Strategies for patients with recurrent nasopharyngeal carcinoma involved internal carotid artery who are intolerant to embolization

Wen-Bin Wu[1,2], Xiao-Bin Zhang[3], Zheng-Kai Feng[1,2,#], Hui-Feng Li[1,2,#], You-Ping Liu[1,2], Jiong-Lin Liang[1,2], Yu-Long Xie[1,2], Yi-Jun Hua[1,2], Rui Sun[1,2], Shun-Lan Wang[4], Jin-Hua Chen[3], Ming-Yuan Chen[1,2]

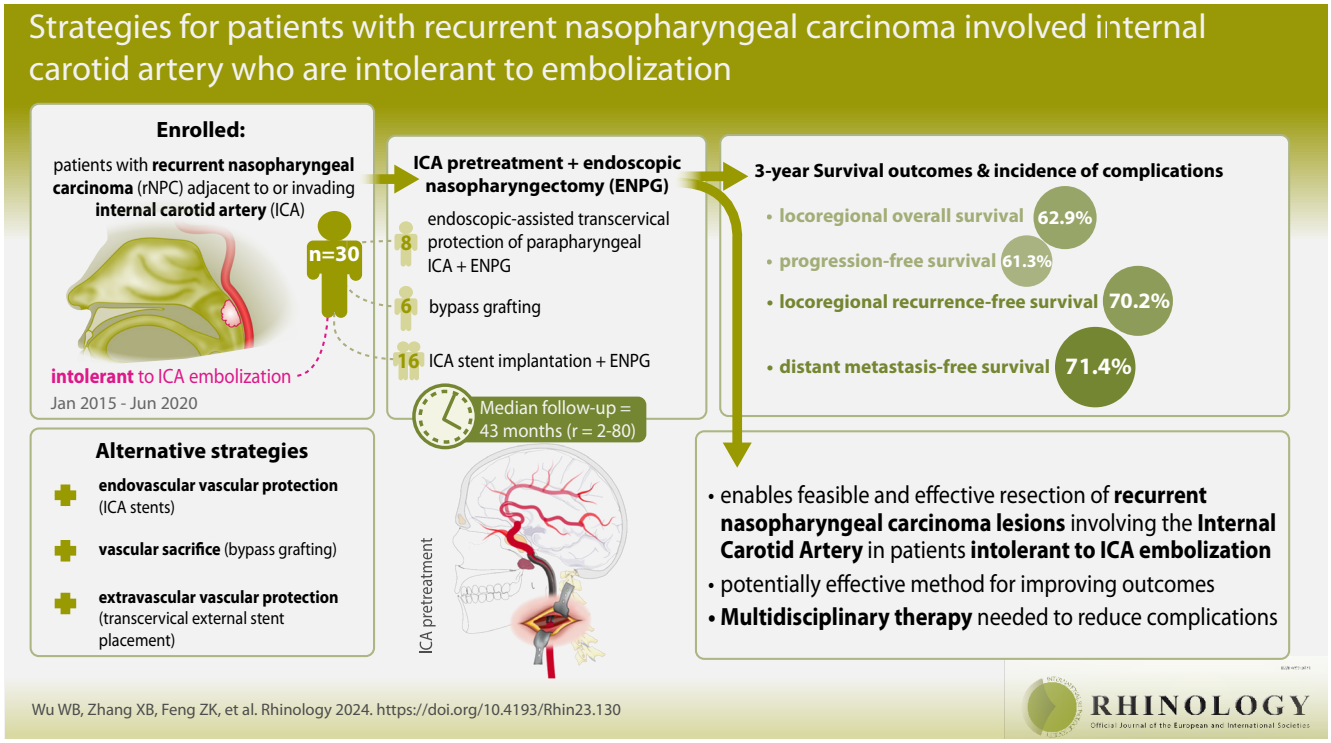
Rhinology 62: 3, 342 - 352, 2024
https://doi.org/10.4193/Rhin23.130

Abstract

Background: The surgical treatment of recurrent nasopharyngeal carcinoma (rNPC) involving the internal carotid artery (ICA) is challenging, as the massive bleeding caused by intraoperative rupture of the ICA is life-threatening. We reported that ICA embolization is an effective pretreatment to avoid fatal bleeding, but some patients cannot tolerate the procedure. We used endovascular vascular protection (ICA stents), vascular sacrifice (bypass grafting) and extravascular vascular protection (transcervical external stent placement) of the ICA to provide alternative options for these patients. **Methodology:** This study enrolled patients with rNPC adjacent to or invading the ICA who were unsuitable for ICA embolization from January 2015 to June 2020. ICA pretreatment combined with endoscopic nasopharyngectomy (ENPG) was performed for the 30 patients. We report the survival outcome and incidence of complications after ICA pretreatment. **Results:** ICA pretreatment was performed for the 30 enrolled patients, among whom 8 underwent endoscopic-assisted transcervical protection of the parapharyngeal ICA combined with ENPG, 6 underwent bypass grafting, and 16 underwent ICA stent implantation followed by ENPG. After pretreatment, at a median follow-up of 43 months (range, 2-80 months), the 3-year locoregional overall survival (OS), progression-free survival (PFS), locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS) were 62.9%, 61.3%, 70.2%, and 71.4%, respectively. **Conclusions:** ICA pretreatment combined with salvage ENPG enables the feasible and effective resection of rNPC lesions involving the ICA in patients who cannot tolerate ICA embolization. Therefore, this treatment may be an effective method for improving outcomes. Multidisciplinary therapy is needed to reduce operation-related complications.

Key words: recurrent nasopharyngeal carcinoma, internal carotid artery, stents, bypass graft, endoscopic nasopharyngectomy

Graphical abstract



Introduction

Nasopharyngeal carcinoma (NPC) is a type of head and neck cancer characterized by a distinct geographical distribution, aetiology, and biology (1). As a consequence of the excellent loco-regional control rates attained using the generally accepted treatment paradigms involving sequential chemoradiotherapy for NPC, only 5-10% of patients will suffer from recurrent nasopharyngeal carcinoma (rNPC) after primary treatment (2-5). According to the National Comprehensive Cancer Network guidelines for the management of head and neck cancer with resectable locoregional recurrence that has been previously treated with radiotherapy, surgery or reirradiation is recommended as a treatment option for rNPC. However, the occurrence of severe late toxicities (grade 3-5) following reirradiation is alarmingly high, reaching a rate up to 70.3% (6-9). These adverse events have a profound impact on patients' survival outcomes and quality of life. Thus, salvage nasopharyngectomy may be considered the preferred treatment option for resectable rNPC (2,10). We first introduced the concept of a "resectable region", defined as the area including the nasopharyngeal cavity (rT1), the posterior naris, nasal septum, or superficial parapharyngeal space (rT2), the base wall of the sphenoid sinus (rT3), and lesions located more than 5 mm away from the ICA (11). However, a substantial proportion of lesions remain unresectable due to their proximity or invasion of the ICA (12), especially for recurrent retropharyngeal lymph nodes (RPLNs) located in the parapharyngeal space near the ICA, and the posterior cranial nerves pose a significant challenge in terms of surgical intervention. This is due to the deep location of the lesions and the need to locate or protect the ICA during or prior to surgery to prevent potential ICA rupture, as extensive resection may result in life-threatening bleeding (13).

Pretreatment of the ICA is necessary to mitigate this risk of massive bleeding and make the surgery more feasible for a larger number of patients with rNPC. ICA embolization has proven to be an effective solution to concerns regarding ICA rupture. In 2021, we conducted a retrospective study in which ICA embolization was applied prior to salvage nasopharyngectomy to treat rNPCs near the ICA. The procedure allowed for complete resection of the lesions invading the ICA without significant ICA bleeding (14). However, certain patient populations, such as those with positive balloon occlusion test (BOT) results, lesions involving both ICAs, or negative BOT results and prior unilateral ICA embolization, are not eligible for ICA embolization (15). This highlights the need for alternative techniques to address this issue.

Over time, our team has collaborated with interventional surgeons to offer surgical treatments for patients with rNPC near the ICA. In this retrospective study, we present 3 innovative strategies aimed at facilitating rNPC removal while preserving blood flow to the brain, including 1) endovascular vascular protection (ICA stenting), 2) vascular sacrifice (bypass grafting) and 3) extravascular vascular protection (transcervical external stent placement). The objective of the study was to analyse the clinical characteristics and evaluate the management techniques and prognostic factors for patients with rNPC involving the ICA who are not eligible for ICA embolization.

Methods

A retrospective review of patients diagnosed with rNPC presenting with tumour lesions involving the ICA with a maximum diameter of less than 5 mm who underwent salvage nasopharyngectomy at the Sun Yat-sen University Cancer Center (SYSUCC) between January 2015 and June 2020 was performed. The inclusion criteria for this study were as follows: 1) a prior history of definitive radiotherapy, 2) classification as rT2-3 according to the seventh edition of the Union for International Cancer Control/American Joint Committee on Cancer clinical staging system prior to surgery, 3) unsuitability for ICA embolization, 4) a confirmed pathological diagnosis of rNPC and (5) lesions located less than 5 mm away from the ICA. The exclusion criteria were as follows: 1) the presence of recurrent local lesions or regional lymphatic nodes that cannot be radically removed, 2) pathologically confirmed or radiographically suspected presence of distant metastases and 3) physical conditions affecting suitability for surgery.

The Clinical Research Ethics Committee of the SYSUCC approved this study and waived the need for written informed consent.

Preoperative examinations

The BOT was routinely conducted before the surgery to determine if the ICA could be safely occluded without causing cerebral ischaemia (15,16). ICA embolization is the preferred type of pretreatment for rNPCs adjacent to or invading the ICA if the BOT results are negative. MRI of the head and neck, nasopharyngoscopy, and plasma Epstein–Barr virus (EBV) DNA within 1 month before surgery were assessed and designated the baseline data. Positron emission tomography/computed tomography (PET-CT) was required to exclude patients with distant metastases.

Surgical procedures

Pretreatment

We proposed 3 ICA pretreatment options for this group of patients: 1) ICA stenting; 2) endoscopic-assisted transcervical protection of the parapharyngeal ICA; and 3) bypass grafting followed by ENPG.

Stent pretreatment

An 8-French guiding catheter (90 cm, produced by Cordis, USA) was successfully positioned in the targeted ICA via a right femoral approach. Control angiograms were then obtained to assess changes in the artery and aid in the selection of an appropriate

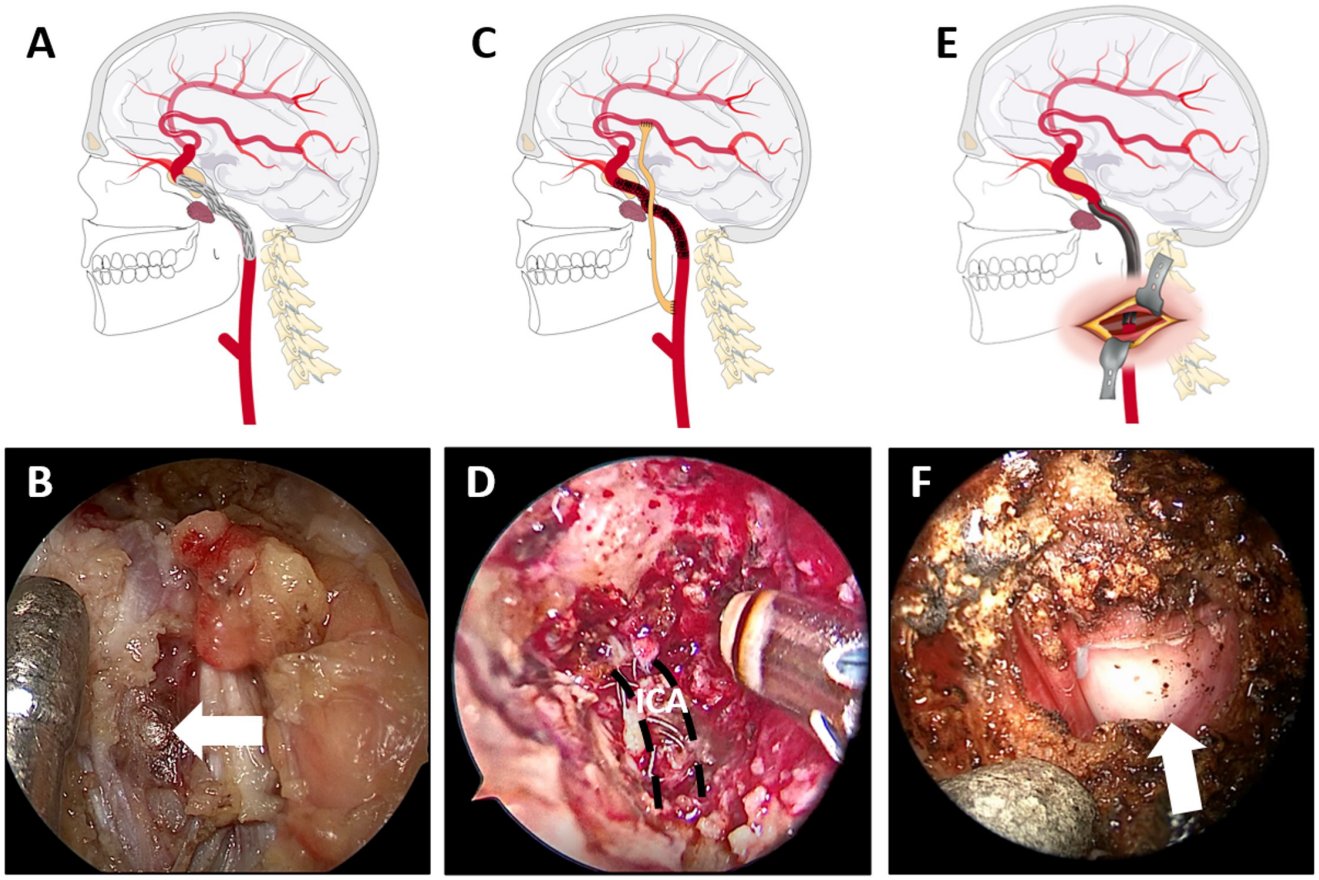


Figure 1. Application of ICA pretreatment in patients with rNPC invading the ICA. (A) Application of ICA stents in patients with rNPCs adjacent to the ICA. (B) No intraoperative bleeding is seen after rupture of the carotid wall (white arrow) pretreated with a stent. (C) Application of vascular bypass in patients with rNPC invading the ICA. (D) After resection of the ICA, the matrix coils (white arrow) were exposed, and no intraoperative bleeding is observed. (E) The neighbouring ICA is protected by placing an external artery stent through a cervical incision. (F) After tumour resection, the ICA at the base is covered by an extravascular stent (white arrow), and no major intraoperative bleeding is observed.

stent type. VIABAHN stents (manufacturer: Gore & Associates; headquarters: Newark, DE, USA) were deemed suitable for the C1-2 segment of the ICA, while WILLIS stents (manufacturer: MicroPort Medical Company; headquarters: Shanghai, China) were primarily utilized for the C2-4 segments. The placement, length, and size of the stents were determined based on radiographic results in consultation with specialists in nasopharyngeal cancer and neurosurgeons. A V-18 microwire (200 cm, produced by Boston Scientific, USA) was navigated to the cavernous sinus segment of the ICA using a VIABAHN stent, and a confirmatory angiogram was performed to verify proper stent positioning. An angiogram was then performed to confirm the position of the self-expanding stent. Subsequently, a 0.014-inch Transend microwire (200 cm, produced by Boston Scientific, USA) was navigated to the cavernous sinus segment utilizing a WILLIS stent based on the roadmap. An angiogram was then performed to verify proper stent placement. The balloon was inflated to deploy the stent, and an immediate angiogram was conducted to assess the imaging results (Figures 1 and 2). If an endoleak was detected, the balloon was inflated a second time. If the endoleak either disappeared or was reduced to a minimal flow volume, the procedure was ceased. In the event that these conditions were not met, another stent was considered.

Two seasoned neurosurgeons performed all the procedures described in this study. Upon discharge, the patients were placed on a 3-month course of dual antiplatelet agents, followed by aspirin therapy for at least 9 months.

Transcervical protection

For endoscopic-assisted transcervical protection of the parapharyngeal ICA (Figures 1, 2, and 3), a horizontal incision in the upper neck was typically made to create an artificial passage to the nasopharyngeal fat gap, we typically performed a horizontal neck incision approximately 2 cm from the lower edge of the mandible. Following neck dissection, we exposed the ICA, vagus nerve, accessory nerve, hypoglossal nerve, and carotid sinus. To obtain a relatively adequate space, a retractor was used to draw the mandibular angle [13]. During the procedure, the extravas-

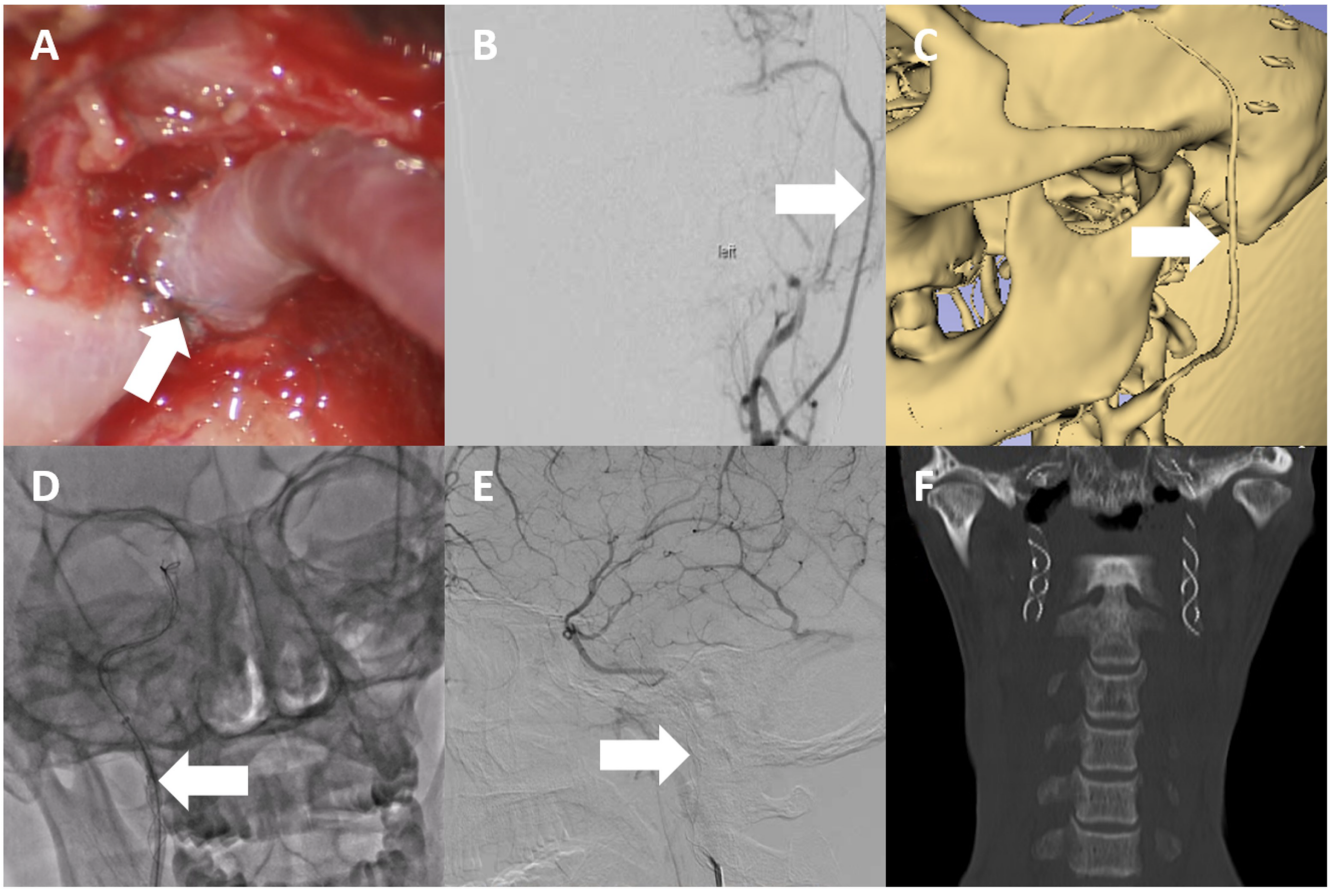


Figure 2. Imaging findings following intravascular ICA pretreatment. A-C Vascular bypass. D-F ICA stents. (A) End-to-side anastomosis (white arrow) was performed between the graft and the ICA or common carotid artery (CCA) of the neck. (B) Left ICA angiography and (C) three-dimensionally reconstructed images from spiral CT after vascular bypass (white arrow) and ICA embolization show that the proximal anastomosis of the bypass graft is at the ICA, passing through the preauricular subcutaneous region, and terminating at the M2 branch of the MCA. (D) Right ICA angiography shows that the stent (white arrow) was positioned to cover the petrous and cervical segments of the ICA. (E) Right ICA angiography after stenting and (F) CT image after stent implantation show that the stent is covering both sides of the petrous and cervical segments of the ICA.

cular stent was advanced along the internal carotid artery (ICA) in an upward direction. It was pushed until reaching the bony landmark known as the external opening of carotid canal. After the ICA was separated and protected, the patient was placed in a supine position, and a sterile environment was maintained for the neck wound following endoscopic nasopharyngectomy (ENPG). For rNPC patients with ipsilateral retropharyngeal lymph node involvement, the ipsilateral level I and level II lymph nodes and the retropharyngeal lymph nodes were also resected [14].

Vascular bypass grafting

The radial artery was utilized as a bypass graft in this procedure. A subcutaneous tunnel was established at the preauricular region linking the neck wound and craniotomy site. Microvascular anastomosis was performed under microscopic visualization in an end-to-side configuration between the graft and the M2 branch of the middle cerebral artery (MCA) and between the graft and either ICA in the neck. For patients receiving low-flow bypass surgery, microvascular anastomosis was performed between the graft and the M2 branch of the MCA and between the graft and the superficial temporal artery (STA) (Figures 2 and 4). Subsequently, an angiogram was performed to evaluate the embolization of the ICA and determine if the external carotid artery demonstrated intracranial compensation. After the surgical procedure, patients were transferred to the intensive care unit (ICU) for postoperative monitoring.

ENPG

The details of ENPG are presented in the Supplementary Materials [11].

Follow-up

All patients underwent regular endoscopic evaluations to remove any accumulated nasal secretions and assess wound reconstruction progress. The evaluations were conducted every 2 weeks until the wound was fully re-epithelialized following

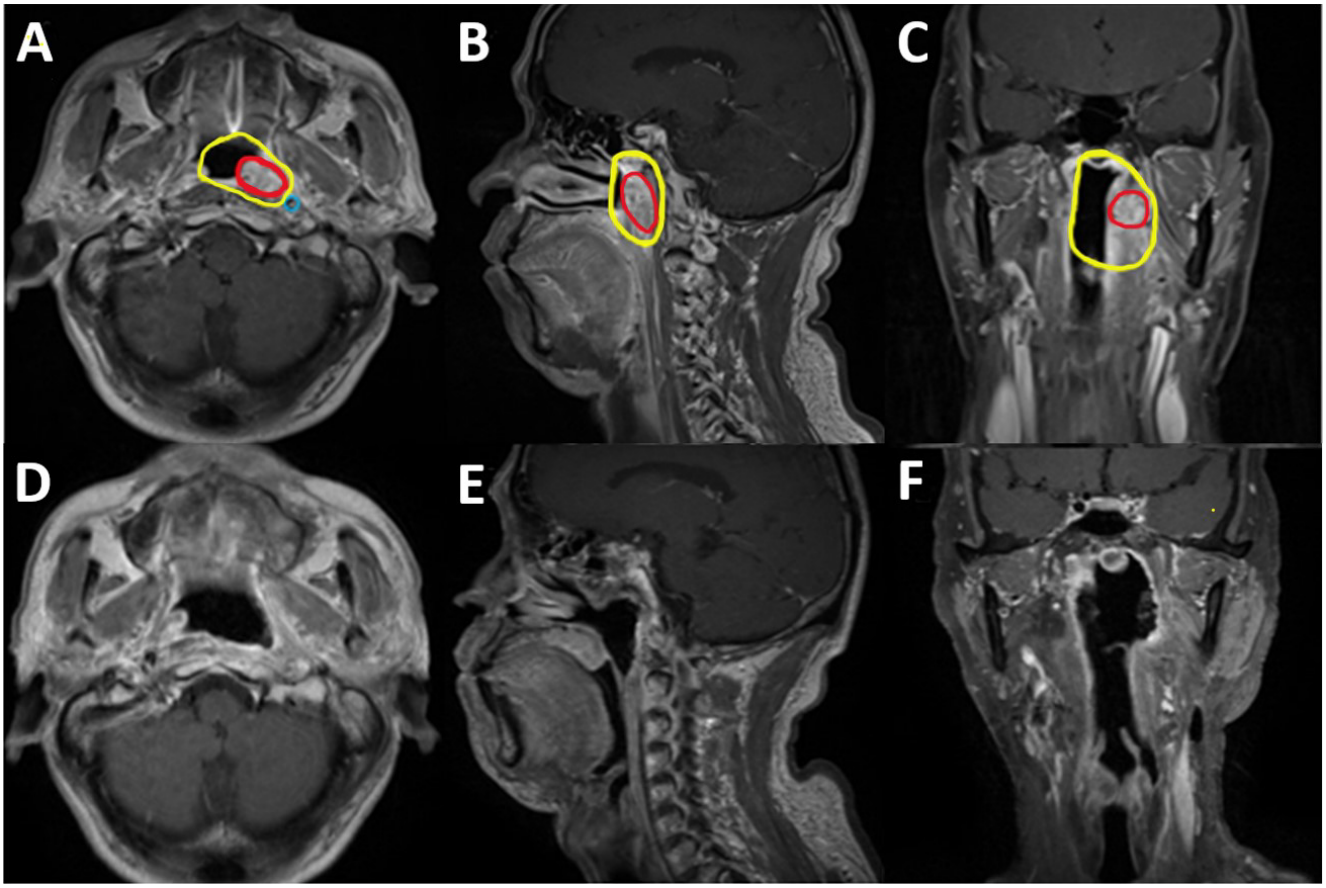


Figure 3. The patient underwent endoscopic-assisted transcervical protection combined with endoscopic nasopharyngectomy. There is a clear normal interstitial space between the lesion and internal carotid artery. Red circle: tumour lesion. Yellow circle: theoretical resection range. Blue circle: internal carotid artery. A-C Gross tumour volume on preoperative T1-weighted MR images in horizontal, coronal, and sagittal views, respectively. D-F show the corresponding postoperative images 3 months after surgery.

surgery. Long-term operation-related morbidities were defined according to the Common Terminology Criteria for Adverse Events 4.0 as those that persisted for more than three months following surgery and were assessed through physical examination and symptom evaluations during the postoperative and follow-up periods.

Statistical methods

Categorical variables were compared by the chi-square test or Fisher's exact test. The time period between the start of treatment and death was used to calculate the OS. The Kaplan-Meier method and the log-rank test were used to test for differences in the survival functions between strategies, as defined by clinical variables. To identify predictors of outcome, we applied a multistep process to perform a univariable analysis. The first step was to study the correlation between OS and each covariate via a univariable analysis; then, those covariates with a univariable $P < 0.1$ were included in a preliminary multivariable Cox proportional hazards regression model to allow for a comprehensive evaluation of potential predictors. Variables that remained statistically significant ($P < 0.05$) were included in the final multivariable model [17,18].

All statistical testing was two tailed. The significance level was set to an alpha of 0.05. All statistical testing was completed using SPSS software (Statistical Package for the Social Sciences version 25.0; Chicago, IL, USA) and the R language environment for statistical computing version 3.1.3 (open source).

Results

Patients

Thirty patients were selected for this study. Table 1 presents the patients' clinical characteristics. Among the enrolled patients, 28 had positive BOT results, while 2 had negative results. Among these 2 patients, in one case, the recurrent rNPC was located near both ICAs, leading to the performance of ICA embolization on one side and stent placement in the contralateral ICA. In another case, the patient had a history of previous ICA embolization due to hemorrhage, and therefore underwent contralateral vascular bypass grafting. All 30 enrolled patients experienced rNPC in the nasopharyngeal region, with 20 patients exhibiting

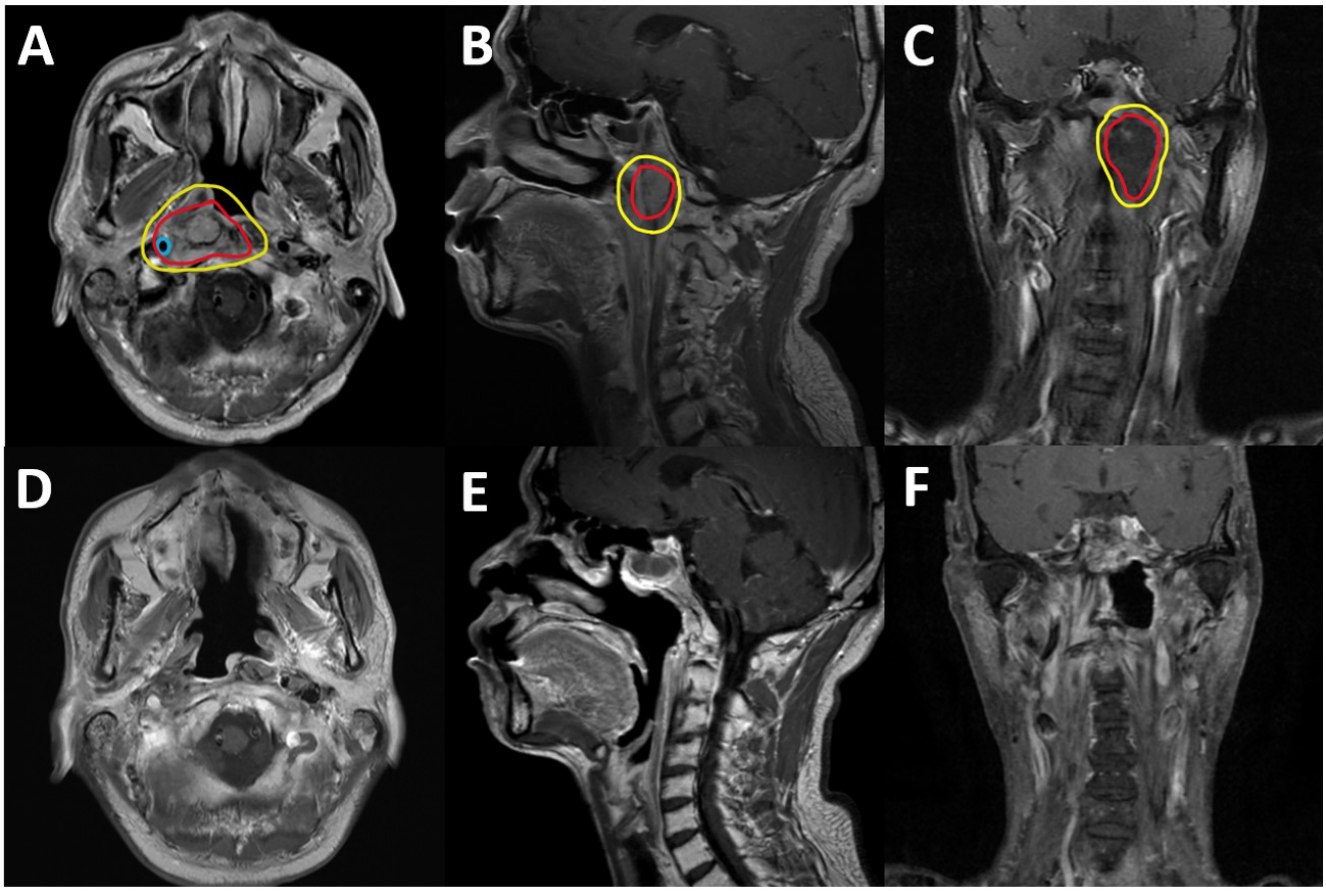


Figure 4. The patient underwent vascular bypass followed by endoscopic nasopharyngectomy. There is no distinct normal interstitial space between the lesion and internal carotid artery. A-C Gross tumour volume on preoperative T1-weighted MR images in horizontal, coronal, and sagittal views, respectively. D-F show the corresponding postoperative images 3 months after surgery.

concurrent cervical lymph node recurrence, including 9 who exhibited ipsilateral retropharyngeal lymph node recurrence and 12 who exhibited level II lymph node recurrence. Eight patients underwent endoscopic-assisted transcervical protection of the parapharyngeal ICA combined with ENPG, 16 patients underwent ICA stent implantation followed by ENPG, and 6 patients underwent vascular bypass grafting followed by ENPG, including 2 patients with rNPC accompanied by nasopharyngeal necrosis invading the ICA.

Patient survival outcomes

The last follow-up date was December 30, 2022. The postoperative follow-up time ranged from 2 to 80 months (median, 43 months). Two of the 30 patients had a positive margin and underwent salvage radiotherapy after the surgery. Seven of the 30 patients developed locoregional recurrence or distant metastasis. Of the 8 patients who underwent endoscopic-assisted transcervical protection of the parapharyngeal ICA combined with ENPG, 2 developed distant metastasis, and 2 developed locoregional recurrence, both within the surgical field. Three patients from this group died during the median follow-up of 56 months (range, 12-80 months). Of the 16 patients who underwent ICA stenting followed by ENPG, 3 were noted to have locoregional recurrence, including 2 with recurrence within the nasopharynx surgical field and 1 with recurrence outside the surgical field but still within the nasopharynx. One of these patients died. The median follow-up of this group was 11.5 months (range, 4-23 months). Of the 6 patients who underwent vascular bypass followed by ENPG (Figure 6), 2 patients died of aspiration pneumonia, and no patient developed locoregional recurrence or distant metastasis. The median follow-up of this group was 41 months (range, 2-43 months). Overall, the 3-year estimated OS, PFS, LRRFS, and DMFS rates of salvage ENPG for rNPC involving the ICA were 62.9%, 61.3%, 70.2%, and 71.4%, respectively. The univariate analysis revealed that a positive margin (HR 6.61, 95% CI [1.21-36.26], P = 0.030) was adverse factor for OS, while sex, age, rT classification, rN classification, reirradiation, preoperative EBV DNA copies and pretreatment methods had no significant effect on survival (Table 2). Multivariate Cox regression analysis revealed that a positive margin (HR 9.32, 95% CI [1.26-68.87], P = 0.029) and reirradiation (HR 13.59, 95% CI [1.26-146.93], P = 0.032) were independent adverse factors for

Table 1. Characteristics and clinical data of the patients.

Patient characteristics	Patients (%)
Patients	30
Demographics	
Gender (%male)	20(66.7%)
Smoking	7(23.3%)
Age (y, Mean ± SD)	48.0±9.1
Initial T classification	
T2	5(16.7%)
T3	19(63.3%)
T4	6(20%)
Initial N classification	
N0	2
N1	11(20.4%)
N2	16(53.3%)
N3	1(3.3%)
Initial M classification	
M0	30(100.0%)
Radiotherapy Course	
1st Course	25(83.3%)
2nd Course	5(16.7%)
rT classification	
rT2	19(63.3%)
rT3	11(36.7%)
rN classification	
rN0	10(33.3%)
rN1	20(66.7%)
Preoperative EBV DNA copies	
>0	22(73.3%)
0	8(26.7%)
Previous internal carotid artery hemorrhage	3(10%)
BOT results	
Positive	28 (93.3%)
Negative	2 (6.7%)
Pretreatment	
Stent Implantation	16 (53.3%)
Transcervical protection	8(26.7%)
vascular bypass	6(20.0%)

OS (Table 2).

Surgery-related complications

At the time of the last follow-up, 14 patients had surgery-related complications, and the incidences of grade 1-2 and grade 3-5 postoperative complications were 30% and 16.7%, respectively. The complication with the highest incidence was swallowing problems (23.3%). During the follow-up period, three patients experienced massive nasopharyngeal bleeding. One case occurred in the endoscopic-assisted transcervical protection group 12 months after surgery and resulted in fatality due to massive nasopharyngeal bleeding outside the hospital. The other two cases transpired at 4 and 18 months post-surgery, respectively, in the ICA stent implantation group. One patient experienced a massive bleeding at home and died, while the other sought emergency medical care for diagnosed extracranial carotid artery branch bleeding. After successful embolization treatment, the latter patient achieved hemostasis and survival.

Among the patients who underwent endoscopic-assisted transcervical protection of the parapharyngeal ICA combined with ENPG, the incidence of grade 3-5 complications, including pharyngeal fistula, swallowing problems, postoperative haemorrhage, limited shoulder range of motion, tongue atrophy, and headache, was 25%. Tongue atrophy (5 patients (62.5%)) was the most common complication. Among these patients, 1 (12.5%) required a permanent nutrient tube for nutrition supply. Among the 16 patients who underwent ICA stent implantation followed by ENPG, three (18.8%) developed ischaemic stroke postoperatively. After interventional thrombectomy and symptomatic treatment, one patient died of pulmonary infection. Among the 6 patients who underwent vascular bypass, 2 developed ischaemic stroke, and the patient's condition improved after conservative treatment. Two patients with rNPC accompanied by nasopharyngeal necrosis had persistent headache after surgery (Figure 5).

Discussion

Our study presents the application of ICA pretreatment followed by ENPG in patients with rNPC adjacent to or invading the ICA who are not suitable for ICA embolization. We report satisfactory survival outcomes with 3-year OS, PFS, LRRFS, and DMFS values of 62.9%, 61.3%, 70.2%, and 71.4%, respectively. Our findings suggest that reirradiation and positive margins are independent adverse prognostic factors for rNPC. Nevertheless, it is crucial to take note of potential severe complications, such as postoperative haemorrhage and ischaemic stroke.

For patients with rNPC adjacent to the ICA, complete removal of the tumour without inducing ICA rupture is crucial for a successful ENPG outcome. In 2020, we proposed ICA embolization as a means of expanding the extent of surgical resection and enabling complete removal of the tumour, thereby ensuring negative margins and reducing the likelihood of residual disease and recurrence (14). A matched pair study by Li et al. showed that ICA embolization during endoscopic surgery for patients with rNPCs invading the ICA significantly improved the survival rate (19). However, patients with lesions involving the bilateral ICAs, and patients with negative BOT results who have undergone unilateral ICA embolization are not suitable for ICA embolization. In 2015, Wei reported on the use of staged vascular bypass and a combined craniofacial approach for the treatment of rT3 to rT4 NPC lesions. Thirteen patients (46.4%) achieved clear resection margins, with a 5-year OS rate of 52%. Despite the promising outcomes, this approach can only be performed in a limited number of cancer centres. Additionally, this approach also leads to facial scarring, which impairs facial aesthetics and causes severe trauma and numerous complications, significantly impacting the postoperative quality of life of the patients. In our

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

Patient characteristics	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	P value	Unadjusted HR (95% CI)	P value
Gender		0.740		
Male	Reference			
Female	0.78 (0.22-2.76)			
Age		0.700		
<48 years	Reference			
≥48 years	0.79 (0.20-3.09)			
rT classification		0.438		
T1-T2	Reference			
T3-T4	1.66(0.46-5.95)			
rN		0.370		
N0	Reference			
N1	1.80(0.50-6.49)			
Pretreatment		0.467		
Transcervical protection	Reference			
Stent Implantation	2.23(0.40-12.43)			
Vascular bypass	0.64(0.12-3.52)			
Positive margin		0.030		0.029
No	Reference		Reference	
Yes	6.61(1.21-36.26)		9.32(1.26-68.87)	
Preoperative EBV DNA copies		0.165		0.268
0	Reference		Reference	
>0	3.50(0.63-14.71)		2.52(0.49-12.97)	
Reirradiation		0.067		0.032
No	Reference		Reference	
Yes	6.78(0.88-52.41)		13.59(1.26-146.93)	

Table 3. Complications and long-term morbidities of patients after ICA pretreatment followed by ENPG.

Parameter	No. of patients (%)
Transcervical protection of the ICA	
Pharyngeal fistula	1(12.5%)
Swallowing problems	3(37.5%)
Postoperative hemorrhage	1(12.5%)
Limited shoulder range of motion	4(50%)
Tongue atrophy	5(62.5%)
Headache	2(25%)
ICA stents	
Ischemic stroke	3(18.8%)
Stroke caused deaths	1(6.3%)
Postoperative hemorrhage	2(12.5%)
Swallowing problems	2(12.5%)
Vascular bypass grafting	
Ischemic stroke	2(33.3%)
Stroke caused deaths	0
Headache	2(33.3%)
Swallowing problems	2(33.3%)

study, we present 3 distinct techniques for pretreating the ICA prior to performing ENPG without interrupting blood flow. Our methods resulted in successful and complete removal of the tumour lesion.

We stratified rNPCs into two groups based on the distance of the tumour from the ICA. For lesions adjacent to the ICA, we attempted to preserve the integrity of the artery during complete tumour resection through two approaches. The first method is extravascular protection, which involves the use of endoscopic-assisted transcervical protection of the parapharyngeal ICA combined with ENPG technology. This approach effectively addressed the issue of the close proximity of rNPC lesions to the ICA by implanting an extravascular stent to shield the ICA. However, due to the establishment of an artificial passage to the nasopharyngeal fat gap, this combined surgery resulted in a relatively high degree of surgical trauma, including complications such as nasal regurgitation, dysphagia, headache and limited shoulder range of motion. More recently, we have been favouring the use of intravascular protection to address this issue. Second, we performed ICA stent implantation followed by ENPG to treat rNPCs, which for all patients was performed safely without ICA bleeding. Although this method achieved a high therapeutic effect, the risk of stent thrombosis persists after surgery. It is noteworthy that all three patients with stent thrombosis also presented with postradiation nasopharyngeal necrosis (PRNN). This may be related to the inflammation around the ICA and the poor nutritional status of the patients. Hemorrhage associated with post-radiation nasopharyngeal necrosis (PRNN), particularly when it invades the ICA, often proves fatal. However, there is a relative scarcity of research focusing on nasopharyngeal

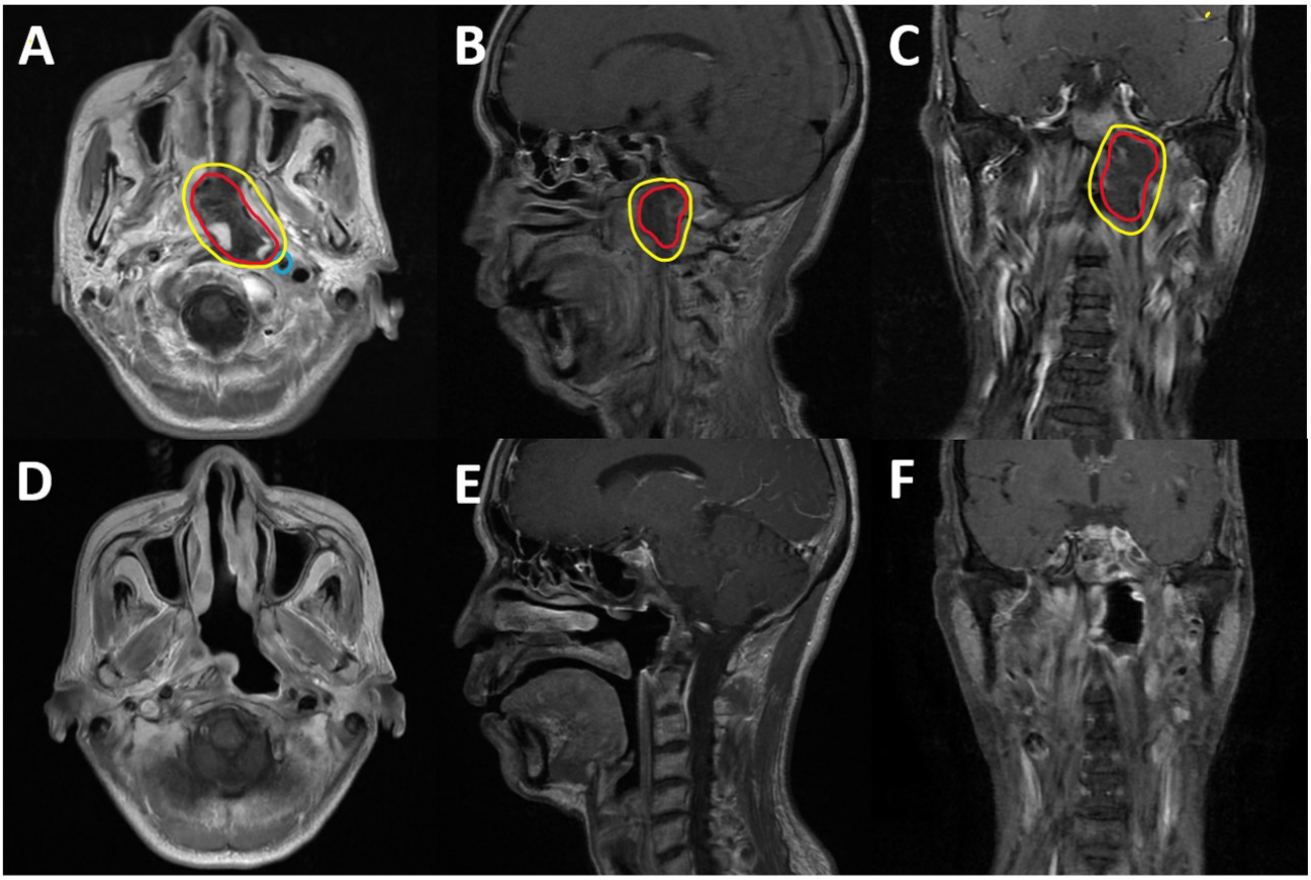


Figure 5. Nasopharyngeal MRI before and after ENPG of an rNPC with necrosis invading the ICA. The patient underwent vascular bypass followed by endoscopic nasopharyngectomy. A-C Gross tumour volume on preoperative T1-weighted MR images in horizontal, coronal, and sagittal views, respectively. D-F show the corresponding postoperative images 3 months after surgery.

radiation necrosis and the utilization of innovative management techniques. This gap in research provides a promising direction for future investigations. Moreover, although protected by stents, the ICA is still at risk of rupture during the surgery, which increases the concern of surgeons when removing the rNPC. Among the patients who underwent stent implantation followed by ENPG, 2 developed locoregional recurrence within the surgical field. This indicates the importance of accurately determining the proximity of the tumour lesion to the ICA during preoperative evaluation. In cases where preservation of the ICA may pose a challenge to the surgeon, consideration should be given to alternative methods that may involve sacrificing the ICA, such as vascular bypass.

In cases where the rNPC invaded or encased the ICA, we performed bypass grafting and ICA occlusion followed by ENPG to safely sacrifice the ICA. Previously, tumour invasion or encasement of the ICA was considered an absolute contraindication for surgery when the artery could not be safely embolized. However, in our study, we were able to achieve clear margins by resecting the tumours en bloc with the ICA. Among the 6 patients who underwent bypass grafting followed by ENPG, none suffered from massive bleeding after the operation, while 2 developed stroke, but the symptoms were mild and improved after conservative treatment. This indicated the effectiveness of vascular bypass grafts in the prevention of ICA bleeding in the present study. In the past, ICA embolization was heavily relied upon to prevent massive bleeding in cases where the lesions had invaded or encased the ICA. However, a report by Chan et al. documented a case in which a patient with a normal BOT result experienced a major neurovascular event intraoperatively after undergoing ICA embolization. The authors postulated that blood flow across the Circle of Willis could become unpredictable following prolonged hypotension during surgery despite a normal preoperative BOT result (20). Furthermore, in patients who have previously undergone unilateral ICA embolization or who have positive BOT results, ICA embolization may result in fatal extensive cerebral infarction. As such, bypass grafting followed by ENPG may represent the sole viable option for these patients. For patients with American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) grade 0–1, we grafted the ICA to the MCA (high-flow bypass graft) for revascularization, while STA to

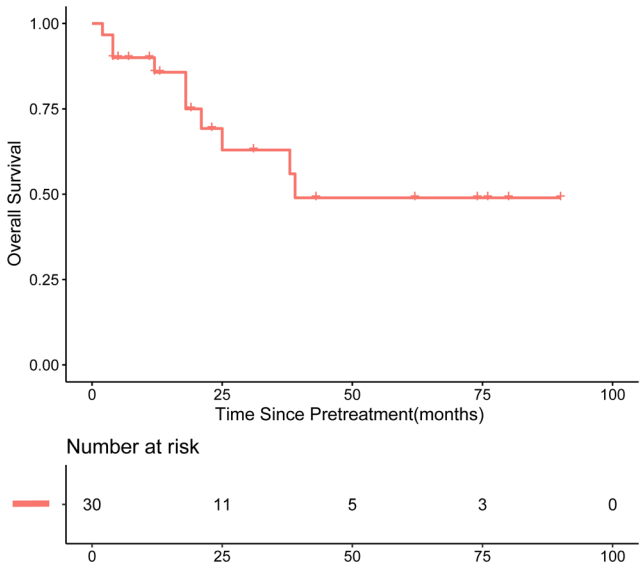


Figure 6. Kaplan-Meier plot showing overall survival (OS) curves for rNPCs involving the ICA.

MCA anastomosis (low flow bypass grafting) was performed in patients with ASITN/SIR grade 2–3.

The limitations and challenges associated with ICA pretreatment combined with ENPG should not be overlooked. Our retrospective study has inherent limitations. Although ICA pretreatment can effectively prevent intraoperative bleeding, it may cause nerve injury-related complications, such as nerve traction, excessive nerve dissection, and excessive muscle detachment, which can lead to long-term morbidity. Additionally, a considerable proportion of patients in our study developed cerebral ischaemia following pretreatment, and some patients died due to pulmonary infection and stroke, highlighting the need for multidisciplinary treatment after surgery. Therefore, more prospective studies are required to optimize the treatment regimens and minimize the risks of surgery-related complications.

Conclusion

ICA pretreatment combined with salvage ENPG enables the feasible, effective and safe resection of rNPC lesions invading or adjacent to the ICA. Positive surgical margins and previous ICA bleeding might be factors affecting the prognosis. Multidisciplinary therapy is needed to reduce operation-related complications.

Authorship contribution

Study concepts: MYC, JHC and SLW; Study design: MYC, JHC, and WBW; Data acquisition: WBW, XBZ, ZKF and HFL; Quality control of data and algorithms: WBW and ZKF; Data analysis and interpretation: WBW, XBZ and MYC; Statistical analysis: WBW, YPL and MYC; Manuscript preparation: WBW, XBZ, ZKF and MYC; Manuscript editing: WBW and MYC; Manuscript review: all the authors.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

Funding was provided by the Program of Sun Yat-Sen University for Clinical Research 5010 Program (No.201310, 2018015, 2018029), the National Natural Science Foundation of China (No. 81772895, 81874134, 82071024), the National Postdoctoral Program for Innovative Talents (BX2021387), Guangdong Province Science and Technology Development Special Funds (Frontier and Key Technology Innovation Direction – Major Science and Technology Project) (No. 2017B020226004), The Key-Area Research and Development of Guangdong Province (2020B1111190001), CSCO-JunShi Cancer Immunotherapy Clinical Research Fund (No. Y-JS2019-002), Jiangxi Provincial Technical Innovation Guidance Program (20212BDH80023), Central Guiding Local Science and Technology Development Fund Project (20231ZDE04024).

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Prof. Ming-Yuan Chen
Department of Nasopharyngeal Carcinoma
Sun Yat-sen University Cancer Center
651 Dongfeng East Road
Guangzhou
Guangdong 510060
P. R. China

Tel: +86-20-8734-3361
Fax: +86-20-87343624
E-mail: chmingy@mail.sysu.edu.cn

Prof. Jin-Hua Chen
Department of Neurosurgery
The third affiliated hospital of Southern Medical University
183 Zhongshan West Road
Guangzhou 510060
P. R. China

Tel: +86-13-92885 1974
E-mail: onyxchen@gmail.com

Prof. Shun-Lan Wang
The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine Department of Otolaryngology
16 Jichang Road
Guangzhou 510060
P. R. China

Tel: +86-18-66601 2286
E-mail: wangsl0718@163.com

Wen-Bin Wu[1,2], Xiao-Bin Zhang[3], Zheng-Kai Feng[1,2,#], Hui-Feng Li[1,2,#], You-Ping Liu[1,2], Jiong-Lin Liang[1,2], Yu-Long Xie[1,2], Yi-Jun Hua[1,2], Rui Sun[1,2], Shun-Lan Wang[4], Jin-Hua Chen[3], Ming-Yuan Chen[1,2]

[1] Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China
[2] Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine; Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China
[3] Department of Neurosurgery, The Third Affiliated Hospital of Southern Medical University, Guangzhou, China
[4] The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Department of Otolaryngology, Guangzhou, China

Rhinology 62: 3, 342 - 352, 2024
https://doi.org/10.4193/Rhin23.130

Received for publication:
April 17, 2023
Accepted: November 12, 2023

Assocociate Editor: Sietze Reitsma

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Methods

ENPG

Our approach entails discontinuing administration of antiplatelet and anticoagulant medications 72 hours prior to the ENPG and resuming them 48 hours post-surgery when confirming that there is no active bleeding. ENPG can be performed 2 weeks after vascular bypass grafting or stent pretreatment, taking into consideration the clinical requirements of individual patients. All surgical procedures were performed under general anaesthesia and orotracheal intubation. ENPG and elective neck dissection (END) were performed approximately 2 weeks after the pretreatment1. The XPS 3000 powered ENT system (Medtronic, Minneapolis, MN, USA) was utilized to resect the rNPC until the underlying normal tissue was visualized. Electrocoagulation using a long head electrotome (Covidien, Saint Louis, MO, USA) was performed to remove connective tissue surrounding the resected tissue. In cases involving the skull base bone, it was removed utilizing a high-speed electric microdrill (Stryker, Kalamazoo, MI, USA). Surgical specimens from the lateral and basal surgical margins and any tissue suspected of malignancy were subjected to pathological examination. After the removal of the rNPC, the nasopharyngeal defect was covered with posterior pedicle nasal septum and floor mucoperiosteum flap based on the posterior nasal septal artery. If the flap from one side was insufficient to cover the defect, a flap from the opposite side of the nasal septum was simultaneously harvested. In addition to ENPG for the primary lesions, we also conducted extensive salvage neck dissection for patients presenting with concurrent neck recurrence.

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