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Skull Base Surgery

Surgical management of advanced sinonasal cancer: a 10-year mono-institutional experience

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SUMMARY

Objective. Endoscopic endonasal surgery is effective in the treatment of sinonasal cancers. However, in cases of well-differentiated locally advanced neoplasms as well as recurrences, the most appropriate treatment is debated. The purpose of this study is to report a mono-institutional experience on craniofacial surgery performed in a tertiary-care referral centre.

Methods. This was a retrospective analysis of 90 patients treated with transcranial and/or transfacial resection for sinonasal cancer between 2010 and 2020. Outcome measures included overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS) and recurrence-free survival (RFS).

Results. The 5-year OS, DSS and DFS were 48.2%, 60.6% and 28.7%, respectively. Factors correlated with prognosis were pT-classification (p = 0.002), histotype (p = 0.012) and dural involvement (p = 0.004). Independent prognostic factors were orbital apex infiltration (p = 0.03), age (p = 0.002) and adjuvant therapy (p = 0.03).

Conclusions. When endoscopic endonasal surgery is contraindicated and chemoradiotherapy is not appropriate, craniofacial and transfacial approaches still represent an option to consider, despite the non-negligible morbidity.

KEY WORDS: craniofacial surgery, paranasal sinus, cancer, skull base, treatment outcome

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Introduction

It is commonly accepted that a combination of surgery and radiotherapy is the mainstay in the management of well-differentiated sinonasal cancer [1-3]. Traditionally, because of the complexity of the sinonasal anatomy and close proximity with orbit and brain, craniofacial surgery has been regarded as the standard treatment to obtain 'en-bloc' resection [4,5]. Over the past two decades, with advances in endoscopic endonasal surgical techniques and skull base reconstruction methods, minimally-invasive surgery has emerged as an alternative to an open surgical approach, with the advantages of lower post-operative morbidity and higher quality of life than open surgery [2,6,7]. On the other hand, the appropriateness of endoscopic endonasal surgery has been questioned especially when managing locally-advanced cases, thus opening a diatribe between supporters of the two techniques. What is universally accepted is that a free-margins resection should be obtained in patients considered suitable for surgery after a multidisciplinary consultation. The surgical technique used to reach such a primary goal should be based on the local extension of tumour and the patient's general conditions.

The purpose of this study is to report a mono-institutional experience on craniofacial surgery performed in a tertiary-care referral centre renewed for endoscopic endonasal approaches, to offer a reappraisal of current evidence on indications and contraindications for traditional open surgery.

Materials and methods

Design and setting

Medical records of patients treated for sinonasal malignancies via transcranial and/or transfacial approaches between April 2010 and May 2020 at a tertiary-care referral Institution were retrospectively reviewed. Patients with (a) missing relevant data (*e.g.,* pre-operative imaging, follow-up); (b) unresectable cancer; (c) distant metastases at presentation and (d) less than 12 months of follow-up were excluded.

Demographic data, tumour characteristics, imaging studies, surgical reports, previous treatments, and adjuvant therapy were collected and reviewed. All cases were re-classified according to the 8th edition of the "TNM classification of malignant tumours" for sinonasal cancer [8].

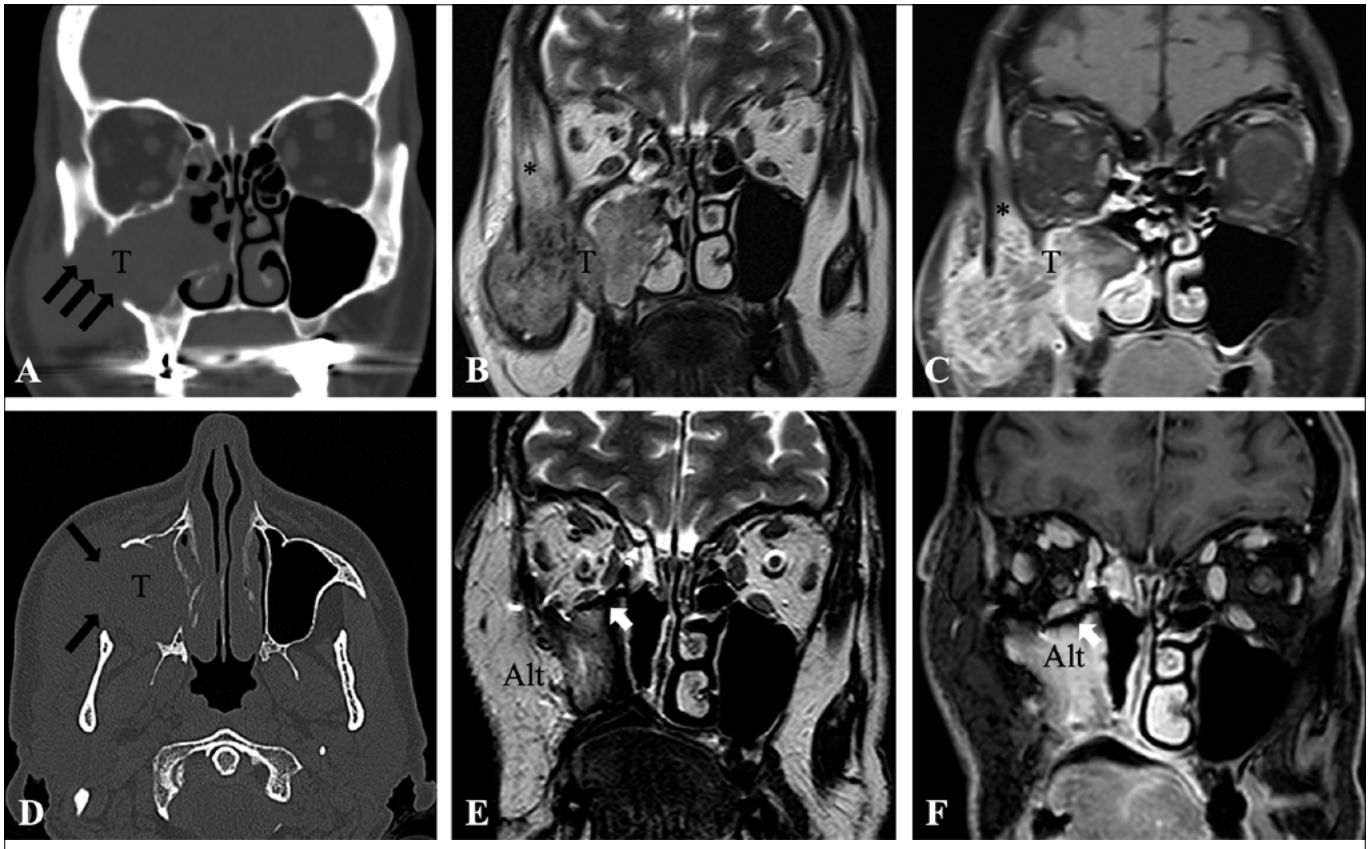
Histological classification was adapted to the 4th edition of the "WHO classification of head and neck tumours" [9].

Participants

A cohort of 90 patients treated with a transcranial and/or transfacial approach was identified through electronic medical records review.

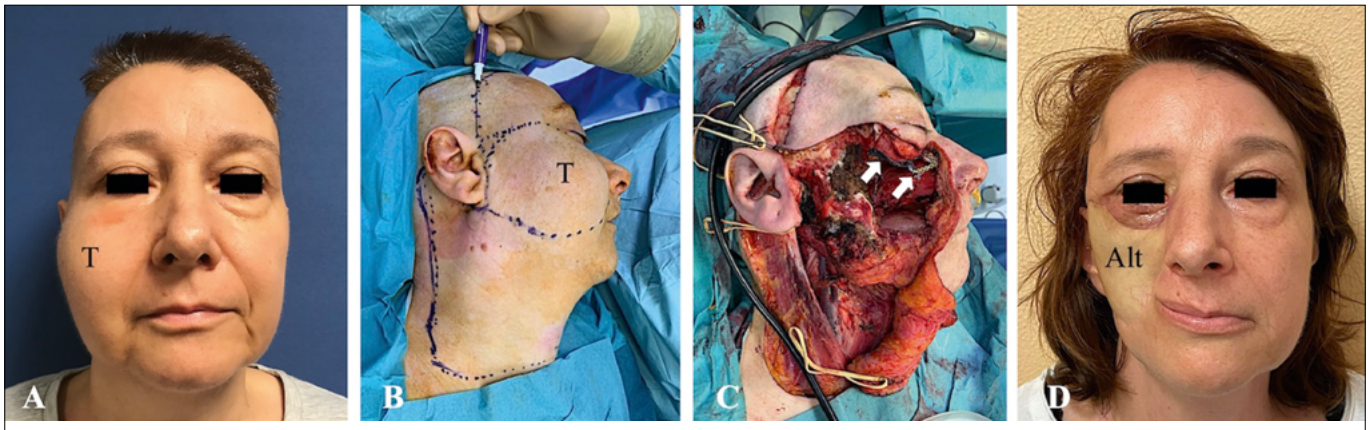
Pre-operative work-up and surgical technique

Local extension of disease was assessed by multiplanar computed tomography (CT) scan and contrast-enhanced magnetic resonance imaging (MRI) in all cases. Based on pre-operative radiological exams no involvement of unresectable areas was apparent. All patients underwent pre-operative nasal endoscopy and biopsy. Neck ultrasound and total body contrast-enhanced CT scan and/or positron emission tomography (PET) scan were obtained to rule out



Alt: anterolateral *thigh free flap;* T: *tumour; black arrows: erosion of the anterolateral maxillary wall; black asterisks: infiltration of the right temporalis muscle; white arrows: mesh plate used to reconstruct the right orbital floor.*

Figure 1. Pre-operative CT (**A** and **D**) and MRI scans (**B**, T2W; **C**, T1W contrast enhanced) in coronal sections show a right maxillary squamous cell carcinoma eroding the anterolateral maxillary bony walls (black arrows in **A** and **D**), extending into the premaxillary soft tissues and infiltrating the infratemporal fossa and the temporalis muscle (black asterisks in **B** and **C**). MRI scans in coronal views (**E**, T2W; **F**, T1W contrast enhanced) performed one year after transfacial surgery. The patient is currently alive without disease at 5 years after treatment.



Alt: anterolateral *thigh free flap;* T: *tumour; white arrows: mesh plate used to reconstruct the right orbital floor.*

Figure 2. A 54-year-old woman affected by right maxillary sinus squamous cell carcinoma G1 involving the infratemporal fossa, parotid gland, temporalis muscle and subcutaneous premaxillary soft tissues (T4aN0M0). (**A**) Clinical appearance, with noticeable right premaxillary swelling; (**B**) Intra-operative surgical planning of skin incisions; (**C**) Intra-operative appearance of the surgical defect resulting after the transfacial resection (right selective neck dissection of the neck levels I to IV, right radical parotidectomy, "en bloc" excision of the neoplasm by radical maxillectomy with extension to overlying skin, temporalis muscle and ramus of the mandible. Reconstruction was performed with an anterolateral thigh free flap and a mesh plate was used for the orbital floor (white arrows in **C**). The patient underwent post-operative radiotherapy. (**D**) Post-operative outcome after 2 years of follow-up.

regional or systemic spread, respectively. Surgical resection was tailored to the local extension of disease (Figs. 1-2, Tab. I). Transfacial surgery included orbital exenteration, total maxillectomy, facial skin excision and/or total rhinectomy. Transcranial surgery was required in case of intracranial extension, massive involvement of the frontal sinus, or infiltration of its posterior wall. Skull base reconstruction was performed whenever required.

Multimodal therapies and neck management

Patients with locally advanced poorly-differentiated cancers were submitted to induction chemotherapy, according to histology-driven protocols [10,11]. Lymphovascular or perineural invasion and T3-T4 categories were considered indications for adjuvant radiotherapy (RT) [1] and concurrent cisplatin-based chemoradiotherapy (CRT) was administered in cases with positive surgical margins [12].

Patients affected by high-grade advanced stage epithelial sinonasal cancers submitted to reconstruction with free flap were treated with elective neck dissection, since the surgical field was already approached for the vascular anastomosis. In the other cases requiring elective neck treatment but without the need of surgical reconstruction, an elective neck irradiation was preferred. Clinically-positive neck lymph nodes were treated with therapeutic neck dissection. All patients were addressed to standardised clinical-radiological follow-up [6].

Main outcome measures

Overall survival (OS), disease-free survival (DFS) and recurrence-free survival (RFS) were analysed. Relapses were classified as exclusive local recurrence (T+, N-, M-), regional recurrence (T±, N+, M-) and distant recurrence (T±, N±, M+). OS was defined as the time from surgery to the last follow-up or death for any cause. DFS was defined as the time from surgery to the first relapse at any site or death for any causes. LRFS, RRFS and DRFS were defined as time from surgery until relapse at local, regional or distant sites, respectively.

Data analysis

Survival probability was assessed using the Kaplan-Meier survival analysis and the log rank test was performed to compare survivals. A multivariate proportional hazard Cox-regression was used for the same endpoints (OS, DFS, LRFS, DRFS). Results are presented in term of hazards ratios (HR), 95% confidence intervals (CIs), and p values. All statistical tests were two-tailed and statistical significance was considered when p value ≤ 0.05. IBM SPSS software, version 25 (Chicago, IL, USA), was used to perform all statistical analysis.

Results

Clinical and pathological characteristics of the population

During the 10-year time span, a total of 502 patients were treated for sinonasal cancer. Among these, 41 patients (8.2%) affected by poorly differentiated histologies received non-surgical based treatment with concurrent CRT, and 371 patients (73.9%) underwent endoscopic endonasal resection, while the remaining 90 cases (17.9%) were treat-

Table I. Indications and contraindications, according to the authors' opinion, for surgical approaches based on anatomical sites involved.

Site	Endoscopic endonasal resection	Trans-cranial resection	Trans-facial resection	Unresectable
Maxillary sinus and palate	Involvement of medial maxillary wall, orbital floor	-	Involvement of lateral and/or inferior walls, hard and/or soft palate involvement	-
Frontal sinus	Lesion abutting into the sinus; lesions originating from the lower half of the sinus with adequate anatomy (large AP diameter and interorbital distance)	Origin from the upper half of the sinus; erosion of the posterior wall Small AP diameter and interorbital distance Massive involvement of the sinus Massive lateral supraorbital attachment in laterally pneumatised sinus	Erosion of the anterior wall; forehead skin or subcutaneous tissue involvement	-
Sphenoid sinus	Involvement of the anterior wall	Posterior planum sphenoidale involvement	-	Involvement of posterior/ lateral wall and/or cavernous sinus, optic chiasm, cavernous ICA
ITF/PPF/UPS	PPF involvement; limited ITF extension	-	Massive ITF involvement, masticatory space involvement	Parapharyngeal ICA encasement
Orbit	Erosion of lamina papyracea (grade 1) Invasion of periorbital layer and/or focal invasion of extraconic periorbital fat (grade 2)	-	Invasion of the anterior 2/3 (grade 3)	Orbital apex (grade 4)
Brain and dura	Limited dural infiltration; olfactory bulb involvement; focal midline brain invasion	Dural infiltration extended laterally over the orbital roofs or posteriorly beyond planum sphenoidale Brain infiltration	-	Massive brain infiltration
Skin	-	-	Facial skin involvement	-

AP: anteroposterior; AW: anterior wall; FS: frontal sinus; ICA: internal carotid artery; ITF: infratemporal fossa; PPF: pterygopalatine fossa; UPS: upper parapharyngeal space.

ed with a transcranial or transfacial approach and included in the study. The male to female ratio was 2.5:1 and the mean age of the population was 61.2 years (range, 4-83; median, 65.5). Table II summarises histology distribution, previous treatments and TNM classification of the patients enrolled. A total of 25 patients affected by pT2-3 tumours were not manageable with endonasal surgery due to hard palate infiltration in 18 maxillary cancers (pT2 in 10 cases and pT3 in 8 cases with simultaneous involvement of ethmoid) and subcutaneous premaxillary soft tissue infiltration in 3 maxillary cancers (staged as pT3). Furthermore, in 4 patients submitted to salvage surgery after CRT the final histology report resulted in a pathological downstage of disease compared to the pre-operative radiological stage.

Treatment and complications

The type of surgical resection and surgical margin status are provided in Table II. Overall, 27 transcranial and 63 transfacial resection were performed. Reconstruction of the surgical defect was required in 51 patients (56.7%) and performed as follows: anterolateral thigh flap in 33 cases (36.7%), temporal muscle flap in 7 cases (7.7%), fibula free flap in 4 cases (4.4%), radial forearm flap in 3 cases (3.3%), vastus lateralis free flap in 2 cases (2.2%), scapular tip free flap and medial sural artery perforator flap in one case each (1.1%). Skull base reconstruction was performed in 27 patients (30%), using pericranial flap in 14 cases and multilayered technique with either flaps or grafts in 13 cases.

Peri-operative complications occurred in 31 patients (34.4%): free flap failure (9 cases, 29%); bleeding (6 cases,

Table II. Clinicopathological characteristics of the study population.

Variable	N/tot (%)	N/TCR (%)	N/TFR (%)
Age (years)			
Mean [range]	61.2 [4-83]	63.1 [27-83]	60.5 [4-82]
Gender			
Male	64/90 (71.1)	23/27 (85.2)	41/63 (65.1)
Female	26/90 (28.9)	4/27 (14.8)	22/63 (34.9)
Previous treatments			
Surgery	16/90 (17.8)	4/27 (14.8)	12/63 (19)
Surgery + radiotherapy	10/90 (11.1)	2/27 (7.4)	8/63 (12.7)
Chemo-radiotherapy	9/90 (16.6)	2/27 (7.4)	7/63 (11.1)
pT classification			
T2	10/90 (11.1)	-	10/63 (15.9)
T3	15/90 (16.7)	1/27 (3.7)	14/63 (22.2)
T4a	36/90 (40)	3/27 (11.1)	33/63 (52.4)
T4b	29/90 (32.2)	23/27 (85.2)	6/63 (9.5)
N classification			
N0	87/90 (96.7)	27/27 (100)	60/63 (95.2)
N1	3/90 (3.3)	-	3/63 (4.8)
Tumour site of origin			
Ethmoid sinus	24/90 (26.7)	11/27 (40.7)	13/63 (20.6)
Frontal sinus	7/90 (7.8)	6/27 (22.2)	1/63 (1.6)
Maxillary sinus	48/90 (53.3)	4/27 (14.8)	44/63 (69.8)
Nasal septum	6/90 (6.7)	2/27 (7.4)	4/63 (6.3)
Olfactory cleft	4/90 (4.4)	1/27 (3.7)	3/63 (4.8)
Pterygoid	1/90 (1.1)	-	1/63 (1.6)
Histologic group			
Squamous cell carcinoma	38/90 (42.2)	10/27 (37)	28/63 (44.4)
Intestinal-type adenocarcinoma	13/90 (14.4)	8/27 (29.6)	5/63 (7.9)
Other epithelial tumours	20/90 (22.2)	1/27 (3.8)	19/63 (30.3)
Malignant soft tissue tumours	10/90 (11.1)	3/27 (11.1)	7/63 (11.1)
Mucosal melanoma	6/90 (6.7)	2/27 (7.4)	4/63 (6.3)
Olfactory neuroblastoma	3/90 (3.3)	3/27 (11.1)	-
Surgery			
Radical maxillectomy	39/90 (43.3)	-	39/63 (62)
Orbital exenteration	12/90 (13.3)	-	12/63 (19)
Cranio-endoscopic resection	12/90 (15.6)	12/27 (44.4)	-
Combined approaches	27/90 (30)	15/27 (55.6)	12/63 (19)
Skull base reconstruction	27/90 (30)	27/27 (100)	-
Neck dissection	17/90 (18.9)	2/27 (7.4)	15/63 (23.9)
Reconstruction	51/90 (56.7)	11/27 (40.7)	40/63 (63.5)
Surgical margins			
Negative	62/90 (68.9)	12/27 (44.4)	50/63 (79.4)
Positive	28/90 (31.1)	15/27 (55.6)	13/63 (20.6)
Adjuvant treatment			
Exclusive radiotherapy	51/90 (56.7)	17/27 (63)	34/63 (54)
Exclusive chemotherapy	4/90 (4.4)	1/27 (3.8)	3/63 (4.8)
Chemo-radiotherapy	9/90 (10)	4/27 (14.8)	5/63 (7.9)
Recurrence			
Overall recurrence rate	39/90 (43.3)	15/27 (55.6)	24/63 (38)
Local (T+, N0, M0)	19/90 (21.1)	4/27 (14.8)	15/63 (23.8)
Regional (T±, N+, M0)	7/90 (7.7)	2/27 (7.4)	5/63 (7.9)
Distant (T±, N±, M+)	13/90 (14.4)	9/27 (33.4)	4/63 (6.3)
Status			
NED	36/90 (40)	4/27 (14.8)	32/63 (50.8)
AWD	18/90 (20)	6/27 (22.2)	12/63 (19)
DOD	28/90 (31.1)	13/27 (48.2)	15/63 (23.9)
DOC	8/90 (8.9)	4/27 (14.8)	4/63 (6.3)

AWD: alive with disease; DOC: dead of other causes; DOD: dead of disease; M: distant disease; N: regional disease; NED: no evidence of disease; T: local disease; TCR: transcranial resection; TFR: transfacial resection.

19.3%); fever, pneumocephalus and donor site morbidity (3 cases respectively, 9.7%); cerebrospinal fluid (CSF) leak, meningitis and pneumonia (2 cases respectively, 6.4%); deep vein thrombosis (one case, 3.2%). The mean time interval for complications was 8.3 days (range, 1-28, median, 9), categorised as early (within 15 days) in 21 cases, and late (after 15 days) in 10 cases.

Most of the patients received adjuvant treatment (64 cases, 71.1%, Tab. II), whereas 26 patients did not as it was not indicated after multidisciplinary discussion for several reasons: surgery performed as salvage treatment after previous RT or CRT (14 cases, 15.5%); radical resection performed for an early-stage cancer (i.e. pT2) in 9 cases (10%); multiple comorbidities with compromised performance status in 2 cases (2.2%); patient's refusal in one case (1.1%).

Survival analysis

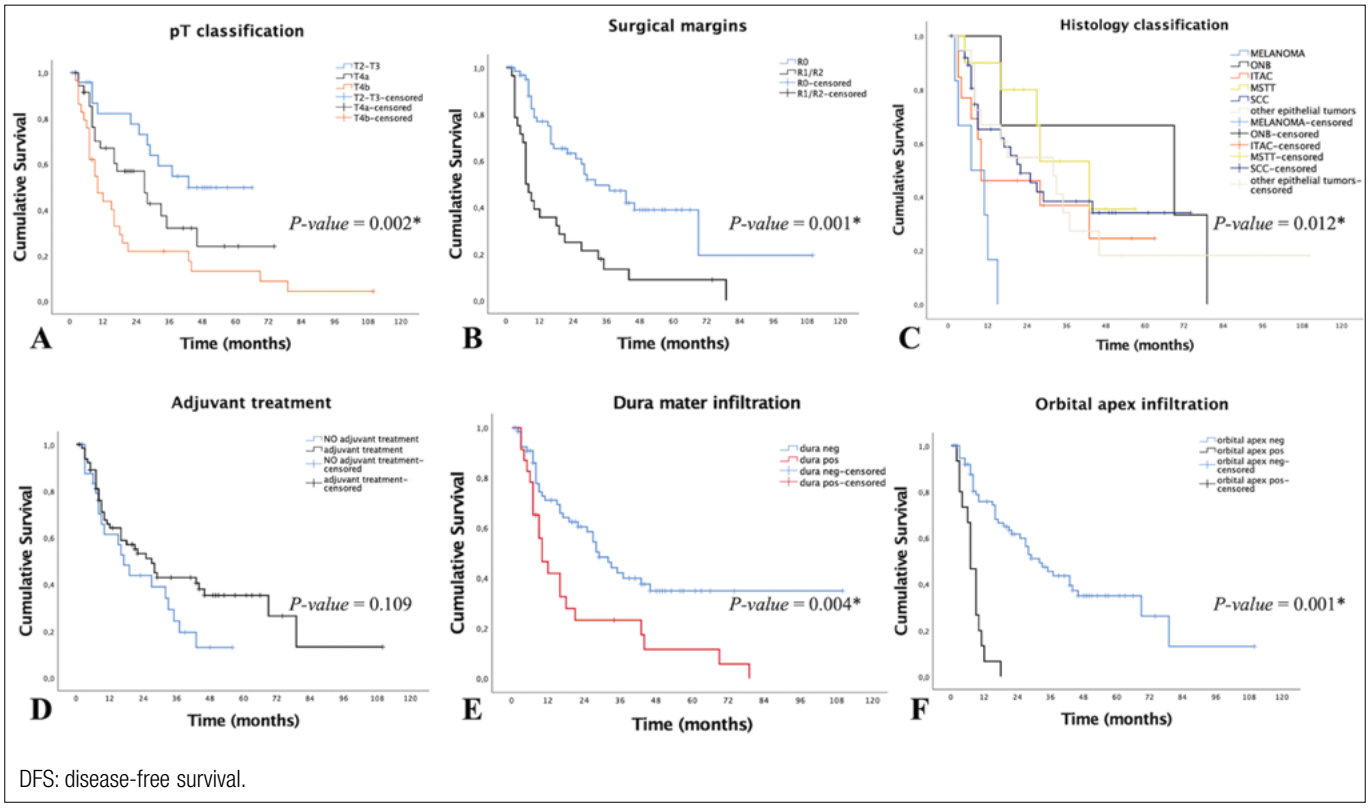
After a mean follow-up of 32.8 months (range, 1-125; median, 26), only 36 patients (40%) were alive without evidence of disease (Tab. II). Five-year OS, DSS and DFS were 48.2%, 60.6% and 28.7%, respectively. Five-year LRFS, RRFS and DRFS were 59.4%, 83.2% and 70.8%, respectively.

The main prognosticators observed were pT classification, surgical margins status, dural infiltration, and orbital apex infiltration, which were associated with reduced survival rates in terms of OS, DFS and DSS (Tab. III, Fig. 3). Histopathological classification was associated with significant differences only in terms of DFS ($p = 0.012$). No significant differences in survivals between patients treated with transfacial and transcranial resection were observed in univariate analysis.

Table III. Survival analysis of the study population: univariate analysis of OS, DFS, DSS, LRFS and DRFS.

Variable	Overall survival		Disease free survival		Disease specific survival		Local recurrence free survival		Distant recurrence free survival	
	5-yr OS	p value	5-yr DFS	p value	5-yr DSS	p value	5-yr LRFS	p value	5-yr DRFS	p value
pT classification		0.011*		0.002*		0.023*		0.124		0.029*
pT2-T3	70.9		49.8		79.9		69.6		86.3	
pT4a	56.8		24.0		61.5		56.4		64.4	
pT4b	34.6		13.1		43.8		47.9		63.4	
Surgical margins		0.001*		0.001*		0.001*		0.010*		0.166
Negative	63.7		38.9		72.5		63.6		72.9	
Positive	29.1		8.9		35.8		47.4		67.5	
Histology		0.099		0.012*		0.112		0.186		0.007*
SCC	43.8		34.2		56.2		76.7		69.8	
ITAC	53.8		24.6		65.3		55.5		61.5	
Other epithelial tumour	56.9		18.2		56.9		27.3		87.1	
MSTT	56.3		NA		75		NA		66.7	
Melanoma	33.3		NA		33.3		66.7		22.2	
ONB	100		33.3		100		66.7		100	
Adjuvant treatment		0.648		0.109		0.682		0.007*		0.169
No	50.2		NA		56.3		31.6		86.3	
Yes	53		35.3		62		70.1		65.8	
Dural infiltration		0.001*		0.004*		0.002*		0.316		0.029*
Negative	62.1		34.9		62.8		63.4		74.4	
Positive	26.4		11.6		33.4		41.9		42.8	
Orbital apex infiltration		0.001*		0.001*		0.001*		0.001*		0.031*
Negative	59.9		34.9		69.7		63.7		74.5	
Positive	17.8		NA		19.4		NA		50.8	
Surgical approach		0.096		0.401		0.404		0.237		0.089
TFR	23.8		29.8		61.2		53.6		77.6	
TCR	47.3		26.5		59.9		72.3		55.9	

*DFS: disease-free survival; DRFS: distant recurrence-free survival; ITAC: intestinal-type adenocarcinoma; LRFS: local recurrence-free survival; MSTT: malignant soft tissue tumour; NA: not applicable; ONB: olfactory neuroblastoma; OS: overall survival; SCC: squamous cell carcinoma; TCR: transcranial resection; TFR: transfacial resection; *Statistically significant values.*



DFS: disease-free survival.

Figure 3. Kaplan-Meier curves for DFS according to pT classification, surgical margins, histopathologic classification, adjuvant treatment, dural and orbital apex infiltration.

Recurrence analysis

The total recurrence rate was 43.3% (39/90 patients, Tab. II) with a mean time to recurrence of 18.5 months. Local recurrence was the most frequent pattern of relapse (19/39 cases, 48.7%). Distant sites of failure were multi-organ (6 cases), brain (3 cases), liver (2 cases), lungs and bones (one case each). Treatment of recurrences was surgically-based in 15/39 cases (38.5%) and non-surgical (RT and/or CRT) in 13/39 cases (33.3%), while 11/39 (28.2%) patients were addressed to best supportive care.

The main factors associated with recurrence risk are summarised in Table III. Orbital apex infiltration was significantly associated with increased risk of local and distant failures; dural infiltration, pT and histopathologic classification were associated with increased risk of systemic dissemination of disease; finally, positive surgical margins were associated with increased risk of local recurrences.

Multivariate analysis

On multivariate analysis (Tab. IV), orbital apex infiltration was associated with significantly increased risk of death and recurrence (HR 2.53 in OS; HR 4.92 in DFS; HR 6.01 in LRFS). Moreover, the delivery of adjuvant treatment emerged as a protective factor, significantly reducing the global risk of recurrence (HR 0.51 in DFS; HR 0.28 in LRFS). Finally, age was confirmed to be an independent prognostic factor in terms of OS. Type of surgical resection (transcranial or transfacial) was not tested on multivariate analysis because of the lack of statistical significance in univariate analysis.

Discussion

The management of sinonasal malignancies has significantly evolved during the last decades [1,3]. Histology-driven protocols are now recognised as the standard of care, which contributed to the reduction of surgical resection as an up-front treatment strategy, particularly in the case of poorly differentiated neoplasms [1,12]. Moreover, the growing experience acquired in sinonasal endoscopic surgery has prompted a wide diffusion of endoscopic resection in the surgical management of these cancers and the concept of "oriented disassembling" of the lesion has definitely proved its validity in terms of oncological safety, with outcomes comparable to those of the classical "en bloc" resection [6]. In the last decade, the progressive development of endoscopic techniques has allowed to manage difficult regions such as

Table IV. Survival analysis of the study population: multivariate analysis of OS, DFS, and LRFS.

Variable	Overall survival			Disease-free survival			Local recurrence-free survival		
	5-yr OS	HR (95% CI)	p value	5-yr DFS	HR (95% CI)	p value	5-yr LRFS	HR (95% CI)	p value
Age (continuous)		1.05 (1.01-1.08)	0.002*		1.01 (0.99-1.03)	0.08		1.00 (0.98-1.02)	0.67
Surgical margins		1.67 (0.71-3.89)	0.23		1.58 (0.83-2.99)	0.15		1.34 (0.51-3.55)	0.54
Negative	63.7			38.9			63.6		
Positive	29.1			8.9			47.4		
Adjuvant treatment		1.04 (0.47-2.29)	0.91		0.52 (0.29-0.95)	0.03*		0.28 (0.12-0.66)	0.004*
No	50.2			NA			31.6		
Yes	53			35.3			70.1		
Dural infiltration		2.11 (0.95-4.69)	0.06		1.24 (0.61-2.54)	0.54		1.05 (0.34-3.18)	0.92
Negative	62.1			34.9			63.4		
Positive	26.4			11.6			41.9		
Orbital apex infiltration		2.53 (1.08-5.94)	0.03*		4.92 (2.20-11.01)	< 0.0005*		6.01 (1.78-20.31)	0.004*
Negative	59.9			34.9			63.7		
Positive	17.8			NA			NA		

*CI: confidence interval; HR: hazard ratio. *Statistically significant; NA: not available*

the frontal sinus [13], various areas of the maxillary sinus [14,15], the infratemporal fossa [16] and orbit [17].

Data from the present analysis confirm this trend over time, considering that in the last 10 years only 90 patients were treated with transcranial or transfacial approaches compared to 371 patients (73.9%) treated by endoscopic endonasal resection.

Nonetheless, traditional transcranial and transfacial procedures are still indicated in selected cases and can be used not only as primary treatment for locally-advanced cases, but also as salvage procedures for local failures in sites that are no longer manageable with minimally-invasive techniques [18]. This is confirmed by the present series, where more than half of the patients were treated for recurrent or persistent disease (52 cases, 57.8%).

After a mean follow-up time of 32.8 months, 5-year survival rates in the present study were 48.2%, 60.6%, 28.7% for OS, DSS, and DFS, respectively. Survival rates from the largest series available are similar to those of the present study, with 5-year OS and DSS rates being 53.6% and 59.9%, respectively [19]. Moreover, a recent review [20] confirmed this trend, reporting median 5-year OS 54% and median 5-year DSS 60%. These data corroborate the appropriateness of the treatments provided in the present series, but also emphasise that there is still space for improvement of outcomes, considering that only small progresses in survival rates have been observed in the last decades when considering advanced-stage sinonasal cancers.

Survival analysis confirmed the role of the most recognised prognosticators: pT classification, status of surgical margins, dural invasion and orbital apex infiltration were significantly associated with reduced survival rates in terms of OS, DFS and DSS (Tabs. III-IV). Achieving negative surgical margins is significantly more important than the way a tumour is removed (en bloc *vs* piecemeal resection), and therefore it should be the surgical goal regardless of the technique chosen, whenever possible. Dural and intracranial extension have been recognised as the most adverse prognostic factors [21]. Our study is in line with this trend, even though the role of dural invasion was not significant in multivariate analysis, suggesting that other elements might act as confounding factors. On the contrary, orbital apex invasion resulted as a high-risk negative prognostic factor for almost all the survival endpoints, in both univariate and multivariate analysis. In particular, orbital apex infiltration significantly worsens outcomes because a free-margin resection is virtually impossible, regardless of the type of surgery performed [5], and results of the present study support this evidence (Tab. IV).

The total recurrence rate of the present series was 43.3% with a mean time to recurrence of 18.5 months, with 5-year LRFS, RRFS and DRFS being 59.4%, 83.2% and 70.8%, respectively. Ganly et al. [22] reported 5-year RFS rates of 45.8%, with median time to recurrence of 7 months, while Higgins et al. [23] reported a 5-year locoregional control rate of 48%. In line with previous series [19,21], local recurrence was the most frequent pattern of relapse (19/39 cases, 48.7%), followed by distant failure (13/39, 33.3%).

Analysis of RFS showed that dural infiltration (p = 0.029) and pT classification (0.029) were the factors associated

with increased risk of systemic dissemination of disease. This was also the case of histopathologic classification ($p = 0.07$), as 4/6 patients affected by mucosal melanoma developed metastases and died of disease. Positive surgical margins were associated with increased risk of local recurrence in univariate analysis ($p = 0.01$). With regards to adjuvant treatments, our results suggest that post-operative radiotherapy might correlate with improved locoregional control: this confirms that in appropriately selected high-risk cases adjuvant treatments might lower the risk of death and recurrence [24].

When dealing with open craniofacial surgery, postoperative morbidity deserves mention. This type of surgery is, in fact, associated with non-negligible rates of complications with an average mortality of 4% as demonstrated by König et al. [20].

Among 1193 patients studied, Ganly et al. [25] reported a postoperative mortality rate of 4% and morbidity rate of 33%. Except for the absence of treatment-related deaths, our study showed a perioperative complication rate (34.4%) in line with those already mentioned. Complications were more frequently represented by free flap failure (9 cases, 29%), followed by bleeding requiring revision (6 cases) and intracranial complications. This highlights that expanding the surgical field can increase the chances to obtain radical removal in tumours that are not amenable to endoscopic endonasal resection, but at a cost of increased risk of mortality and morbidity: it should always be discussed pre-operatively with the patient and balanced considering performance status, comorbidities and residual quality of life.

This study has some limitations that should be mentioned. First, it is based on a retrospective analysis of patients treated over a 10-year period, with intercurrent changes that inevitably introduced bias in the analysis. Second, a significant heterogeneity was observed in the study, considering that different histologies with different biological behaviours were treated with different open surgical approaches. Third, the reduced number of events of interest may have limited the factors evaluated in multivariate analyses, especially for RRFS.

Conclusions

Progresses in multimodal treatment strategies, as well as refinements in endoscopic endonasal surgical techniques have progressively reduced the role of transcranial and transfacial resections during the last decade, which are still associated with non-negligible rates of peri-operative morbidity and significant impact in post-operative quality of life. Nonetheless, craniofacial surgery should remain part of the armamentarium of the head and neck surgeon in order to increase the chances to obtain radical resection in advanced-stage disease and in selected cases of local recurrences involving sites that are not amenable to endoscopic salvage surgery.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

GS: conceptualisation, formal analysis, investigation, data curation, writing original draft, visualisation; ADA: conceptualisation, investigation, writing original draft; PB: resources, supervision; MB: resources, supervision; MC: resources, supervision; LV: resources, supervision; PA: resources, supervision; DL: resources, supervision; PC: conceptualisation, investigation, resources, supervision; MTZ: conceptualisation, investigation, resources, supervision, writing review & editing.

Ethical consideration

The study was approved by the Institutional Review Board (Insubria Board of Ethics, approval number 0033025/2015). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each participant/patient for study participation and data publication.

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