Endoscopic surgery versus conservative treatment in nasopharyngeal carcinoma patients with nasopharyngeal necrosis

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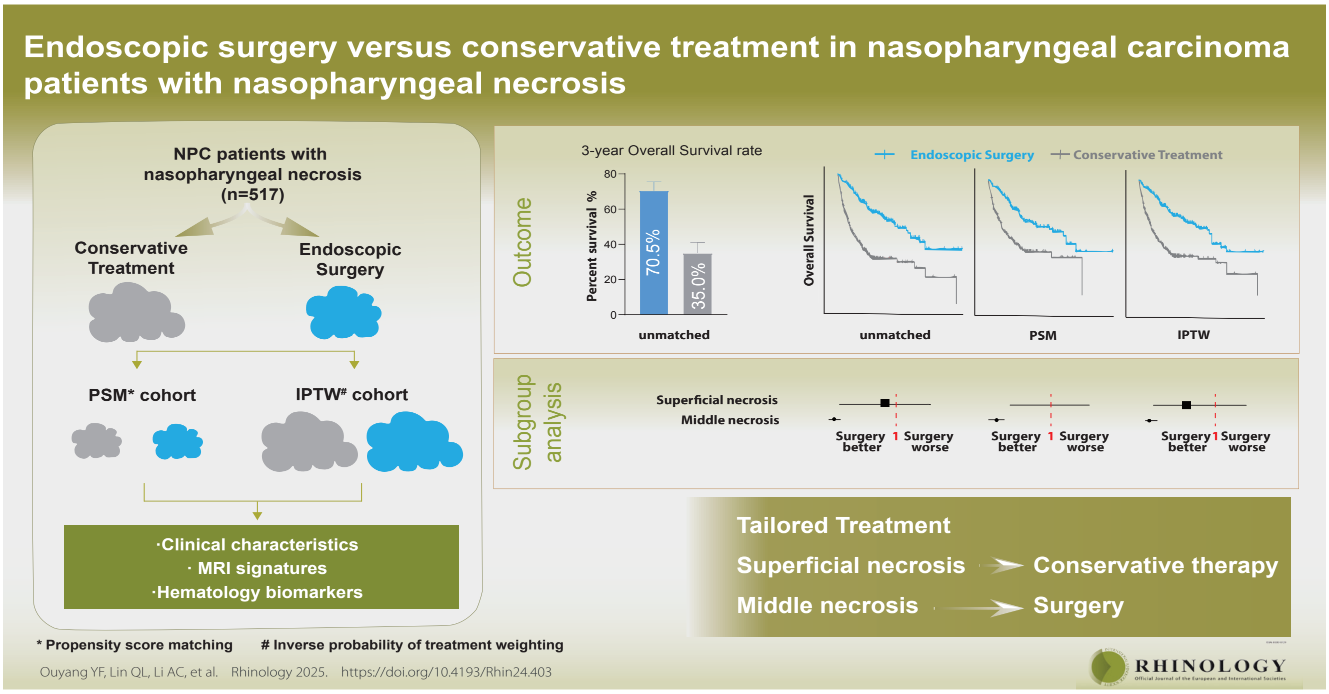

Abstract

Background: Nasopharyngeal necrosis is a common sequela after treatment for nasopharyngeal carcinoma (NPC). This study aims to compare the effectiveness of the main interventions, endoscopic surgery and conservative therapy, on nasopharyngeal necrosis and identify potential beneficiaries.

Methodology: This retrospective study was conducted on patients with nasopharyngeal necrosis from September 2008 to December 2020 at the Cancer Hospital of Sun Yat-sen University. The overall survival (OS) of patients with nasopharyngeal necrosis and their mucosal healing status were assessed. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were used to balance confounding factors between the two groups.

Results: A total of 517 patients (124 females; 393 males) with nasopharyngeal necrosis were included in this analysis, among whom 287 received conservative therapy and 230 underwent endoscopic surgical treatment. In the unmatched cohort, the endoscopic surgery group had a higher 3-year OS rate than the conservative therapy group. Patients who underwent surgery had higher cure rates than did those who received conservative therapy. PSM and IPTW analyses yielded similar results. Multivariate analyses of the unmatched, PSM, and IPTW cohorts revealed that nasal endoscopic surgery was an independent protective factor for the OS of patients with nasopharyngeal necrosis.

Conclusions: In this retrospective research, endoscopic surgery demonstrated better efficacy than conservative therapy for nasopharyngeal carcinoma patients with nasopharyngeal necrosis, while conservative therapy may be preferred for patients with superficial mucosal necrosis.

Key words: nasopharyngeal carcinoma, nasopharyngeal necrosis, endoscopic surgery, conservative therapy, efficiency

Introduction

Nasopharyngeal carcinoma (NPC) stands as a prominent malignancy in the head and neck area, particularly widespread in southern China and Southeast Asia [1,2]. Radiotherapy (RT) either with or without chemotherapy is the primary treatment for NPC. Advancements in RT techniques and utilization of adjuvant chemotherapy in locoregionally advanced NPC patients have led to enhanced survival outcomes, 5-year overall survival (OS) rates range from 63.0% to 87.4% [3-6]. However, complications arising from irradiation fields are unavoidable, such as nasopharyngeal necrosis (NN), which historically refers specifically to post-radiation nasopharyngeal necrosis (PRNN) [7-10].

NN is one of the most severe sequelae of RT for NPC [8]. It involves the coagulative necrosis of nasopharyngeal tissues including the nasopharyngeal mucosa, musculus longus capitis, parapharyngeal tissues, and skull base. Symptoms typically encompass headaches, foul odor from the nasal cavity, and nasopharyngeal bleeding, significantly impacting the patient's quality of life. More importantly, NN may affect the skull and major blood vessels and often leads to death due to massive nasopharyngeal hemorrhage, infection, and cachexia, with mortality rates ranging from 41.8% to 42.9% [11-13]. When NN is complicated with the internal carotid artery rupture, the mortality rate can rise to 72.7% [11-13]. Thus, NPC patients with NN have a poor prognosis, the 3-year OS rate was reported to be 54.7% with NN, compared to 84.4% without NN [14].

Because NN significantly affects the effectiveness and safety of NPC treatment, especially in recurrent cases, proper management of NN is essential for improving patient outcomes and quality of life. Nowadays, treatment options for NN mainly include conservative therapy and nasal endoscopic surgery. Conservative treatments such as endoscopic irrigation, debridement, systemic antibiotics, hyperbaric oxygen therapy, and nutritional support [15]. However, these conservative measures may fail due to incomplete debridement and poor wound healing [11]. Nasal endoscopic surgery, which involves radical endoscopic necrectomy followed by reconstruction with a posterior pedicle nasal septum and floor mucoperiosteum flap, has shown a 70.8% effectiveness rate, outperforming conservative treatments [13]. Despite its benefits, its adoption is limited by technical complexities and a roughly one-third failure rate in nasal flap reconstruction. Currently, there is a lack of head-to-head comparative studies between surgical and conservative therapy for NN, and existing research is limited by comparisons with contemporaneous data and confounding factors between the two treatment groups.

In addition, studies have found that the mucosal repair rates in early to middle necrosis can reach 63.2% and 50.9% with improved conservative treatment, respectively [16]. It remains to be investigated which is superior between endoscopic surgery and conservative treatment for NN, and the characteristics of their respective suitable populations. Therefore, conducting comparative effectiveness research between surgical and conservative therapy for NN, along with subgroup analyses, is essential for guiding treatment decisions for patients with this condition.

Materials and methods

Patient selection

We retrospectively reviewed clinical data from September 2008 to December 2020 at the Cancer Hospital of Sun Yat-sen University. This study was approved by the ethics committee of Sun Yat-sen University Cancer Center. Written informed consent was obtained from all patients. Patients were included if they met the following criteria: confirmed NN by nasopharyngoscopy or magnetic resonance images (MRI) with undetected EBV-DNA level; MRI data available at necrosis onset; complete medical records at necrosis occurrence; detailed necrosis treatment records; history of radical intensity-modulated radiotherapy; and complete follow-up information. Exclusion criteria included: confirmed nasopharyngeal recurrence or metastasis, secondary tumours, or necrosis with pathological biopsy-confirmed nasopharyngeal recurrence. Inflammatory markers analysed were the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR).

Diagnosis of nasopharyngeal necrosis

Necrosis was diagnosed through nasopharyngeal endoscopy and MRI. The endoscopic diagnosis criteria for NN were ulceration and necrotic secretions, microbial flora, or exposure of skull base bone observed under nasal endoscopy. Discontinuation of mucosal lines and/or low signal areas on T1C-enhanced sequences. The staging of necrosis was mainly based on the patient's MRI images: early necrosis (mucosal necrosis) was defined as limited to the nasopharyngeal mucosa without soft tissue necrosis; middle necrosis (soft tissue necrosis) was defined as necrotic lesions involving the mucosa, muscle tissue, and parapharyngeal fascia without skull base bone necrosis; severe necrosis represents osteoradionecrosis, which defined as necrotic lesions involving bone tissues such as the sphenoid bone and clivus [8, 17] (Figure 1).

Treatments

Conservative therapy involves endoscopic debridement, excision of the necrotic tissues, and systemic therapy. Patients receive conservative endoscopic therapy under topical anesthesia. Debridement was performed every 2-4 weeks with irrigation using 2% hydrogen peroxide or saline and surface application of recombinant human epidermal growth factor. Systemic treatment included antibiotics, nutritional support, and pain management. The endpoint was ulcer healing and symptom relief.

The specific procedure for nasal endoscopic surgery for the treatment of NN is consistent with the previous reports by our research group [18]. Necrotic tissue was removed using the XPS

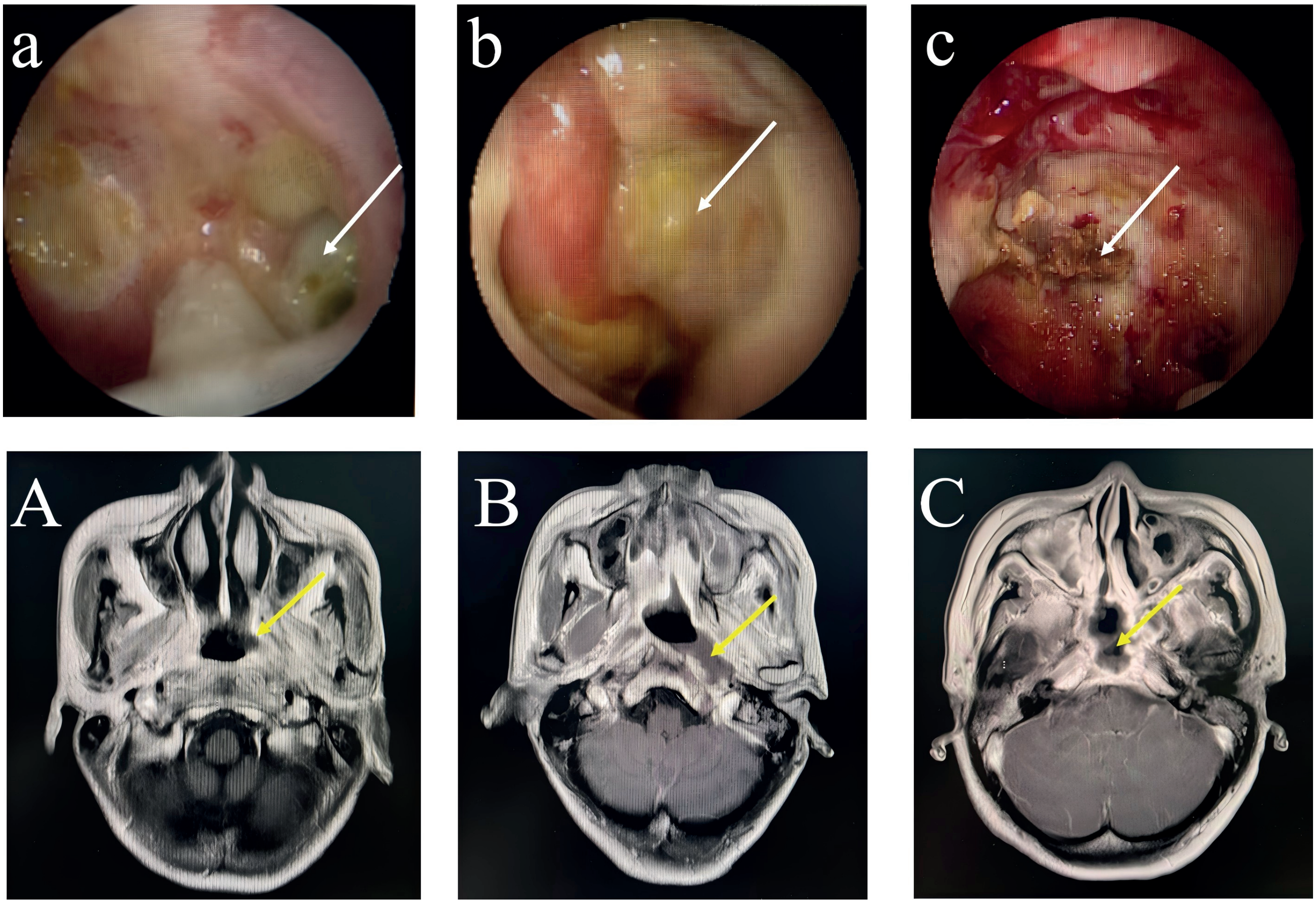

Figure 1. Endoscopic images and magnetic resonance images (MRIs) of nasopharyngeal necrosis. (a) Endoscopic image and (A) transverse, contrast enhanced T1 weighted MRI of early necrosis (arrow). (b) Endoscopic image and (B) transverse, contrast enhanced T1 weighted MRI of middle necrosis (arrow). (c) Endoscopic image and (C) transverse, contrast enhanced T1 weighted MRI of osteoradionecrosis (arrow).

3000 ENT Power System (Medtronic, Minneapolis, MN, USA) and electric micro-drill (Stryker, Kalamazoo, MI, USA). Reconstruction involved posterior pedicle nasal septum and floor mucoperiosteum flaps, supported by an absorbable gelatin sponge and rapid rhino. The dissection was largely extradural. Postoperatively, patients received antibiotics for 5-7 days and an MRI for flap blood supply evaluation. Patients with necrosis near the internal carotid artery (≤ 5mm), which measured in T1-weighted MRI images (23), underwent a balloon occlusion test, with embolization performed if necessary.

Follow-up

Patients were followed up every 3 months during treatment, every 6 months after necrosis healing, and annually after 3 years or until death. The primary endpoint was OS, defined as the time from the necrosis treatment start to the last follow-up or death. The secondary endpoint was mucosal healing, defined as complete healing or significant ulcer reduction and symptom relief. Lack of change or worsening necrosis was deemed ineffective. The last follow-up date was December 8th, 2022.

Statistical analysis

Baseline characteristics were compared using t-tests or Wilcoxon rank-sum tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. Propensity score matching (PSM) with a 1:1 ratio and inverse probability of treatment weighting (IPTW) adjusted for confounders. The PSM cohort comprised 175 patients in each treatment group, while the IPTW cohort included 516 patients in the conservative treatment group and 517 in the endoscopic surgery group. In the IPTW cohort, all standardized mean difference (SMD) values were < 0.10 and all p-values were > 0.1, indicating balanced data. In the PSM cohort, except for the SMD value for secondary radiotherapy being 0.176 (P = 0.100), other SMD values were < 0.10, demonstrating comparability groups (Table 1 and Table S1). Kaplan-Meier method was used for survival curves, with log-rank tests for comparisons. Cutoff values for continuous variables were determined via time-dependent ROC analysis or clinical relevance. Univariate and multivariate analyses identified prognostic factors using the Cox model. The Variance Inflation Factor was employed to detect the multicollinearity in regression analysis. Subgroup and interaction analyses explored treat-

Table 1. Summary of clinical characteristics in the unmatched, the PSM and the IPTW cohort

Characteristic	Unmatched, no. (%)		P-value	Propensity matched, no. (%)		P-value	IPTW, no. (%)		P-value
	Conservative treatment	Surgery		Conservative treatment	Surgery		Conservative treatment	Surgery	
No. of patients	287	230		175	175		516	517	
Sex			0.581			0.463			0.787
female	72 (25.09)	52 (22.61)		48 (27.43)	42 (24.00)		126 (24.42)	130 (25.15)	
male	215 (74.91)	178 (77.39)		127 (72.57)	133 (76.00)		390 (75.58)	387 (74.85)	
Age			0.212			0.562			0.963
≤ 45 years	93 (32.40)	62 (26.96)		56 (32.00)	51 (29.14)		157 (30.43)	158 (30.56)	
> 45 years	194 (67.60)	168 (73.04)		119 (68.00)	124 (70.86)		359 (69.57)	359 (69.44)	
Diabetes			0.051			0.769			0.994
No	282 (98.26)	218 (94.78)		170 (97.14)	168 (96.00)		499 (96.70)	500 (96.71)	
Yes	5 (1.74)	12 (5.22)		5 (2.86)	7 (4.00)		17 (3.30)	17 (3.29)	
Smoking			0.586			0.480			0.961
No	201 (70.03)	167 (72.61)		127 (72.57)	121 (69.14)		370 (71.71)	370 (71.57)	
Yes	86 (29.97)	63 (27.39)		48 (27.43)	54 (30.86)		146 (28.29)	147 (28.43)	
Lesion area*			**<0.001**			0.407			0.987
Mucosa	79 (27.53)	30 (13.04)		35 (20.00)	29 (16.57)		110 (21.32)	110 (21.28)	
Beyond mucosa	208 (72.47)	200 (86.96)		140 (80.00)	146 (83.43)		406 (78.68)	407 (78.72)	
Osteoradionecrosis			0.954			0.911			0.862
No	189 (65.85)	150 (65.22)		113 (64.57)	114 (65.14)		341 (66.09)	339 (65.57)	
Yes	98 (34.15)	80 (34.78)		62 (35.43)	61 (34.86)		175 (33.91)	178 (34.43)	
Distant to ICA #			0.743			0.592			0.928
≤ 5mm	160 (55.75)	124 (53.91)		96 (54.86)	91 (52.00)		285 (55.23)	287 (55.51)	
> 5mm	127 (44.25)	106 (46.09)		79 (45.14)	84 (48.00)		231 (44.77)	230 (44.49)	
Primary RT method			0.553			0.407			0.862
2DRT	54 (18.82)	49 (21.30)		29 (16.57)	35 (20.00)		98 (18.99)	96 (18.57)	
IMRT	233 (81.18)	181 (78.70)		146 (83.43)	140 (80.00)		418 (81.01)	421 (81.43)	
Re-irradiation			**0.006**			0.100			0.950
No	148 (51.57)	147 (63.91)		114 (65.14)	99 (56.57)		293 (56.78)	295 (57.06)	
Yes	139 (48.43)	83 (36.09)		61 (34.86)	76 (43.43)		223 (43.22)	222 (42.94)	
BMI			0.004			0.630			0.890
≤ 18.50 kg/m^2	54 (18.82)	69 (30.00)		49 (28.00)	45 (25.71)		125 (24.22)	127 (24.56)	
> 18.50 kg/m^2	233 (81.18)	161 (70.00)		126 (72.00)	130 (74.29)		391 (75.78)	390 (75.44)	
NLR			0.528			0.826			0.928
≤ 4.16	117 (40.77)	101 (43.91)		69 (39.43)	67 (38.29)		215 (41.67)	214 (41.39)	
> 4.16	170 (59.23)	129 (56.09)		106 (60.57)	108 (61.71)		301 (58.33)	303 (58.61)	
LMR			**0.014**			0.575			0.819
≤ 3.51	245 (85.37)	176 (76.52)		142 (81.14)	146 (83.42)		424 (82.17)	422 (81.62)	
> 3.51	42 (14.63)	54 (23.48)		33 (18.86)	29 (16.58)		92 (17.83)	95 (18.38)	
ALB			0.518			1.000			0.854
≤ 35 g/L	35 (12.20)	23 (10.00)		18 (10.29)	18 (10.29)		58 (11.24)	60 (11.61)	
> 35 g/L	252 (87.80)	207 (90.00)		157 (89.71)	157 (89.71)		458 (88.76)	457 (88.39)	
HGB			**0.047**			0.435			0.929
< 110 g/L	110 (38.33)	68 (29.55)		66 (37.71)	59 (33.71)		181 (35.08)	180 (34.82)	
≥ 110 g/L	177 (61.67)	162 (70.45)		109 (62.29)	116 (66.29)		335 (64.92)	337 (65.18)	

Table 1 *continued*. Summary of clinical characteristics in the unmatched, the PSM and the IPTW cohort.

Characteristic	Unmatched, no. (%)		P-value	Propensity matched, no. (%)		P-value	IPTW, no. (%)		P-value
	Conservative treatment	Surgery		Conservative treatment	Surgery		Conservative treatment	Surgery	
CRP/ALB			0.500			0.655			0.681
< 0.31	113 (39.37)	83 (36.09)		64 (36.57)	60 (34.29)		192 (37.21)	186 (35.98)	
≥ 0.31	174 (60.63)	147 (63.91)		111 (63.43)	115 (65.71)		324 (62.79)	331 (64.02)	

*Necrosis confined to the mucous and interrupted mucosal line that could be seen with MRI. # Distant to ICA refers to the minimal axial distance from necrosis lesion to internal carotid in MRI. Abbreviations: PSM: propensity score matching; IPTW: inverse probability of treatment weighting; ICA: internal carotid artery; RT: radiotherapy; 2DRT: two-dimensional radiotherapy; IMRT: intensity modulated radiation therapy; BMI: body mass index; NLR: lymphocyte ratio; LMR: lymphocyte to monocyte ratio; ALB: albumin; HGB: hemoglobin; CRP: c-reaction protein.

ment efficacy. Statistical analyses used R software 4.2.1, with P < 0.05 considered significant.

Results

Patient demographics and surgical results

This study included a total of 517 patients with NN from 2008 to 2020, among whom 287 received conservative treatment and 230 underwent endoscopic surgical treatment (Table 1). Of these, 285 patients experienced recurrent NN and 232 patients developed necrosis after initial radiotherapy. The proportion of recurrence in NN patients were higher in conservative treatment group than in the surgery group (63.4% vs. 44.8%, P < 0.01). Among the patients, 23.98% were female and 76.02% were male, with a median age of 51 years (range, 44-59 years). And 77% (398/517) of patients were pathologically confirmed without nasopharyngeal recurrence, others were with undetected EBV-DNA level was at diagnosis. Early necrosis accounted for 21.08% (109/517), and 34.43% (178/517) of patients exhibited osteoradionecrosis, while 54.93% (284/517) had necrotic lesions adjacent to the internal carotid artery. Overall, 70.9% (163/230) was reconstructed with local intranasal flaps after radiotherapy. In the surgery group, 104 patients underwent ICA embolization, and ICA stent were applied in 1 patient.

By the end of the last follow-up, a total of 250 patients had died, including 79 in the endoscopic surgery group and 171 in the conservative treatment group (Table S2). The primary causes of death were massive bleeding (n=108), followed by local tumour recurrence (n=49), and distant tumour metastasis (n=25). Patients who received conservative therapy had a higher mortality rate due to massive bleeding compared to those in the surgical group (P < 0.001, Table S2). The incidence of complications that were specific to surgery was 53 (23.0%) of 230 patients, including postoperative haemorrhage (n=20), nasal adhesion (n=17), flap necrosis (n=10), and others (n=13).

Through time-dependent ROC curve analysis, we set critical values for some continuous variables. The critical value for the distance between necrotic lesions and the internal carotid artery was 5mm, the NLR was 4.16, the LMR was 3.51, and the C-reactive protein (CRP) to albumin (ALB) ratio was 0.31. The critical values for body mass index (BMI), ALB, and hemoglobin (HGB) were primarily based on clinical significance. The characteristics of the endoscopic surgery group and the conservative treatment group are shown in Table 1. In the endoscopic surgery group, there were significantly higher proportions of diabetic patients (5.22%), those with middle necrosis (86.96%), and those with BMI ≤ 18.50 kg/m^2 (30.00%) compared to the conservative treatment group. Conversely, the conservative treatment group had more patients with prior re-irradiation, LMR ≤ 3.51, and HGB < 110 g/L. To address baseline imbalances, we applied 1:1 PSM and inverse IPTW. Both the PSM cohort and IPTW cohort showed balanced characteristics between the two groups (Table 1 and Table S1).

Outcome of survival analysis

The median follow-up time was 39.50 months (range, 0.60-124.10 months). In the unmatched cohort, the 3-year OS rate was 35.00% (95% CI, 29.30-41.80%) for conservative treatment and 70.50% (95% CI, 64.50-77.10%) for endoscopic surgery, showing a significant advantage for endoscopic surgery (P < 0.001). Similar results were observed in the PSM and IPTW cohorts. In the PSM cohort, 3-year OS rate was 47.20% (95% CI, 40.00-55.70%) for conservative treatment versus 75.00% (95% CI, 68.60-82.00%) for endoscopic surgery (P < 0.001). In the IPTW cohort, 3-year OS rate was 44.30% (95% CI, 37.30-50.30%) for conservative treatment and 77.60% (95% CI, 71.80-84.00%) for endoscopic surgery (P < 0.001). Endoscopic surgery consistently showed superior efficacy across all cohorts (Figure 2 and Table S3).

Univariate and multivariate Cox regression analyses were performed. In the unmatched cohort, the hazard ratio (HR) for endoscopic surgery versus conservative treatment was 0.28 (95% CI, 0.21-0.38, P < 0.001). This finding was consistent in the

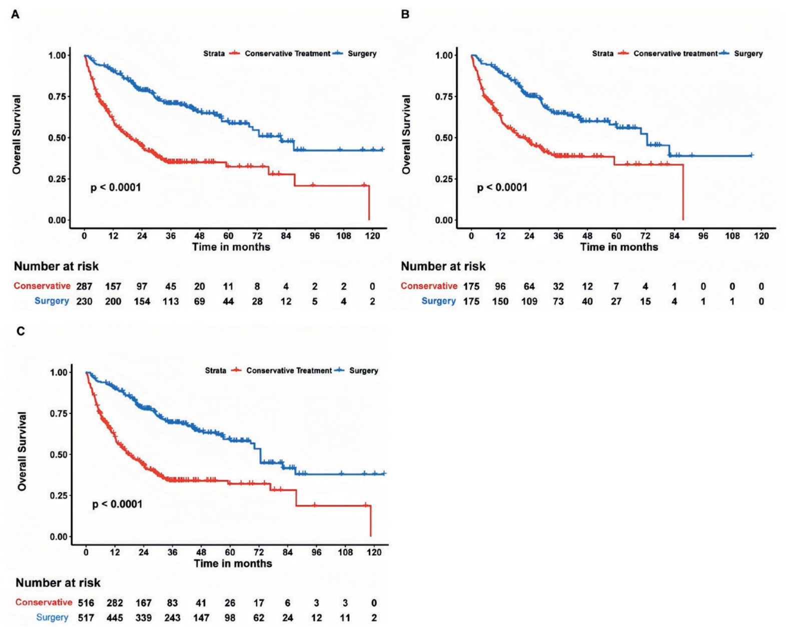

Figure 2. Kaplan–Meier curves of overall survival with endoscopic surgery and conservative treatment in the unmatched (A), the PSM (B) and the IPTW cohort (C).

PSM cohort (HR = 0.33, 95% CI = 0.23-0.45, P < 0.001) and the IPTW cohort (HR = 0.30, 95% CI = 0.22-0.41, P < 0.001). These results indicate that endoscopic surgery is an independent protective factor for survival in patients of NN (Table 2). Not surprisingly, endoscopic surgery prolonged the overall survival of NN patients without recurrence during follow-up, compared to conservative treatments (P < 0.05, Table S4; Figure S1).
In univariate Cox regression, patient sex, age, and diabetes history were not significantly linked to survival (P > 0.05), so we excluded them from further analysis. In multivariate Cox regression, the independent adverse prognostic factors for necrosis survival, beyond treatment factors, included middle necrosis, osteoradionecrosis, necrotic lesions ≤ 5mm from the internal carotid artery, history of re-irradiation, ALB ≤ 35 g/L, and a CRP/ALB ratio ≥ 0.31. These factors were consistent across the unmatched, PSM, and IPTW cohorts (Table 2). Multicollinearity did not exist in our model detecting by Variance Inflation Factor.

Subgroup analysis

To evaluate the efficacy of endoscopic surgery versus conservative treatment, we performed subgroup analyses across the unmatched, PSM, and IPTW cohorts. Subgroup factors included lesion extent, osteoradionecrosis, necrosis distance from the internal carotid artery, re-irradiation, BMI, ALB, and CRP/ALB.
In the unmatched cohort, an interaction between treatment modality and lesion extent was observed (P = 0.001). For early necrosis, endoscopic surgery and conservative treatment were comparable (HR: 0.87, 95% CI: 0.31-2.39). For middle necrosis, endoscopic surgery was significantly more effective (HR: 0.23, 95% CI: 0.17-0.32). No interaction was found with other factors; endoscopic surgery was superior in all other subgroups (Figure 3A). In the PSM cohort, an interaction with lesion extent was noted (P = 0.002). No significant difference was observed for early necrosis (HR: 2.82, 95% CI: 0.51-15.51). Endoscopic surgery was more effective in other subgroups (Figure 3B). In the IPTW cohort, interaction with lesion extent was significant (P = 0.001). Endoscopic surgery did not show benefit for early necrosis (HR: 0.76, 95% CI: 0.29-2.02), but was significantly beneficial for middle necrosis (HR: 0.25, 95% CI: 0.19-0.35). Endoscopic surgery was more effective across all other subgroups (Figure 3C).
Among the conservative treatments, 242 patients received medical treatment, 32 patients underwent endoscopic debridement combined with medical treatment, and 13 patients for others (Table S5). Endoscopic debridement combined with medical treatment had similar clinical outcomes as other two groups (P > 0.05, Table S6).

Discussion

Endoscopic surgery and conservative treatment are key approaches for NN, yet no prospective randomized controlled trials have directly compared their effectiveness [13]. Retrospective studies suggest endoscopic surgery may be superior, but these findings are limited by small sample sizes, selection biases, and confounding factors [12, 14, 17, 19, 20]. Our study, the largest in this field, found that endoscopic surgery generally offers better OS and necrosis healing compared to conservative treatment in the unmatched cohort, PSM cohort, and IPTW cohort. It also emerged as an independent protective factor for OS. However, for early necrosis, endoscopic surgery's efficacy is comparable to conservative treatment. Advances in endoscopic technology

Table 2. Univariate and multivariate analyses of variables correlated with overall survival.

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Treatment (surgery vs. conservative treatment)				
Unmatched	0.35 (0.26-0.46)	**<0.001**	0.28 (0.21-0.38)	**<0.001**
Propensity-score matched	0.42 (0.31-0.58)	**<0.001**	0.33 (0.23-0.45)	**<0.001**
IPTW matched	0.36 (0.27-0.47)	**<0.001**	0.30 (0.22-0.41)	**<0.001**
Smoking (Yes vs. No)				
Unmatched	1.33 (1.03-1.73)	**0.032**	1.19 (0.91-1.55)	0.211
Propensity-score matched	1.28 (0.92-1.77)	0.137	--	--
IPTW matched	1.31 (1.00-1.72)	**0.050**	1.27 (0.95-1.68)	0.104
Lesion area (Beyond mucosa vs. mucosa)				
Unmatched	3.47 (2.26-5.34)	**<0.001**	2.21 (1.36-3.61)	**0.001**
Propensity-score matched	4.15 (2.23-7.49)	**<0.001**	2.34 (1.22-4.50)	**0.011**
IPTW matched	3.13 (2.02-4.86)	**<0.001**	1.75 (1.01-3.04)	**0.047**
Osteoradionecrosis (Yes vs. No)				
Unmatched	2.27 (1.77-2.92)	**<0.001**	1.49 (1.13-1.96)	**0.005**
Propensity-score matched	2.18 (1.60-2.98)	**<0.001**	1.57 (1.12-2.20)	**0.009**
IPTW matched	2.19 (1.68-2.85)	**<0.001**	1.64 (1.20-2.24)	**0.002**
Distant to ICA (≤ 5 vs >5 mm)				
Unmatched	2.45 (1.90-3.15)	**<0.001**	1.63 (1.23-2.18)	**0.001**
Propensity-score matched	2.14 (1.57-2.94)	**<0.001**	1.50 (1.06-2.13)	**0.024**
IPTW matched	2.20 (1.67-2.89)	**<0.001**	1.48 (1.07-2.04)	**0.017**
Primary RT method (2DRT vs. IMRT)				
Unmatched	0.72 (0.54-0.95)	**0.021**	1.01 (0.74-1.38)	0.956
Propensity-score matched	0.82 (0.57-1.19)	0.297	--	--
IPTW matched	0.73 (0.53-1.00)	**0.048**	0.95 (0.68-1.33)	0.785
Re-irradiation (Yes vs. No)				
Unmatched	2.71 (2.09-3.50)	**<0.001**	2.07 (1.57-2.74)	**<0.001**
Propensity-score matched	1.75 (1.28-2.39)	**<0.001**	1.61 (1.16-2.22)	**0.004**
IPTW matched	2.11 (1.58-2.83)	**<0.001**	2.00 (1.47-2.72)	**<0.001**
BMI (>18.5 vs. ≤ 18.5 kg/m^2)				
Unmatched	0.72 (0.54-0.95)	**0.019**	0.78 (0.58-1.05)	0.101
Propensity-score matched	0.53 (0.39-0.74)	**<0.001**	0.72 (0.50-1.03)	0.071
IPTW matched	0.60 (0.45-0.80)	**0.001**	0.68 (0.45-0.94)	**0.017**
NLR (≤ 4.16 vs. >4.16)				
Unmatched	1.61 (1.24-2.10)	**<0.001**	1.21 (0.89-1.65)	0.231
Propensity-score matched	1.61 (1.16-2.25)	**0.005**	1.14 (0.76-1.73)	0.522
IPTW matched	1.52 (1.16-2.00)	**0.003**	1.18 (0.86-1.63)	0.312
LMR (≤ 3.51 vs. >3.51)				
Unmatched	0.47 (0.32-0.70)	**<0.001**	0.72 (0.47-1.12)	0.146
Propensity-score matched	0.57 (0.36-0.91)	**0.019**	0.68 (0.38-1.20)	0.183
IPTW matched	0.53 (0.36-0.78)	**0.001**	0.66 (0.41-1.08)	0.096
ALB (>35 vs. ≤ 35 g/L)				
Unmatched	0.39 (0.28-0.54)	**<0.001**	0.52 (0.36-0.74)	**<0.001**
Propensity-score matched	0.41 (0.27-0.64)	**<0.001**	0.44 (0.28-0.71)	**0.001**
IPTW matched	0.50 (0.33-0.78)	**0.002**	0.57 (0.38-0.85)	**0.006**

Table 2 *continued*. Univariate and multivariate analyses of variables correlated with overall survival.

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
HGB (≥110 vs. <110g/L)				
Unmatched	0.60 (0.47-0.78)	**<0.001**	1.04 (0.78-1.38)	0.786
Propensity-score matched	0.66 (0.48-0.90)	**0.009**	1.12 (0.80-1.58)	0.512
IPTW matched	0.71 (0.54-0.93)	**0.013**	1.07 (0.78-1.46)	0.674
CRP/ALB (≥ 0.31 vs. <0.31)				
Unmatched	2.31 (1.73-3.08)	**<0.001**	1.72 (1.24-2.38)	**0.001**
Propensity-score matched	2.52 (1.72-3.68)	**<0.001**	1.73 (1.14-2.63)	**0.010**
IPTW matched	2.02 (1.50-2.73)	**<0.001**	1.55 (1.09-2.22)	**0.015**

Abbreviations: PSM: propensity score matching; IPTW: inverse probability of treatment weighting; ICA: internal carotid artery; RT: radiotherapy; 2DRT: two-dimensional radiotherapy; IMRT: intensity modulated radiation therapy; BMI: body mass index; NLR: lymphocyte ratio; LMR: lymphocyte to monocyte ratio; ALB: albumin; HGB: hemoglobin; CRP: c-reaction protein.

have led to increased reports on its use for NN. A study of 27 patients treated surgically found that 96% experienced headache relief, all had resolved foul nasal odor, and the mucosal healing rate was 77.8% [19]. Zou et al. reported a 2-year OS rate of 77.9% and a complete mucosal healing rate of 78% using a combined excision and flap technique [13]. Our study, involving 230 patients, showed a 3-year OS rate of 70.5% and a postoperative mucosal healing rate of 73.0% with endoscopic surgery, significantly outperforming conservative treatment. Endoscopic surgery effectively removes necrotic tissue, enhancing epithelialization and improving survival and healing rates [12, 13, 18, 20, 21].

It is worth noting that subgroup analyses in the unmatched, PSM, IPTW cohort showed that for patients with early necrosis, endoscopic surgery and conservative debridement were equally effective. Indeed, the effectiveness of conservative treatment for early necrosis has been demonstrated in several studies. Hua et al. found that out of 10 patients with necrosis limited to the nasopharyngeal mucosa, 8 achieved long-term survival after conservative treatment [8]. Another retrospective study involving 113 necrotic patients found that 63.2% of patients with early NN achieved mucosal repair after conservative treatment, with a 2-year OS rate of 86.7% [16]. In our study, 79 patients with early necrosis who received conservative treatment had a mucosal repair rate of 82.30%. The 2-year OS rate was 83.80% (95% CI, 75.00-92.60%) in the conservative group, similar to the surgical group (86.30% [95% CI, 73.80-98.80%]). This effectiveness can be attributed to the superficial nature of the lesions and relatively mild local infections in these patients, allowing thorough debridement under local anesthesia. Additionally, antibiotic therapy, hydrogen peroxide irrigation, and epidermal growth factors contributed to repair. Therefore, conservative treatment can be as effective as surgery for early necrosis. We categorized endoscopic debridement as conservative group due to its minimally invasive approach. Patients in the surgical group experienced extensive tissue removal, longer hospital stays, and general anesthesia, compared with the conservative group.

For patients in settings where endoscopic surgery is not available, conservative treatment may be preferable. However, among 109 cases of early necrosis in this study, only 30 underwent nasal endoscopic surgery. Further prospective clinical trials are needed to compare the efficacy of endoscopic surgery and conservative treatment in this subgroup, with ongoing trial NCT05228093 expected to provide more insights.

In the multivariate Cox regression analysis across the three cohorts, we identified several independent adverse prognostic factors for necrosis: middle necrosis, combined osteoradionecrosis, necrotic lesion distance to the internal carotid artery ≤ 5mm, prior re-irradiation, ALB ≤ 35 g/L, and CRP/ALB ratio ≥ 0.31. Exposure of the internal carotid artery in necrotic lesions is a well-established adverse prognostic factor, with mortality rates between 67.2% and 72.7%, and a high risk of fatal nasopharyngeal hemorrhage [8, 15, 22]. In this study, 108 patients (43.20% of deaths) died from severe bleeding, highlighting the importance of vascular protection in necrosis treatment. Carotid artery embolization can significantly reduce bleeding risk and enhance tissue repair, improving survival rates [13, 23, 24]. For patients with a positive balloon occlusion test (BOT), internal carotid artery stenting before necrosis treatment reduced nasopharyngeal bleeding risk to 8.3% and increased the OS rate to 73.2% [25]. In this study, 105 patients who underwent endoscopic surgery with vascular pretreatment had an 8.60% bleeding mortality rate. These findings suggest that effective vascular protection improves survival and reduces bleeding risk in patients with lesions near the internal carotid artery. However, carotid artery embolization or stenting also increases the risk of stroke and cerebral ischemia [25, 26], and predicting this risk remains an area

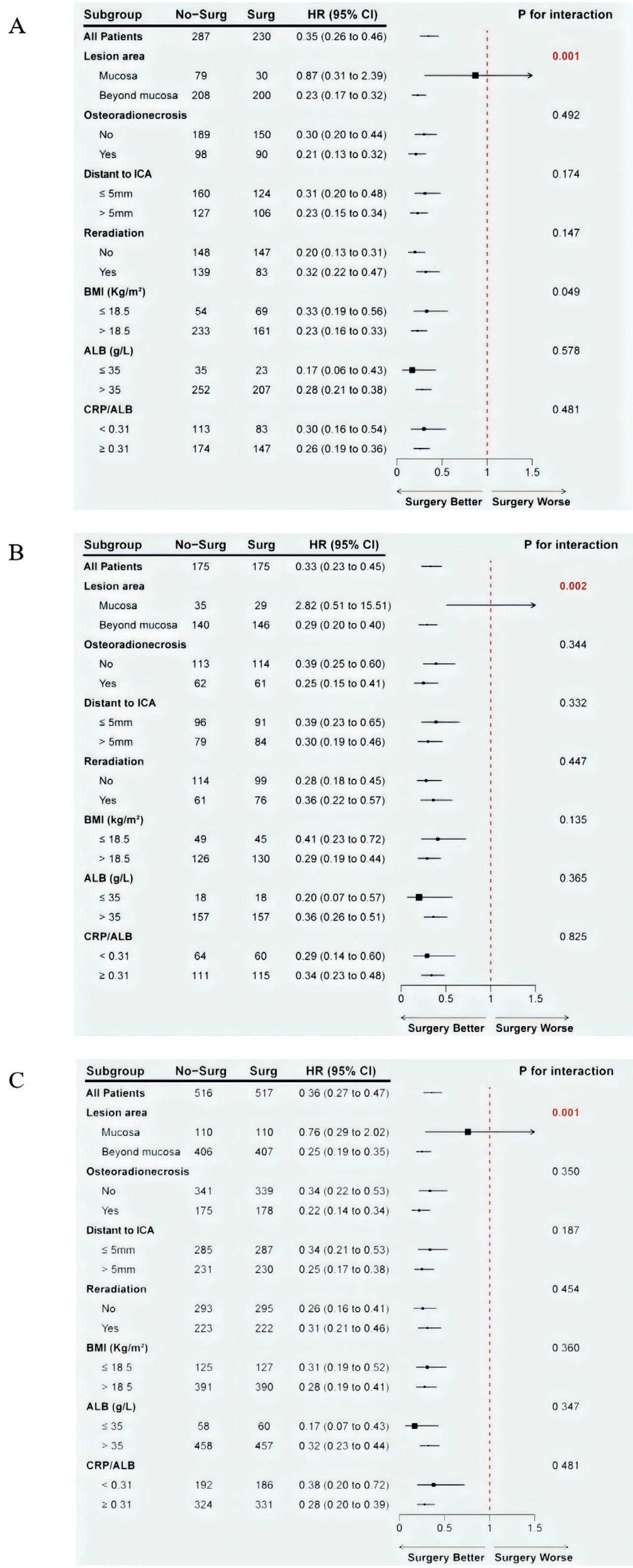

Figure 3. Forest plots for subgroup analyses in the unmatched(A), the PSM(B) and the IPTW cohort(C).

for further research.

Re-irradiation is an essential salvage treatment for locally advanced recurrent NPC, but it significantly increases the incidence of NN, with rates up to 51.5% compared to primary cases, and NN is one of the major serious adverse reactions [9, 27-29]. This heightened risk is due to the higher radiation doses received by the nasopharyngeal mucosa, which impairs mucosal repair [30]. Both our study and others have identified re-irradiation as an independent adverse prognostic factor for NN, with a hazard ratio for death of 2.706 (95% CI: 2.092-3.500) compared to radiotherapy alone [12, 16]. Subgroup analysis shows that endoscopic surgery is significantly more effective than conservative treatment for NN following re-irradiation (HR=0.32, 95% CI: 0.22-0.47, P = 0.147). Thus, endoscopic surgery is preferred for managing NN after re-irradiation.

ALB levels and the CRP/ALB ratio are established inflammatory markers linked to poor tumour prognosis [31-33]. Our study reveals that ALB ≤ 35g/L and a CRP/ALB ratio ≥ 0.31 are independent adverse prognostic factors for patients with NN, indicating that poor nutritional and inflammatory status significantly affect treatment outcomes. Cachexia and intracranial infections are noted as common causes of death in necrosis cases [11]. Thus, in addition to standard debridement, enhanced nutritional and antimicrobial support is crucial for patients with NN.

Our study identified 49 patients who died from local nasopharyngeal recurrence. Research shows that recurrence combined with necrosis leads to a worse prognosis compared to simple necrosis [13]. Effective diagnostic indicators are lacking, but endoscopic surgery can differentiate between simple necrosis and recurrent nasopharyngeal carcinoma, providing essential pathological evidence and alleviating necrosis symptoms.

Limitations exist in our study. Despite employing PSM and IPTW to adjust for confounding factors, some may still be unaccounted for. Large-scale phase III trials are needed to definitively compare the efficacy of nasal endoscopic surgery and conservative treatment for NN. Additionally, as all cases were from a single centre, the findings may not be generalizable due to potential differences in treatment approaches across centres. Lastly, the subgroup analysis is post hoc and provides only preliminary insights for the clinical treatment of NN.

Conclusion

Our study suggests that nasal endoscopic surgery offers superior OS and efficacy compared with conservative treatment for NN. While conservative treatment is as effective as endoscopic surgery for early necrosis, endoscopic surgery is significantly better for other patients. It also serves as an independent protective factor for survival. Independent adverse prognostic factors include middle necrosis, combined osteoradionecrosis, necrotic lesions within 5 mm of the internal carotid artery, re-irradiation history, ALB ≤ 35 g/L, and a CRP/ALB ratio ≥ 0.31. Multicentre phase III trials are needed to further evaluate the comparative effectiveness of these treatments.

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Authorship contribution
Study concepts: RLX, JYS; Study design: RLX, JYS; Data acquisition: YFOY, QLL, ACL; Quality control of data and algorithms: YFOY, QLL, ACL; Data analysis and interpretation: YFOY, RLX; Statistical analysis: YFOY, QLL, RLX; Manuscript preparation: YFOY, QLL, RLX; Manuscript editing: YFOY, QLL, RLX, JYS; Manuscript review: all the authors.

Conflict of interest
The authors declare that no conflict of interest.

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References
1. Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol. 2002;12(6):421-9.
2. Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. Lancet. 2016;387(10022):1012-24.
3. Ma J, Mai HQ, Hong MH, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol. 2001;19(5):1350-7.
4. Zhang W, Dou H, Lam C, et al. Concurrent chemoradiotherapy with or without adjuvant chemotherapy in intermediate and locoregionally advanced nasopharyngeal carcinoma. Tumour Biol. 2013;34(3):1729-36.
5. Zhang MX, Li J, Shen GP, et al. Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: A 10-year experience with a large cohort and long follow-up. Eur J Cancer. 2015;51(17):2587-95.
6. Mao YP, Tang LL, Chen L, et al. Prognostic factors and failure patterns in non-metastatic nasopharyngeal carcinoma after intensity-modulated radiotherapy. Chin J Cancer. 2016;35(1):103.
7. Huang XM, Zheng YQ, Zhang XM, et al. Diagnosis and management of skull base osteoradionecrosis after radiotherapy for nasopharyngeal carcinoma. Laryngoscope. 2006;116(9):1626-31.
8. Hua YJ, Chen MY, Qian CN, et al. Postradiation nasopharyngeal necrosis in the patients with nasopharyngeal carcinoma. Head Neck. 2009;31(6):807-12.
9. Yu YH, Xia WX, Shi JL, et al. A model to predict the risk of lethal nasopharyngeal necrosis after re-irradiation with intensity-modulated radiotherapy in nasopharyngeal carcinoma patients. Chin J Cancer. 2016;35(1):59.
10. Kuan EC, Wang EW, Adappa ND, et al. International Consensus Statement on Allergy and Rhinology: Sinonasal Tumors. Int Forum Allergy Rhinol. 2024;14(2):149-608.
11. Hua YJ, Chen MY, Hong MH, et al. [Short-term efficacy of endoscopy-guided debridement on radiation-related nasopharyngeal necrosis in 20 nasopharyngeal carcinoma patients after radiotherapy]. Ai Zheng. 2008;27(7):729-33.
12. Yang Q, Zou X, You R, et al. Proposal for a new risk classification system for nasopharyngeal carcinoma patients with post-radiation nasopharyngeal necrosis. Oral Oncol. 2017;67:83-8.
13. Zou X, Wang SL, Liu YP, et al. A curative-intent endoscopic surgery for postradiation nasopharyngeal necrosis in patients with nasopharyngeal carcinoma. Cancer Commun (Lond). 2018;38(1):74.
14. Yang K, Ahn YC, Nam H, Hong SD, Oh D, Noh JM. Clinical features of post-radiation nasopharyngeal necrosis and their outcomes following surgical intervention in nasopharyngeal cancer patients. Oral Oncol. 2021;114:105180.
15. Chen MY, Mai HQ, Sun R, et al. Clinical findings and imaging features of 67 nasopharyngeal carcinoma patients with postradiation nasopharyngeal necrosis. Chin J Cancer. 2013;32(10):533-8.
16. Xiao Y, Peng S, Tang Y, et al. Retrospective analysis of a modified irrigation method for nasopharyngeal carcinoma patients with post-radiation nasopharyngeal necrosis. Front Oncol. 2021;11:663132.
17. Ryu G, So YK, Seo MY, et al. Using the nasoseptal flap for reconstruction after endoscopic debridement of radionecrosis in nasopharyngeal carcinoma. Am J Rhinol Allergy. 2018;32(1):61-5.
18. Chen MY, Wang SL, Zhu YL, et al. Use of a posterior pedicle nasal septum and floor mucoperiosteum flap to resurface the nasopharynx after endoscopic nasopharyngectomy for recurrent nasopharyngeal carcinoma. Head Neck. 2012;34(10):1383-8.
19. Song B, Kim HY, Jung YG, Baek CH, Chung MK, Hong SD. Endoscopic debridement of post-radiation nasopharyngeal necrosis: the effects of resurfacing with a vascularized flap. Clin Exp Otorhinolaryngol. 2022;15(4):354-63.
20. Shah SR, Wu A, Sindwani R, Tang D. Presentation and optimal management of anterior and central skull base osteoradionecrosis: systematic review and meta-analysis. Laryngoscope. 2025 Mar;135(3):982-990.
21. Hao SP, Chen HC, Wei FC, Chen CY, Yeh AR, Su JL. Systematic management of osteoradionecrosis in the head and neck. Laryngoscope. 1999;109(8):1324-7; discussion 7-8.
22. Wu JX, Xu LY, Yang BH, et al. [Clinical analysis of 60 cases with radiative nasopharyngeal necrosis in nasopharyngeal carcinoma]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2012;47(3):185-90.
23. Wang ZQ, Xie YL, Liu YP, et al. Endoscopic nasopharyngectomy combined with internal carotid artery pretreatment for recurrent nasopharyngeal carcinoma. Otolaryngol Head Neck Surg. 2022;166(3):490-7.
24. Liu YL, Wen K, Zhang WJ, et al. Assessment of prophylactic internal carotid artery management in postradiation nasopharyngeal necrosis patients. Otolaryngol Head Neck Surg. 2024;170(2):447-56.
25. Wu WB, Zhang XB, Liu YP, et al. Stent pretreatment for internal carotid artery exposed to necrotic lesions in nasopharyngeal carcinoma. Rhinology. 2023.61,3:246-254.
26. Whisenant JT, Kadkhodayan Y, Cross DT, 3rd, Moran CJ, Derdeyn CP. Incidence and mechanisms of stroke after permanent carotid artery occlusion following temporary occlusion testing. J Neurointerv Surg. 2015;7(6):395-401.
27. Tian YM, Zhao C, Guo Y, et al. Effect of total dose and fraction size on survival of patients with locally recurrent nasopharyngeal carcinoma treated with intensity-modulated radiotherapy: a phase 2, single-center, randomized controlled trial. Cancer. 2014;120(22):3502-9.
28. Chan OS, Sze HC, Lee MC, et al. Reirradiation with intensity-modulated radiotherapy for locally recurrent T3 to T4 nasopharyngeal carcinoma. Head Neck. 2017;39(3):533-40.
29. Li XY, Sun XS, Liu SL, et al. The development of a nomogram to predict post-radiation necrosis in nasopharyngeal carcinoma patients: a large-scale cohort study. Cancer Manag Res. 2019;11:6253-63.
30. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. J Oral Maxillofac Surg. 1983;41(5):283-8.
31. Sun P, Chen C, Xia Y, et al. The Ratio of

C-Reactive Protein/Albumin is a Novel Inflammatory Predictor of Overall Survival in Cisplatin-Based Treated Patients with Metastatic Nasopharyngeal Carcinoma. Dis Markers. 2017;2017:6570808.
32. Tao CJ, Chen YY, Jiang F, et al. The C-reactive Protein/Albumin Ratio Is an independent Prognostic Factor for Overall Survival in Patients with Nasopharyngeal Carcinoma Receiving Intensity-Modulated Radiotherapy. J Cancer. 2016;7(14):2005-11.
33. Oei RW, Ye L, Huang J, et al. Prognostic value of nutritional markers in nasopharyngeal carcinoma patients receiving intensity-modulated radiotherapy: a propensity score matching study. Onco Targets Ther. 2018;11:4857-68.

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SUPPLEMENTARY MATERIAL

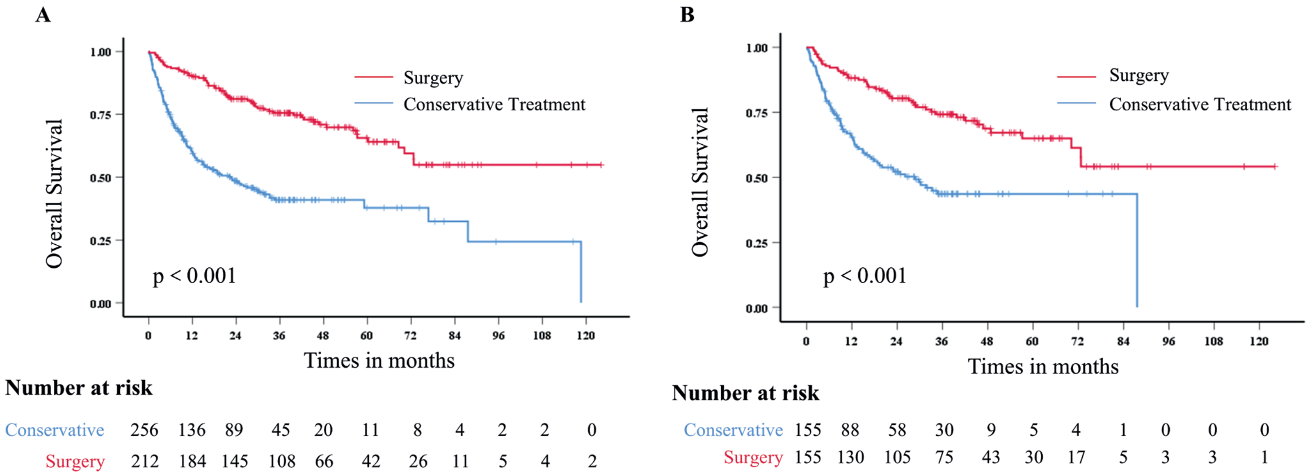

Figure S1. Kaplan–Meier curves of overall survival with endoscopic surgery and conservative treatment in the unmatched (A) and the PSM (B) cohort without recurrence

Table S1. Standardized mean difference between conservative treatment and surgery group after matching.

Characteristics	Unmatched	Propensity matched	IPTW
Sex (Male vs. Female)	0.058	0.079	0.021
Age (≤ 45 vs >45 years)	0.119	0.062	0.001
Diabetes (Yes vs. No)	0.190	0.063	0.002
Smoking (Yes vs. No)	0.057	0.076	0.005
Lesion area* (Mucosa vs Beyond mucosa)	0.366	0.089	0.002
Osteoradionecrosis (Yes vs. No)	0.013	0.012	0.011
Distant to ICA (≤ 5 vs >5 mm)[#]	0.037	0.057	0.004
Primary RT method (2DRT vs. IMRT)	0.062	0.089	0.008
Re-irradiation (Yes vs. No)	0.252	0.176	0.005
BMI (≤ 18.5 vs. >18.5 kg/m^2)	0.263	0.052	0.009
NLR (≤ 4.16 vs. >4.16)	0.064	0.023	0.004
LMR (≤ 4.16 vs. >4.16)	0.227	0.060	0.014
ALB (≤ 35 vs. >35 g/L)	0.070	<0.001	0.016
HGB (<110 vs. ≥110 g/L)	0.186	0.084	0.006
CRP/ALB (<0.31 vs. ≥ 0.31)	0.068	0.048	0.027

* Necrosis confined to the mucous and interrupted mucosal line that could be seen with MRI. [#] Distant to ICA refers to the minimal axial distance from necrosis lesion to internal carotid in MRI. Abbreviations: IPTW, Inverse Probability Treatment Weighting; ICA, internal carotid artery; RT, radiation therapy; 2DRT, two-dimensional radiotherapy; IMRT, intensity-modulated radiation therapy; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; ALB, albumin; HGB, hemoglobin; CRP/ALB, C-reactive protein (CRP) to albumin ratio.

Table S2. Causes of death between the conservative and surgery group.

Cause of death	Total (n=250)	Endoscopic surgery (n=79)	Conservative treatment (n=171)	P-value
Massive bleeding	108 (43.2%)	18 (22.8%)	90 (52.6%)	**< 0.001**
Local tumour recurrence	49 (19.6%)	18 (22.8%)	31 (18.1%)	0.389
Distant tumour metastasis	25 (10.0%)	11 (13.9%)	14 (8.2%)	0.160
Cachexia	24 (9.6%)	11 (13.9%)	13 (7.6%)	0.632
Cerebrovascular accidents	23 (9.2%)	11 (13.9%)	12 (7.0%)	0.115
Aspiration pneumonia	12 (4.8%)	6 (7.6%)	6 (3.5%)	0.079
Intracranial infection	9 (3.6%)	4 (5.1%)	5 (2.9%)	0.277

Table S3. Treatment outcome with conservative treatment and surgery in patients with post-radiation nasopharyngeal necrosis.

Treatment outcome	Conservative treatment, rate (95%CI)	Surgery, rate (95%CI)	P-value
1-year OS			
Unmatched	60.30 (54.80-66.40)	89.90 (86.00-93.90)	**<0.001**
PSM	62.90 (56.0-70.70)	89.00 (84.50-93.80)	**<0.001**
IPTW	60.70 (54.90-67.10)	89.7 (85.60-94.10)	**<0.001**
3-year OS			
Unmatched	35.00 (29.30-41.80)	70.50 (64.50-77.10)	**<0.001**
PSM	47.20 (40.00-55.70)	75.00 (68.60-82.00)	**<0.001**
IPTW	44.30 (37.30-50.30)	77.60 (71.80-84.00)	**<0.001**
5-year OS			
Unmatched	32.30 (25.50-40.90)	58.50 (50.80-67.40)	**<0.001**
PSM	33.60 (24.00-47.00)	55.80 (46.90-66.30)	**0.005**
IPTW	32.10 (25.4-40.50)	58.10 (49.90-67.50)	**<0.001**
Efficiency			
Unmatched	33.10 (27.90-38.70)	73.00 (67.00-78.40)	**<0.001**
PSM	38.20 (31.40-45.70)	74.80 (68.00-80.70)	**<0.001**
IPTW	33.40 (29.50-37.60)	64.20 (60.00-68.20)	**<0.001**

Abbreviations: PSM, Propensity-score matched; IPTW, Inverse Probability Treatment Weighting.

Table S4. Baseline characteristics in the patients without recurrence.

Characteristic	Unmatched, no. (%)			Propensity matched, no. (%)		
	Conservative treatment	Surgery	P-value	Conservative treatment	Surgery	P-value
No. of patients	256	212		155	155	
Sex			0.505			0.609
female	66 (25.8)	49 (23.1)		44 (26.5)	40 (25.8)	
male	190 (74.2)	163 (76.9)		111 (73.5)	115 (74.2)	
Age						1.000
≤ 45 years	78 (30.5)	55 (25.9)	0.280	41 (26.5)	41 (26.5)	
> 45 years	178 (69.5)	157 (74.1)		114 (73.5)	114 (73.5)	
Diabetes						1.000
No	251 (98.0)	201 (94.8)	0.055	150 (96.8)	150 (96.8)	
Yes	5 (2.0)	11 (5.2)		5 (3.2)	5 (3.3)	
Smoking			0.393			0.524
No	183 (71.5)	159 (75.0)		115 (74.2)	110 (71.0)	
Yes	73 (28.5)	53 (25.0)		40 (25.8)	45 (29.0)	
Lesion area*			**<0.001**			0.165
Mucosa	76 (29.7)	28 (13.2)		38 (24.5)	28 (18.1)	
Beyond mucosa	180 (70.3)	184 (86.8)		117 (75.5)	127 (81.9)	
Osteoradionecrosis			0.712			0.344
No	172 (67.2)	139 (65.6)		103 (66.5)	95 (61.3)	
Yes	84 (32.8)	73 (34.4)		52 (33.5)	60 (38.7)	
Distant to ICA[#]			0.219			0.209
≤ 5mm	134 (52.3)	123 (58.0)		80 (51.6)	91 (58.7)	
> 5mm	122 (47.7)	89 (42.0)		75 (48.4)	64 (41.3)	
Primary RT method			0.494			0.121
2DRT	49 (19.1)	46 (21.7)		26 (16.8)	37 (23.9)	
IMRT	207 (80.9)	166 (78.3)		129 (83.2)	118 (76.1)	
Re-irradiation			**0.024**			
No	139 (54.3)	137 (64.6)		107 (69.0)	90 (58.1)	0.059
Yes	117 (45.7)	75 (35.4)		48 (31.0)	65 (41.9)	
BMI			**0.004**			
≤ 18.50 kg/m^2	46 (18.0)	62 (29.2)		40 (25.8)	37 (23.9)	0.693
> 18.50 kg/m^2	210 (82.0)	150 (70.8)		115 (74.2)	118 (76.1)	
NLR			0.371			0.908
≤ 4.16	103 (40.2)	94 (44.3)		65 (41.9)	66 (42.6)	
> 4.16	153 (59.8)	118 (55.7)		90 (58.1)	89 (57.4)	
LMR			**0.016**			0.394
≤ 3.51	216 (84.4)	160 (75.5)		127 (81.9)	121 (78.1)	
> 3.51	40 (15.6)	52 (24.5)		28 (18.1)	34 (21.9)	
ALB			0.240			0.570
≤ 35 g/L	33 (12.9)	20 (9.4)		14 (9.0)	17 (11.0)	
> 35 g/L	223 (87.1)	192 (90.6)		141 (91.0)	138 (89.0)	
HGB			**0.023**			0.633
< 110 g/L	98 (38.3)	60 (28.3)		56 (36.1)	52 (33.5)	
≥ 110 g/L	158 (61.7)	152 (71.7)		99 (63.9)	103 (66.5)	

Table S4 *continued*. Baseline characteristics in the patients without recurrence.

Characteristic	Unmatched, no. (%)			Propensity matched, no. (%)		
	Conservative treatment	Surgery	P-value	Conservative treatment	Surgery	P-value
CRP/ALB			0.408			0.814
< 0.31	105 (41.0)	79 (37.3)		59 (38.1)	57 (36.8)	
≥ 0.31	151 (59.0)	133 (62.7)		96 (61.9)	98 (63.2)	

* Necrosis confined to the mucous and interrupted mucosal line that could be seen with MRI. # Distant to ICA refers to the minimal axial distance from necrosis lesion to internal carotid in MRI. Abbreviations: PSM: propensity score matching; IPTW: inverse probability of treatment weighting; ICA: internal carotid artery; RT: radiotherapy; 2DRT: two-dimensional radiotherapy; IMRT: intensity modulated radiation therapy; BMI: body mass index; NLR: lymphocyte ratio; LMR: lymphocyte to monocyte ratio; ALB: albumin; HGB: hemoglobin; CRP: c-reaction protein.

Table S5. Baseline characteristics in the conservative treatments.

Characteristic	Medical treatment, no. (%)	Endoscopic debridement combined with medical treatment, no. (%)	Others, no. (%)	P-value
No. of patients	242	32	13	
Sex				0.245
female	65 (26.9)	5 (15.6)	2 (15.4)	
male	177 (73.1)	27 (84.4)	11 (84.6)	
Age				0.470
≤ 45 years	82 (33.9)	8 (25)	3 (23.1)	
> 45 years	160 (66.1)	24 (75)	10 (76.9)	
Diabetes				1.000
No	237 (97.9)	32 (100)	13 (100)	
Yes	5 (2.1)	0 (0)	0 (0)	
Smoking				0.143
No	174 (71.9)	21 (65.6)	6 (46.2)	
Yes	68 (28.1)	11 (34.4)	7 (53.8)	
Lesion area*				**0.001**
Mucosa	59 (24.4)	18 (56.3)	2 (15.4)	
Beyond mucosa	183 (75.6)	14 (43.8)	11 (84.6)	
Osteoradionecrosis				**0.010**
No	154 (63.6)	28 (87.5)	7 (53.8)	
Yes	88 (36.4)	4 (12.5)	6 (46.2)	
Distant to ICA#				**< 0.001**
≤ 5mm	139 (57.4)	6 (18.8)	8 (61.5)	
> 5mm	103 (42.6)	26 (81.2)	5 (38.5)	
Primary RT method				0.096
2DRT	49 (20.2)	2 (6.3)	3 (23.1)	
IMRT	193 (79.8)	30 (93.7)	10 (76.9)	
Re-irradiation				**< 0.001**
No	114 (47.1)	28 (87.5)	6 (46.2)	
Yes	128 (52.9)	4 (12.5)	7 (53.8)	

Table S5 *continued*. Baseline characteristics in the conservative treatments.

Characteristic	Medical treatment, no. (%)	Endoscopic debridement combined with medical treatment, no. (%)	Others, no. (%)	P-value
BMI				0.824
≤ 18.5 kg/m²	47 (19.4)	5 (15.6)	2 (15.4)	
> 18.5 kg/m²	195 (80.6)	27 (84.4)	11 (84.6)	
NLR				0.408
≤ 4.16	96 (39.7)	14 (43.8)	7 (53.8)	
> 4.16	146 (60.3)	18 (56.2)	6 (46.2)	
LMR				**0.008**
≤ 3.51	211 (87.2)	27 (84.4)	7 (53.8)	
> 3.51	31 (12.8)	5 (15.6)	6 (46.2)	
ALB				0.156
≤ 35 g/L	32 (13.2)	1 (3.1)	2 (15.2)	
> 35 g/L	210 (86.8)	31 (96.9)	11 (84.6)	
HGB				0.162
< 110 g/L	88 (36.4)	14 (43.8)	8 (61.5)	
≥ 110 g/L	154 (63.6)	18 (56.2)	5 (38.5)	
CRP/ALB				0.866
< 0.31	94 (38.8)	14 (43.8)	5 (38.5)	
≥ 0.31	148 (61.2)	18 (56.2)	8 (61.5)	

* Necrosis confined to the mucous and interrupted mucosal line that could be seen with MRI. # Distant to ICA refers to the minimal axial distance from necrosis lesion to internal carotid in MRI. Abbreviations: PSM: propensity score matching; IPTW: inverse probability of treatment weighting; ICA: internal carotid artery; RT: radiotherapy; 2DRT: two-dimensional radiotherapy; IMRT: intensity modulated radiation therapy; BMI: body mass index; NLR: lymphocyte ratio; LMR: lymphocyte to monocyte ratio; ALB: albumin; HGB: hemoglobin; CRP: c-reaction protein.

Table S6. Univariate and multivariate analyses of variables correlated with overall survival within the patients within conservative treatments.

Characteristics	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Treatment				
Others	Reference		Reference	
Medical treatment	1.336 (0.626 - 2.851)	0.454	1.433 (0.652 - 3.149)	0.371
Endoscopic debridement combined with medical treatment	0.278 (0.088 - 0.878)	**0.029**	0.756 (0.231 - 2.470)	0.643
Lesion area*				
Beyond mucosa	Reference		Reference	
mucosa	0.102 (0.055 - 0.189)	**< 0.001**	0.243 (0.122 - 0.482)	**< 0.001**
Osteoradionecrosis				
No	Reference		Reference	
Yes	3.068 (2.258 - 4.169)	**< 0.001**	1.412 (1.008 - 1.977)	**0.045**
Distant to ICA#				
>5 mm	Reference		Reference	
≤ 5 mm	4.400 (3.111 - 6.222)	**< 0.001**	1.654 (1.110 - 2.467)	**0.013**

Table S6 *continued*. Univariate and multivariate analyses of variables correlated with overall survival within the patients within conservative treatments.

Characteristics	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Primary RT method				
IMRT	Reference		Reference	
2DRT	1.744 (1.239 - 2.455)	**0.001**	0.982 (0.675 - 1.430)	0.926
Re-irradiation				
Yes	Reference		Reference	
No	0.407 (0.297 - 0.558)	**< 0.001**	0.616 (0.437 - 0.868)	**0.006**
HGB				
< 110 g/L	Reference		Reference	
≥ 110 g/L	0.708 (0.521 - 0.962)	**0.027**	1.177 (0.842 - 1.647)	0.340
NLR				
> 4.16	Reference		Reference	
≤ 4.16	0.494 (0.357 - 0.684)	**< 0.001**	0.651 (0.438 - 0.968)	**0.034**
LMR				
≤ 3.51	Reference		Reference	
> 3.51	0.463 (0.276 - 0.775)	**0.003**	0.807 (0.439 - 1.483)	0.490
ALB				
> 35 g/L	Reference		Reference	
≤ 35 g/L	3.551 (2.383 - 5.293)	**< 0.001**	1.907 (1.239 - 2.935)	**0.003**
CRP/ALB				
≥ 0.31	Reference		Reference	
< 0.31	0.352 (0.248 - 0.500)	**< 0.001**	0.679 (0.459 - 1.003)	0.052

* Necrosis confined to the mucous and interrupted mucosal line that could be seen with MRI. # Distant to ICA refers to the minimal axial distance from necrosis lesion to internal carotid in MRI. Abbreviations: ICA: internal carotid artery; RT: radiotherapy; 2DRT: two-dimensional radiotherapy; IMRT: intensity modulated radiation therapy; NLR: lymphocyte ratio; LMR: lymphocyte to monocyte ratio; ALB: albumin; CRP: c-reaction protein.