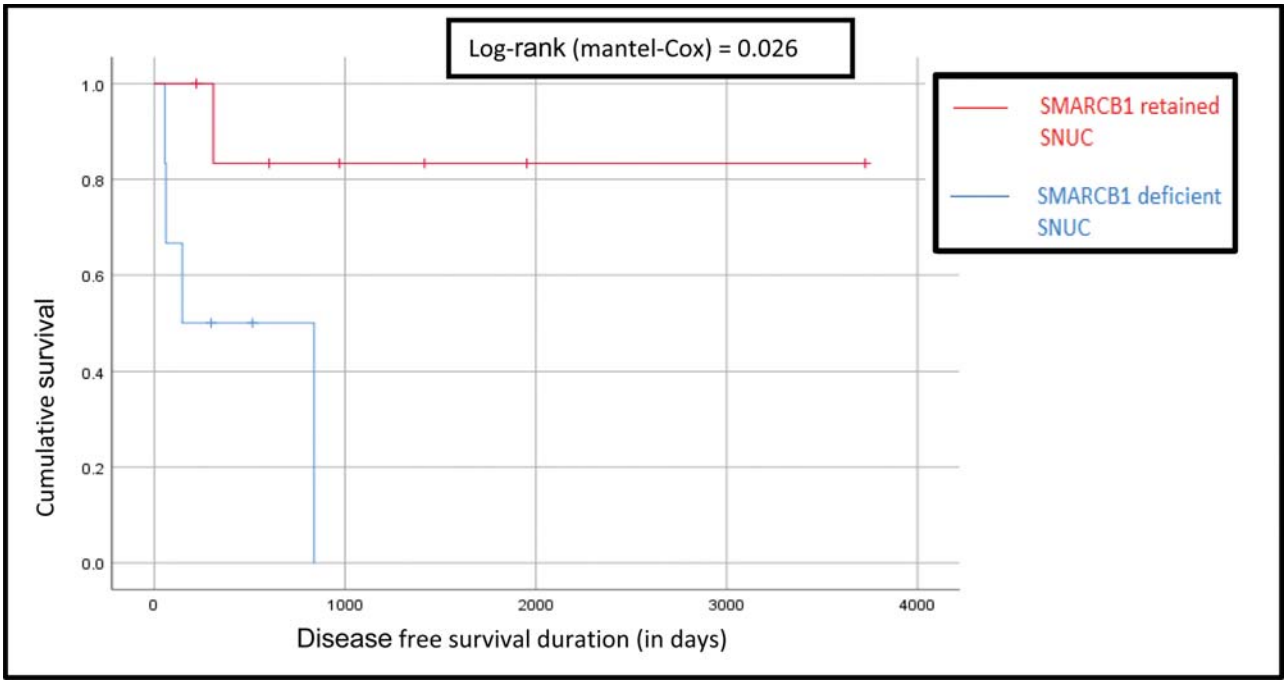

Fig. 4 Comparison of Kaplan–Meier survival curves for disease free progression survival between SR-SNUC and SD-SNUC. X axis denotes the duration of survival (in days) and Y axis denoted the cumulative survival. Vertical lines on each of the curves denote censored patients. SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC.

Table 5 Comparison of 5-year survival probabilities (SP) between SR-SNUC and SD-SNUC

Time period (y)	SP of SR-SNUC (95% limits)	SP of SD-SNUC (95% limits)
1	1.00 (0.56–1.00)	0.66 (0.24–0.94)
2	0.85 (0.42–0.99)	0.66 (0.24–0.94)
3	0.85 (0.42–0.99)	0.66 (0.24–0.94)
4	0.85 (0.42–0.99)	0.66 (0.24–0.94)
5	0.85 (0.42–0.99)	0.33 (0.05–0.75)

Abbreviations: SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC.

Table 6 Comparison of survival durations between SR-SNUC and SD-SNUC

	SR-SNUC	SD-SNUC	*p*-Value	Effect size index (Cohen's "d")
Overall survival duration (mo)				
Mean	53.24	28.82	0.23	0.7 (medium)
Standard deviation	37.50	31.15		
Disease free survival duration (mo)				
Mean	43.79	10.62	0.08	1.07 (large)
Standard deviation	40.97	10.26		

Abbreviations: SD-SNUC, SMARCB1-deficient sinonasal undifferentiated carcinoma; SR-SNUC, SMARCB1-retained SNUC.

outcomes, especially those related to disease progression, were consistently poorer for SD-SNUC (Kaplan-Meier curve; $p = 0.02$). Considering the fact that both these subgroups shared similar pretreatment and treatment related variables, this stark difference in prognosis may be attributed to differential expression of *SMARCB1*. This is the first study of its kind to report differential expression of *SMARCB1* in SNUC and to analyze the survival outcomes of SNUC based on this genetic aberration.

We acknowledge the limitations of this study, especially those related to retrospective study design including incomplete and inconsistent data in medical records. Additionally low-sample size, owing to rarity of the tumor is also recognized. Future investigations, however, may be similarly hampered by the low incidence of SNUC and, therefore, a deeper investigation of the genetic signature of these samples is advised. It is necessary to better understand this genetic aberration by evaluating whether differential gene expression is responsible for variations in clinical tumor behavior and aggressiveness, and, furthermore, to elucidate whether it may represent a viable basis for tumor subtyping and stratification of patients for targeted therapy.

Conclusion

SNUC represent a heterogeneous group of undifferentiated sinonasal malignancies. This study demonstrates that tumors with and without *SMARCB1* expression by IHC have marked differences in survival and, therefore, may represent distinct clinical entities. We propose that *SMARCB1* expression may represent a viable option to subtype morphologically undifferentiated sinonasal tumors in an effort to develop more individualized treatment protocols.

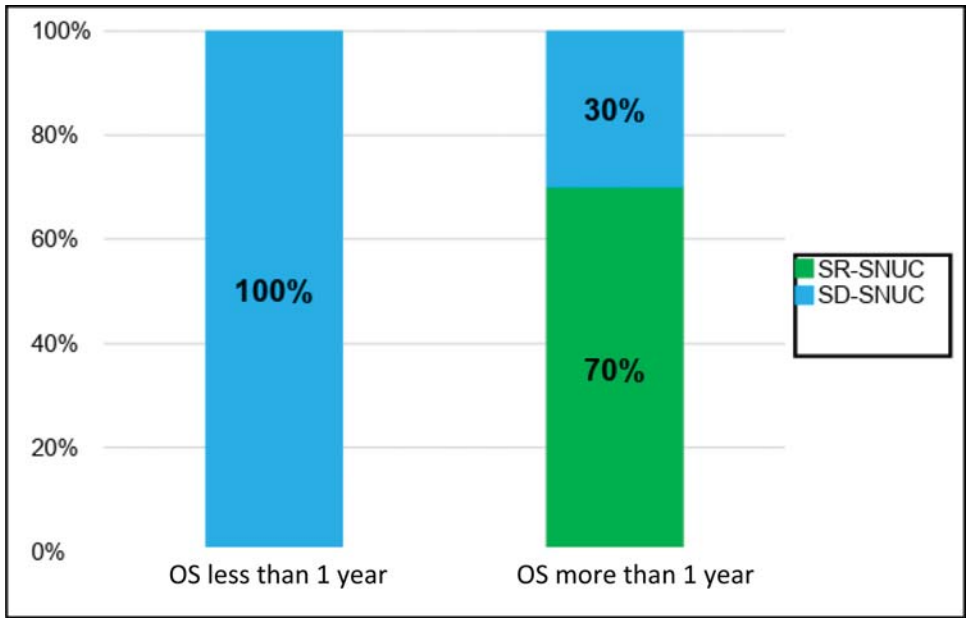

Fig. 5 Comparison of overall survival less than and more than 1 year between SR-SNUC and SD-SNUC. X axis denotes the duration of DFS and Y axis denoted the proportion of patients. Values inside each of these boxes represent respective proportion of patients. OS, overall survival; SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC.

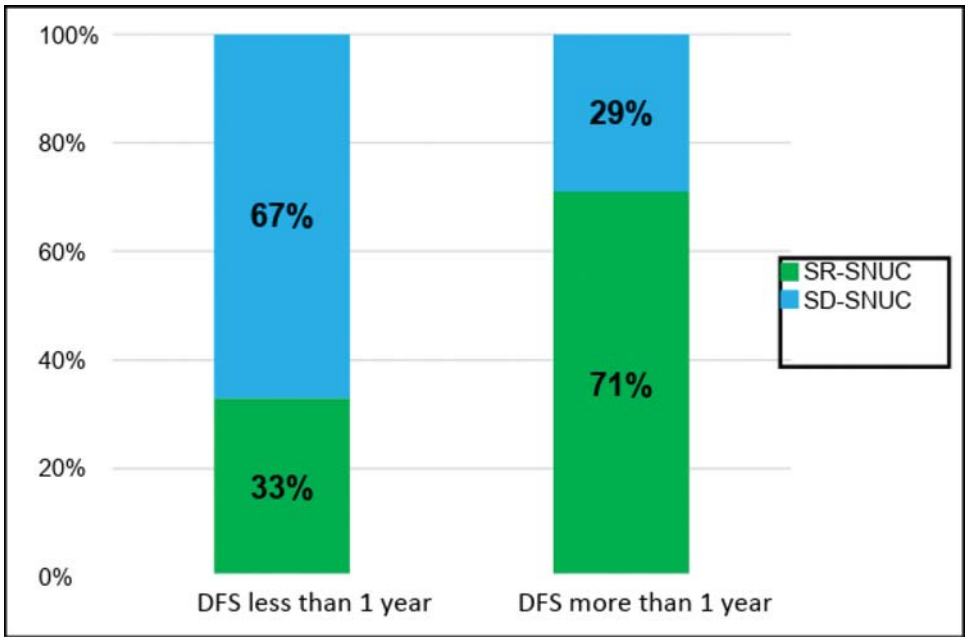

Fig. 6 Comparison of disease free survival less than and more than one year between SR-SNUC and SD-SNUC. X axis denotes the duration of DFS and Y axis denoted the proportion of patients. Values inside each of these boxes represent respective proportion of patients. DFS, disease free survival; SD-SNUC, *SMARCB1*-deficient sinonasal undifferentiated carcinoma; SR-SNUC, *SMARCB1*-retained SNUC.

Financial Disclosure
None.

Conflict of Interest
None.

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