Patterns of recurrences in sinonasal cancers undergoing an endoscopic surgery-based treatment: Results of the MUSES* on 940 patients *MUlti-institutional collaborative Study on Endoscopically treated Sinonasal cancers

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A B S T R A C T

Objectives: The improvements in survival with expansion of the survivors' population, along with evolution of endoscopically-based treatment modalities, have contributed to emphasize the clinical relevance of recurrences in sinonasal cancers. However, at present, literature is scant regarding the pattern of recurrences and the therapeutic strategies available to manage long survivors who experienced single or multiple failures. The aim of the present study was to analyze sinonasal cancers recurrences to provide data regarding rates and patterns of relapse, predictors of failure and prognostic impact of the recurrence.
Materials and Methods: All patients receiving multimodal treatments including endoscopic surgery between 1995 and 2021 in three European referral centers were included. Statistical analysis of survival was performed through univariable, multivariable and unidirectional multistate models. Survival after recurrence analysis was implemented for patients experiencing at least one recurrence.
Results: The 5- and 10-year recurrence free survival rates were 34.1% and 38.4% for the whole population. With a mean follow-up time of 60 months, a global recurrence rate of 32.9% was observed. The 5- and 10-year survival after recurrence rates were 27.2% and 21.7%, respectively. Incidence and rates of recurrences were significantly associated with histology subtypes.
Conclusion: This study provides valuable oncologic outcomes regarding a large homogenous cohort of patients affected by sinonasal malignances treated within a multimodal framework, emphasizing the strong correlation of histologic type with prognosis, as well as with pattern of recurrences.

Introduction

During the last two decades, data from retrospective studies and population-based registry analyses have re-shaped the panorama of therapeutic strategies employed in the management of sinonasal cancers. During this time span, literature has progressively shifted its focus from analyzing outcomes of different surgical approaches to explore which multimodal treatment protocol could offer the best oncologic outcome, driven by histological subtypes. The implementation of such histology-driven strategies in multidisciplinary settings have allowed to achieve better survival outcomes [1–4]. Therefore, the survivors' population progressively expanded, so as did recurrences, the management of which has now become a critical issue. If most studies focused on global oncologic outcomes and investigated on prognostic factors, literature is scant regarding pattern of recurrence, the factors which might influence their specific occurrence and their prognostic impact for the different histological types. Moreover, in the last three decades, endoscopic surgery has progressively proven to be safe and effective in the treatment of sinonasal malignancies, and has progressively replaced open surgery by virtue of its lower morbidity, shorter hospital stay and at least equal ability to achieve uninvolved margins. However, at present, a definitive shift toward endoscopic surgery has not been completely established, since the major cohort of patients described in literature so far were focused on traditional open surgery [5].

The aim of the present study is to retrospectively analyze a large multicentric cohort of patients affected by sinonasal cancers undergoing an endoscopic surgery-based treatment within a multimodal treatment management with the purposes of further validating the efficacy of this technique in the treatment of these cancers and in order to investigate: (a) rates and patterns of recurrences for the entire cohort and specifically for each histological type; (b) patient-related and tumor-related predictors of recurrence; (c) the prognostic impact of the failure in term of survival after recurrence (SAR).

Materials and methods

Dataset preparation

A multicentric retrospective observational cohort study of a series of patients treated in three European tertiary care referral centers for the management of sinonasal cancers was performed [6]. The following criteria were applied to select patients to be included into the main dataset:

- Patients were affected by primary or recurrent resectable sinonasal cancer.
- Surgery included an endoscopic transnasal approach and was performed as part of a curative treatment at one of the three principal centers of the MUSES (*i.e.*, "ASST Spedali Civili di Brescia" – University of Brescia [Brescia, Italy], "Ospedale di Circolo e Fondazione Macchi" – University of Insubria [Varese, Italy], "Hôpital Lariboisière" – University of Paris [Paris, France]).
- Period of inclusion: 1995–2018.
- Treatment was performed within a multidisciplinary frame (*i.e.*, at least a head and neck surgeon with expertise in endoscopic skull base surgery, a radiation oncologist, a medical oncologist, and a radiologist were involved) in accordance with current guidelines and evidences [1,7–10].

The following exclusion criteria were used:

- Patients affected by systemic lymphoproliferative disorders with sinonasal localization.
- Distant metastasis at presentation.
- Patients receiving any of the following surgical procedures: open maxillectomy, open craniofacial resection, rhinectomy, Riedel's operation, osteoplastic frontal approach, midfacial degloving approach, lateral rhinotomy approach, orbital exenteration/clearance.

Demographic data, tumor characteristics, imaging studies, surgical and pathological reports, previous treatments and adjuvant therapy, complications and follow-up were retrieved [4]. All patients of the series were retrospectively staged according to the 8th edition of the AJCC/UICC staging system for head and neck cancer [11]. Histological types and grading were classified according to the 4th Edition of the WHO Classification of Head and Neck Tumours [12]. The Kadish staging system [13] and the Dulguerov-Calcaterra staging system [14] were additionally used to stage the tumors histologically classified as olfactory neuroblastoma (ONB). Tumors were grouped in the following categories according to histopathological diagnosis: sinonasal adenocarcinomas (SNAC), sinonasal carcinomas (SNC), mucosal melanomas (MM), olfactory neuroblastomas (ONB), salivary gland cancers (SGC), soft tissue tumors (STT), borderline / low grade malignant soft tissue tumors (LGMSFT), undifferentiated tumors. Informed consent was obtained from all participants included in the study. All procedures were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board (Insubria Board of Ethics, approval number

0033025/2015).

Recurrence analysis

Recurrences were stratified according to the location of the relapse, as follows: patients with exclusively local relapse (T+, N-, M-); patients with regional relapse, with or without local recurrence (T±, N+, M-); patients with distant relapse, regardless of failure at other sites (T±, N±, M+).

Statistical analysis

All analyses were performed with R (version 4.1.2, r-project.org). The main endpoints were overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), recurrence-free survival (RFS) and recurrence free survival considering local, regional and distant sites (L-RFS, R-RFS, D-RFS, respectively). OS was defined as time from surgical treatment to death for all causes, DFS as the time from surgical treatment until the first event between relapse at any site or death for all causes. Cause-specific end-points were also considered: DSS was defined as time from surgical treatment to death for causes related to the sinonasal malignant tumor (death for other causes was considered as a competing event); RFS was defined as time from surgical treatment until relapse at any site (death for all causes was considered as a competing event); for L-RFS, R-RFS, D-RFS only relapse at each respective site (local, regional and distant) was considered. For OS and DFS outcomes, the Kaplan-Meier method was used to estimate the survival probability. For outcomes with competitive risk (DSS, RFS, L-RFS, R-RFS, D-RFS), the Aalen-Johansen method was used to estimate the crude cumulative incidences for each competitive event. Survival and crude incidence curves within levels of each factor were estimated and compared based on either the log rank test or Gray test according to the considered outcome. Age at diagnosis, as a continuous variable, was analyzed using univariable Cox models. Univariable analyses and multivariable proportional hazard Cox-regression models were also implemented.

A unidirectional multistate model was implemented with descriptive purpose to depict the rate of patients experiencing each disease state (free of disease, locoregional recurrence, distant recurrence, death) over time, separately for each histological group.

SAR analysis was performed considering patients who experienced at least one recurrence during the follow-up. The Kaplan-Meier method was used to estimate the survival probability, considering the first recurrence as the starting point of the observation. For each of the five most represented histological groups a multivariable proportional hazard Cox-regression model was implemented considering age at recurrence (AAR), time to recurrence (TTR) and site of recurrence (SOR), classified as either distant or locoregional, as prognostic factors.

Results of Cox regression analysis are shown in term of hazards ratios (HR), 95% confidence intervals (CIs), and p values. All statistical tests were two tail and p values were considered significant when < 0.05. P-values within the interval 0.05–0.10 were defined as close-to-significant. Subgroup analysis was performed only on groups including at least 75 patients.

Results

Patients' characteristics

The patients considered eligible for the present study were 940: 493/940 (52.5%) treated at "Ospedale di Circolo e Fondazione Macchi – University of Insubria" in Varese, 290/940 (30.8%) treated in "ASST Spedali Civili di Brescia" and 157/290 (16.7%) treated at "Hôpital Lariboisière – University of Paris"). The clinicopathological feature of the population are depicted in Table 1. The study population included a total of 39 different histological types, the distribution of which is shown in Table S1. All patients underwent surgical resection of the tumor

Table 1
Clinical features of the study population.

Variable		N	%
Age	Mean	61.2	
	Median	64	
	IQR	52–73	
Gender	Male	642/940	68.3
	Female	298/940	31.7
Presentation	Naive	745/940	79.3
	Relapses	195/940	20.7
Previous treatment	Surgery (±RT ± CHT)	146/940	15.5
	RT (±CHT)	38/940	4.0
	Exclusive CHT	7/940	0.8
Site of origin	Naso-ethmoid	843/940	89.7
	Maxillary	76/940	8.1
	Sphenoid	16/940	1.7
	Frontal	5/940	0.5
T classification	T1	150/940	16
	T2	199/940	21.2
	T3	186/940	19.8
	T4a	158/940	16.8
	T4b	246/940	26.2
N classification	N0	920/940	97.9
	N+	20/940	2.1
	1	7	
	2a	1	
	2b	7	
	2c	2	
	3b	3	
Induction CHT		59/940	6.3
Surgery	ER	373/940	39.9
	ERTC	464/940	49.5
	CER	84/940	8.9
	Multiportal approaches	19/940	1.7
Surgical margins	R0	723/940	76.9
	R+	217/940	23.1
Adjuvant treatment	None	375/940	39.9
	Exclusive RT	528/940	56.2
	CRT	37/940	3.9
Follow-up	Mean	60	months
	Median	46	months
	Range	1–272	months
Status	NED	587/940	62.4
	DOD	185/940	19.7
	AWD	82/940	8.7
	DOC	72/940	7.7
	Lost	14/940	1.5

Abbreviations: AWD, alive with disease; CER, cranio-endoscopic resection; CHT, chemotherapy; CRT, chemoradiotherapy; DOC dead of other causes; DOD, dead of disease; ER, endoscopic endonasal resection; ERTC, endoscopic resection with transnasal craniectomy; IQR, inter-quartile range; NED, no evidence of disease; R0, free margin resection; R+, residual disease; RT, radiotherapy.

through an approach tailored to the extension of disease. Complete resection (R0) was obtained in 723 (76.9%) cases. After surgery, 565/940 (60.1%) patients received adjuvant treatments.

Survival analysis

The follow-up of the study population ranged from 1 to 272 months (mean, 60 months; median, 46 months). Since 14 patients were lost at follow-up, the survival and recurrence analyses were performed on a total of 926 patients. The 5- and 10-year OS rates were 73.6% and 61.2%, while 5- and 10-year DFS rates were 59.6% and 49.6%, respectively. Kaplan-Meier curves for composite outcomes (OS and DFS) and curves of cumulative incidence for competitive risks (DSS, RFS, L-RFS and D-RFS) are shown in Fig. S1. Table S2 reports incidences of events of interest and competitive events, along with confidence interval for such outcomes.

Univariable analysis showed statistically significant differences in survival rates according to the parameters most widely recognized in the literature as prognostic factors (Table S3). Remarkably, statistically significant differences were observed in terms of OS, DFS, RFS, LRF and

D-RFS (p < 0.001) according to histological groups, reflecting the different biological behavior of these neoplasms (Fig. 1). Finally, multivariable analysis was performed for OS, DFS, L-RFS and D-RFS for the whole study population to investigate the impact on prognosis of selected variables explored in univariable analysis (Table S3).

Recurrence analysis

During follow-up, a total of 305/926 patients (32.9%) developed at least a recurrence: local failures in 155/926 cases (16.7%), regional in 22/926 (2.4%) and distant in 130/926 (14%) (Table 2). Mean and median time to the first recurrence were 21.4 months and 10.5 months respectively (range 1–163 months). As regards treatment of recurrences, surgical resection was mainly used in case of local relapse (77/155, 49.7%) for all the histological groups. Exclusive surgical resection was used in 58 cases, surgery followed by RT in 16 cases and ChT (chemotherapy) was part of the treatment in 3 cases. Regional recurrences were uncommon events considering overall histologies and were more frequent for olfactory neuroblastoma, occurring in 5.4% of the cases (6/112 patients). Salvage treatment was almost exclusively performed in the form of neck dissection, in 68.2% of the cases (15/22 patients). Systemic dissemination was the most frequent event of relapse for MM and undifferentiated tumors, occurring in 43.7% and 24.1% of the cases, respectively. In these cases, chemotherapy was the main modality of treatment for all histological groups (51/130 patients, 39.2%), with immunotherapy mainly used in cases of metastatic MM (10 cases). To note, a considerable percentage of metastatic patients were addressed to best supportive care (49/130, 37.7%). Rates, time, patterns of recurrence and follow-up status were considerably different among different histological types (Table 2). The multistate model was implemented to depict the rate of patients experiencing each disease state (free of disease, locoregional recurrence, distant recurrence, death) over time for each of the five most represented histological groups - SNAC, SNC, ONB, MM, SGC (Fig. 2). Table 3 shows DFS, tested with both univariable and multivariable analysis, L-RFS and D-RFS, analyzed in a histology-specific multivariable model, for each of the five considered histological groups.

Survival after recurrence analysis

Considering only patients experiencing at least one recurrence during follow-up (305/926 patients, 32.9%), SAR analysis showed that 5- and 10-year rates were 27.2% (20.7–33.6) and 21.7% (14.9–28.5)

respectively. Univariable analysis showed that SAR was significantly different across the histological groups (p < 0.001) (Fig. 3). Table 4 shows the multivariable model considering the role of AAR, TTR and SOR as prognostic factors for the different histologies. TTR was associated with slight improvement in prognosis (the later the relapse, the better the prognosis) for most of the considered histological groups, while SOR was significantly associated with difference in prognosis only for SNACs with HR 4.411 (2.358–8.250, p < 0.001).

Discussion

Nearly two decades have passed since the introduction of endoscopic techniques for the surgical treatment of sinonasal malignancies. Nevertheless, the rarity and high degree of heterogeneity of these cancers resulted in a paucity of evidence-based results, as most of the available data are related to case series with small sample sizes and short follow-up [15]. To the best of our knowledge, the MUSES study represents the largest multicentric series of endoscopically-treated sinonasal malignancies with an adequate mean follow-up time of 60 months. The 5- and 10-year OS rates were 73.6% and 61.2%, while 5- and 10-year DFS rates were 59.6% and 49.6%, respectively. These outcomes are worse if compared to the *meta*-analysis published by Rawal et al. [16]. However, caution should be paid when comparing oncologic outcomes with earlier endoscopic series, where lower stages of disease with shorter follow-up time have been reported [17]. A recent study from the MD Anderson Cancer Center (Houston, Texas) [3], reports outcomes for 293 patients treated by means of endoscopic and endoscopic-assisted resection, showing 10-year OS, DSS and RFS of 61.7%, 79.7%, and 40.2% respectively, which is in line with the present experience, confirming that even though oncologic outcomes have been steadily improving over the last 4 decades [18], prognosis is to be globally considered poor and continues to decrease for a long period of time after treatment. The mean follow-up time of 60 months is a considerable strength point of the present analysis, and it is the longest ever reported for endoscopically-treated sinonasal malignancies. This has allowed to observe disease-related events occurring even more than 10 years after surgery, as reflected by the decrease in OS and DFS from the 5th to 10th year of follow-up. This confirms that failures significantly impact on prognosis and suggests that follow-up for sinonasal malignancies is to be prolonged, at least for specific histologies, for more than 10 years [9].

Although the global recurrence rate was 32.9% (305/926 patients), our study showed that the distribution of recurrences significantly varied according to histology. The highest recurrence rate was observed for
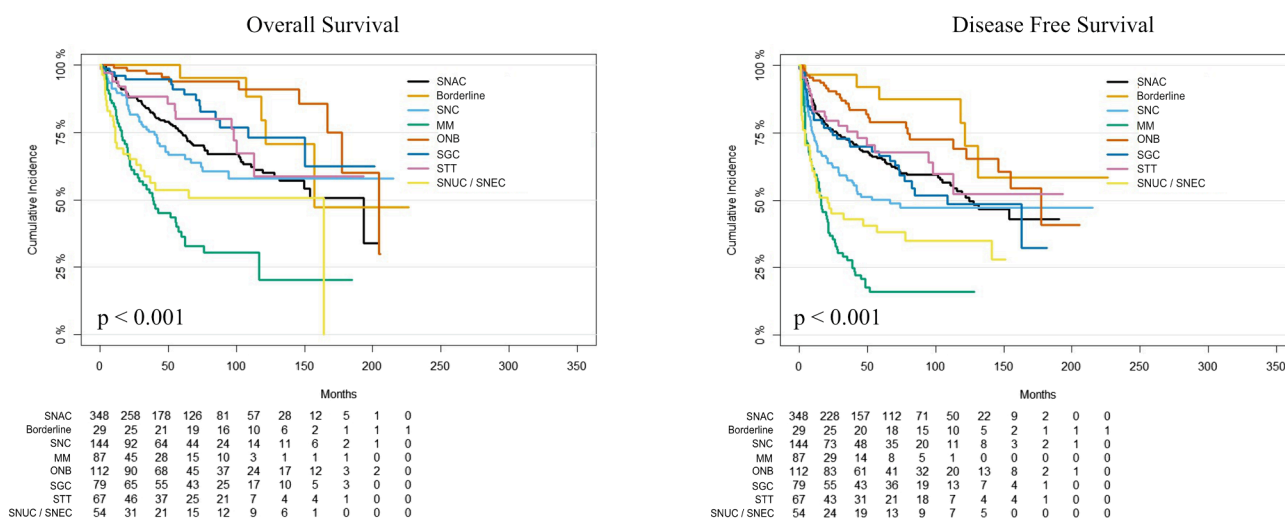

Fig. 1. Univariable analysis: Kaplan-Meier curves for OS and DFS according to histologic groups. *Abbreviations: MM, malignant melanoma; ONB, olfactory neuroblastoma; SGC, salivary gland cancer; SNAC, sinonasal adenocarcinoma; SNC, sinonasal carcinoma; SNEC, sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; STT, soft tissue tumor.*

Table 2
Rates, time, patterns of recurrence and follow-up status of the study population, according to the histologic group.

		SNAC		SNC		MM		ONB		SGC		STT		SNUC / SNEC		Borderline Tumor		H-L tumor	Total	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	n/TOT	%
Cases*		348/926	37,6%	144/926	15,6%	87/926	9,4%	112/926	12,1%	79/926	8,5%	67/926	7,2%	54/926	5,8%	29/926	3,1%	6/926	926/926	100%
Patients with recurrence		90/348	26,1%	56/144	39,6%	63/87	72,4%	22/112	19,6%	28/79	35,4%	13/67	19,4%	30/54	55,6%	3/29	10,3%	0/6	305/926	32.9%
Time	Mean	22,4	months	14,3	months	14,5	months	44,8	months	29,8	months	19,9	months	17,8	months	58,9	months	NA	21,4	months
	Median	11,7	months	8,8	months	9,5	months	30,4	months	13,6	months	9	months	7,5	months	42,1	months	NA	10,5	months
	Range	1–124	months	1–53	months	1–48	months	2–154	months	1–163	months	2–94	months	1–140	months	4–130	months	NA	1; 163	months
Patients' status	DOC	5/348	1,4%	2/144	1,4%	2/87	2,3%	0/112	0,0%	1/79	1,3%	1/67	1,5%	0/54	0,0%	0/29	0,0%	0	11/926	1,2%
	DOD	53/348	15,2%	33/144	22,9%	44/87	50,6%	5/112	4,5%	7/79	8,9%	5/67	7,5%	21/54	38,9%	2/29	6,9%	0	170/926	18,4%
	AWD	18/348	5,2%	10/144	6,9%	15/87	17,2%	11/112	9,8%	13/79	16,5%	3/67	4,5%	6/54	11,1%	0/29	0,0%	0	76/926	8,2%
	NED	14/348	4,0%	11/144	7,6%	2/87	2,3%	6/112	5,4%	7/79	8,9%	4/67	6,0%	3/54	5,6%	1/29	3,4%	0	48/926	5,2%
Local recurrences (T+, N-, M-)		48/348	13,8%	31/144	21,5%	22/87	25,3%	8/112	7,1%	19/79	24,1%	10/67	14,9%	14/54	25,9%	3/29	10,3%	0	155/926	16,7%
Time	Mean	26,3	months	11,7	months	17,9	months	34,8	months	36,6	months	21	months	17	months	58,9	months	NA	22,7	months
	Range	1–125	months	2–53	months	2–102	months	4–80	months	1–163	months	2–94	months	1–77	months	4–130	months	NA	1–163	months
Treatment	S (±RT ± CHT)	24/348	6,9%	15/144	10,4%	14/87	16,1%	4/112	3,6%	8/79	10,1%	4/67	6,0%	6/54	11,1%	2/29	6,9%	0	77/926	8,3%
	RT (±CHT)	11/348	3,2%	6/144	4,2%	2/87	2,3%	2/112	1,8%	7/79	8,9%	2/67	3,0%	3/54	5,6%	1/29	3,4%	0	34/926	3,7%
	BSC	13/348	3,7%	10/144	6,9%	6/87	6,9%	2/112	1,8%	4/79	5,1%	4/67	6,0%	5/54	9,3%	0/29	0,0%	0	44/926	4,8%
Patients' status	DOC	4/348	1,1%	2/144	1,4%	1/87	1,1%	0/112	0,0%	0/79	0,0%	1/67	1,5%	0/54	0,0%	0/29	0,0%	0	8/926	0,9%
	DOD	20/348	5,7%	16/144	11,1%	16/87	18,4%	2/112	1,8%	5/79	6,3%	4/67	6,0%	7/54	13,0%	2/29	6,9%	0	72/926	7,8%
	AWD	12/348	3,4%	6/144	4,2%	3/87	3,4%	4/112	3,6%	9/79	11,4%	3/67	4,5%	6/54	11,1%	0/29	0,0%	0	43/926	4,6%
	NED	12/348	3,4%	7/144	4,9%	2/87	2,3%	2/112	1,8%	5/79	6,3%	2/67	3,0%	1/54	1,9%	1/29	3,4%	0	32/926	3,5%
Regional recurrences (T±, N+, M-)		3/348	0,8%	3/144	2,1%	3/87	3,4%	6/112	5,4%	1/79	1,3%	1/67	1,5%	3/54	5,6%	0/29	0	0	22/926	2,4%
Time	Mean	25,8	months	10,9	months	18	months	39,3	months	34,7	months	20	months	17,5	months	58,9	months	NA	22,8	months
	Range	1–124	months	2–53	months	2–102	months	2–122	months	1–163	months	2–94	months	1–77	months	4–130	months	NA	1–163	months
Treatment	S (±RT ± CHT)	1/348	0,3%	2/144	1,4%	2/87	2,3%	6/112	5,4%	1/79	1,3%	0/67	0,0%	2/54	3,7%	0/29	0,0%	0	14/926	1,5%
	RT (±CHT)	1/348	0,3%	1/144	0,7%	1/87	1,1%	0/112	0,0%	0/79	0,0%	0/67	0,0%	1/54	1,9%	0/29	0,0%	0	4/926	0,4%
	BSC	1/348	0,3%	0/144	0,0%	0/87	0,0%	0/112	0,0%	0/79	0,0%	1/67	1,5%	0/54	0,0%	0/29	0,0%	0	2/926	0,1%
Patients' status	DOC	1/348	0,3%	0/144	0,0%	0/87	0,0%	0/112	0,0%	0/79	0,0%	0/67	0,0%	0/54	0,0%	0/29	0%	0	1/926	0,1%
	DOD	2/348	0,6%	1/144	0,7%	1/87	1,1%	0/112	0,0%	0/79	0,0%	0/67	0,0%	1/54	1,9%	0/29	0%	0	5/926	0,5%
	AWD	0/348	0,0%	0/144	0,0%	2/87	2,3%	2/112	1,8%	0/79	0,0%	0/67	0,0%	0/54	0,0%	0/29	0%	0	4/926	0,4%
	NED	0/348	0,0%	2/144	1,4%	0/87	0,0%	4/112	3,6%	1/79	1,3%	1/67	1,5%	2/54	3,7%	0/29	0%	0	10/926	1,1%
						38/87		8/112		8/79		2/67		13/54		0/29	0%	0		14,0%

Table 2 (continued)

	SNAC n	SNAC %	SNC n	SNC %	MM n	MM %	ONB n	ONB %	SGC n	SGC %	STT n	STT %	SNUC / SNEC n	SNUC / SNEC %	Borderline Tumor n	Borderline Tumor %	H-L tumor n	Total n/TOT	Total %
Distant recurrences (T±, N±, M+)	39/348	11,2%	22/144	15,3%		43,7%		7,1%		10,1%		3,0%		24,1%	NA		NA	130/926	
Time — Mean	20	months	19,8	months	16,1	months	43	months	28,3	months	31,2	months	19,2	months	NA		NA	20,7	months
Time — Range	1–115	months	1–45	months	1–55	months	3–112	months	5–82	months	28–33	months	1–140	months	NA		NA	1–140	months
Treatment — S (±RT ± CHT)	5/348	1,4%	6/144	4,2%	0/87	0,0%	1/112	0,9%	2/79	2,5%	0/67	0,0%	0/54	0,0%	0/29	0%	0	14/926	1,5%
Treatment — RT (±CHT)	4/348	1,1%	2/144	1,4%	4/87	4,6%	4/112	3,6%	0/79	0,0%	0/67	0,0%	3/54	5,6%	0/29	0%	0	17/926	1,8%
Treatment — BSC	30/348	8,6%	14/144	9,7%	34/87	39,1%	3/112	2,7%	6/79	7,6%	2/67	3,0%	10/54	18,5%	0/29	0%	0	99/926	10,7%
Patients' status — DOC	0/348	0,0%	0/144	0,0%	1/87	1,1%	0/112	0,0%	1/79	1,3%	0/67	0,0%	0/54	0,0%	0/29	0%	0	2/926	0,2%
Patients' status — DOD	31/348	8,9%	16/144	11,1%	27/87	31,0%	3/112	2,7%	2/79	2,5%	1/67	1,5%	13/54	24,1%	0/29	0%	0	93/926	10,0%
Patients' status — AWD	6/348	1,7%	4/144	2,8%	10/87	11,5%	5/112	4,5%	4/79	5,1%	0/67	0,0%	0/54	0,0%	0/29	0%	0	29/926	3,1%
Patients' status — NED	2/348	0,6%	2/144	1,4%	0/87	0,0%	0/112	0,0%	1/79	1,3%	1/67	1,5%	0/54	0,0%	0/29	0%	0	6/926	0,6%

Abbreviations: AWD, alive with disease; BSC, best supportive care (including all patients receiving treatment without curative purposes or no treatment); CHT, chemotherapy; DOC, dead of disease; DOD, dead of other causes; H-L, hemato-lymphoid tumors; M, distant recurrence; N, regional recurrence; NA, not applicable; NED, no evidence of disease; ONB, olfactory neuroblastoma; T, local recurrence; RT, radiotherapy; SGC, salivary gland cancer; SNAC, sinonasal adenocarcinoma; SNC, sinonasal carcinoma; SNEC, sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; STT, soft tissue tumor.
* Only cases with available follow-up were considered in the analysis of recurrence patterns and outcomes (excluding 14 patients lost at follow-up).

MM (63/87, 72.4%), followed by undifferentiated tumors (SNUC – sinonasal undifferentiated carcinoma – and SNEC – sinonasal neuroendocrine carcinoma) (30/54, 55.6%), SNC (56/144, 39.6%), SGC (28/79, 35.4%), SNAC (90/348, 26.1%), ONB (22/112, 19.6%) and borderline tumors (3/29, 10.3%). Moreover, most of the prognostic factors investigated appeared to be histology-specific in influencing the prognosis, standing the important role of margins' infiltration which acts as a transversal prognostic factor for most of the histologic groups considered. This emphasizes the importance of free-margin resection in the management of sinonasal cancers, which is paramount to achieve sound oncologic results. However, considering the crucial role of histology subtypes for survival outcomes and the histology-specific role of most of the other prognostic factor analyzed, the discussion regarding characteristic patterns of recurrence and their impact on prognosis will be provided separately for each one of the major histological groups.

Sinonasal adenocarcinoma (SNAC)

In the present series, SNAC accounted for 37.3% (355/941) of the population, proportion almost entirely represented by intestinal type adenocarcinoma (ITAC), with 10-year OS and DFS of 60% and 52.3%, respectively. This defines SNAC as an intermediate prognosis group, which is in line with most of the reported series, where 5-year OS, DSS, and DFS rates are 53–83%, 82–83%, and 62–74%, respectively [19].

We found that local extent of disease (pT), grading, dural involvement and surgical margins were significantly associated with reduced DFS in univariable analysis ($p < 0.001$), in line with previous studies [7,20–22]. Surgical margins' status appeared to be the strongest prognosticator for SNAC, significantly associated with both L-RFS and D-RFS, with HR of 3.169 ($p < 0.001$) and 2.93 ($p = 0.009$), respectively. This suggests that infiltrated postoperative margins represent a highly unfavorable risk factor not only for local recurrence, but also for delayed systemic dissemination. Conversely, advanced-staged lesions were significantly associated only with L-RFS (HR = 3.283, $p = 0.001$), which might indicate that ITAC classified $\geq$ pT3 might be associated with an increased risk of local failure. In addition, dural invasion showed a trend close to statistical significance with D-RFS (HR = 2.079, $p = 0.086$), suggesting that invasion of the dura might be a predisposing factor for the occurrence of systemic relapse.

A total of 91 recurrences among 348 cases (26.1%) were observed in the present study, with a mean and median time to recurrence of 22.4 and 11.7 months, respectively. Local failure was the most frequent pattern of recurrence (48/348 cases), which is consistent with the literature [7,20–22]. The non-negligible rate of distant recurrences observed in our analysis (39/348, 11.2%) is in contrast with previous studies [20–22]. This might be due to the intensive follow-up program, if compared to other follow-up policies. When occurring, systemic dissemination of disease significantly affects the prognosis. In the study by Camp et al. [22], the occurrence of metastases significantly influenced the OS ($p < 0.0001$), DSS ($p < 0.0001$), and RFS ($p < 0.0001$). In our study, the majority of these patients were not suitable for any form of treatment and were addressed to best supportive care (30/39, 76.9%). This emphasizes the detrimental effect of the relapse on prognosis for SNAC, considering that SAR of SNACs is not dissimilar to that of undifferentiated tumors or MM (Fig. 3), with 5- and 10-year SAR values of 22.4% (IC 9.9–34.9%) and 19.2% (IC 7–31.4%), respectively. Univariable analysis of SAR identified TTR and SOR significantly associated with different prognosis, with better survival for patients failing later during surveillance (TTR HR = 0.97, IC 0.96–0.99, $p = 0.002$), while patients with distant dissemination of disease experienced worse prognosis (SOR HR = 4.41, IC 2.36–8.25, $p < 0.001$).

Sinonasal squamous cell carcinoma (SNSCC)

SNSCC represented the second most frequent histologic group of the series (15.6%), which is consistent with epidemiologic data from
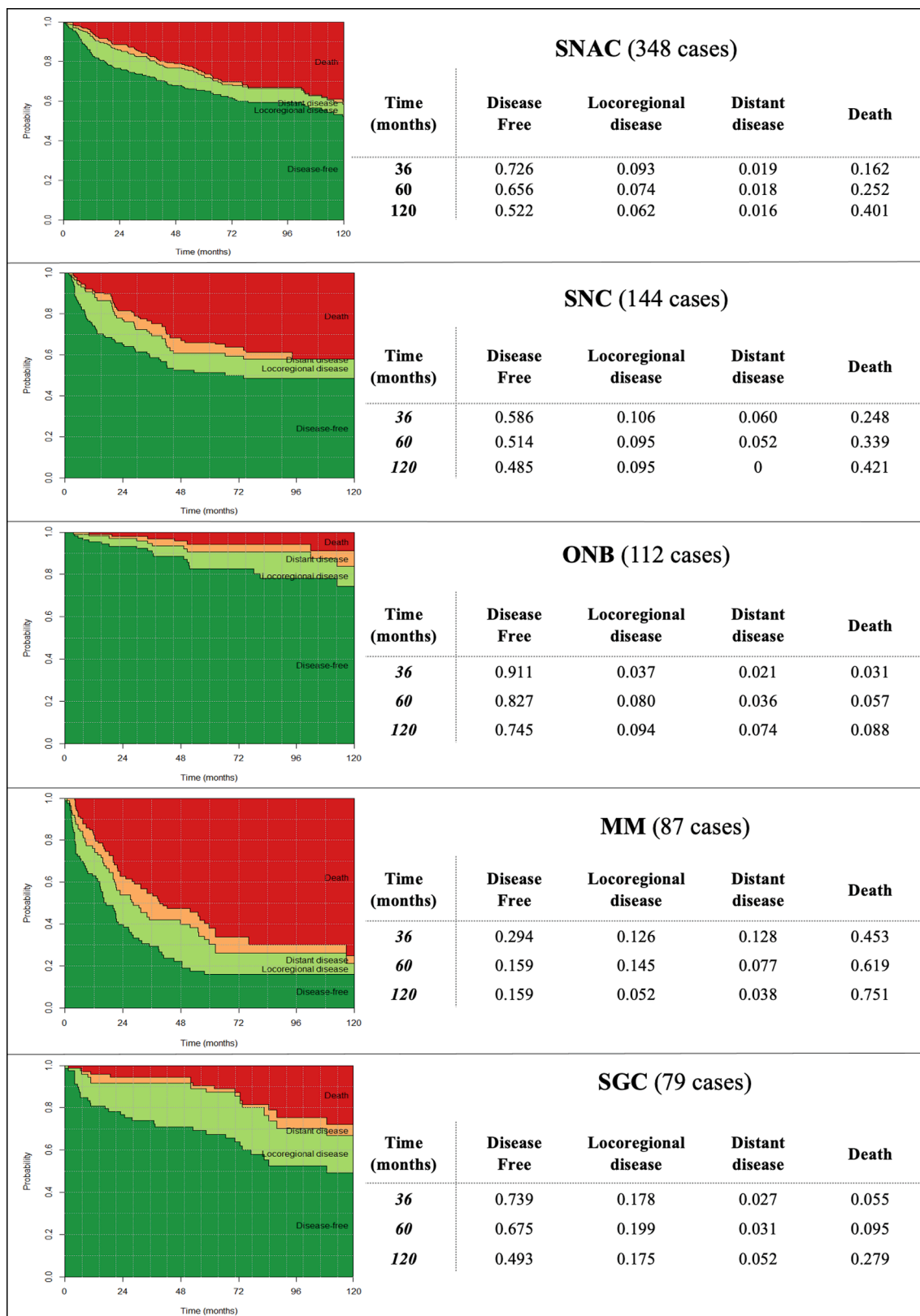
SNAC (348 cases)

Time (months)	Disease Free	Locoregional disease	Distant disease	Death
36	0.726	0.093	0.019	0.162
60	0.656	0.074	0.018	0.252
120	0.522	0.062	0.016	0.401

SNC (144 cases)

Time (months)	Disease Free	Locoregional disease	Distant disease	Death
36	0.586	0.106	0.060	0.248
60	0.514	0.095	0.052	0.339
120	0.485	0.095	0	0.421

ONB (112 cases)

Time (months)	Disease Free	Locoregional disease	Distant disease	Death
36	0.911	0.037	0.021	0.031
60	0.827	0.080	0.036	0.057
120	0.745	0.094	0.074	0.088

MM (87 cases)

Time (months)	Disease Free	Locoregional disease	Distant disease	Death
36	0.294	0.126	0.128	0.453
60	0.159	0.145	0.077	0.619
120	0.159	0.052	0.038	0.751

SGC (79 cases)

Time (months)	Disease Free	Locoregional disease	Distant disease	Death
36	0.739	0.178	0.027	0.055
60	0.675	0.199	0.031	0.095
120	0.493	0.175	0.052	0.279

Fig. 2. Unidirectional Multistate Model analysis of the five most represented histologic groups of the series. *Abbreviations: MM, malignant melanoma; ONB, olfactory neuroblastoma; SGC, salivary gland cancer; SNAC, sinonasal adenocarcinoma; SNC, sinonasal carcinoma.*

Table 3

Histology-specific multivariable model for DFS, L-RFS and D-RFS.

	Variable	DFS (univariable analysis) 10-y DFS (%)	p-value	DFS (multivariable analysis) HR	95% CI	p-value	L-RFS (multivariable analysis) HR	95% CI	p-value	D-RFS (multivariable analysis) HR	95% CI	p-value
SNAC	*Age*	NA	NA	1.013	0.995–1.032	0.164	1.012	0.987–1.038	0.345	0.971	0.940–1.004	0.083
	*Exposure**		0.645	0.941	0.612–1.447	0.780	0.872	0.483–1.572	0.648	2.323	0.846–6.378	0.102
	Leather	40.7										
	Wood	57.9										
	None	52.9										
	Grading		< 0.001	1.192	0.776–1.831	0.422	1.187	0.662–2.128	0.566	1.569	0.728–3.380	0.250
	G1-2 vs	57.0										
	G3	39.4										
	Margins		< 0.001	3.049	1.992–4.669	**<0.001**	3.169	1.770–5.673	**<0.001**	2.930	1.315–6.530	**0.009**
	R + vs	15.7										
	R0	58.5										
	Dura		< 0.001	1.916	1.203–3.051	**0.006**	1.521	0.807–2.867	0.195	2.079	0.901–4.801	0.086
	Positive vs	15.3										
	Negative	58.3										
	pT		< 0.001	2.268	1.452–3.545	**<0.001**	3.283	1.672–6.446	**0.001**	2.189	0.884–5.421	0.090
	pT ≥ 3 vs	39.1										
	pT1-2	64.3										
SNC	Age	NA	NA	0.997	0.977–1.018	0.807	1.001	0.974–1.03	0.345	0.992	0.960–1.025	0.611
	Presentation		**0.011**	2.426	1.394–4.22	**0.002**	2.368	1.166–4.81	**0.001**	2.730	1.041–7.158	**0.041**
	Relapses vs	31.1										
	Naïve	54.2										
	Grading		0.034	1.172	0.639–2.148	0.609	0.882	0.404–1.93	0.648	0.941	0.354–2.504	0.904
	G1-2 vs	57.0										
	G3	39.4										
	Margins		<0.001	4.843	2.653–8.841	**<0.001**	5.933	2.75–12.79	**<0.001**	2.239	0.786–6.377	0.131
	R + vs	15.7										
	R0	58.5										
	Site of origin		0.929	1.782	0.938–3.384	0.077	2.363	1.073–5.2	**<0.001**	0.232	0.031–1.751	0.156
	Maxillary vs	47.6										
	Naso-ethmoid	47.3										
	pT		**0.004**	1.775	0.881–3.575	0.108	2.374	0.954–5.91	0.195	2.158	0.565–8.240	0.261
	pT ≥ 3 vs	40.0										
	pT1-2	65.5										
ONB	Age	NA	NA	1.036	1.003–1.07	**0.033**	1.007	0.959–1.058	0.770	1.040	0.973–1.112	0.249
	Grading (Hyams)		0.416	1.872	0.466–7.52	0.377	0.966	0.222–4.202	0.963	1.926	0.364–10.2	0.441
	III-IV vs	66.1										
	I-II	68.5										
	Margins		< 0.001	2.716	1.148–6.42	**0.023**	4.063	0.889–18.57	0.071	1.640	0.279–9.656	0.584
	R + vs	48.1										
	R0	73.4										
	Dura		**0.026**	2.361	0.965–5.78	0.060	0.740	0.138–3.958	0.724	21.63	1.91–244.5	**0.013**
	Positive vs	27.3										
	Negative	78.4										
MM	Age	NA	NA	1.003	0.984–1.021	0.786	0.991	0.968–1.014	0.428	0.997	0.975–1.019	0.779
	Margins		**0.004**	1.881	1.129–3.132	**0.015**	2.142	1.139–4.029	**0.018**	1.465	0.711–3.019	0.301
	R + vs	4.2										
	R0	21.5										
	RT		0.144	0.609	0.368–1.010	0.055	0.478	0.246–0.928	**0.029**	0.903	0.469–1.741	0.761
	Yes vs	23.6										
	No	9.9										
	pT		**0.021**	1.930	1.140–3.268	**0.014**	1.350	0.706–2.583	0.364	4.048	1.888–8.682	**< 0.001**
	pT ≥ 4a vs	10.2										
	pT 3	22.7										
SGC	Age	NA	NA	1.020	0.993–1.048	0.156	1.020	0.988–1.054	0.227	1.008	0.951–1.067	0.796
	Margins		<0.001	2.905	1.159–7.280	**0.023**	6.291	1.966–20.14	**0.002**	7.778	0.46–131.5	0.155
	R + vs	44.8°										
	R0	82.9°										
	RT		**0.032**	1.290	0.445–3.736	0.639	1.430	0.403–5.072	0.580	1.013	0.046–22.17	0.994
	Yes vs	30.6										
	No	73.5										
	Grading		< 0.001	3.867	1.777–8.416	**<0.001**	2.950	1.201–7.251	**0.018**	8.010	1.433–44.78	**0.018**
	G3 vs	16.7										
	G1-2	60.7										
	pT		**0.001**	1.420	0.469–4.304	0.535	0.740	0.202–2.714	0.650	0.813	0.025–25.97	0.907
	pT ≥ 3 vs	26.1										
	pT1-2	74.5										

Abbreviations: CI, confidence interval; DFS, disease free survival; HR, hazard ratio; MM, mucosal melanoma; NA, not applicable; ONB, olfactory neuroblastoma; RT, radiotherapy; SGC, salivary gland cancer; SNAC, sinonasal adenocarcinoma; SNC, sinonasal carcinoma; L-RFS, local recurrence free survival; D-RFS, distant recurrence free survival.

* in the multivariable model, exposure to leather and dust was analyzed vs no exposure. ° 5-year DFS rates.

Survival After Recurrence
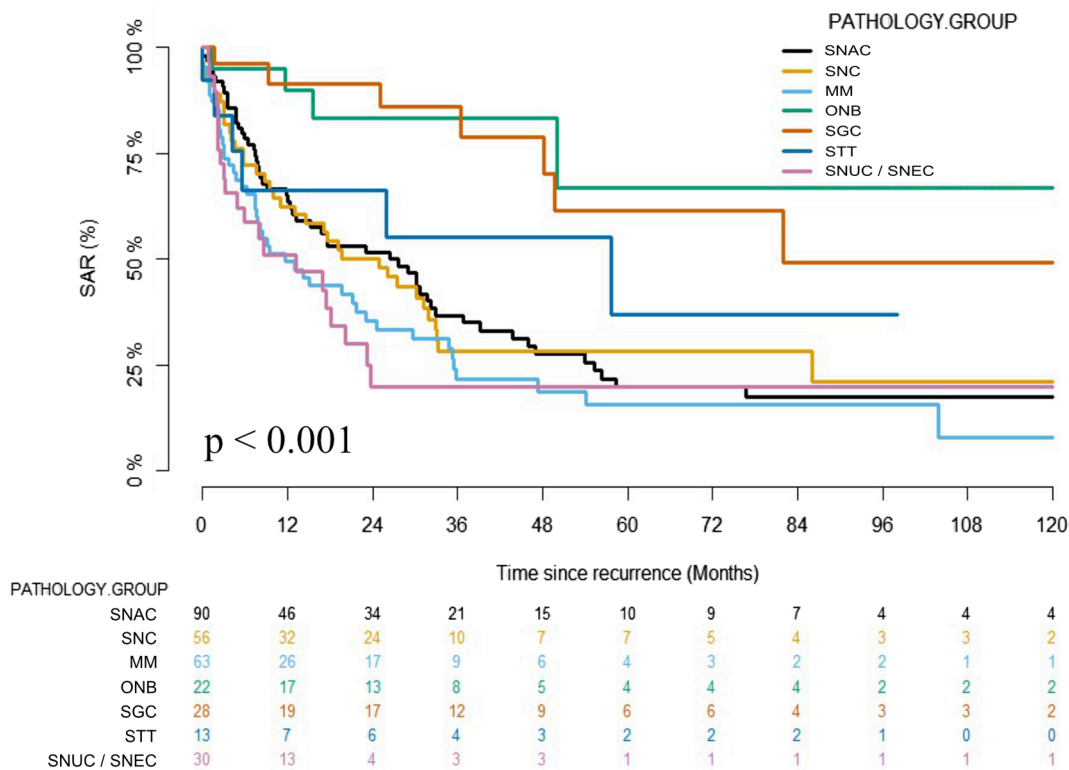
Fig. 3. Survival After Recurrence univariable analysis: Kaplan-Meier curves according to histologic groups. *Abbreviations: MM, malignant melanoma; ONB, olfactory neuroblastoma; SGC, salivary gland cancer; SNAC, sinonasal adenocarcinoma; SNC, sinonasal carcinoma; SNEC, sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; STT, soft tissue tumor.*

European countries [23]. Our analysis showed 10-year OS and DFS of 57.9% and 47.3%, which is in line with literature [24,25]. With regard to prognostic factors, previous treatments (HR = 2.426, p = 0.002) and positive surgical margins (HR = 4.843, p < 0.001) were significantly associated with reduced DFS in multivariable analysis. Interestingly, previous treatments were significantly associated with both worse L-RFS (HR = 2.368, p = 0.001) and D-RFS (HR = 2.730, p = 0.041). This finding underlines the importance of an upfront adequate treatment, since the failure might impede a curative goal of the re-treatment and profoundly affect the prognosis [26]. Moreover, positive margins significantly associated with worse DFS (HR = 4.843, p < 0.001) in the multivariable model, as well as with reduced L-RFS (HR 5.933, p < 0.001), in accordance with previous studies [27,28]. In addition, the impact on prognosis and recurrence risk of the site of origin of the disease (maxillary vs naso-ethmoid tumors) was studied in our series since differences have been described in literature [29]. In our analysis, maxillary sinus carcinomas showed a reduced L-RFS in the multivariable model (HR = 2.363, p < 0.001). This might be explained by the intrinsic difficulty in obtaining free-margin resection especially in case of infratemporal fossa involvement.

Overall recurrence rate for SNSCC in our analysis was 39.6% (56/144 patients), which is in line with data available in literature: 27% reported by Lund et al. [23] and 38.2% reported by de Almeida et al. [27]. The most frequent pattern of recurrence for SNC was represented by isolated local recurrence (31/144, 21.5%), followed by systemic dissemination (22/144, 15.3%), while regional relapses accounted for a minority of the cases (3/144, 2.1%). Overall, the event of a recurrence profoundly impacted on prognosis, considering that 5-year SAR for SNSCC was 31.2% (IC 12.2–50.2%), with 63% of the patients with a recurrence dead of disease at last follow-up. In multivariable analysis of SAR only TTR was found to be associated with prognosis (TTR HR 0.968,

IC 93.9–100, p = 0.048), while SOR did not show any significant impact on prognosis after recurrence (p = 0.198).

Olfactory neuroblastoma (ONB)

The present series counted a total of 112 cases of ONB, with 10-year OS and DFS of 90.9% and 69.1%, respectively, comparing equal or better with other series [30–32]. According to the literature, most recognized negative prognostic factors for ONB are advanced Kadish stage, high Hyams grade, the presence of nodal metastasis and infiltrated postoperative surgical margins [30,31,33–36]. In our analysis, margins' status and dural infiltration were significantly associated with DFS in univariable (p < 0.001 and p = 0.026, respectively) and multivariable analysis. These results are in line with evidence from the multicentric experience reported by Patel et al. [37].

Regarding dural infiltration, the present analysis showed a strong association with D-RFS (HR = 21.63, p = 0.013), while no influence on L-RFS was observed. This might suggest that local recurrence is not impacted by dural invasion provided that the resection is accomplished with negative margins. On the other hand, the presence of dural invasion might lead to a significant increase in the risk of distant recurrences, which in our series were represented mainly by meningeal spread; this suggests that dural infiltration might be considered as a factor to intensify postoperative treatment (e.g. adrotherapy instead of conventional radiotherapy). In this high-risk group of patients, careful radiological examination during follow-up is warranted to detect recurrences still amenable to salvage therapy, usually in the form of stereotactic radiosurgery. Rimmer et al. [38] observed that distant metastasis can present up to 10 years after treatment, and our data confirm this finding, with meningeal metastasis found up to 112 months postoperatively. The overall recurrence rate for ONB was 19.6% (22/112 patients) in the

Table 4
Histology-specific multivariable model of Survival After Recurrence analysis.

Variable	SNAC			SNC			ONB			MM			SGC		
	Value	HR [95% CI]	p-value	Value	HR [95% CI]	p-value	Value	HR [95% CI]	p-value	Value	HR [95% CI]	p-value	Value	HR [95% CI]	p-value
AAR (years) [IQR]	68.16 [62.4,73.4]	1.02 [0.99–1.05]	0.278	65.90 [48.4,72.9]	1.019 [0.99–1.04]	0.144	62.73 [53.7,71.2]	0.966 [0.89–1.04]	0.383	72.04 [66.3,79.6]	1.014 [0.99–1.04]	0.287	62.33 [49.99,69.04]	0.986 [0.93–1.05]	0.651
TTR (years) [IQR]	11.74 [6.4,27.3]	0.97 [0.96–0.99]	**0.002**	8.58 [3.9,19.9]	0.968 [0.94–1.00]	**0.048**	30.35 [15.9,71.7]	1.016 [0.99–1.04]	0.200	9.49 [3.9,21.3]	0.971 [0.95–0.99]	**0.026**	13.57 [5.55, 41.30]	0.980 [0.94–1.02]	0.323
SOR* (N, [%])	T: 64 [71.1] N: 2 [2.2] M: 24[26.7]	4.41 [2.36–8.25]	**<0.001**	T: 37 [66.1] N: 6 [10.7] M: 13[23.2]	1.780 [0.74–4.28]	0.198	T: 9 [40.9] N: 7 [31.8] M: 6 [27.3]	7.762 [0.6–100]	0.117	T: 38 [60.3] N: 5 [7.9] M: 20 [31.7]	1.541 [0.82–2.90]	0.182	T: 24 [85.7] N: 1 [3.6] M: 3 [10.7]	5.238 [0.44–61.86]	0.189

Abbreviations: AAR, age at recurrence; CI, confidence interval; HR, hazard ratio; MM, mucosal melanoma; ONB, olfactory neuroblastoma; SGC, salivary gland cancer; SNAC, sinonasal adenocarcinoma; SNC, sinonasal carcinoma; SOR, site of recurrence; TTR, time to recurrence.
* For multivariable analysis of the variable SOR, distant recurrence (M) vs locoregional recurrence (T-N) was tested.

present study, which is slightly lower than what described in literature [39–41]. However, the distribution of failures among local (7.1%, 8/112 patients), regional (5.4%, 6/112 patients) and distant sites (7.1%, 8/112 patients), appears to be similar between our study and previous reports [30,39–41]. Noticeably, this distribution has been re-shaped by the protective role of elective neck irradiation in Kadish C ONBs, which has been introduced in the last decade in many centers worldwide [36,42]. In the present series, mean TTR was similar between local and regional recurrences (34.8 and 39.3 months, respectively), and slightly higher for relapses occurring at distant sites (43 months). The shorter time to first recurrence observed in our series might be attributable to the intensive endoscopic and radiologic follow-up policy adopted [9]. In their metanalysis, Dulguerov et al. [34] reported that salvage after local recurrence is possible in 33–50% of cases, regional recurrence is salvageable by further treatment in a third of cases, while distant metastases carry a very poor prognosis. In our experience, salvage treatment encompassing surgical resection and/or radiotherapy was employed overall in 77% of the recurrences (17/22 cases). Salvage treatments were curative in most cases due to the early detection of recurrence. This might account for the high survival after recurrence rate of ONB, which was the highest among all the histologic groups (10-year SAR, 66.7%).

Mucosal melanoma (MM)

Consistently with the literature [43,44], our experience confirmed that MM should be considered as the most aggressive histologic group, with 10-years OS and DFS being 20.3% and 15.9%, respectively. Remarkably, D-RFS was significantly associated with high-stage disease, with lesions staged pT4 showing a 4-fold risk of distant recurrences compared to pT3 neoplasms. This might suggest that increased depth of infiltration (e.g. cartilage or bony structures of the paranasal sinus region) significantly raises the risk for systemic dissemination, while local control might be guaranteed provided that surgical margins are negative and RT is part of the treatment. To support this hypothesis, in our study, infiltrated margins were significantly associated with a decrease in DFS (HR = 1.881, p = 0.015) and in L-RFS (HR = 2.142, p = 0.018), but not with lower D-RFS. Similarly, RT was significantly associated only with improved L-RFS (HR = 0.478, p = 0.029) and not with either reduced D-RFS or DFS. Our data are in line with previous findings which support the role of RT in improving local control of disease [45], without any benefits in terms of OS [46,47]. The high tendency towards distant recurrences has a pivotal impact on OS for MM [48], suggesting that further investigation into novel, systemic therapies is required to improve outcomes in this disease entity. When analyzing patterns of treatment failure in the largest institutional cohorts of MM, Amit et al. [43] reported an overall recurrence rate of 48%, the most common failure being represented by distant metastasis in 69 patients (35%). This compared lower than our data, where an overall recurrence rate of 72.4% (63/87 cases), with a mean and median time to recurrence of 14.5 and 9.5 months, respectively, were observed. This may be due to the longer follow-up time of the present series. Systemic recurrences were observed in 38/87 (43.7%) cases, followed by local failures (22/87 cases, 25.3%), while regional failures were observed only in 3 cases (3.4%). Amit et al.]reported that the site of metastasis had a significant impact on both OS (p = 0.004) and DSS (p = 0.002). Similarly, our analysis confirmed that MM has the worst SAR among all the considered histologic groups, with 10-years SAR being 9.4% (0–23.9%). However, due to the high percentage of patients suffering from diffuse systemic localization of disease (28/38, 73.6% of the cases), the role of SOR was not significantly associated with survival in multivariable analysis, as opposed to TTR which showed association with SAR, with an HR of 0.971 (IC 0.945–0.996, p = 0.026). Altogether, with the very high rate and early onset of systemic failures, further research into immunotherapies and targeted therapies is urgently needed to improve on standard of care [49].

Salivary gland cancers (SGC)

The salivary gland cancers accounted for 8.5% of the total study sample (79/926 cases), being mostly represented by ACC (62%, 49/79 cases) and salivary adenocarcinoma NOS (10.1%, 8/79), as described in literature [50]. The 10-year OS and DFS rates were 73% and 48.5%, respectively, for this histologic group. These figures reflect the biological behavior of ACC, for which OS exceeds that of other sinonasal malignancies, but have a propensity towards indolent local and distant recurrences, which justify the considerably low DFS and high disease-specific mortality. In the series by Lupinetti et al. [50] the local recurrence and distant metastasis rates were 30% and 38%, respectively. Overall recurrence rate for SGC in our series was 35.4%. Most frequent site of failure was represented by isolated local relapse (19/79 cases, 24.1%), which were amenable to curative treatments in most of the cases (surgical resection in 8/19 cases, 42.1%, and radiotherapy in 7/19 cases, 36.8%). Systemic dissemination of disease may occur late in the follow-up: the lungs are by far the most frequently involved site, followed by liver, bone, and brain [50–52]. In the present series, distant recurrences were observed in a lower percentage of patients (10.1%), as only 8 patients experienced systemic spread of the disease (5 pulmonary metastases and 3 bone metastases). In our analysis, infiltrated surgical margins, RT, grading and advanced-stage (pT greater than 3) were significantly associated with worse 10-year DFS. In the multivariable model, only infiltrated margins and high-grade emerged as independent prognostic factors for DFS (HR = 2.905, p = 0.023 and HR = 3.867, p < 0.001, respectively). In detail, infiltrated margins were associated with reduced L-RFS (HR = 6.291, p = 0.002), while high-grade were associated with reduced D-RFS (HR = 8.010, p = 0.018). Finally, it's worth mentioning that ACC patients might recur after a prolonged time span. Kim et al. [17] found that 11.1% of initially cured ACC patients developed a local recurrence within the 10- to 15-year period, and 5.6% of our patients developed a distant metastasis in the 5- to 10-year period. In our experience, distant recurrences tended to occur earlier than local recurrences, being the mean time to recurrence of 36.6 months for local relapse and 28.3 months for distant failures. However, we also observed cases of recurrences diagnosed up to 163 months after initial treatment. This emphasizes that for this specific histologic group, a prolonged follow-up of at least 15 years, and possibly lifelong, is advisable [9]. Nonetheless, our analysis confirmed that patients experiencing recurrences can show prolonged survival rates, since SAR for SGC resulted to be the second most favorable among all the histologic groups (5 and 10-years SAR, 60.3 and 48.2%, respectively).

Study limitations

The present study has some limitations that cannot be neglected. First, it is based on a retrospective analysis of patients over a 23-year period. If on the one hand this represented a strength point, as it analyzed recurrence patterns over a long follow-up period, it also may have introduced biases related to the inevitable changes in staging systems and treatment modalities. Second, the variety of different histologies within the panorama of sinonasal malignancies forced us to a simplistic stratification of tumors in few groups; in this regard, greater variability is to be considered if we take into account the presence of undifferentiated histological types (e.g. SNUC), which were not analyzed in detail, or other histologies that only recently were classified as separate entities (e.g. INI1-deficient sinonasal carcinoma). Third, this paper analyses oncologic outcomes and pattern of recurrences of patients undergoing an endoscopic surgery-based treatment for sinonasal malignancies. If this, on the one hand, inevitably introduces a selection bias due to indications for such a surgical treatment (e.g. especially in the early 2000s due to lack of experience, mostly early-stage tumors were addressed to endoscopic resection), the aim of the paper was to validate the effectiveness of such a surgical approach to achieve at least comparable oncologic outcomes to previous series analyzing open

approaches. Moreover, endoscopic resection has progressively replaced open surgery by virtue of its lower morbidity, shorter hospital stay and at least equal ability to achieve uninvolved margins, so that the present study is of particular interest considering the current trends in treatment of sinonasal malignancies. Finally, the multicentric nature of the study was performed based on a common philosophy of treatment developed during years but might have introduced a certain degree of data heterogeneity, which could not be completely corrected.

Conclusion

Sinonasal cancer still represent a rare tumor with high risk for local and distant recurrences. Surgical margins' status confirmed to be a trasversal negative prognostic factor considering the overall population, which points out the importance of the adequacy of the surgical treatment at the time of the first diagnosis. More importantly, our results emphasize the concept that histology is the milestone factor in determining the incidence and pattern of recurrence. Therefore, nowadays, multimodal treatment protocols as well as the schedule of postoperative surveillance should be histology-based and patient-tailored, in order to maximize the chance to cure also in the case of recurrences.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2022.106123.

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