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Morbidity of multimodal treatments including endoscopic surgery for sinonasal malignancies: Results of an international collaborative study on 940 patients (MUSES)

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Abstract

Introduction: In the management of sinonasal malignancies treatment-induced morbidity and mortality is gaining relevance both for surgical approaches (endoscopic and open resection) and non-surgical therapies. The aim of this multicenter study is to assess complications associated with endoscopic surgery and non-surgical treatments (neoadjuvant and/or adjuvant) for malignant sinonasal tumors.

Methods: All patients with nasoethmoidal malignancies treated with curative intent with endoscopic or endoscopic-assisted surgery at three referral centers with uniform management policies were included. Neo- and/or adjuvant (chemo)radiotherapy was administered according to histology and pathological

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report. Demographics, treatment characteristics, and complications related both to the surgical and non-surgical approaches were retrieved. The data were analyzed with univariate and multivariate statistics to assess independent predictors of complications.

Results: Nine hundred and forty patients were included, 643 males (68%) and 297 females (32%). A total of 225 complications were identified in 187 patients (19.9%): cerebrospinal fluid (CSF) leak (3.5%), mucocele (2.3%), surgical site bleeding (2.0%), epiphora (2.0%), and radionecrosis (2.0%) were the most common. Treatment-related mortality was 0.4%. Variables independently associated with complications at multivariate analysis were principally dural resection (OR 1.92), cranioendoscopic or multiportal resection (OR 2.93), dural repair with multilayer technique with less than three layers (OR 2.17), and graft different from iliotibial tract (OR 3.29).

Conclusion: Our study shows that modern endoscopic treatments and radiotherapy for sinonasal malignancies are associated with limited morbidity and treatment-related mortality. CSF leak and radionecrosis, although rare, remain the most frequent complications and should be further addressed by future research efforts.

1 | INTRODUCTION

Transnasal endoscopic surgery to treat malignancies of the sinonasal cavity has progressively replaced open approaches due to its ability to achieve non-inferior survival outcomes while reducing surgical invasiveness.[1–4] Indeed, a modern comprehensive management of sinonasal malignancies should not only aim at disease control but also consider treatment-induced morbidity and mortality. In this evolving scenario, several authors have increasingly focused their attention on post-treatment quality of life (QOL), relative to both surgery (endoscopic [ER] vs. open craniofacial resection [CRF]) and adjuvant therapy.[5–13]

Currently, the morbidity associated with transnasal ER for sinonasal malignancies is considered superior compared with CFR.[14] This difference has been attributed to the less invasive ER approach, which results in a decreased operative time, reduced bleeding, and shorter hospitalization.[9,14–16] However, this evidence is based on relatively small and mostly single institution series, thus limiting its reliability.

Integral to the treatment of sinonasal malignancies is also radiotherapy (RT), alone or combined with chemotherapy. Specific complications related to this treatment modality have also been described, along with the reduction of morbidity associated with the introduction of modern technologies such as intensity-modulated RT (IMRT) over the last two decades.[8,10,17]

Indeed, the technical and technological changes that have taken place over the last 20–25 years have profoundly changed the morbidity of therapies on sinonasal cancer patients, thus mandating a reappraisal of large, modern series.

The aim of the present paper is to assess the treatment related morbidity and mortality of multimodal treatment including endoscopic resection in a large multi-institutional study.

2 | METHODS

A multicenter retrospective observational study was performed in the Otorhinolaryngology Departments of "Università degli Studi di Brescia—Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili di Brescia" (Brescia, Italy), "Università dell'Insubria—ASST Sette Laghi Ospedale di Circolo e Fondazione Macchi di Varese" (Varese, Italy), and "Assistance Publique—Hôpitaux de Paris (APHP)—Hôpital Lariboisère" (Paris, France). The project was named MUlti-institutional collaborative Study on Endoscopically treated Sinonasal cancers (MUSES)

and provided data that were analyzed to assess prognosis and patterns of recurrence after multimodal treatment.[4,18]

Data on patients treated for sinonasal malignancies between October 1995 and March 2021 were collected in the three centers of MUSES,[4,18] which shared the same principles of treatment of sinonasal cancers throughout the study period, thus ensuring a reasonable degree of uniformity in terms of treatment policy. Patients with a benign sinonasal tumor and those treated without endoscopic or endoscopic-assisted surgery (e.g., CFR) were excluded from the study. Complete details on MUSES inclusion and exclusion criteria have been previously reported[4,18] and treatment principles were thoroughly discussed.

Standard deep vein thrombosis prevention strategy included compression stockings and low-molecular-weight heparin at prophylactic dosage.

Follow-up strategy was in keeping with European recommendations.[19]

2.1 | Ethical aspects

The study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards, and in compliance with the guidelines of the International Conference on Harmonization for Good Medical Practice. The study was approved by the appropriate institutional research ethics committee of each participating center ("ASST Spedali Civili di Brescia" and University of Brescia: protocol NP3616; "Ospedale di Circolo e Fondazione Macchi" and University of Insubria: Insubria Board of Ethics, approval number 0033025/2015; "Hopital Lariboisiere and University of Paris": REFCOR database approval CNIL #91204 and CCTIR #11.337).

2.2 | Multicenter database

Patient records in each center were reviewed to collect the following data: demographics, medical history, comorbidity-polypharmacy score (CPS),[20] smoking, previous tumor treatments (including neoadjuvant/induction therapies), clinical TNM, type of surgery (classified as either endoscopic resection [ER], endoscopic resection with transnasal craniectomy [ERTC], cranioendoscopic resection [CER] or endoscopic-assisted CFR [EACFR]),[4] length of postoperative hospital stay, type of skull base reconstruction (number of layers, type of graft [ileotibial tract or other], pedicled flap, free flap), histopathological diagnosis (post-surgical TNM, grading, site of origin and involved anatomical subsites), adjuvant treatments and treatment-related death.

The MUSES database was then searched for treatment-related complications.

First, we examined complications that occurred after surgery, defined as: (1) early post-surgical when they occurred within 1 month after surgery; (2) late post-surgical when occurred later than 1 month after surgery in patients who did not receive further adjuvant treatments.

Early post-surgical complications were rated according to Clavien–Dindo classification.[21]

Second, we examined complications that occurred at any time after adjuvant (chemo)RT that were classified according to their mortality risk in three groups: (1) no mortality risk; (2) at risk of mortality if untreated; (3) causing death.

After data anonymization, the databases of the three centers were merged for data analysis.

2.3 | Statistical analysis

2.3.1 | Descriptive and univariate

The variables that were selected were analyzed with descriptive and univariate statistics, calculating the odds ratio (OR) as a measure of association between the variables and the occurrence of complications. The same analysis was repeated on the subset of patients who underwent dural resection to assess the risk of postoperative CSF leak.

2.3.2 | Multivariate analysis

The measure of independence between type of surgery and all complication outcomes was assessed using chi-square statistics, a $p < 0.05$ was considered significant.

Based on the variables that were significantly associated with complications at univariate analysis, a stepwise linear regression model was applied. A bidirectional approach based on Akaike Information Criterion (AIC) was used to measure the quality of the multivariate model. Variables that presented an excessively wide/implausible confidence interval (e.g., 0-infinite) were excluded from this multivariate analysis.

2.3.3 | Testing for sensitivity and specificity with receiver operating characteristic (ROC) curves

Once linear regression was performed, different probability thresholds were used in the regression model and were analyzed in terms of both sensitivity and specificity.

The threshold with best sensitivity and specificity was then selected for further analysis.

2.3.4 | Testing for accuracy of the multivariate model

After choosing the probability threshold, the model was tested by randomly selecting 75% of the cases (training set) and then retested on the remaining 25% of the patients (validation set) refitting the model based on the same variables selected for multivariate analysis.

3 | RESULTS

A total of 940 patients were included. The main characteristics of the series are shown in Table 1. The mean length of hospitalization was 8 days (median 7 days; interquartile range (IQR) 4–10). The average follow-up duration after surgery was 59 months (range: 6–272 months). Data on smoking status were available in 277 cases, 141 were active smokers. Comorbidity-polypharmacy score (CPS) could be calculated in 147 patients and ranged between 0 and 20, the median score was 5 (IQR 2–8).

3.1 | Complications analysis

Two hundred and twenty-five complications were reported in 187 patients, accounting for a complication rate of 19.9%. More than one complication occurred in 30 patients (16%), among which two complications were reported in 25 (13%) patients, three in three (2%), four in one (0.5%), and five in one (0.5%) for a total of 68 complications. The rate of patients with complications according to the type of surgery was: 14% (52/373) after ER, 21% (97/464) after ERTC, 36% (30/84) after CER, and 41%

TABLE 1 Main characteristics of patients enrolled in the presented series.

	$N = 940$ (%)	Peculiarities
Gender, male:female	643:297	–
Primary vs. secondary malignancy	745 (79.3%) vs. 195 (20.7%)	Previous treatment consisted of surgery (101 patients), surgery and adjuvant RT (36 patients), definitive ChT-RT (29 patients), surgery and adjuvant ChT-RT (18 patients), definitive RT (13 patients), and surgery and adjuvant ChT (7 patients)
Surgical approach		
Type of surgical approach	ER: 373 (39.7%) ERTC: 464 (49.4%) CER: 84 (8.9%) EACFR: 19 (2.0%)	The surgical approach was unilateral in 366 (38.9%) patients
Extension to the skull base	839 (89.3%)	Resection of 275 (29.3%) skull base mucosa, 23 (2.4%) bony skull base, 515 (54.8%) dura mater, 26 (2.8%) brain
Extension to the orbit	429 (45.6%)	Resection of 285 (30.3%) lamina papyracea, 97 (10.3%) periorbit, and 49 (5.2%) extraconal fat
Extension to the intracranial lateral spaces	99 (10.5%)	Resection of 51 (5.4%) pterygopalatine fossa, 22 (2.3%) pterygoid plates, and 28 (3.0%) infratemporal fossa
Skull base reconstruction	629 (66.9%)	ITT used in 470 (74.7%), synthetic and heterologous grafts (e.g., TachoSil, Duragen) used in 104 (16.5%) cases. Pedicle and free flaps employed in 94 (14.9%) and 2 (0.3%) cases, respectively Layers of skull base reconstruction were 1, 2, 3, and 4 in 78 (12.4%), 75 (11.9%), 429 (68.2%), and 2 (0.3%) cases, respectively
Adjuvant treatment	$N = 580$ (61% of total)	
Radiotherapy	526 (90%)	Radiotherapy was administered either pre- (80, 8%) or postoperatively (563, 60%) to a total of 643 patients (68%)
Radiotherapy + chemotherapy	37 (7%)	
Chemotherapy	17 (3%)	

Abbreviations: CER, cranioendoscopic resection (ER combined with a coronal incision, frontal craniotomy and sub-frontal approach); CHT, chemotherapy; ER, endoscopic resection; ERTC, ER with transnasal craniectomy; ITT, iliotibial tract graft; RT, radiotherapy.

TABLE 2 Severity of early postoperative surgical complications classified according to the Clavien–Dindo classification.

	Complications	N
Grade 1 (14 cases, 1.5%)	Temporary visual dysfunction (diplopia, amaurosis fugax)	7
	Asymptomatic, small intracranial hematoma	3
	Hypokalemia	2
	Persistent olfactory dysfunction (dysosmia/cacosmia)	1
	Postoperative CSF leak not requiring surgery	1
	Subdural hematoma	1
	Pneumocephalus	2
	Headache	1
Grade 2 (31 cases, 3.3%)	Delirium	7
	Arrhytmia	3
	Fever of unknown origin	6
	Pulmonary thromboembolism	3
	Anemia	4
	Slowly remitting pneumocephalus	3
	Meningitis	2
	Acute rhinosinusitis	2
	Pneumonia	1
	Rhabdomyolysis	1
	Spontaneous bacterial peritonitis	1
	Deep venous thrombosis	1
Grade 3a (37 cases, 3.9%)	Epistaxis	14
	Postoperative CSF leak	10
	ITT donor site complications (e.g., seroma, hematoma)	12
Grade 3b (35 cases, 3.7%)	Postoperative CSF leak	13
	Cerebral abscess	5
	Tension pneumocephalus	4
	Epistaxis	2
	ICA aneurism bleeding	1
	Cerebral herniation	2
	Tension pneumocephalus with cerebral herniation	1
	Hygroma	1
	Pneumocephalus and infectious meningitis	2
	Skull base reconstruction infection	1
	CSF leak, cerebral abscess, pneumocephalus, paraplegia and urinary incontinence	5
	CSF leak and meningitis	1 + 1
	Intracranial foreign body	1
	Intracranial foreign body and cerebral abscess	1 + 1
Grade 4a (2 cases, 0.2%)	Stroke	2
Grade 4b (5 cases, 0.5%)	Sepsis	5
Grade 5 (2 cases, 0.2%)	Hygroma	1
	Carotid blowout	1
	Total	139

Abbreviations: CSF, cerebrospinal fluid; ICA, internal carotid artery; ITT, ileotibial trait.

TABLE 3 Severity of complications occurred after completion of adjuvant (chemo)radiotherapy classified according to mortality risk.

	Complications	N
Complication with no risk of mortality (37 cases, 3.9%)	Nasolacrimal duct obstruction	15
	Mucocele/mucopyocele	9
	Cataract	2
	Oronasal/oroantral fistula	2
	Asymptomatic post-radiation cerebral edema	1
	Eustachian tube dysfunction	1
	Frontal depression	1
	Epilepsy	1
	Trismus	1
	Persistent conjunctival chemosis	1
	Glaucoma	1
	Unilateral loss of vision	1
	Optic neuritis	1
Complication with risk of mortality if not adequately treated (19 cases, 2.0%)	Uncomplicated radionecrosis	11
	Radionecrosis with CSF leak	4
	Late-onset CSF leak (no radionecrosis reported)	2
	Extradural abscess	2
Complication as cause of death of the patient (2 cases, 0.2%)	Radionecrosis with CSF leak	1
	Carotid blowout	1

Abbreviation: CSF, cerebrospinal fluid.

(8/19) after EACFR. Despite a constant trend toward a higher complication rate for more complex procedure, the correlation with the type of surgery did not reach statistical significance ($p > 0.05$).

One hundred and sixty-four complications (73%) in 143 (15%) patients occurred after surgical treatment, either early or late post-surgical ones. Early complications were the majority of post-surgical complications and were 139 (61%) in 118 patients (12%). They are detailed and grouped according to Clavien–Dindo classification in Table 2. Late post-surgical complications were found in 25 (2%) patients treated exclusively with surgery, whereas other 62 (27%) complications, reported in 51 (5.4%) patients, occurred after adjuvant RT and were defined as post-(chemo)RT complications (Table 3). Details on all treatment-related complications are summarized in Table 4.

Treatment-related mortality was 0.4% (4 cases). Two (0.2%) events occurred early postoperatively, 1 case of severe hygroma causing brain herniation and 1 carotid blowout. Other two (0.2%) happened after adjuvant RT, 1 carotid blowout and 1 anterior skull base radionecrosis with CSF leak and subsequent infection-related death.

3.2 | Univariate analysis

Variables significantly associated with complications in the entire series are reported in Table 5. Complications and variables significantly associated with CSF leak in the subgroup of patients who underwent transnasal craniectomy with dural resection and skull base reconstruction are reported in Table 6.

3.3 | Multivariate analysis

Multivariate analysis and independent variables associated with complications in the entire series are reported in Table 7. Multivariate analysis of the subgroup of 543 (57.8%) patients who underwent transnasal craniectomy with dural resection is reported in Table 8.

Multivariate analysis and independent variables associated with postoperative CSF leak in the subgroup of 543 (58%) patients who underwent trans nasal craniectomy with dural resection are reported in Table 9.

A further multivariate analysis on the subgroup of cases with data about comorbidity-polypharmacy score (CPS) was performed: in this subanalysis, CPS was the only independent variable associated with a higher risk of complications.

3.4 | Validation of multivariate models

Considering variables predicting complications in the entire series (Table 7), the selected threshold was 0.3 and the accuracy model test showed a result of 2.3%.

Whereas, among variables predicting complications in the subgroup who underwent ERTC, and variables predicting CSF leak in the subgroup who underwent ERTC, the selected threshold was respectively 0.25 and 0.05, with an accuracy model test of 4% and 13.7%, respectively (Figures S1–S3).

4 | DISCUSSION

Among all included patients, the complication rate was 20% (225 complications), with a greater prevalence of post-surgical complications (163 cases, 72%) compared with post-(chemo)radiotherapy (62 cases, 28%). The most common post-surgical complication was CSF leak (3.5%),

TABLE 4 Characteristics, incidence, timing, and treatment of complications experienced by the enrolled patients.

Complication	N = 940 (%)	Post-surgical treatment <1 month (%, time to onset)	Post-surgical treatment >1 month or after adjuvant radiotherapy (%, time to onset)	Treatment
CSF leak	33 (3.5% of whole series and 6.1% of cases with dural resection)	26 (78.8%, within 2 weeks)	7 (21.2%, 4–48 months)	*Early cases:* 15 (57.7%) treated with revision surgery, 10 (38.5%) cases were managed with lumbar drainage and 1 (3.8%) had a spontaneous resolution of the leak *Late cases:* treated with revision surgery, 1 patient died from extended infection and radiation necrosis
Mucocele and mucopyocele	22 (2.3%)	0	22 (100%, 6 months-8 years)	Surgical treatment was necessary in 21 (95.5%) cases
Nasolacrimal duct obstruction	19 (2%)	0	19 (100%, within 6 months)	Dacryocystorhinostomy was necessary in 13 (68.4%) cases
Epistaxis or surgical cavity bleeding	19 (2%)	18 (94.7%, perioperative)	1 (5.3%, after 10 years)	Cauterization and/or nasal packing were used in 14 (73.7%) cases, while surgical revision was required in 3 (15.8%) cases. Lethal carotid blowout happened in one case of skull base radiation necrosis 10 years after the end of RT
Radiation necrosis	19 (1.9% of the whole series, 2.8% of the subgroup who underwent adjuvant RT-CHT)	0	19 (100%, onset after 7–60 months)	Eight patients (with anterior skull base necrosis, 7 of whom had concomitant CSF-leak), underwent surgery with debridement and skull base reconstruction with pericranial flap. Other two patients (necrosis of the maxillary bone and nasal septum) required endoscopic debridement One patient had concomitant radionecrosis of brain and skull base reconstruction, CSF leak, infection of skull base (see discussion), a fatal outcome could not be avoided despite revision surgery The remaining 8 patients (necrosis of brain, septum, frontal and maxillary bone) were treated with antibiotics, pentoxifylline, tocopherol, and steroid (the last only in case of cerebral edema)
Ophthalmic complications (diplopia, cataract, conjunctival chemosis and glaucoma)	13 (1.4%)	7 (53.8%, up to 2 weeks after surgery)	6 (46.2%)	Treated accordingly Of note, after radiotherapy, one unilateral non-reversible blindness, and one case of post radiation optic neuritis
Iliotibial tract donor site complication	12 (1.3%)	12 (100%, during postoperative hospital stay)	0	Hematoma were evacuated and bleeding points were controlled by bipolar coagulation with the patient under general anesthesia; seromas were treated with a syringe drainage followed by application of compressive dressing. Wound infections were successfully treated with antibiotics
Symptomatic pneumocephalus	8 (0.9%)	8 (100%, 2 days-3 weeks)	0	Revision surgery was performed in 6 (75.0%) cases, the remining had spontaneous resolution

(Continues)

TABLE 4 (Continued)

Complication	N = 940 (%)	Post-surgical treatment <1 month (%, time to onset)	Post-surgical treatment >1 month or after adjuvant radiotherapy (%, time to onset)	Treatment
Brain abscess	8 (0.9%)	3 (37.5%, perioperative)	5 (62.5%, up to 7 months)	Surgical drainage (7 cases) or needle aspiration under radiological guidance (1 case) were curative
Meningitis	5 (0.5%)	5 (100%, during postoperative hospital stay)	0	In all cases the complication was treated successfully with antibiotic therapy, and with revision surgery in cases of concomitant CSF-leak (2) or pneumocephalus (1)
Sepsis	5 (0.5%)	5 (100%, during postoperative hospital stay)	0	All cases were treated successfully with antibiotic therapy
Brain hematoma	3 (0.3%)	3 (100%, during postoperative hospital stay)	0	This complication did not implicate symptoms and did not require any intervention
Subdural hygroma	3 (0.3%)	2 (66.7%, during postoperative hospital stay)	1 (33.3%, 3 months)	*Early:* One case was treated successfully with revision surgery, the other did not undergo revision surgery and died after 2 months for neurological complications related to the hygroma. The *late* onset case had a benign evolution and no intervention was required
Brain herniation	3 (0.3%)	3 (100%, during postoperative hospital stay)	0	All patients were successfully treated with revision surgery through an open access
Cerebral ischemia	3 (0.3%)	2 (66.7%, during postoperative hospital stay)	1 (33.3%, 2 months)	Late case had undergone chemoradiation before salvage surgery
Extradural abscess	2 (0.2%)	0	2 (100%, 3–18 months after adjuvant RT)	Both cases were treated successfully with surgical drainage
Intracranial foreign body	2 (0.2%)	2 (100%, detected before discharge from hospital)	0	Surgical removal
Infection of the skull base reconstruction	2 (0.2%)	1 (50%, perioperative)	1 (50%, 4 months after the end of RT)	The early case was treated with revision surgery; the late case, associated with CSF-leak and brain radiation necrosis, and died because of the complication
Nasal obstruction (functional synechiae)	2 (0.2%)	0	2 (100%, >1 month after exclusive surgical treatment)	Revision surgery was resolutive in both cases
Oronasal/oroantral fistula	2 (0.2%)	0	2 (100%, 4 and 31 months after the end of adjuvant RT)	In both cases the resection was extended to the floor of maxillary sinus

TABLE 4 (Continued)

Complication	N = 940 (%)	Post-surgical treatment <1 month (%, time to onset)	Post-surgical treatment >1 month or after adjuvant radiotherapy (%, time to onset)	Treatment
Stroke	3 (0.3%)	2 (66.7%, within 2 weeks after surgery)	1 (33.3%, 2 months)	In the late case chemoradiation was performed before surgery and is probably associated with the event
Other post-radiation complications	5 (0.5%)	0	5 (100%, variable onset after RT)	Brain edema (1 case), eustachian tube dysfunction (1 case), frontal syndrome (1 case); post-radiation epilepsy (1 case), and post-radiation trismus (1 case)
Other medical complications	38 (4.0%)	38 (100%, during postoperative hospital stay)	0	• Delirium in 9 (23.7%) cases • Fever of unknown origin in 6 (15.8%) cases • Anemia requiring blood transfusions in 4 (10.5%) cases • Pulmonary embolism in 4 (10.5%) cases • Hypokalemia in 2 (5.3%) cases • Acute sinusitis in 2 (5.3%) cases • Paraplegia and urinary incontinence in 1 (2.6%) case • Persistent headache in 1 (2.6%) case • Olfactory dysfunction in 1 (2.6%) case • Spontaneous bacterial peritonitis in 1 (2.6%) case • Epilepsy in 1 (2.6%) case • Rhabdomyolysis in 1 (2.6%) case • Pneumonia in 1 (2.6%) case

Note: Early complications were defined when they occurred within 1 month after surgery, whereas late complications occurred later than 1 month.

Abbreviations: CHT, chemotherapy; CSF, cerebrospinal fluid; RT, radiotherapy.

TABLE 5 Variables associated with complications in the entire series at univariate analysis.

Univariate analysis			
Variable	***p* value**	**Odds ratio**	**95% CI**
Patient-related variables			
Male gender	0.01	1.59	1.10–2.29
Preoperative ChT	0.03	2.03	1.07–3.85
CPS	<0.001	1.10	1.04–1.15
Surgery-related variables			
Hospitalization (days)	<0.001	1.13	1.09–1.16
Skull base resection	<0.001	1.29	1.11–1.49
Dural resection	<0.001	2.02	1.43–2.85
Skull base reconstruction	<0.001	1.85	1.28–2.68
Extranasal or Intranasal Pedicled flap vs. no flap	0.02	1.47	1.06–2.03
ER vs. other approaches	**<0.001**	**0.52**	**0.37–0.74**
No graft used	**<0.001**	**0.53**	**0.37–0.77**
Graft non-ITT	0.03	1.67	1.05–2.66
Resection limited to bony SB	**<0.001**	**0.39**	**0.26–0.59**
Resection of dura or brain	<0.001	2.02	1.43–2.85
Two-layer SB reconstruction	<0.001	3.02	1.84–4.96
Unilateral extension	**<0.001**	**0.50**	**0.35–0.72**
Bilateral extension	<0.001	1.98	1.39–2.83
CER or multiportal approach	<0.001	2.83	1.82–4.40
Disease/pathology-related variables			
Extraconal fat involvement	0.02	3.48	1.24–9.74
Infratemporal fossa involvement	0.02	2.60	1.16–5.83
Nasopharyngeal involvement	0.01	2.04	1.18–3.52
Orbital apex involvement	0.01	2.34	1.22–4.50
Bony skull base involvement	0.01	1.55	1.12–2.14
Brain involvement	0.01	2.25	1.20–4.23
Anterior skull base reconstruction with graft vs. no reconstruction or other techniques (pedicled, etc.)	<0.001	1.88	1.29–2.73
ITAC vs. other histologies	0.01	1.57	1.13–2.18
MM vs. other histologies	**<0.001**	**0.31**	**0.14–0.69**
pT4b vs. other T stages	<0.001	1.68	1.19–2.37

Note: Variables significantly associated with better outcomes are highlighted in bold.

Abbreviations: CER, cranioendoscopic resection; CHT, chemotherapy; CPS, comorbidity-polypharmacy score; ER, endoscopic resection; ITAC, intestinal-type adenocarcinoma; ITT, iliotibial tract; MM, mucosal melanoma; SB, skull base.

while post-(chemo)radiotherapy was radionecrosis (2.7%). The overall rate of mortality was 0.4% (four cases), and only 2 (0.2%) deaths were associated with the lethal progression of a post-surgical complication.

To the best of our knowledge, this manuscript represents the largest cohort of sinonasal malignancies that underwent an endoscopic surgery-based multimodal treatment in the literature, focusing on complications and their management.

4.1 | Complications after surgery

Our results show that endoscopic surgical approaches are relatively safe, with an early post-surgical complication rate of 15% and minimal mortality (0.2%).

ER morbidity has been previously investigated and the two largest series reported to date report complication rates of 9%–11% and mortality of 0%–1%.[22,23] Nevertheless, while a large study of patients undergoing CFR

TABLE 6 Variables associated with complications in the subgroup of 543 (57.8%) patients who underwent dural resection and skull base (SB) reconstruction at univariate analysis.

Univariate analysis			
Variable	*p* value	Odds ratio	95% CI
Patient-related variables			
Hospitalization (days)	<0.001	1.15	1.11–1.19
Preoperative RT-CHT	<0.001	3.35	1.55–7.22
Surgery-related variables			
CER or multiportal approach	<0.001	2.83	1.82–4.40
Resection of intraconal fat	0.02	2.77	1.21–6.34
Resection of ITF	**0.05**	**0.51**	**0.26–1.00**
Grafts: non-ITT	0.01	2.19	1.20–4.01
Two-layer SB reconstruction	<0.001	2.47	1.41–4.31
Three or more layer SB reconstruction	**<0.001**	**0.49**	**0.30–0.79**
Disease/pathology-related variables			
pT1	**0.04**	**0.41**	**0.17–0.98**
Orbital apex	<0.001	5.48	2.22–13.52
Brain invasion	0.03	2.12	1.09–4.10
Unilateral extension	**<0.001**	**0.50**	**0.35–0.72**
Bilateral extension	<0.001	1.98	1.39–2.83

Note: Variables significantly associated with better outcomes are highlighted in bold.
Abbreviations: ITF, infratemporal fossa; ITT, iliotibial tract graft; RT-CHT, chemoradiation; SB, skull base.

TABLE 7 Variables associated with complications in the entire series at multivariate analysis.

Multivariate analysis			
Variable	*p* value	Odds ratio	95% CI
Nasopharynx	<0.001	2.93	1.41–6.07
Resection of ITF	0.02	3.2	1.18–8.64
Dural resection +/− subpial dissection	<0.001	1.92	1.25–2.94
Two-layer SB reconstruction	0.01	2.17	1.24–3.78
CER or multiportal approaches	<0.001	2.93	1.56–5.51

Abbreviations: CER, cranioendoscopic resection; ITF, infratemporal fossa; SB, skull base.

TABLE 8 Variables associated with complications in the subgroup of 543 (57.8%) patients who underwent dural resection and skull base (SB) reconstruction at multivariate analysis.

Multivariate analysis			
Variable	*p* value	Odds ratio	95% CI
Orbital apex	0.02	3.46	1.12–9.91
ERTC	**0.01**	**0.41**	**0.21–0.78**
Resection extended to the brain	0.05	2.02	0.99–4.41
Three or more layer SB reconstruction	**0.02**	**0.48**	**0.27–0.88**

Note: Variables significantly associated with better outcomes are highlighted in bold.
Abbreviation: ERTC, endoscopic resection with transnasal craniectomy.

dating before the advent of ER found an overall complication rate of 36.3% and a mortality rate of 4.5%,[24] more recent studies on CFR found complication rates that are more comparable to concurrent endoscopic series, ranging between 9.7% and 25% in studies published after 2008.[22,23,25] Indeed, a direct comparison between CFR and endoscopic techniques cannot be made based solely on the described data because of heterogeneity of patient

TABLE 9 Variables associated with CSF leak at multivariate analysis in the subgroup of 543 (57.8%) patients who underwent dural resection and skull base reconstruction.

Multivariate analysis			
Variable	*p* value	Odds ratio	95% CI
Grafts: non-ITT	0.01	3.29	1.26–8.55
Two-layer SB reconstruction	0.03	2.72	1.09–6.78

Abbreviations: ITT, iliotibial tract graft; SB, skull base.

selection criteria and different sample size among case series. Overall, our data indicate that extended lesions that warrant a more aggressive surgical approach present a higher likelihood to experience complications (Tables 5–9). Specifically, in our multivariate analysis, CER/EACFR, dural resection and extension to the ITF or nasopharynx have been demonstrated to be independent risk factors associated with complications (OR between 2.93 and 3.2, Table 7).

Among all early post-surgical complications, the most frequent were related to dural resection and failure of subsequent reconstruction, namely CSF leak, pneumocephalus, and brain herniation (Table 4). CSF leak has recently been described in 0.5%–6% of patients treated with endoscopic/open craniectomy with dural reconstruction,[9,26,27] which is in line with our findings (2.7% of patients). Multivariate analysis conducted on the whole patient cohort and on those patients who underwent ERTC indicated an overall higher risk of complications (OR 2.17) and a higher risk of CSF leak among patients undergoing skull base reconstruction using only two layers (OR 2.72). Conversely, three-layer SB reconstruction was a protective factor in the development of complications in cases of skull base resection and dural reconstruction (OR 0.48). Indeed, as already demonstrated, three-layer SB reconstruction with ITT has emerged as the gold-standard procedure in cases of large defects of the central portion of the anterior skull base.[28] Most cases of early post-surgical CSF leak (15, 58%) were treated with revision surgery while 11 (42%) cases of mild leak were treated conservatively, either with minor revision under local anesthesia (i.e., sealing of the leak with fibrin glue and bolstering of the duraplasty with resorbable material) or with lumbar drain.

Together with CSF leak, failure of SB reconstruction can also lead to two other early complications: pneumocephalus and brain herniation. The presence of intracranial air after ERTC is a relatively common finding on postoperative imaging studies with a prevalence of over 40%.[29] In the majority of cases, this event is asymptomatic and benign (consequent to the entry of air during the surgical procedure), although it can be a warning sign for dural reconstruction failure and CSF leak.[30] A retrospective study on 256 endoscopic anterior skull base surgery cases with dural opening showed that a frontal or intraventricular pneumocephalus is not correlated with postoperative CSF leak and can be consequently defined as benign pneumocephalus, since it is completely absorbed within a week. However, intracranial air at the level of the convexity, interhemispheric fissure, sellar, parasellar, and perimesencephalic region is correlated with postoperative CSF leak (OR 4.9).[29] In our cohort, we took into account only severe symptomatic pneumocephalus independently of its location, which was found in 8 patients (0.9%) and was variably associated with other complications (e.g., CSF leak, meningitis, brain herniation). The condition was treated in the majority of cases (75%) with revision surgery; in two patients, it resolved spontaneously.

Brain herniation after endoscopic surgery for sinonasal malignancies is an extremely rare condition (0.64%) that was treated in all cases with revision surgery. This adverse event seems unrelated to the size of the defect or technique of anterior SB reconstruction, but rather to the presence of increased intracranial pressure associated with obesity or obstructive sleep apnea.[31]

Considering early infectious adverse events, meningitis was reported in four postoperative cases, which was isolated (without CSF leak or pneumocephalus) in two cases. The presence of uncomplicated meningitis after endoscopic endonasal skull base surgery is relatively rare (0.9%–1.8%).[32] A single preoperative dose of antibiotic (third generation cephalosporine) is routinely administered in all three centers, unless an infected surgical field is noted. Only presence of infection during intraoperative examination or evidence of postoperative meningitis warrant culture-guided long-term antibiotic therapy. A recent meta-analysis demonstrated that neither long-term-antibiotics nor multiple prophylactic antibiotics were associated with a significant reduction of infectious complications.[33] In our series, all cases of postoperative meningitis without CSF leak were successfully treated with antibiotic therapy (Table 4).

Another infectious adverse event, brain abscess, was reported early after surgery in three cases and resolved by surgical/radiological drainage. The cause of the complication was recognized in only two early cases: SB

reconstruction failure and presence of a retained foreign body (surgical cottonoid). Uncomplicated retention of intracranial cottonoids was reported in another patient in this series and was treated with surgical revision. Count of surgical materials after each procedure, proper communication among staff nurses and surgeons and use of cottonoids wired and/or marked with radiopaque material are all proven measures to prevent such complications and should be consistently implemented.[34]

Early postoperative bleeding occurred in 18 patients, and most cases (14 cases, 73.7%) were moderate and properly treated conservatively with nasal packing. Only three cases (15.8%) needed revision surgery. Only one case of fatal carotid blowout occurred on postoperative day six after an extended multiportal approach to a sinonasal chondrosarcoma after which the parapharyngeal carotid artery was left uncovered. Covering of ICA after resection should always be attempted in order to minimize inflammation and/or infection of exposed arterial walls and consequent rupture.

In addition, subdural hygroma was reported in three cases (two early cases and one late). This complication is rare in transnasal endoscopic approaches, but well known for decompressive craniotomy and endoscopic third ventriculostomy and can be fatal.[35,36] One of our patients who developed a hygroma early in the postoperative period died 2 months later of neurological complications related to this condition. Park et al. recently demonstrated that one of the risk factors for subdural hygroma is extended dissection of the arachnoid,[37] and it could be speculated that this also applies to our series in which subdural hygroma occurred only in advanced cases (all pT4b) requiring craniectomy and dural resection.

4.2 | Complications occurring after adjuvant (chemo)radiotherapy

Radiation therapy plays a significant role in the multimodal treatment of sinonasal malignancies and more than half of the patients (580, 61%) underwent that treatment. Among all complications experienced in our cohort, radionecrosis represented the fifth most common, whereas considering only post-radiotherapy complications, it was the most frequent with 19 cases (3% of the subgroup who underwent adjuvant (chemo)radiotherapy). Radionecrosis usually presents an incidence between 3% and 24% depending on many factors (e.g., radiation dose, age, and fractionation)[38]; symptoms are variable with a frequent asymptomatic radiological presentation.[39] Compared with other case series, our cohort had a relative low rate of radionecrosis (2.7%), which could be mostly explained by its retrospective design that

could have led to underestimation of mild, asymptomatic cases. Anterior SB and frontal lobe were the most common areas of radiation induced necrosis and in such cases the association with CSF leak is frequent.[40] The management of this complication varies in relation to its severity. In fact, as happened in our series, all cases with uncomplicated radionecrosis were treated with antibiotics, and steroids only if associated with cerebral edema. In some cases, the use of pentoxifylline, tocopherol, and clorodronate, initially described to treat mandibular osteoradionecrosis, were applied because of the similar pathogenic mechanisms and the increasing evidence of their efficacy.[41,42] On the contrary, if the radionecrosis was associated with a complication (i.e., CSF leak, internal carotid artery exposure or exposed osteomyelitis) debridement of the necrotic bone associated with a vascularized flap coverage was performed in addition to standard medical therapy. In our series, radionecrosis evolved into a fatal condition in two cases (1) one case of skull base reconstruction radionecrosis, CSF leak and infection that could not be salvaged despite repeated attempts at repairing the skull base with local and free vascularized flaps, and (2) one case of carotid blowout. Indeed, carotid blowout is a feared consequence of SB irradiation with a mortality rate as high as 50% in surgically-treated and 76% in re-irradiated patients.[43,44]

Finally, two cases of extradural abscess with late onset (3 and 18 months after the end of RT) occurred. These infectious complications could be related to supra-infection of a focal area of radionecrosis, and one case progressed to fatal brain and systemic infection.

Among the other complications that occurred after radiation therapy (Table 4), the most relevant ones involved the brain (frontal syndrome, epilepsy, brain edema, stroke) or the eye and the optic system (cataract, conjunctival chemosis, glaucoma, amaurosis, post-irradiation optic neuritis), and were recorded in a minority of irradiated patients (10, 1.7%).

4.3 | Study limitations

We presented multicentric data characterized by homogeneity of treatment philosophy with a relative long follow-up (mean 59 months); however, the retrospective nature of the study, together with the lack of data of non-surgical treatments (e.g., dose and type of chemo/radiotherapy) and the potential underestimation of minor complications or complications occurring more distantly after surgery or radiotherapy could be seen as major limitation. In addition, it should be noted that as data on non-surgical treatments are collected in a surgical setting, it is reasonable to assume that there could have been an underestimation of post-chemo/radiotherapy complications.

5 | CONCLUSION

The present analysis confirms that the transnasal endoscopic surgery for sinonasal malignancies is associated with acceptable morbidity and mortality. Considering only severe adverse events (life threatening and/or requiring surgical treatment), the rates of complications related to surgery and adjuvant therapies are 4.7% and 3.2%, respectively, with CSF leak and radionecrosis being the most common post-surgical and radiation-induced complications. Multivariate analysis confirmed the importance of three-layer ITT for SB reconstruction; more extended endoscopic-assisted surgery (CER and multiportal approaches) had higher morbidity than purely endoscopic endonasal procedures. Further studies focusing on recently introduced irradiation modalities (e.g., heavy ion particle therapy) and the role of patient comorbidities are needed to further personalize care and improve outcomes.

AUTHOR CONTRIBUTIONS

G. Bertazzoni, A. Vinciguerra, D. Camous, M. Turri Zanoni, M. Ferrari, D. Mattavelli, A. Schreiber, S. Taboni, A.D. Arosio B. Verillaud and V. Rampinelli made substantial contributions to conception, design and acquisition of data, drafted the article, revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; C. Piazza, M. Bignami, A. Deganello, P. Battaglia, P. Nicolai, P. Castelnuovo, P. Herman made substantial contributions to conception of the data, revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request to the corresponding author.

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