International, multi-institutional evaluation of practice patterns and outcomes for recurrent and metastatic sinonasal undifferentiated carcinoma (SNUC)

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ABSTRACT

Objectives. Analyze clinical characteristics of patients with recurrent and metastatic SNUC and evaluate current treatment strategies to help guide future management.

Design. Retrospective cohort study.

Setting. Six international tertiary treatment centers.

Participants. Patients with documented diagnoses of recurrent or metastatic SNUC since 1983.

Main Outcome Measures. Patient demographics and clinical characteristics were collected. Primary outcome measures included disease-specific survival (DSS), overall survival (OS), and time to recurrence following initial treatment (TTR). Further univariable and multivariable analyses were performed to assess for prognostic factors.

Results. A total of 97 patients with a mean [SD] age of 52.4 [15.6] were identified, 15 of whom presented with metastatic SNUC and 90 of whom developed recurrence. Management in both populations was widely variable. For patients with metastatic disease, 1-year DSS probability was 33.3% [95% CI, 10.8%-100%]. For patients with recurrent SNUC, 1- and 5-year DSS probabilities were 45.7% [95%CI, 31.9%-65.6%] and 8.6% [95%CI, 2.9%-25.3%], respectively. Median [IQR] TTR was 8 months [3–18.5 months]. Multivariable analyses revealed a significant association between orbital involvement on initial presentation and TTR (HR=3.28, 95%CI [1.45-7.42], p=0.004).

Conclusions. To our knowledge, this is the first study addressing metastatic and recurrent SNUC based on a large patient cohort. Orbital extension of primary SNUC may predict a higher probability of recurrence following treatment, suggesting the possible utility of a more aggressive treatment in this subgroup of patients. A heterogenous patient population and wide variability in management emphasize the challenges in standardizing care; however, dismal survival rates demonstrate the necessity for further evaluation of current approaches to improve evidence-based recommendations.

INTRODUCTION

Sinonasal malignancies comprise a vast and diverse group of rare cancers originating along the nasal tract or from the paranasal sinuses. The most common are squamous cell carcinoma and adenocarcinoma, followed by adenoid cystic carcinoma, mucosal melanoma, and olfactory neuroblastoma. Patients presenting with olfactory neuroblastoma and adenocarcinomas appear to demonstrate the highest survival rates in the literature, while mucosal melanomas and squamous cell carcinomas are generally associated with worse prognoses [1,2].

Amongst the rarer, more aggressive high-grade sinonasal malignancies, and generally associated with worse outcomes, are sinonasal undifferentiated carcinomas (SNUC), which are malignancies of the sinonasal tract with broad histological and immunochemical ambiguity. With reported incidence rates of less than 0.02 per 100,000 people, SNUC tends to present predominantly in older, Caucasian patients in their 50's-60's, though presentation ranges from patients in their mid-30s to late 80's across multiple studies [3–5]. Most patients present with nonspecific symptoms attributable to virtually any sinonasal malignancy, including a sensation of nasal obstruction, epistaxis, and various cranial nerve deficits depending on cranial nerve involvement [3,4]. Notably, many patients tend to present with additional symptoms such as periorbital swelling, visual impairments, and/or headache that arise from orbital and/or dural extension of tumor [5,6].

Clinical management of SNUC is variable and involves a combination of surgery, radiation, chemotherapy, and/or, more recently, biological therapies, though the optimal sequencing of treatment strategies has not yet been well-defined. Some studies have described prognostic

benefits associated with a surgical approach coupled with adjunctive chemotherapy or radiotherapy, while others suggest minimal-to-no benefit of resection without reliable negative margins and instead recommend a more aggressive, multimodal approach to treatment [5,7–9]. More recently, several studies have demonstrated advantages of induction chemotherapy as a screen for patients who are likely to benefit from subsequent definitive chemoradiation [10,11].

These treatment strategies, despite their aggressive nature, are only curative for a proportion of patients with primary SNUC, with limited utility in others. Studies have described recurrence occurring in more than 20-30% of patients within the first two years of treatment, with 10-20% of patients developing extension of their disease into regional lymph nodes and 25-30% experiencing metastatic progression [12,13]. Yet, despite this high potential for recurrence, the current literature characterizing this large subset of patients remains limited and relatively unexplored, demonstrating a critical gap in knowledge to support clinical approaches to care. Thus, this study aimed to analyze the clinical presentation and outcomes associated with recurrent and metastatic SNUC and outline the current landscape for treatment strategies in efforts to guide future management. To our knowledge, this study is among the first to address recurrent and metastatic SNUC in a large population cohort spanning multiple institutions across the United States and Europe.

METHODS

Data collection

Data were collected via a multi-institutional, international retrospective review of patients with a documented diagnosis of recurrent or metastatic SNUC since 1983 at six tertiary treatment

centers: Johns Hopkins University School of Medicine, the University of Texas MD Anderson Cancer Center, Michigan Medicine at the University of Michigan, University College London, University of Insubria, and University of Brescia. Patients for whom adequate documentation was not available were excluded from the study. The initial date of SNUC diagnosis was defined according to the date tissue was collected via biopsy for subsequent histopathological confirmation of disease. This study was approved by individual institutional IRBs as well as the Johns Hopkins School of Medicine Institutional Review Board (IRB00303895) for further multi-institutional analysis of collated data.

Various demographic and clinical characteristics of patients were collected including age, sex, primary site of tumor at initial presentation, TNM staging, orbital and dural involvement, and site of recurrence for patients with recurrent disease. Primary site of tumor at presentation was categorized into seven main anatomical locations along the sinonasal tract: the nasal cavity, nasopharynx, frontal, ethmoid, sphenoid, and maxillary sinuses, and the infratemporal fossa. These primary sites were used to further dichotomize the patient population to those with and without sinus involvement, as well as those with and without involvement of the nasal cavity. Tumor recurrence was stratified into local, regional, locoregional, and distant areas of spread along with a combination of distant and local, regional, or locoregional recurrence. Local site of recurrence was defined by recurrent tumor growth in the same sinonasal location as the primary tumor, while regional spread was defined by extension into the regional lymph nodes.

Details regarding treatment following initial and recurrent presentation were also collected, including treatment modality and for patients with recurrent SNUC, time to recurrence following

initial treatment of primary disease. As management of SNUC is not standardized globally, patients at each tertiary treatment center included in this study were treated per their respective institutional guidelines. Management consisted of a combination of one or more of four primary treatment options: surgery, radiation, chemotherapy, or biological therapy.

Outcome data included overall survival (OS), disease-specific survival (DSS), and time to recurrence (TTR). OS of each individual patient spanned from the date of their initial SNUC diagnosis to their date of death. DSS was calculated similarly, but only using patients for whom mortality was specifically attributed to SNUC-related complications. TTR was calculated from the date of the last treatment for primary disease to the date recurrent disease was established.

Statistical Analysis

As the data were not normally distributed for this population, descriptive statistics were summarized primarily using median values with interquartile range (IQR) for continuous variables. Patients were grouped by metastatic or recurrent disease presentation. Kaplan-Meier survival analyses and univariable and multivariable Cox proportional hazards analyses were performed with hazard ratios reported to assess for any effects of patient characteristics or treatment modalities on DSS, OS and TTR. Further subgroup survival analysis was limited by significant heterogeneity in patient characteristics and treatment modality. All analysis of data was performed via R Statistical Software (v4.2.3).

RESULTS

Demographic and clinical characteristics

Patient demographic and clinical data are presented in **Table 1**. Of 218 patients diagnosed with SNUC in our study cohort, 97 total patients with established recurrent or metastatic SNUC were identified, with a median [IQR] age of 52.1 [40.0 – 64.3] years at the time of their diagnosis including 66 (68.0%) male and 31 (32.0%) female patients. Of these patients, 15 presented with metastatic disease and 90 developed recurrence of their tumor following their initial treatment.

Of the 15 patients who presented with metastatic disease, data regarding primary patient characteristics and treatment was available for 13 patients. Patients with metastatic disease presented initially with disease localized to their ethmoid sinuses (6/13, 46.2%) and nasal cavity (3/13, 23.1%), and most patients presented with orbital involvement (8/12, 66.7%). Dural involvement was present in approximately half of this patient population (6/12, 50.0%). Majority of these patients with metastatic spread presented with more locally advanced disease (T_4: 12/13 [92.3%]) (**Table 1**).

On initial presentation with primary tumor, the majority of patients with recurrent disease independently demonstrated invasion of malignancy to adjacent structures (T_4: 49/69 [71.0%]), no lymph node involvement (N_0: 52/69 [75.4%]), and no metastases (M_0: 62/69 [89.9%]). Recurrence was primarily observed in patients after treatment of primary disease in their nasal cavity (33/90, 36.7%) and ethmoid sinuses (22/90, 24.4%). Other patients who developed recurrence demonstrated primary tumor with nasopharyngeal (14/90, 15.6%), maxillary (9/90, 10%), frontal (4/90, 4.4%), sphenoidal (4/90, 4.4%), or infratemporal fossa (3/90, 3.3%) involvement (**Table 1**).

37/73 (43.8%) patients re-presented with local, 7/73 (9.6%) with regional, 9/73 (12.3%) with locoregional, and 14/73 (19.2%) with distant spread of tumor while 11/73 (15.1%) patients demonstrated a combination of distant and either local, locoregional, or regional recurrence. Recurrent disease predominantly occurred in patients with orbital involvement (34/50, 68.0%) and/or dural involvement on initial presentation (30/50, 60.0%) (**Table 1**).

Management and Survival Analyses

Management of metastatic and recurrent disease was widely variable, with numerous regimens involving surgery, chemotherapy, and/or radiation observed across this patient population (**Tables 2-3**). The majority of patients with recurrence had previously been treated with chemoradiation alone (21/81, 25.9%), surgery followed by chemoradiation (14/81, 17.3%), or chemotherapy followed by chemoradiation (13/81, 16.0%) (**Table 4**). Of the patients who experienced recurrence following initial treatment, the median TTR was approximately 8 months [IQR, 3–18.5 months]. Their recurrent tumor was primarily treated with chemoradiation (15/73, 20.5%), chemotherapy alone (12/73, 16.4%), or surgery alone (11/73, 15.1%). Surgery was involved in the management of recurrence in 31/73 patients (42.5%) (**Table 3**).

While patients with metastatic disease exhibited a 1-year DSS rate of 33.3% [95% CI, 10.8% - 100%], 1- and 5-year DSS rates for the recurrent disease patient population were 45.7% [95% CI, 31.9%-65.6%] and 8.6% [95% CI, 2.9%-25.3%], respectively (**Fig. 1**). OS rates for patients with metastatic disease at 1- and 5-years were 54.6% [95% CI, 31.8% - 93.6%] and 9.1% [95% CI, 1.4% - 58.9%], while those for patients with recurrent disease were 69.8% [95% CI, 60.7% - 80.2%] and 22.1% [95% CI, 14.9% - 32.9%], respectively (**Fig. 2**). Notably, only one participant

with metastatic disease was alive beyond 5 years, for whom mortality was not attributed specifically to SNUC-related complications. Univariable Cox proportional hazards regression analyses revealed statistically significant prognostic effects of sinus involvement of primary tumor on DSS, age on OS, and orbital involvement of primary tumor on TTR. Of these associations, statistical significance was maintained on evaluation with multivariable analysis only for the association between orbital involvement and TTR (HR = 3.28, 95% CI [1.45-7.42], p = 0.004) (**Supp. Fig. 1**). Further multivariable Cox proportional hazards regression analyses yielded no other significant associations between DSS, OS, or TTR for recurrent disease and various clinical and tumor characteristics including age, sex, orbital, dural, sinus, or nasal cavity involvement, and T and N staging at presentation (**Supp. Tables 1-3**).

DISCUSSION

To our knowledge, this is the first study to address metastatic and recurrent SNUC in a very large cohort of patients for this rare population. The demographics of our patient population with recurrent SNUC align well with those of primary SNUC as reported in the literature, with majority of patients aged 40's-60's and men presenting at 2-3 times the rate of women [4]. Nearly 59% of patients presented initially with dural and 68% with orbital extension of disease suggesting the aggressive nature of SNUC in line with what has previously been described [6,14,15]. SNUC appears particularly aggressive at initial presentation in patients who proceed to develop metastatic or recurrent disease, further evidenced by the tendency for higher T stages (T3, T4) at presentation in majority of the metastatic and recurrent SNUC patient population studied here.

Interestingly, DSS and OS analysis of this dataset did not suggest any predictive characteristics associated with the prognosis of recurrent or metastatic SNUC with respect to age, sex, or involvement of the orbit, sinuses, or nasal cavity, though these analyses were limited due to a widely heterogenous patient population. Notably, however, patients who presented with orbital extension of primary SNUC appeared to relapse more quickly following initial treatment (Supp. Fig. 1). In conjunction with prior findings highlighting the significant proportion of patients presenting with orbital invasion of SNUC, this emphasizes the potential utility and necessity of more aggressive treatment in this subgroup given the likelihood of recurrence with further implications on DSS [6].

Aggressive surgical intervention via orbital exenteration in this population has been explored previously, though the research is limited to small case series and individual case studies presumably given the rarity of this disease. These studies describe limited utility of orbital exenteration with minimal effects on survival, evidence of recurrence despite intervention, and significantly associated morbidity [16–18]. Other studies have described benefits of extended orbital exenteration in patients presenting with orbital extension of disease, highlighting positive effects on OS and recurrence-free survival [19]. Interestingly, induction chemotherapy for a select population of SNUC patients with orbital involvement has demonstrated promising results with improved orbital preservation [18].

While majority of patients with SNUC across the six institutions included here were treated with either chemoradiation alone or surgery/chemotherapy followed by chemoradiation for their primary disease and either chemoradiation or monotherapies involving chemotherapeutic or

surgical interventions for recurrent disease, the data demonstrated large variability in management, limiting our ability to discern any meaningful survival differences in patients attributable to treatment modality. Coupled with a heterogenous patient population at presentation, this emphasizes the significant challenges that exist in standardizing care for patients with primary disease and even more so for patients with recurrent or metastatic SNUC. However, remarkably lower 1-year DSS for metastatic SNUC (33.3%) and 1- and 5-year DSS for recurrent SNUC (45.7% and 8.6%, respectively) relative to primary disease demonstrate the necessity for further evaluation of our current approaches in hopes of multi-center standardization of management in efforts to improve outcomes. Interestingly, of the patients who developed recurrence, majority appear to have experienced tumor recurrence within 2 years of their initial treatment. Considering a median time to recurrence of 8 months observed in this patient cohort in conjunction with reports in the literature of recurrence occurring in more than 20-30% of patients with primary disease, this may suggest benefit in earlier, more frequent post-treatment surveillance within this time frame[13].

Recent studies have pointed to the efficacy of incorporating induction chemotherapy into management of primary SNUC, followed by definitive chemoradiation for those who respond well [10,11,18]. However, its utility in the recurrent and metastatic population has not yet been well-explored. One area of interest on the horizon involves recent molecular analyses via next-generation sequencing and immunohistochemical studies that have highlighted specific genetic associations reportedly unique to SNUC that may have broad implications for future therapy. Isocitrate dehydrogenase 2 (IDH2) mutations appear particularly prominent in SNUC, reported in ranges of 49-88% of patients in small case series, encouraging several clinical trials that have

been initiated to explore the efficacy of IDH2-targeting therapies, such as enasidenib, on treating this rare, but aggressive, malignancy [20–23]. Recent preclinical studies have demonstrated increased expression of programmed-death ligand 1 (PD-L1) in SNUC cell lines and responsiveness to anti-PD-L1 therapy in combination with interleukin-15 (IL-15) superagonism *in vitro*, suggesting targets for potentially therapeutic benefits of combinatory immunotherapy [24]. Other possible genetic targets of interest for targeted therapy that have been described in the literature include aberrations in growth factor receptors such as HER2 and fibroblast growth factors (FGFR1), though these appear much less frequently associated with SNUC than IDH2 mutations and the clinical implications have not yet been as well-explored [25–27].

CONCLUSION

Research regarding recurrent and metastatic SNUC, a rare and aggressive sinonasal malignancy, is incredibly limited. To our knowledge, this represents one of the first studies to explore recurrent and metastatic SNUC in a large, international, multi-institutional patient cohort, suggesting important prognostic factors for recurrence following initial treatment including orbital extension of disease. The significant link between orbital involvement and time to recurrence potentially warrants more aggressive treatment of initial disease with orbital extension, though further study is necessary to discern the optimal modality of choice. The dismal survival rates of recurrent and metastatic SNUC and wide variability in current management strategies emphasize the necessity of further investigation towards a multi-center standardization of treatment in hopes of improving evidence-based recommendations, with optimistic investigations of new biologic interventions currently under way.

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FIGURE CAPTIONS

Figure 1. Disease-specific survival rates of **a)** patients with metastatic SNUC and **b)** patients with recurrent SNUC

Figure 2. Overall survival rates of **a)** patients with metastatic SNUC and **b)** patients with recurrent SNUC

TABLES

Table 1. Summarized demographics and clinical characteristics of patients on initial presentation with SNUC.

	Metastatic Disease	Recurrent Disease	Total
Age, *mean (SD), y*	52.1 [18.1]	51.7 [15.1]	52.4 (15.6)
Age, median (IQR), y	50.1 [41.1-62.5]	51.5 [39.9 – 64.0]	52.1 [40.0 – 64.3]
Patient sex			
Male	12 (80.0%)	61 (67.8%)	66 (68.0%)
Female	3 (20.0%)	29 (32.2%)	31 (32.0%)
Primary Site			
Nasal Cavity	3 (23.1%)	33 (36.7%)	35 (36.8%)
Ethmoid	6 (46.2%)	22 (24.4%)	22 (23.2%)
Nasopharynx	0	14 (15.6%)	14 (14.7%)
Maxillary	2 (15.4%)	9 (10.0%)	11 (11.6%)
Frontal	1 (7.7%)	4 (4.4%)	4 (4.2%)
Sphenoid	0	4 (4.4%)	4 (4.2%)
Infratemporal Fossa	0	1 (1.1%)	1 (1.1%)
Other	1 (7.7%)	3 (3.3%)	4 (4.2%)
TNM staging			
T			
I	0	2 (2.9%)	2 (2.7%)

II	0	8 (11.6%)	8 (10.7%)
III	1 (7.7%)	10 (14.5%)	11 (14.6%)
IV	12 (92.3%)	49 (71.0%)	54 (72.0%)
N			
0	7 (53.8%)	52 (75.4%)	55 (73.3%)
I	3 (23.1%)	8 (11.6%)	9 (12.0%)
IIa	0	0	0
IIb	0	2 (2.9%)	2 (2.7%)
IIc	2 (15.4%)	6 (8.7%)	7 (9.3%)
III	1 (7.7%)	1 (1.5%)	2 (2.7%)
M			
0	0	62 (89.9%)	62 (82.7%)
I	13 (100%)	7 (10.1%)	13 (17.3%)
Orbital Involvement			
Yes	8 (66.7%)	34 (68.0%)	38 (67.9%)
No	4 (33.3%)	16 (32.0%)	18 (32.1%)
Dural Involvement			
Yes	6 (50.0%)	30 (60.0%)	33 (58.9%)
No	6 (50.0%)	20 (40.0%)	23 (41.1%)

Table 2. Management of patients with metastatic SNUC

Treatment Modality	N = 15
CT	3 (20.0%)
CT → CTRT	1 (6.7%)
CTRT	3 (20.0%)
CTRT → Surgery	1 (6.7%)
Other	2 (13.3%)
Palliative CT	2 (13.3%)
Surgery → CTRT	1 (6.7%)
Surgery → RT	1 (6.7%)
Surgery → CT → CTRT	1 (6.7%)

Table 3. Management of patients with recurrent SNUC stratified by site of recurrence

Treatment Modality	Recurrence Site							Total
	Local	Regional	Locoregional	Distant	Local + Distant	Regional + Distant	Locoregional + Distant	
CT	3 (9.4%)	0	1 (11.1%)	4 (28.6%)	2 (50%)	2 (66.7%)	0	**12 (16.4%)**
CT → CTRT	0	0	0	1 (7.1%)	0	0	0	**1 (1.4%)**
CT → Surgery	3 (9.4%)	0	0	0	1 (25%)	0	0	**4 (5.5%)**
CT → Surgery → RT	0	0	2 (22.2%)	0	0	0	1 (25%)	**3 (4.1%)**
CTRT	5 (15.6%)	1 (14.3%)	2 (22.2%)	4 (28.6%)	0	1 (33.3%)	2 (50%)	**15 (20.5%)**
CTRT → Surgery	0	0	1 (11.1%)	0	0	0	0	**1 (1.4%)**
Immunotherapy	1 (3.1%)	0	0	0	0	0	0	**1 (1.4%)**
Other	1 (3.1%)	4 (57.1%)	1 (11.1%)	3 (21.5%)	0	0	1 (25%)	**10 (13.7%)**
RT	1 (3.1%)	0	0	1 (7.1%)	1 (25%)	0	0	**3 (4.1%)**
Surgery	10 (31.2%)	1 (14.3%)	0	0	0	0	0	**11 (15.1%)**

Surgery → CT	2 (6.3%)	1 (14.3%)	0	0	0	0	0	**3 (4.1%)**
Surgery → CTRT	4 (12.5%)	0	1 (11.1%)	1 (7.1%)	0	0	0	**6 (8.2%)**
Surgery → RT	2 (6.3%)	0	1 (11.1%)	0	0	0	0	**3 (4.1%)**
Total	**32**	**7**	**9**	**14**	**4**	**3**	**4**	**73**

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Table 4. Management of primary disease in patients with recurrent SNUC stratified by site of recurrence

Treatment Modality	Recurrence Site							
	Local	Regional	Locoregional	Distant	Local + Distant	Regional + Distant	Locoregional + Distant	Total
CT	2 (6.5%)	0	1 (10%)	0	0	0	0	**3 (3.7%)**
CT → CTRT	5 (16.1%)	0	1 (10%)	5 (21.7%)	0	2 (66.7%)	0	**13 (16.0%)**
CT → CTRT → Surgery	1 (3.2%)	0	1 (10%)	2 (8.7%)	0	0	0	**4 (4.9%)**
CT → Surgery	0	0	0	0	1 (20%)	0	0	**1 (1.2%)**
CT → Surgery → RT	1 (3.2%)	0	1 (10%)	0	1 (20%)	0	0	**3 (3.7%)**
CT → Surgery →CTRT	1 (3.2%)	0	0	3 (13%)	0	0	1 (25%)	**5 (6.2%)**
CTRT	8 (25.8%)	3 (60%)	3 (30%)	3 (13%)	2 (40%)	1 (33.3%)	1 (25%)	**21 (25.9%)**
CTRT → Surgery	5 (16.1%)	0	0	0	0	0	1 (25%)	**6 (7.4%)**
Other	3 (9.7%)	1 (20%)	0	1 (4.4%)	0	0	0	**5 (6.2%)**
Surgery	0	0	1 (10%)	1 (4.4%)	0	0	0	**2 (2.5%)**

Surgery → CT	1 (3.2%)	0	0	0	0	0	0	**1 (1.2%)**
Surgery → CTRT	2 (6.5%)	1 (20%)	2 (20%)	8 (34.8%)	0	0	1 (25%)	**14 (17.3%)**
Surgery → RT	2 (6.5%)	0	0	0	1 (20%)	0	0	**3 (3.7%)**
Total	**31**	**5**	**10**	**23**	**5**	**3**	**4**	**81**

Supplementary Table 1. Univariable and multivariable cox proportional hazards analyses of prognostic factors for disease-specific survival of patients with recurrent SNUC

			HR (univariable)	HR (multivariable)
Age	Mean (SD)	51.7 (15.1)	1.01 (0.98-1.03, p=0.561)	0.97 (0.93-1.02, p=0.258)
Sex	M	61 (67.8)	-	-
	F	29 (32.2)	1.36 (0.63-2.94, p=0.441)	0.23 (0.04-1.35, p=0.103)
Orbital Involvement	No	16 (32.0)	-	-
	Yes	34 (68.0)	3.24 (0.88-11.94, p=0.077)	5.06 (0.79-32.50, p=0.087)
Dural Involvement	No	20 (40.0)	-	-
	Yes	**30 (60.0)**	**0.32 (0.11-0.89, p=0.029)**	**0.19 (0.04-0.86, p=0.031)**
Sinus Involvement	No	51 (56.7)	-	-
	Yes	**39 (43.3)**	**2.13 (1.05-4.32, p=0.036)**	3.57 (0.78-16.42, p=0.102)
Nasal Cavity Involvement	No	57 (63.3)	-	-
	Yes	33 (36.7)	0.64 (0.31-1.30, p=0.219)	NA (NA-NA, p=NA)
T Stage	<T4	20 (27.4)	-	-
	≥T4	53 (72.6)	0.96 (0.38-2.41, p=0.935)	0.28 (0.02-3.45, p=0.321)
N Stage	<N2	64 (86.5)	-	-
	≥N2	10 (13.5)	0.82 (0.24-2.86, p=0.758)	0.19 (0.01-5.56, p=0.331)

Supplementary Table 2. Univariable and multivariable cox proportional hazards analyses of prognostic factors for overall survival of patients with recurrent SNUC

			HR (univariable)	HR (multivariable)
Age	**Mean (SD)**	**51.7 (15.1)**	**1.03 (1.01-1.04, p=0.002)**	1.01 (0.98-1.04, p=0.405)
Sex	M	61 (67.8)	-	-
	F	29 (32.2)	1.05 (0.66-1.67, p=0.847)	0.95 (0.37-2.50, p=0.925)
Orbital Involvement	No	16 (32.0)	-	-
	Yes	34 (68.0)	1.49 (0.80-2.77, p=0.214)	1.66 (0.85-3.26, p=0.140)
Dural Involvement	No	20 (40.0)	-	-
	Yes	30 (60.0)	0.83 (0.46-1.49, p=0.533)	0.67 (0.27-1.63, p=0.373)
Sinus Involvement	No	51 (56.7)	-	-
	Yes	39 (43.3)	0.96 (0.62-1.49, p=0.844)	0.87 (0.29-2.57, p=0.800)
Nasal Cavity Involvement	No	57 (63.3)	-	-
	Yes	33 (36.7)	0.89 (0.57-1.38, p=0.599)	0.96 (0.30-3.06, p=0.946)
T Stage	<T4	20 (27.4)	-	-
	≥T4	53 (72.6)	1.13 (0.66-1.93, p=0.656)	1.46 (0.45-4.78, p=0.532)
N Stage	<N2	64 (86.5)	-	-
	≥N2	10 (13.5)	0.64 (0.33-1.27, p=0.202)	0.44 (0.14-1.38, p=0.160)

Supplementary Table 3. Univariable and multivariable cox proportional hazards analyses of prognostic factors for time to recurrence for patients with recurrent SNUC

			HR (univariable)	HR (multivariable)
Age	Mean (SD)	51.7 (15.1)	1.00 (0.99-1.02, p=0.768)	0.98 (0.96-1.01, p=0.198)
Sex	M	61 (67.8)	-	-
	F	29 (32.2)	1.15 (0.73-1.81, p=0.539)	0.53 (0.20-1.42, p=0.207)
Orbital Involvement	No	16 (32.0)	-	-
	Yes	**34 (68.0)**	**2.51 (1.27-4.98, p=0.008)**	**3.28 (1.45-7.42, p=0.004)**
Dural Involvement	No	20 (40.0)	-	-
	Yes	30 (60.0)	0.83 (0.46-1.49, p=0.527)	0.48 (0.20-1.16, p=0.102)
Sinus Involvement	No	51 (56.7)	-	-
	Yes	39 (43.3)	1.25 (0.81-1.92, p=0.313)	1.16 (0.36-3.69, p=0.801)
Nasal Cavity Involvement	No	57 (63.3)	-	-
	Yes	33 (36.7)	0.76 (0.49-1.18, p=0.221)	0.54 (0.16-1.83, p=0.323)
T Stage	<T4	20 (27.4)	-	-
	≥T4	53 (72.6)	1.05 (0.62-1.78, p=0.849)	2.28 (0.63-8.27, p=0.209)
N Stage	<N2	64 (86.5)	-	-
	≥N2	10 (13.5)	0.70 (0.35-1.37, p=0.293)	0.34 (0.10-1.12, p=0.076)

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