Long-term Outcomes of Endoscopic Resection Versus Open Surgery for Locally Advanced Sinonasal Malignancies in Combination With Radiotherapy

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Abstract

Objective:

To compare the long-term oncological outcomes of endoscopic resection versus open surgery in combination with radiotherapy for locally advanced sinonasal malignancies.

Methods:

Data for continuous patients with sinonasal epithelial tumors treated in our center between Jan 1999 and Dec 2016 were retrospectively reviewed. Those who received surgery (endoscopic or open surgery) combined with radiotherapy were identified, and 1:1 matching with propensity scores was performed. The primary endpoints of overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan-Meier method and Cox proportional hazards modeling. The local recurrence rate (LRR) was assessed by competing risk analysis.

Results:

We identified 267 eligible patients, 90 of whom were included after matching: 45 patients in the endoscopy group and 45 in the open group. The median follow-up time was 87 months. In the endoscopic group, 84.4% of patients received intensity-modulated radiotherapy (IMRT), with a mean gross tumor volume (GTV) dose of 68.28 Gy; in the open surgery group, 64.4% of patients received IMRT, with a mean GTV dose of 64 Gy. The 5-year OS, PFS and LRR were 69.9%, 58.6%, and 24.5% in the endoscopic group and 64.6%, 54.4%, and 31.8% in the open surgery group, respectively. Multivariable regression analysis revealed that surgical approach was not associated with lower OS, PFS or LRR. Age, histopathology and stage were independent risk factors for OS.

Conclusion:

For patients with locally advanced sinonasal carcinoma, minimally invasive endoscopic resection, in combination with a higher radiation dose and new radiation techniques such as IMRT, yields survival outcomes similar to those of open surgery in combination with radiotherapy.

Introduction

Malignant sinonasal tumors represent 3%-5% of head and neck malignancies and less than 1% of all malignancies[1–3]. Due to the insidiousness of these tumors in the early stage, patients are frequently diagnosed at locally advanced stages. Based on evidence from some retrospective studies, a combination of surgery and radiotherapy is the mainstay of sinonasal cancer management[4].

Because of the complexity of the sinonasal anatomy, open surgery has traditionally been regarded as the standard treatment to achieve en bloc resection[5]. However, these patients are at a high risk for developing postoperative complications as well as facial incisions and scarring. With advances in endoscopic surgical techniques, imaging guidance, and reconstruction methods, minimally invasive surgery has been introduced over the past two decades as an alternative to open surgery for the treatment of advanced sinonasal malignancies. Indeed, retrospective studies have shown that compared to open surgery, endoscopic resection is associated with a lower risk of postoperative morbidity, shorter hospital stay, and a higher quality of life (QoL) score[6–8]. According to recent data, these two procedures offer an equivalent survival rate for patients with early-stage disease and limited invasion[9–11]. However, a challenge with endoscopic surgery is that tumors cannot be removed en bloc in some cases. Nevertheless, some studies have indicated that en bloc procedures are not always indispensable and that piecemeal resection is acceptable if radical removal of the tumor is guaranteed[12, 13]. In recent years, an increasing number of groups have begun to explore the application of endoscopic surgery for locally advanced malignant nasal cavity and paranasal sinus tumors. However, for patients with locally advanced sinonasal malignancies, it remains unknown whether outcomes of endoscopic surgery combined with radiotherapy are equivalent to those of open surgery combined with radiotherapy.

Theoretically, a combination of endoscopic resection with radiotherapy offers some advantages; for example, the lesion can tolerate higher radiation doses than the open wound after surgery, which may result in a high local control rate. Due to a shorter healing time and fewer adverse events, endoscopic surgery offers the benefit of significantly decreased delays in adjuvant radiotherapy compared to open surgery[14]. Moreover, new radiation techniques such as intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), tomotherapy, and proton-beam therapy enable achieving well-defined and steep dose gradients close to the target volumes[15, 16].

Regardless, randomized controlled trials comparing endoscopic surgery with open surgery are lacking to date, and previous observational studies have been limited by high heterogeneity regarding histopathologic subtype, tumor staging, and adjuvant therapy and short follow-up times. We assessed long-term survival outcomes after endoscopic versus open surgery using propensity score analysis to minimize bias. Furthermore, to the best of our knowledge, this is the largest report on the clinical effect of endoscopic surgery versus open surgery combined with radiotherapy for locally advanced sinonasal malignancies. Finally, our study provides insight into Asian populations, whereas other studies have mainly involved Western populations.

Materials And Methods

Patients [Figure 1]

Between Jan 1999 and Dec 2016, all consecutive patients at stage T3–4b (according to the 8th edition of the AJCC staging system) who underwent a combination of surgery and radiotherapy with a histopathological diagnosis of epithelial malignancy arising from the nasal cavity and paranasal sinus in our center were included. Patients were excluded if pathology revealed olfactory neuroblastoma, neuroendocrine carcinoma or mucosal melanoma, if they had a newly diagnosed malignant tumor in the previous five years, or if follow-up information was incomplete. This study was approved by the local institutional review board (IRB).

Treatment

After clinical assessment and review of additional investigations, the final treatment modality was decided by the multidisciplinary team.

All patients underwent preoperative or postoperative radiotherapy. If the primary tumor invaded the orbital structure, pterygopalatine fossa, or brain parenchyma, preoperative radiotherapy was preferred. A total dose of 50 to 60 Gy was delivered to 95% of the planning treatment volume (PTV) in 1.8–2.0 Gy per fraction, with 25–30 fractions (5 fractions per week) over 5–6 weeks. When the tumor extended into the pterygopalatine fossa or orbit, the dose was increased to more than 60 Gy, and 70 Gy was often considered. Postoperative radiotherapy was recommended for selected risk factors, including advanced T stage, perineural/lymphatic/vascular invasion, nonnegative surgical margin, and multiple positive nodes with or without extranodal extension. The prescribed dose was given in 30 fractions at 60 Gy over six weeks. Higher doses of postoperative RT (70 Gy) were recommended for extranodal extension or positive margins.

Systemic therapy was administered at the discretion of the multidisciplinary team, as based on clinicopathologic factors, patient comorbidities and preference. In most cases, the patients were treated with 80–100 mg/m^2 intravenous cisplatin every three weeks for 2–3 cycles or 50–60 mg/m^2 intravenous cisplatin weekly for 5–6 cycles. Alternatively, the patients were treated with nimotuzumab at a dose of 200 mg/m^2 once per week for a total of 6–7 cycles.

Outcomes

The primary objective was to separately assess survival outcomes between the endoscopic group and the open surgery group. Overall survival (OS) was defined as the date of initial diagnosis to death due to any cause or the last follow-up. Progression-free survival (PFS) was defined as the date of diagnosis to the date of recurrence or death from any cause; patients who were lost to follow-up were censored. The local recurrence rate (LRR), which was defined as recurrence at the site of the initial primary tumor, was also analyzed.

Statistical Methods

Before matching, normally distributed continuous data were compared using the independent samples t-test; the results are presented as means with standard deviations (SDs). Nonnormally distributed continuous data were compared using the Mann-Whitney U test, and the results are presented as medians with interquartile ranges (IQRs). Categorical data, which are presented as frequencies with percentages, were compared using the chi-square test with correction for continuity when necessary. Univariate and multivariate analyses were carried out to identify prognostic factors associated with OS, PFS and LRR for the entire dataset. Variables with a p-value < 0.2 in univariate analysis were included in multivariate analysis using Cox regression.

Logistic regression was performed to estimate predictors of endoscopic or open surgery use. Propensity scores were calculated given the covariates of variables estimated from the logistic regression mentioned above (including primary site, histopathologic subtype, T-stage and N-stage) using another logistic regression model with a caliper of 0.2; 1:1 matching was performed with the nearest-neighbor algorithm. After matching, normally distributed continuous data were compared using the paired-samples t-test[17]. The Wilcoxon signed-rank test was used for nonnormally distributed continuous data; categorical data were compared with McNemar's test. OS and PFS are described by the Kaplan-Meier (KM) curve, and comparison of survival probabilities was performed using a Cox proportional hazards model due to the matched nature of the data[18].

The local recurrence rate, which was compared using the Fine & Gray test, is depicted as cumulative incidence plots. Death without the event of interest was considered a competing risk event. The statistical analyses were performed with SPSS version 26 (IBM Corp) and R version 3.2 (http://www.R-project.org). All analyses were 2-sided, with p-value < 0.05 indicating significance.

Results

Patient Characteristics

A total of 267 patients with T3–4b sinonasal carcinomas were identified. Of these, 46 (17.2%) underwent endoscopic surgery and 221 (82.8%) open surgery. All patients in the endoscopy group received postoperative radiotherapy, and 82.6% (38/46) who underwent IMRT. The mean dose of the primary gross tumor volume (GTVp) or tumor bed volume (GTVtb) was 68.31 Gy (SD 5.05 Gy). For patients who underwent open surgery, 134 (60.6%) received preoperative radiotherapy; 56.10% (124/221) underwent IMRT. The mean dose of GTVp or GTVtb was 63.88 Gy (SD 7.89 Gy). Other baseline demographic features and clinicopathological characteristics are shown in Table 1, and other treatment-level data are provided in Table 2.

Table 1
Patient characteristics and clinicopathological features

	Entire Cohort (n = 267)					Matched Cohort (n = 90)				
	Endoscopic surgery		Open Surgery			Endoscopic Surgery		Open Surgery		
	n = 46	(17.2%)	n = 221	(82.8%)	p	n = 45	(%)	n = 45	(%)	p
Sex					0.511					0.239
Male	30	65.20%	155	70.10%		30	66.70%	35	77.80%	
Female	16	34.80%	66	29.90%		15	33.30%	10	22.20%	
Age (SD)	53	14	51	12	0.604	53	14	50	13	0.284
Primary site					0.000					0.832
Nasal cavity	27	58.70%	50	22.60%		26	57.80%	25	55.60%	
Paranasal sinuses	19	41.30%	171	77.40%		19	42.20%	20	44.40%	
Histopathology					0.219					0.832
SCC	26	56.50%	146	66.10%		25	55.60%	26	57.80%	
AdenoCA	20	43.50%	75	33.90%		25	44.40%	26	42.20%	
Differentiation degree					0.156					0.370
low	16	34.80%	46	20.80%		13	28.90%	10	22.20%	
mediate	8	17.40%	60	27.10%		7	15.60%	14	31.10%	
high	4	8.70%	29	13.10%		4	8.90%	3	6.70%	
unknown	18	39.10%	86	38.90%		21	46.70%	18	40.00%	
T stage (AJCC 8th)					0.186					0.830
T3-4a	27	58.70%	152	68.80%		27	60.00%	26	57.80%	
T4b	19	41.30%	69	31.20%		18	40.00%	19	42.20%	
N stage					0.104					0.553
N0	44	95.70%	193	87.30%		43	95.60%	44	97.80%	
N+	2	4.30%	28	12.70%		2	4.40%	1	2.20%	

Abbreviation: SD, Standard deviation; SCC, Squamous Cell Carcinoma; AdenoCA, Adenocarcinoma; N+, N-positive.

Table 2
Treatment-level characteristics

	Entire Cohort (n = 267)					Matched Cohort (n = 90)				
	Endoscopic surgery		Open Surgery			Endoscopic Surgery		Open Surgery		
	n = 46	(%)	n = 221	(%)	p	n = 45	(%)	n = 45	(%)	p
Year of diagnosis					0.018					0.099
1999-2007	10	21.70%	89	40.30%		9	20.00%	16	35.60%	
2008-2016	36	78.30%	132	59.70%		36	80.00%	29	64.40%	
Orbital exenteration					0.107					0.056
No	46	100.00%	204	92.30%		45	100.00%	40	88.90%	
Yes	0	0.00%	17	7.70%		0	0.00%	5	11.10%	
Treatment modality										0.000
RT+S	46	100.00%	134	60.60%		45	100.00%	34	75.60%	
S + RT	0	0.00%	87	39.40%		0	0.00%	11	24.40%	
RT technology					0.001					0.030
non-IMRT	8	17.40%	97	43.90%		7	15.60%	16	35.60%	
IMRT	38	82.60%	124	56.10%		38	84.40%	29	64.40%	
GTVp/GTVtb dose					0.002					0.023
< 66Gy	9	19.60%	97	43.90%		9	20.00%	19	42.20%	
≥66Gy	37	80.40%	124	56.10%		36	80.00%	26	57.80%	
GTVp/GTVtb dose (SD)	68.31	5.05	63.88	7.89	0.000	68.28	5.10	64.33	7.39	0.004
Chemotherapy					0.502					0.777
No	39	84.80%	178	80.50%		38	84.40%	37	82.20%	
Yes	7	15.20%	43	19.50%		7	15.60%	8	17.80%	
Surgical margin					0.000					0.000
Negative	7	15.20%	142	64.30%		7	15.60%	30	66.70%	
Positive	39	84.80%	79	35.70%		38	84.40%	15	33.30%	

Abbreviation: SD, Standard deviation; RT: Radiotherapy; S: Surgery; IMRT: Intensity-Modulated Radiotherapy; GTVp: primary gross tumor volume; GTVtb: tumor bed volume.

PSM Analysis and Oncologic Outcomes

Factors associated with the use of endoscopic and open surgery were examined using logistic regression models, and the primary site, histopathology subtype and T stage were retained in the regression model. Moreover, N-stage was considered an essential survival predictor and was also included in the propensity score calculation. The 1:1 matching for endoscopic surgery versus open surgery resulted in 45 matched pairs, and tests indicated negligible differences across all demographic and

clinicopathological variables in the matched cohort. However, there were some differences in treatment-level characteristics. For the endoscopy group, IMRT was applied in 84.4% of patients, and the median dose of GTVp/GTVtb was higher, at 68.28 Gy (SD 5.1 Gy), than in the open surgery group. Of the patients who underwent open surgery, 64.4% were treated with IMRT, and the median dose of GTVp/GTVtb was 64.33 Gy (SD 7.39 Gy).

OS distributions estimated by the Kaplan-Meier method for the unmatched and matched treatment groups are depicted in Figure 2. For the unmatched group, the median follow-up time was 76 months (IQR 45–98 months) for endoscopic surgery and 100 months (IQR 60–136 months) for open surgery. There was no difference in OS or PFS. The 5-year and 10-year OS rates were 69.9% and 44.7% for patients receiving endoscopic surgery and 64.6% and 56.1% for patients receiving open surgery, respectively (HR = 0.10, 95% CI: 0.590–1.671, p = 0.98). The 5-year and 10-year LRRs were 24.5% and 43.4% for patients in the endoscopic group and 31.8% and 36.3% for patients in the open group, respectively (HR = 0.79; 95% CI: 0.426–1.449; p = 0.28). The cumulative incidence of LR is illustrated in Figure 3.

After PSM, the median follow-up time was 75 months (IQR 45–99 months) for endoscopic surgery and 99 months (IQR 57–120 months) for open surgery. Sixteen patients in the endoscopic group and 14 in the open group died. The median OS was 98 months in the endoscopic group; however, the median OS was not estimable in the open group. Additionally, 5- and 10-year OS rates were 69.2% and 47.6% in the endoscopic group and 76.4% and 58.2% in the open group, respectively (HR = 1.30; 95%CI: 0.634–2.666; p = 0.47); 5- and 10-year PFS rates were 60.9% and 48.5% and 62.1% and 46.7% in the endoscopic and open groups, respectively (HR = 0.93; 95%CI: 0.494–1.766; p = 0.83). For 5- and 10-year LR, rates were 25.3% and 45% in the endoscopic group and 28.3% and 42% in the open group, respectively (HR = 0.73; 95% CI: 0.347–1.530; p = 0.4).

Univariate and Multivariate Analyses

Factors associated with OS, PFS and LR were estimated in proportional hazards models for the unmatched cohort. In univariate analysis, the surgical approach did not show a significant correlation with OS or PFS. There was still no difference in multivariate analysis after adjustment for age, primary site, histopathological subtype, T stage, N stage and adjuvant chemotherapy. In multivariate analysis, age older than sixty years, T4b and squamous cell carcinoma appeared to be independent negative prognostic factors for OS, though only T stage was an independent prognostic factor for PFS. Adenocarcinoma and early T-stage tumors had a lower risk of developing LR, and surgical approach seemed to have no impact on LRR. The detailed multivariate analysis data are shown in Table 3.

Table 3

Multivariate analysis of predictors for OS, PFS and LR

	OS				PFS				LR			
Variable	HR	95%CI		p	HR	95%CI		p	HR	95%CI		p
Age				0.000				0.280				0.289
<60	1				1				1			
≥60	2.205	1.482	3.278		1.249	0.834	1.87		1.293	0.804	2.08	
Primary site				0.464				0.927				0.203
Nasal cavity	1				1				1			
Paranasal sinuses	1.198	0.739	1.94		1.02	0.669	1.555		0.726	0.443	1.189	
Histopathology				0.007				0.205				0.003
SCC	1				1				1			
AdenoCA	0.507	0.31	0.828		0.766	0.507	1.157		0.441	0.258	0.755	
T staging				0.003				0.047				0.016
T3-4a	1				1				1			
T4b	1.866	1.242	2.804		1.47	1.005	2.149		1.743	1.11	2.737	
N staging				0.461				0.162				0.256
N0	1				1				1			
N+	0.785	0.412	1.495		0.624	0.322	1.209		0.652	0.312	1.363	
Adjuvant chemo				0.366				0.482				0.719
No	1				1				1			
Yes	1.256	0.766	2.058		1.191	0.732	1.936		1.11	0.628	1.964	
Surgical approach				0.665				0.526				0.281
Open	1				1				1			
Endoscopy	1.132	0.645	1.987		0.845	0.502	1.422		0.699	0.365	1.34	
Abbreviation: SCC, Squamous Cell Carcinoma; AdenoCA, Adenocarcinoma; N+, N-positive.												

Discussion

The long-term outcomes of patients with locally advanced sinonasal malignancies who received endoscopic surgery combined with radiotherapy remains unclear. In this retrospective study, we found that in combination with a higher radiation dose and new radiation techniques such as IMRT, minimally invasive endoscopic resection yielded survival outcomes similar to those of open surgery for locally advanced sinonasal carcinoma.

Previous work has shown that survival outcomes with endoscopic resection are comparable to those of open resection for early-stage sinonasal squamous cell carcinomas, adenoid cystic carcinomas, mucosal melanoma, and esthesioneuroblastoma[19-24]. In a meta-analysis, Rawal et al. [24] evaluated 35 studies and found that the 2- and 5-year OS rates of patients who underwent endoscopic endonasal resection were similar and sometimes higher than those of patients who underwent open craniofacial

resection. In their study, 63% of patients had T1/T2 tumors, but staging data were not available for 22% of the cohort. Moreover, histopathologic subtype had a high degree of heterogeneity, with the majority being esthesioneuroblastoma. In another pooled analysis of 15 studies, Higgins et al.[23] observed similar 5-year OS between these two surgical management strategies in early-stage adenocarcinoma and esthesioneuroblastoma. Meccariello et al.[25] performed another pooled analysis, showing that compared to open surgery, endoscopic management is associated with better OS and disease-free survival (DFS) across almost all T stages. However, 54.2% of patients in the endoscopic surgery group had T1/T2 tumors, whereas 38% of patients in the open surgery group had T1/T2 tumors. Additionally, there was no T-stage information available for 33% of the patients. The proportion of patients who received adjuvant RT was also different in these two groups. By analyzing National Cancer Database (NCDB), Kilic et al.[21] found no difference in OS and DFS between the two approaches for patients with sinonasal squamous cell carcinoma (SNSCC). Similar to the studies mentioned above, the proportion of clinical stage was significantly different between the endoscopy group and the open surgery group. Additionally, we could not determine from the results whether the patients received adjuvant RT or chemotherapy.

Furthermore, studies have reported higher rates of OS or disease-specific survival (DSS) among patients undergoing endoscopic resection than those undergoing open surgery[9][10]. Both of these studies included a higher proportion of early-stage tumors in the endoscopy group than in the open group, as they set strict inclusion criteria for selecting patients to receive endoscopic resection. Although it is true that smaller tumors are more likely to be treated endoscopically, with the application of endoscopic surgery in sinonasal malignancies, surgeons have begun to explore its use for locally advanced tumors. Patients with early-stage disease accounted for the majority in the endoscopic group, but some locally advanced patients still underwent endoscopic surgery in previous studies. Even in Kilic's study[21], more patients with IVB received endoscopic surgery than open surgery. The author speculated that the reason is that the surgeons may have been more skilled in endoscopic technique and prefer this approach for sinonasal malignancy. Therefore, for patients with locally advanced sinonasal carcinoma who undergo endoscopic surgery, it remains unknown whether survival outcomes after adjuvant radiotherapy are comparable to those of open surgery combined with radiotherapy.

Oncologic outcomes in our study were slightly worse than those in previous studies. The primary reason might be that we enrolled patients with T3–4b-stage disease and that other authors included all stages or more early-stage disease. Hagemann et al.[20] performed Kaplan-Meier analysis stratified by T stage and reported a 5-year OS of 73.2% and 52% for T3 and T4 tumors, respectively, which was consistent with our results. For local recurrence, our results were no worse than those of other studies. In their single-arm study, Nakamaru et al.[11] found that the 5-year local control rate (LCR) was 92.9% for patients with highly selected early-stage SNSCC who underwent endoscopic surgery. In adenocarcinoma, Grosjean et al.[26] reported a 3-year LCR of 71% in the transfacial group and 81.4% in the endoscopic group ($p = 0.392$). According to our results, the surgical approach does not appear to have an impact on OS, PFS or LRR.

Surgical margin status is regarded as an independent risk factor for recurrence and survival[20, 27, 28]. Some scholars have found that these two surgical groups are similar with regard to negative surgical margin rate, at approximately 70–80%[19, 21, 22, 29, 30]. Regretfully, the status of the surgical margin cannot be compared between the two surgical groups in our series because some patients in the open surgery group underwent preoperative radiotherapy, promoting a higher R0 resection rate[30, 31]. Although the preoperative radiotherapy strategy is inconsistent with the practice of surgery combined with postoperative radiotherapy adopted by most international institutions, it does not violate the multimodality therapy in advanced disease recommended by National Comprehensive Cancer Network (NCCN) Guidelines. As the largest cancer treatment center in Asia, the preoperative RT strategy has been successfully utilized for head and neck carcinoma for decades[32, 33], and the results of clinical practice show that preoperative radiotherapy can improve the orbital retention rate without affecting survival outcomes[31, 34]. Furthermore, in our study, the rate of negative surgical margins was lower than that previously reported, especially in the endoscopic group, which may be explained by the fact that we enrolled patients with T3–4b disease. However, the high positive margin rate did not affect local control or OS for patients in the endoscopic group. The following two factors may explain this result. On the one hand, more patients in the endoscopic group were treated with IMRT instead of 2D RT or 3D CRT. On the other hand, patients in

the endoscopic group received higher radiation doses than those in the open group. Given the advancement of sophisticated radiation technology, good tumor coverage and normal organ sparing, even better survival outcomes can be achieved[15, 16, 35-37].

Our analysis had several limitations. First, as we mentioned above, preoperative radiotherapy is not a mainstream treatment mode. Due to the treatment preference, rather than contraindications, of our multidisciplinary tumor board, no patients in the endoscopic group received preoperative radiotherapy. Nevertheless, based on our previous study revealing that preoperative or postoperative radiotherapy is not associated with survival outcomes in SNSCC[31], we believe that this bias would not have much impact on the results of the comparison analysis in the current study. Second, the number of patients included in the propensity score analysis was limited; thus, limited statistical power may have contributed to the statistically nonsignificant comparisons. Thus, larger cohorts are required to validate the results.

In conclusion, for patients with locally advanced sinonasal carcinoma, minimally invasive endoscopic resection in combination with a higher radiation dose and new radiation techniques such as IMRT yields survival outcomes similar to those of open surgery in combination with radiotherapy.

Abbreviations

Not applicable.

Declarations

Ethics approval and consent to participate:

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Institutional Review Board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academic of Medical Sciences and Peking Union Medical College. Informed consent was obtained from all individual participants included in the study.

Consent for publication:

All authors approved the submitted version for publication.

Availability of data and material:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions:

QL contributed conception and design of the study; QL organized the database; QL performed the statistical analysis; QL wrote the first draft of the manuscript; QL wrote sections of the manuscript. All authors contributed to manuscript revision and approved the submitted version.

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Conflict of interest statement:

All authors have no conflict of interest to declare.

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Figures

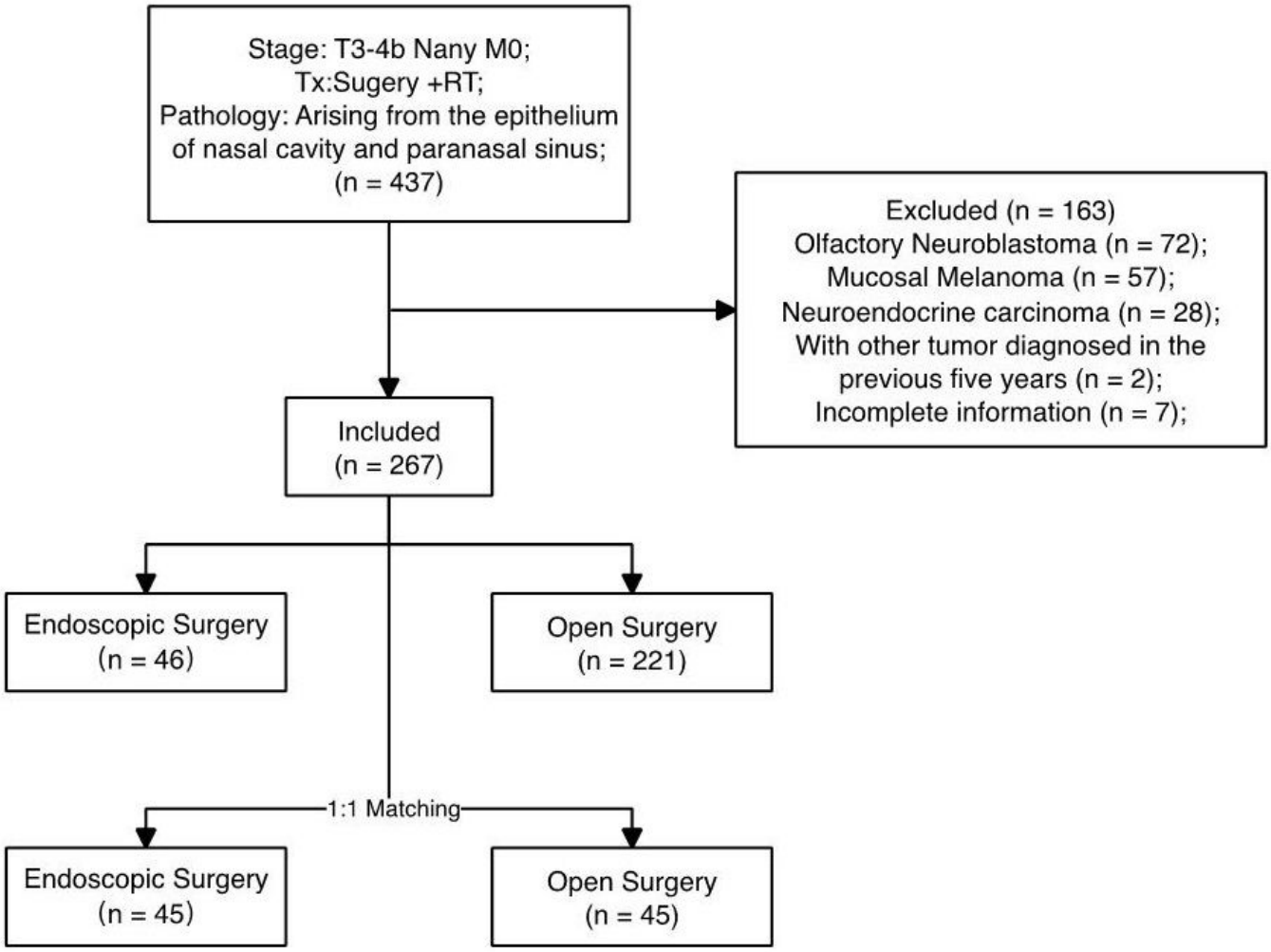

Figure 1

Flowchart of patients' selection

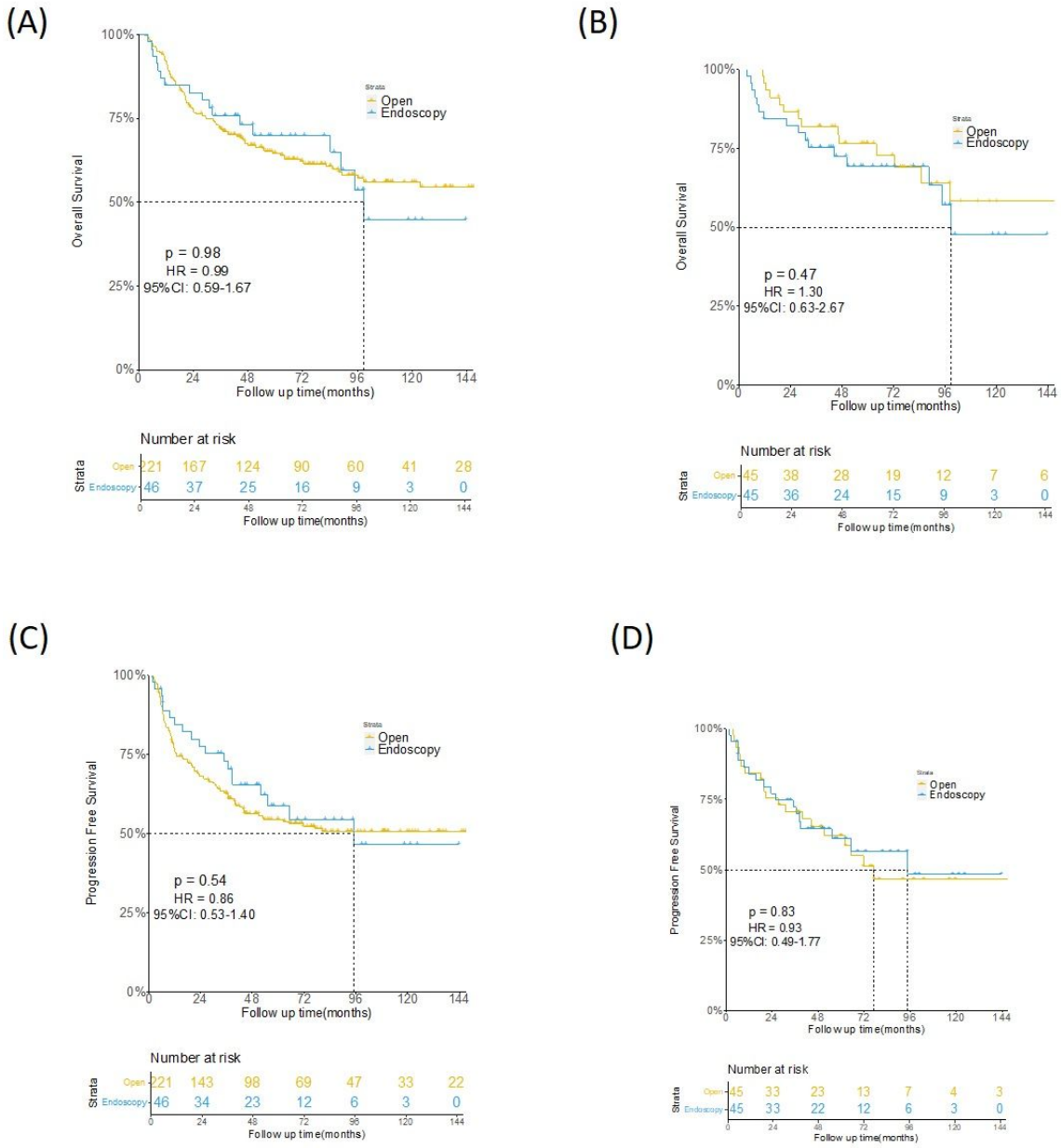

Figure 2

Kaplan-Meier Estimates of Overall Survival, Progression-Free Survival (before & after PSM) (A) Overall Survival in the entire cohort (B) Overall Survival in the matched group (C) Progression-Free Survival in the entire cohort (D) Progression-Free Survival in the matched group

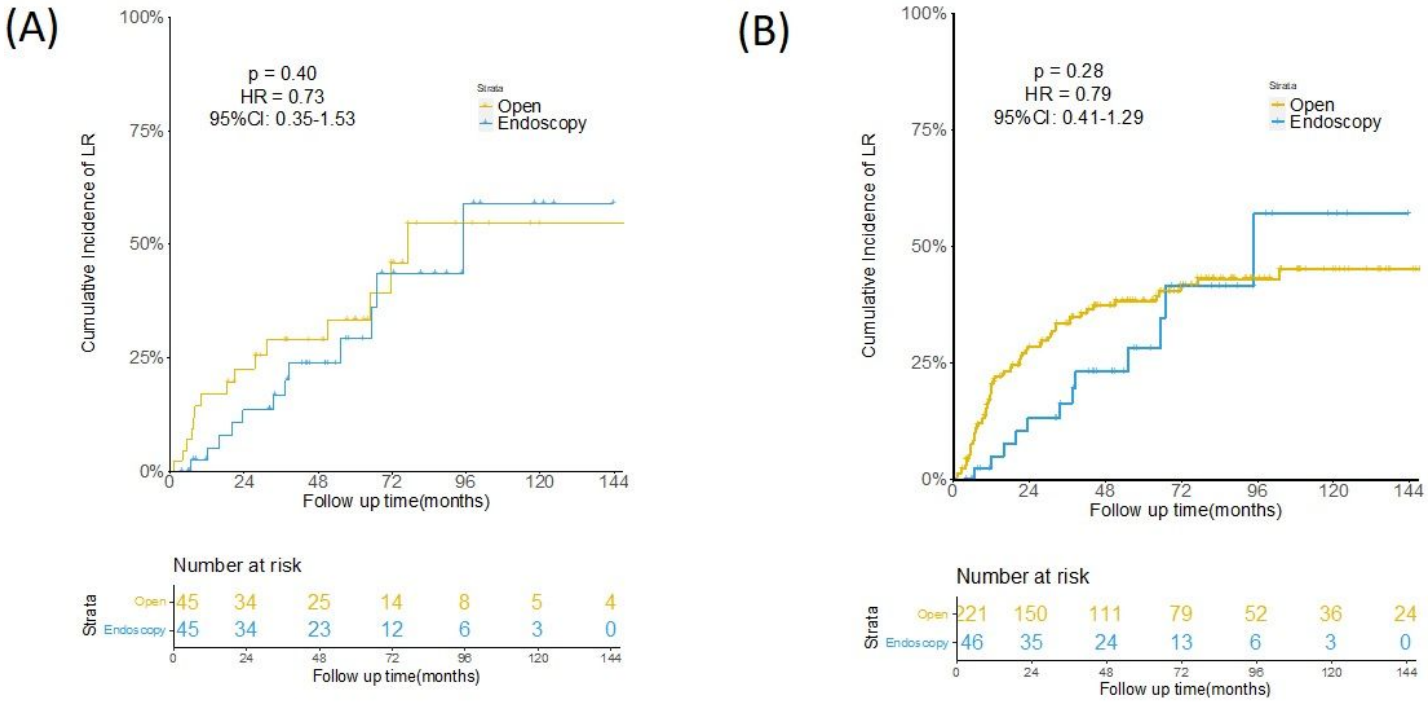

Figure 3

Cumulative Incidence of Local Recurrence (before & after PSM) (A) Local Recurrence in the entire cohort (B) Local Recurrence in the matched cohort