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Matching-adjusted indirect comparison of endoscopic and craniofacial resection for the treatment of sinonasal cancer invading the skull base

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A R T I C L E I N F O

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Skull base surgery
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A B S T R A C T

Aim: The aim of this study was to compare the efficacy and safety of endoscopic endonasal approaches (EEA) with craniofacial resection (CFR) for sinonasal cancers invading the skull base, using an unanchored matching-adjusted indirect comparison (MAIC).

Methods: A MAIC approach was used to analyse data from two large cohorts: the MUlti-institutional collaborative Study on Endoscopically treated Sinonasal cancers (MUSES) cohort, comprising sinonasal cancer patients treated endoscopically, and a historical CFR cohort reported by Ganly et al. Individual patient data were available only for the first cohort. Patients with olfactory neuroblastomas were excluded. Key prognostic factors were used to match and adjust the two cohorts, minimising selection bias. The primary endpoint was overall survival (OS), with secondary endpoints including recurrence-free survival (RFS), perioperative mortality, complication rates, and resection margins.

Results: A total of 724 EEA-treated and 334 CFR-treated patients were included. EEA showed significantly improved OS before (HR= 2.33, 95 % CI= 1.88–2.87) and after MAIC adjustment (HR= 1.93, 95 % CI= 1.60–2.34). Observed RFS was higher in the EEA group (HR= 1.39, 95 % CI = 1.14–1.69) but no longer differed after adjustment (HR= 1.06, 95 % CI= 0.91–1.23). EEA was associated with significantly better Disease Specific Survival (HR= 1.71, 95 % CI = 1.39–2.13), lower perioperative mortality (OR= 8.12, 95 % CI= 3.45–36.7) and fewer complications than CFR (OR= 3.68, 95 % CI= 2.47–5.42).

Conclusion: In this MAIC study based on the 2 largest cohorts of sinonasal cancer with skull base invasion, EEA offered comparable oncologic outcomes to CFR with reduced morbidity, supporting it as a valid alternative when performed in expert centres.

1. Introduction

Sinonasal cancers are rare tumours that present significant treatment challenges. The various histological subtypes exhibit different progression patterns, necessitating the use of distinct therapeutic approaches. The proximity of numerous vital structures, including the brain and

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orbit, renders surgical intervention in these areas challenging and potentially invasive [1]. Historically, these tumours were managed through open surgical techniques. However, the advent of endoscopic surgery has enabled the treatment of nasal tumours in a less invasive manner, initially focusing on benign tumours. As techniques evolved, endoscopic surgery expanded to treat progressively more advanced sinus cancers, including those invading the brain [2]. The adoption of these techniques by specialised teams has not allowed for randomised studies to validate their superiority over open approaches. While retrospective studies have demonstrated that endoscopic surgery can achieve comparable oncological outcomes with reduced morbidity in the treatment of T1-T2 sinonasal cancers [3], controversy remains regarding tumours invading the skull base, where endoscopic approaches are considered an alternative to craniofacial resection [4,5].

Endoscopic approaches have been increasingly applied to more advanced tumours over time, making direct comparisons inconclusive regarding their superiority over external approaches [1]. However, studies accounting for potential biases have only been conducted on small populations, limiting their statistical power [6,7].

This study aims to compare the treatment of sinonasal cancers invading the skull base via endoscopic approaches using data from a large cohort and historical data from craniofacial resections. A matching adjusted indirect comparison (MAIC) was performed to handle the underlying indication bias that may confound the estimate of effects [8].

2. Material and methods

The MUlti-institutional collaborative Study on Endoscopically treated Sinonasal cancers (MUSES) cohort is a previously published, multicentre cohort of patients with sinonasal cancer treated with surgery, including an endoscopic transnasal approach, between 1995 and 2018 in three European centres: "ASST Spedali Civili di Brescia," University of Brescia, Brescia, Italy; "Ospedale di Circolo e Fondazione Macchi," University of Insubria, Varese, Italy; and "Hôpital Lariboisière," University Paris Cité, Paris, France [9]. This cohort was approved by local institutional review boards ('ASST Spedali Civili di Brescia' – University of Brescia: protocol NP3616; 'Ospedale di Circolo e Fondazione Macchi' – University of Insubria: Insubria Board of Ethics, approval number 0033025/2015; 'Hôpital Lariboisière' – University of Paris: REFCOR database approval CNIL #91204 and CCTIR #11.337.

In this study, we conducted a comparative analysis using published data from Ganly et al., which reported the treatment of sinonasal cancers invading the skull base via craniofacial resection, excluding olfactory neuroblastomas [10]. This comparative analysis used an unanchored MAIC, a new propensity score-based approach that allows to correct baseline imbalances in prognostic variables and treatment modifiers across the groups, when individual patient data (IPD) are only available for one intervention, while only aggregated (published) data are available for the comparator [8].

Patients without follow-up or with missing values for prognostic factors were excluded. As the number of missing values was very low, no imputation was performed. Patients from the MUSES cohort with tumours invading the skull base were included, while those with olfactory neuroblastomas were excluded.

Baseline characteristics were summarised and compared between the MUSES cohort (referred to as the endoscopic cohort) and the studies by Ganly et al. (referred to as the CFR cohort). The primary endpoint evaluated in the MAIC analysis was overall survival (OS). Secondary endpoints included disease-specific survival (DSS), recurrence-free survival (RFS), perioperative mortality, clear resection margins, and the frequency of severe perioperative complications.

The survival data from the historical studies were extracted from the published Kaplan-Meier curves. The extraction was performed using Digitizit software, and a pseudo-individual patient dataset (IPD) was constructed from the extracted data, patient numbers, and median survival time using the method developed by Guyot et al. [11]. Kaplan-Meier curves were recreated from the extracted data to check the results in comparison to the original curves. Only 5-year survival was assessed due to the low reliability of longer-term survival data, as the median follow-up was 19 months in the study by Ganly et al. Before matching, the survival between the selected patients from the MUSES study and the data from Ganly et al. was compared by the log-rank test. Hazard ratios (HR), 95 % confidence intervals (CI), were estimated using Cox proportional hazards models.

In the MUSES cohort, treatment-related death was defined as any death occurring within 30 days after the completion of treatment. An operative complication was classified as severe if it led to prolonged hospitalisation, required early revision surgery, or posed a risk of permanent sequelae or mortality. These endpoints were compared with those reported in the studies by Ganly et al. Odds ratios (ORs), along with the corresponding 95 % confidence intervals (CIs) were estimated, and p-values were subsequently calculated using Wald tests.

The selected patients from the MUSES cohort and the data from the Ganly et al. studies were matched based on their aggregated baseline characteristics (means or proportions). Individual patient data from the selected MUSES cohort were weighted to ensure that the weighted means and proportions of the variables of interest aligned with those of the comparative study data. The patients included in the MUSES cohort were weighted according to their propensity score to belong to the Ganly et al. study rather than the MUSES cohort. These weights were calculated using a logistic regression model estimating the probability of inclusion in the historical study versus the MUSES cohort [12]. The matching variables included in the model were identified as prognostic factors in the historical studies, namely tumour histology, age over 70, orbital invasion, brain invasion, dura mater invasion, prior radiotherapy for the tumour, and prior surgery for the tumour.

The characteristics of the historical cohort and those of the individual patient cohort were compared before and after weighting to assess the balance achieved for the variables of interest. Standardised mean differences (SMDs) were used to measure the imbalance between groups, with values over 10 % indicating imbalance. Using observation weighting, the effective sample size was calculated as a measure of precision of the MAIC analysis and overlap, with small ESS indicating highly variable weights due to a lack of population overlap [12]. Unadjusted and weighted survival data were graphically represented using the Kaplan-Meier method. The treatment effect was evaluated using the log-rank test and by estimating the hazard ratio using the Cox method, as well as the odds ratios for secondary endpoints. The 95 % confidence intervals for HRs and ORs were estimated via bootstrapping using 1000 distinct samples and a bias-corrected and accelerated (BCA) bootstrap interval [13].

All statistical analyses were conducted using R version 4.1.3 with the MAIC, boot, and IPDfromKM packages.

3. Results

To study sinonasal cancers invading the skull base, other than olfactory neuroblastomas, an indirect comparison was made between the MUSES database (endoscopic treatment cohort) and the historical cohort of Ganly et al. (CFR treatment cohort). A total of 724 patients, with a sinonasal cancer invading the skull base, treated by endoscopy, were included after the exclusion of ONBs (Fig. 1). Clinical characteristics are displayed in Table 1 and were compared to the Ganly et al. study. A potential confounding-by-indication bias across those groups was observed, as illustrated by the SMDs above 10 % in all the prognostic variables (Table 1). After MAIC weighting, the ESS was 485 in the endoscopic cohort (reduced by 32.7 %) and the proportion of selected variables were perfectly balanced between groups (Table 2).

Before MAIC, OS was better in the endoscopic cohort with an HR = 2.33 (95 %CI, 1.88–2.87, $p < 0.001$). These results persist after MAIC, with a HR = 1.93 (95 %CI, 1.60–2.34, $p < 0.001$) (Fig. 2). As the proportional hazards assumption for the Cox model was not met

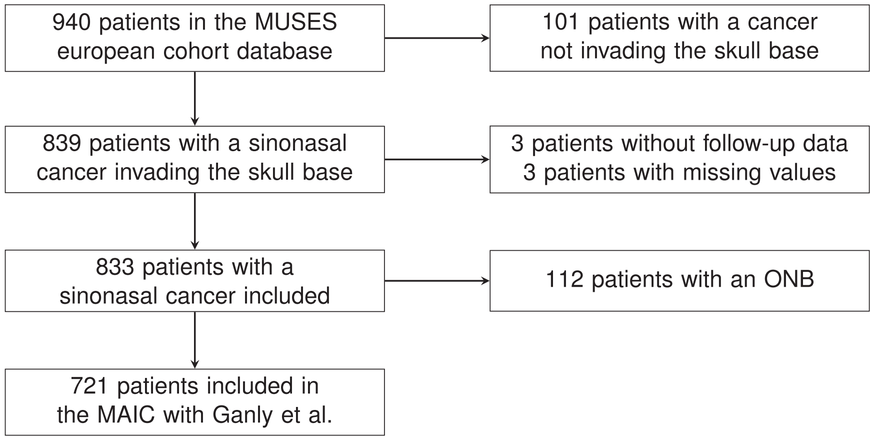

Fig. 1. Flow-chart ONB = olfactory neuroblastoma.

Table 1
Characteristics of the patients in the Ganly et al. study compared to patients included from the MUSES cohort.

Characteristics N (%)	MUSES N = 721	Ganly et al. N = 334	SMD
Male sex	527 (73.1)	218 (65.3)	0.170
Age > 50 years	585 (81.1)	204/313 (65.2)	0.523
Age > 70 years	259 (35.9)	43/313 (13.7)	0.650
Previous treatment			
Previous surgery	119 (16.5)	120 (35.9)	0.453
Previous RT	83 (11.5)	79 (23.7)	0.323
Previous chemotherapy	63 (8.7)	56 (16.8)	0.242
Histology			0.521
Adenocarcinoma	335 (46.5)	107 (32.0)	
Squamous cell carcinoma	112 (15.5)	101 (30.2)	
Minor salivary gland carcinoma	65 (9.0)	32 (9.6)	
High grade sarcoma	19 (2.6)	18 (5.4)	
Low grade sarcoma	27 (3.7)	24 (7.2)	
Melanoma	72 (10.0)	21 (6.3)	
Undifferentiated	16 (2.2)	14 (4.2)	
Other	75 (10.4)	17 (5.1)	
Extent			
Middle cranial involvement	171 (23.7)	25 (7.5)	0.459
Orbital involvement			
Bone	125 (17.3)	218 (65.3)	1.114
Periorbit	97 (13.5)	163 (48.8)	0.826
Intraorbital content	43 (6.0)	50 (15.0)	0.297
Intracranial involvement			
Bone	276 (38.3)	194 (58.1)	0.404
Dura mater	129 (17.9)	120 (35.9)	0.415
Brain	32 (4.4)	31 (9.3)	0.192
Pterygopalatine involvement	53 (7.4)	62/333 (18.6)	0.349

(Supplementary Figure 1), an Aalen additive model was used to confirm the survival difference ($p < 0.001$), revealing a decreasing treatment effect over time (Supplementary Figure 2). Similar results were found focusing on DSS, with a HR = 2.31 (95 %CI, 1.84–2.90, $p < 0.001$) before matching and HR = 1.71 (95 %CI, 1.39–2.13, $p < 0.001$) after MAIC (Fig. 3). RFS was also improved in the endoscopic cohort with an HR = 1.39 (95 %CI, 1.14–1.69, p = 0.001), but lose significance after matching adjustment (HR = 1.06; 95 %CI, 0.91–1.23, p = 0.63) (Fig. 4). No evidence of violation of the proportional hazards assumption of the Cox model was found for both the DSS and the RFS analyses.

Postoperative mortality was reported in 15/334 patients in the CFR cohort (4.5 %), and in 5/723 patients in the endoscopic cohort (0.7 %), corresponding to an OR = 6.73 (95 %CI, 2.43–18.69 $p < 0.001$). Postoperative mortality was still significantly higher in patients treated by CFR after MAIC, with an OR = 8.12 (95 %CI, 3.45–36.7, p = 0.001). Postoperative complications occurred in 110/334 (32.9 %) patients treated with CFR and in 69/723 (9.6 %) patients treated by endoscopy (OR = 4.64; 95 %CI, 3.32–6.52, $p < 0.001$). Postoperative complications were more frequent in patients treated by CFR, even after MAIC (OR = 3.68; 95 %CI, 2.47–5.42, $p < 0.001$). Clear margin resection was obtained in 238/334 (71.3 %) patients treated by CFR and in 568/723 (78.8 %) patients treated by endoscopy (OR = 0.67; CI95 %, 0.50– 0.90, p = 0.008), but it was not significantly different between treatments after MAIC (OR = 1.15; 95 %CI, 0.93– 1.40, p = 0.36).

4. Discussion

4.1. Key results

Our study confirms that endoscopic surgery achieves comparable local control to CFR for anterior skull base malignancies while markedly reducing perioperative morbidity and mortality. The use of MAIC analysis enabled robust comparisons between the two largest cohorts, namely a contemporary cohort of sinonasal cancer patients treated endoscopically (the MUSES cohort) and a historical cohort treated by CFR (Ganly et al.), thereby providing important statistical power.

4.2. Limitations

The use of historical data for the CFR cohort in MAIC analyses introduces inherent differences in data collection quality, follow-up practices, and evolving standards of care over time that may have influenced the outcomes. The CFR cohort in this study reflects treatment approaches from an earlier period, which may no longer fully align with contemporary standards of care; some authors suggest that the morbidity associated with these techniques has declined over time [5]. Consequently, some observed differences in overall mortality may be partially attributed to these temporal variations, in addition to the selection biases that MAIC seeks to correct.

These differences in treatment eras reflect not only advances in adjunctive therapies but also the refinement of surgical techniques, impacting treatment-related toxicity and long-term outcomes. The CFR and MUSES cohorts span different time periods, and improvements in chemotherapy and radiotherapy over this interval may further explain observed differences in overall survival. These therapeutic advances have enhanced survival by reducing the toxicity of adjuvant treatments [21], and induction therapy is now a growing modality in the treatment of undifferentiated sinonasal carcinomas [22] and other sinonasal cancers. However, survival curves and Schoenfeld residuals both demonstrated that the OS benefit from the endoscopic approach was mainly observed in the first months after surgery, potentially suggesting that the survival benefit is primarily mediated by reduced treatment toxicity. Given that recent advancements focus on reducing morbidity, the observed benefit in RFS is likely less affected by these temporal factors.

Table 2
Prognostic variable before and after matching-adjustment, according to the surgery performed for the treatment of sinonasal cancer invading the skull base excluding olfactory neuroblastomas.

Treatment	Before matching			After matching		
Characteristics N (%)	Endoscopic N = 721	CFR N = 334	SMD	Endoscopic N = 485	CFR N = 334	SMD
Age > 70 years	259 (35.9)	43/313 (13.7)	0.65	66.6 (13.7)	43/313 (13.7)	0.00
Previous treatment						
Previous surgery	119 (16.5)	120 (35.9)	0.45	174.3 (35.9)	120 (35.9)	0.00
Previous RT	83 (11.5)	79 (23.7)	0.32	114.7 (23.7)	79 (23.7)	0.00
Histology			0.52			0.00
Adenocarcinoma	335 (46.5)	107 (32.0)		155.4 (32.0)	107 (32.0)	
Squamous cell carcinoma	112 (15.5)	101 (30.2)		146.7 (30.2)	101 (30.2)	
Minor salivary gland carcinoma	65 (9.0)	32 (9.6)		46.5 (9.6)	32 (9.6)	
High grade sarcoma	19 (2.6)	18 (5.4)		26.1 (5.4)	18 (5.4)	
Low grade sarcoma	27 (3.7)	24 (7.2)		34.9 (7.2)	24 (7.2)	
Melanoma	72 (10.0)	21 (6.3)		30.5 (6.3)	21 (6.3)	
Undifferentiated	16 (2.2)	14 (4.2)		20.3 (4.2)	14 (4.2)	
Other	75 (10.4)	17 (5.1)		24.7 (5.1)	17 (5.1)	
Extent of the disease						
Intraorbital content	43 (6.0)	50 (15.0)	0.30	72.6 (15.0)	50 (15.0)	0.00
Intracranial involvement						
Dura mater	129 (17.9)	120 (35.9)	0.42	174.3 (35.9)	120 (35.9)	0.00
Brain	32 (4.4)	31 (9.3)	0.19	45.0 (9.3)	31 (9.3)	0.00

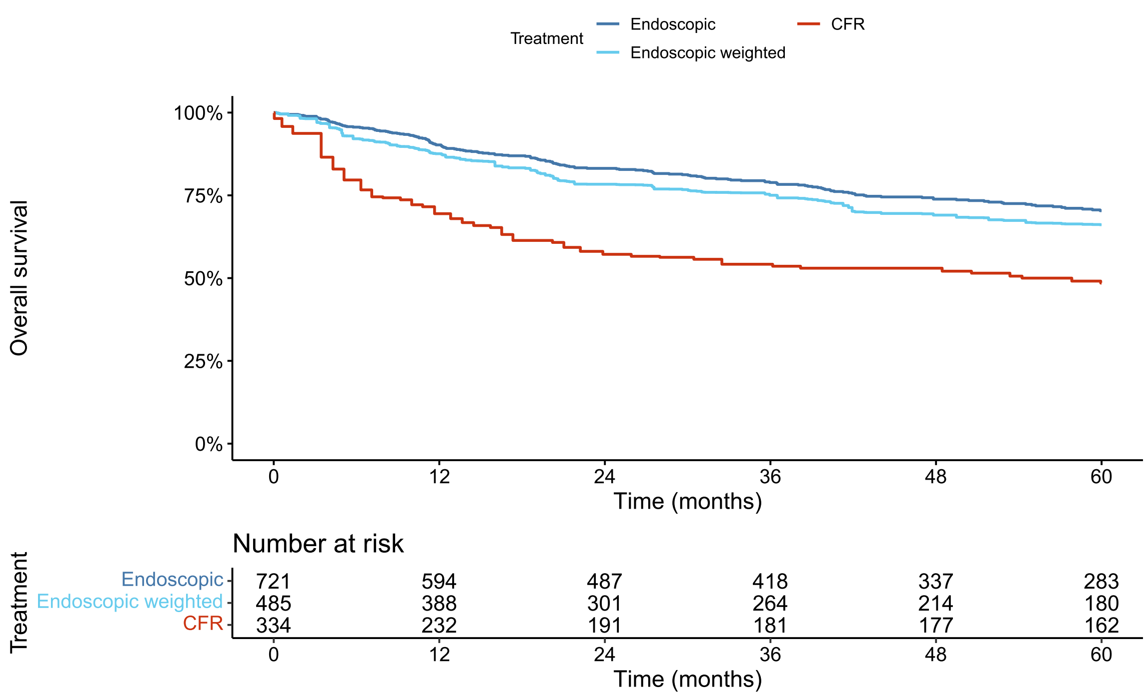

Fig. 2. Survival curves representing the overall survival according to the treatment performed, before and after weighting of the endoscopic cohort. CFR = craniofacial resection.

The proportional hazards assumption was not entirely met for overall survival, with survival advantage associated with endoscopic treatment more pronounced in the early post-treatment period. This early benefit likely reflects the reduction in treatment-related mortality with endoscopic approaches. Over time, however, the mortality advantage diminishes, supporting the use of the Cox model as an averaged estimate across the study period, even with violations of the proportional hazard assumption [23,24]. The results also remained significant when analyzed using an Aalen additive model. Finally, unanchored indirect comparison methods rely on the assumption of adjustment for all prognostic variables and modifiers of treatment effect [12]. While adjustments were made for several key prognostic factors, certain variables such as TNM stage and nodal involvement were not consistently reported. Although nodal involvement is rare in sinonasal cancers, its absence from the Ganly et al. study represents an inherent limitation.

4.3. Interpretation

For several decades, CFR has served as the cornerstone treatment for anterior skull base malignancies. This technique has traditionally been viewed as the gold standard, particularly for advanced sinonasal tumours invading the skull base. However, with the evolution of surgical instrumentation and expertise, endoscopic surgery has emerged as a less invasive alternative, extending its applicability from benign or low-grade lesions to more complex malignancies, including skull base and

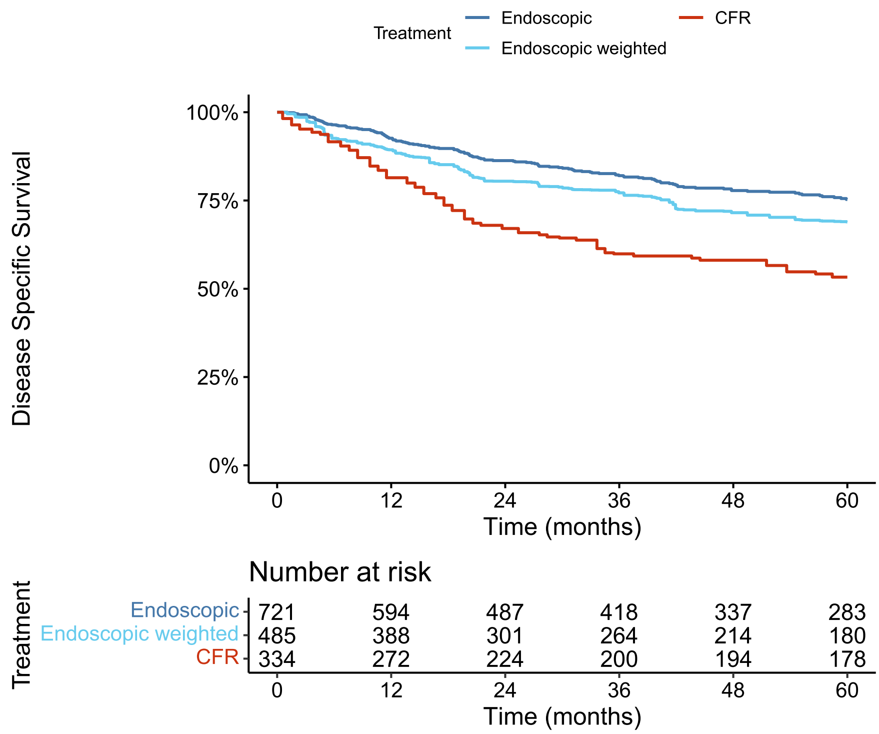

Fig. 3. Survival curves representing the disease specific survival according to the treatment performed, before and after weighting of the endoscopic cohort. CFR = craniofacial resection.

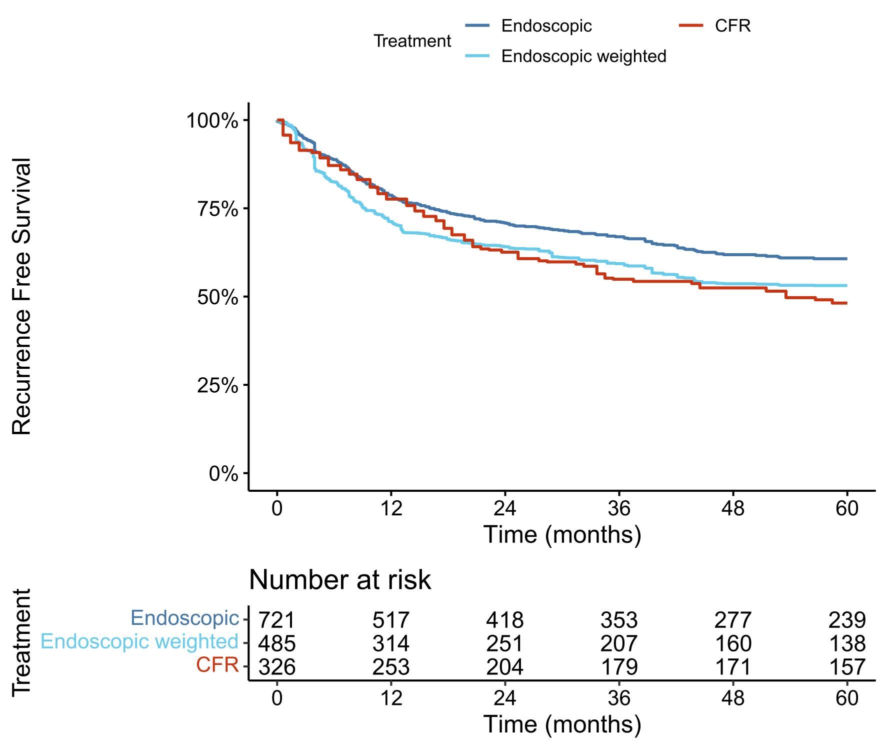

Fig. 4. Survival curves representing the recurrence free survival according to the treatment performed, before and after weighting of the endoscopic cohort. CFR = craniofacial resection.

intracranial invasions. Endoscopic surgery is now recognized as the preferred approach for early-stage tumours (T1-T2), offering equivalent oncologic control with substantially reduced morbidity [3,4,14].

The gradual adoption of endoscopic surgery for sinonasal malignancies has presented challenges in comparing outcomes across studies, as retrospective analyses frequently suffer from selection biases. Early-stage tumours are often managed endoscopically, leading to a predominance of less advanced cases in these cohorts [15], which could explain the oncological equivalence or better outcomes reported in patients treated with endoscopic endonasal resections in several articles [16–18]. Although some studies have adjusted for these biases, they remain limited by small sample sizes [6,7] and residual confounding due to incomplete data [19]. For example, Schur et al. matched 42 patients with sinonasal cancers invading the skull base, treated endoscopically, with 54 patients treated by open surgery. Their results showed a trend towards more frequent positive margins and worse RFS in the endoscopic group, although these differences were not statistically significant. They also found a trend towards better OS and fewer complications in the endoscopic cohort [7]. On the other hand, Kiliç et al. compared endoscopic resections and open approaches using propensity score matching in the National Cancer Database (NCDB), a large database focusing on patients treated for cancer in the USA. They found similar OS between groups, but the analysis lacked information on disease recurrences and tumour location, which are key prognostic factors, limiting the interpretation of the results [19]. Additionally, a potential publication bias has been suggested regarding endoscopic endonasal approaches, as studies showing inferior outcomes with endoscopy may be less likely to be reported, leading to a literature base that disproportionately favours the endoscopic approach [20].

Given these limitations, the use of MAIC analysis in this study represents a significant advancement. By leveraging two large cohorts and addressing selection biases, MAIC enables robust comparisons between individual patient data from a contemporary cohort and aggregated historical data. This statistical approach allows for an accurate assessment of therapeutic effectiveness across the two largest multicenter cohorts of sinonasal cancer patients treated by either endoscopic surgery (the MUSES cohort [9]) or CFR (Ganly et al. cohort [10]). MAIC provides a nuanced method of controlling for prognostic variables, thereby reducing confounding and enhancing comparability [8]. Although the effective sample size in the endoscopic cohort decreased by 33 % to 485, reflecting the reweighting required due to baseline differences between the groups, this reduction still allowed us to preserve a robust level of statistical power for subsequent analyses.

Our findings affirm the viability of endoscopic surgery as a frontline approach for sinonasal cancers invading the skull base. The results indicate that endoscopic techniques achieve comparable local control to CFR with a marked reduction in perioperative morbidity and mortality. This reduced complication rate likely reflects the minimally invasive nature of endoscopic surgery, avoiding the extensive dissection, craniotomy, and facial incisions characteristic of CFR [1]. Consequently, these results reinforce the rationale for recommending endoscopic or hybrid approaches as primary interventions for sinonasal cancers involving the skull base, where feasible. It is however important to underline that craniofacial resection keeps a role in some situations, when clear margin resection cannot be achieved with endoscopic resection.

4.4. Generalisability

It is important to recognize that the outcomes associated with endoscopic endonasal surgery may depend on the experience of the surgical team [25]. The results achieved in this study, which involved three referral centres in the MUSES cohort, may not be generalisable to all facilities. Furthermore, our analysis does not extend to patients with olfactory neuroblastomas, as these were excluded from the Ganly et al. cohort. Consequently, these results are not applicable to this histological subtype, which constitutes approximately 2–6 % of sinonasal cancers [26].

5. Conclusion

This study employed an unanchored matching-adjusted indirect comparison to analyse the two largest published cohorts on the treatment of sinonasal carcinomas invading the skull base, comparing endoscopic resection with craniofacial resection. After adjustment for confounding factors, overall survival was superior in patients treated with endoscopic techniques, while recurrence-free survival was similar between the two groups. Likewise, complications and perioperative mortality were higher in patients treated with craniofacial resection, but both techniques achieved similar rates of clear resection margins after adjustment. In conclusion, our findings demonstrate that endoscopic techniques provide comparable oncologic outcomes to craniofacial resection, with the advantage of lower morbidity.

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CRediT authorship contribution statement

Taboni Stefano: Writing – review & editing, Investigation, Data curation. **Matavelli Davide:** Writing – review & editing, Supervision, Conceptualization. **Nicolai Piero:** Writing – review & editing, Supervision, Resources, Conceptualization. **Ferrari Marco:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Castelnuovo Paolo:** Writing – review & editing, Supervision, Resources, Conceptualization. **Verillaud Benjamin:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization. **Schreiber Alberto:** Writing – review & editing, Supervision, Conceptualization. **Herman Philippe:** Writing – review & editing, Supervision, Resources, Conceptualization. **Turri-Zanoni Mario:** Writing – review & editing, Supervision, Conceptualization. **Battaglia Paolo:** Writing – review & editing, Supervision, Conceptualization. **Vinciguerra Alessandro:** Writing – review & editing, Resources, Data curation, Conceptualization. **Piazza Cesare:** Writing – review & editing, Supervision, Conceptualization. **Chevret Sylvie:** Writing – review & editing, Validation, Software, Methodology, Formal analysis, Conceptualization. **Camous Domitille:** Investigation, Data curation. **Deganello Alberto:** Writing – review & editing, Supervision, Conceptualization. **Bignami Maurizio:** Writing – review & editing, Supervision, Conceptualization. **Bertazzoni Giacomo:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization. **Arosio Alberto Daniele:** Writing – review & editing, Investigation, Data curation. **Chatelet Florian:** Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Rampinelli Vittorio:** Writing – review & editing, Investigation, Data curation.

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. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115382.

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