Stent pretreatment for internal carotid artery exposed to necrotic lesions in nasopharyngeal carcinoma*

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Abstract

Background: Post radiation nasopharyngeal necrosis (PRNN) invading the internal carotid artery (ICA) contributes to the death of 69.2–72.7% of PRNN patients. ICA occlusion is an effective treatment to avoid fatal bleeding, while some patients are intolerant. We present a novel method that allows for these patients without interrupting blood flow through the ICA.

Methodology: This study enrolled patients with PRNN-invaded ICA who were not suitable for ICA occlusion from April 2020 to November 2022. ICA stent pretreatment was performed in the 36 patients and followed the endoscopic nasopharyngectomy (ENPG) or conservative treatment for PRNN. We report the survival outcome and incidence of complications after stent implantation and compare the survival outcomes of ENPG and conservative treatment for PRNN followed by stent implantation.

Results: ICA stent pretreatment was performed in the 36 enrolled patients, among which 14 underwent ENPG, and 22 received conservative treatment. 27.8% patients died after a median follow-up of 15 months. The Kaplan-Meier estimates of overall survival were higher in the ENPG group than in the conservative treatment group. Karnofsky performance status (KPS) was significantly higher in the ENPG group than in the non-ENPG group.

Conclusions: The innovative application of ICA stents is a promising treatment to improve outcomes in patients with PRNN invading the ICA who are unsuitable for ICA embolization, especially when followed by endoscopic surgery. However, methods to avoid postoperative cerebral ischemia and nasopharyngeal hemorrhage still require further study.

Key words: nasopharyngeal carcinoma, necrosis, carotid artery, stents, endoscopy, stroke

Introduction

Nasopharyngeal carcinoma (NPC) is a head and neck cancer with unique geographical, etiological, and biological features. Sequential chemoradiotherapy is a fundamental treatment for NPC, resulting in an approximately 80% 5-year overall survival rate [(1)]. Radiotherapy may exert serious adverse effects on the normal tissues and bones surrounding the nasopharynx [(2-5)]. As the most severe adverse event in patients with NPC, post radiation nasopharyngeal necrosis (PRNN) is observed in some patients with NPC after high-dose irradiation or reirradiation. PRNN is commonly accompanied by a severe headache, foul odor, and epistaxis, which seriously affect the patients' quality of life. As reported by Chen et al., 41.8–42.9% of patients with PRNN die due to various complications, and the risk of death is increased by 69.2%–72.7% when PRNN invades the ICA due to massive nasopharyngeal bleeding [(6, 7)]. Endoscopic nasopharyngectomy (ENPG) is considered the standard treatment option for PRNN [(2, 8)]. However, we also found that a considerable proportion of lesions remain unresectable because they infringe on the ICA [(9)]. Performing endoscopic surgery is still a challenge in patients with lesions invading the ICA because the ICA must be located or protected during surgery, the tissue needs to be separated

carefully to prevent rupture of the ICA, and a large extent of resection may cause ICA injury, which could be life-threatening. Some novel techniques, such as pretreatment of the ICA, are needed to prevent massive nasopharyngeal bleeding or enable ENPG to be suitable for more patients with PRNN. ICA embolization successfully overcomes concerns about ICA rupture. In 2018, we reported the application of ICA embolization followed by radical endoscopic necrectomy to treat nasopharyngeal necrosis adjacent to or invading the ICA, wherein the lesions invading the ICA were completely excised to promote nasopharyngeal tissue healing and prolong the survival of the patients [8, 10]. However, patients with positive balloon occlusion test (BOT) results and patients with negative BOT results who have undergone unilateral ICA embolization are not suitable for ICA embolization. The application of endovascular stent grafting was considered an ideal technique to address the matter, and it had been successfully used for endovascular repair in patients with ICA aneurysm who could not undergo a radical operation. There are two case reports of neck malignancy invading the ICA treated with carotid stents before tumor resection without massive arterial bleeding observed during dissection [11, 12]. Theoretically, the endovascular stent should be effective at protecting the ICA from rupture in the invasion of necrosis or surgical resection.
In this study, we present a novel method that facilitates nasopharyngeal lesion removal without interrupting blood flow through the ICA. The purpose of this retrospective study was to summarize the clinical features and evaluate the management approaches and prognostic factors of patients with PRNN invading the ICA who were treated with ICA stents.

Materials and methods

Patients

From April 2020 to November 2022, 36 patients with NPC who had ICA stents placed as a pretreatment followed by radical endoscopic necrectomy or conservative treatment at the Sun Yat-sen University Cancer Center were selected for enrollment. This study was approved by the ethics committee of Sun Yat-sen University Cancer Center. Written informed consent was obtained from all patients.
The selection criteria were as follows: 1) a history of radiotherapy in the nasopharynx, 2) nasopharyngeal necrosis was proven clinically and pathologically, 3) PRNN lesions invaded the ICA, and 4) patients were not suitable for occlusion of the ICA, such as a positive BOT result, lesions invading both the left and right ICA, or patients who had undergone unilateral ICA embolization. The exclusion criteria for this study were as follows: 1) The patients whose MRI and CT results showed that broad necrosis invaded the cavernous segment of the ICA were excluded, 2) Physical conditions unsuitable for surgery, such as heart failure and cardiac function>grade 3 (New York Heart Association) were excluded.

BOT procedure and stent pretreatment

The balloon was maintained in place for 30 minutes, during which neurological symptoms were observed (Figure 2). ICA occlusion is the first choice for those patients with PRNN invading the ICA to avoid fatal bleeding but is not suitable when BOT is positive, the necrotic lesions invaded both the left and right ICA, or the patients had undergone unilateral ICA embolization. Then, stent pretreatment was performed as an alternative.
An 8-French guiding catheter (90 cm, Cordis, USA) was positioned in the targeted ICA through a right femoral approach. Control angiograms were performed to illustrate the changes in vessels and select the appropriate stent version. The C1-2 segment is suitable for VIABAHN stents, and WILLIS stents are mainly used for ICA segments C2-4. The position, length, and size of stents are determined based on radiography results by nasopharyngeal cancer specialists and neurosurgeons. A V-18 microwire (200 cm, Boston Scientific, USA) was delivered to the cavernous sinus segment of the ICA using a VIABAHN stent based on the roadmap. An angiogram confirmed the position of the self-expanding stent. A 0.014-inch Transend microwire (200 cm, Boston Scientific, USA) was delivered to the cavernous sinus segment of the ICA using a WILLIS stent based on the roadmap. After an angiogram, the position of the stent was confirmed (Figure 1). The balloon was inflated to deploy the stent. An angiogram was immediately performed to evaluate the imaging results. If an endoleak was detected, then the balloon was inflated a second time. If the endoleak disappeared or diminished to a slight flow volume, then the procedure would be ceased. Otherwise, another stent was considered.
Two seasoned neurosurgeons performed all the procedures described in this study. Upon discharge, patients were placed on a 3-month course of dual antiplatelet agents, followed by aspirin therapy for at least 9 months.

Treatment of PRNN

Bacterial cultivation from nasopharyngeal secretions and drug sensitivity assays were performed in patients with PRNN to identify antibiotics to be used. Conservative treatment for PRNN included daily nasopharyngeal irrigation with 2% aqueous hydrogen dioxide or saline, intravenous or gastrostomy nutrition, and systematic antibiotic therapy. Endoscopic cleaning of the necrotic tissues under local anesthesia was also considered conservative treatment, and this procedure was usually performed every 2 or 4 weeks. hyperbaric oxygen therapy was done in 6 patients.
ENPG (Figure 4) for PRNN followed by reconstruction using the posterior pedicle nasal septum and floor mucoperiosteum flap was performed after stent pretreatment in some patients. Since coated stents were used, our strategy is to stop using antiplatelet and anticoagulant medications 72 hours before ENPG and restore 48 hours after surgery when confirming that there is no

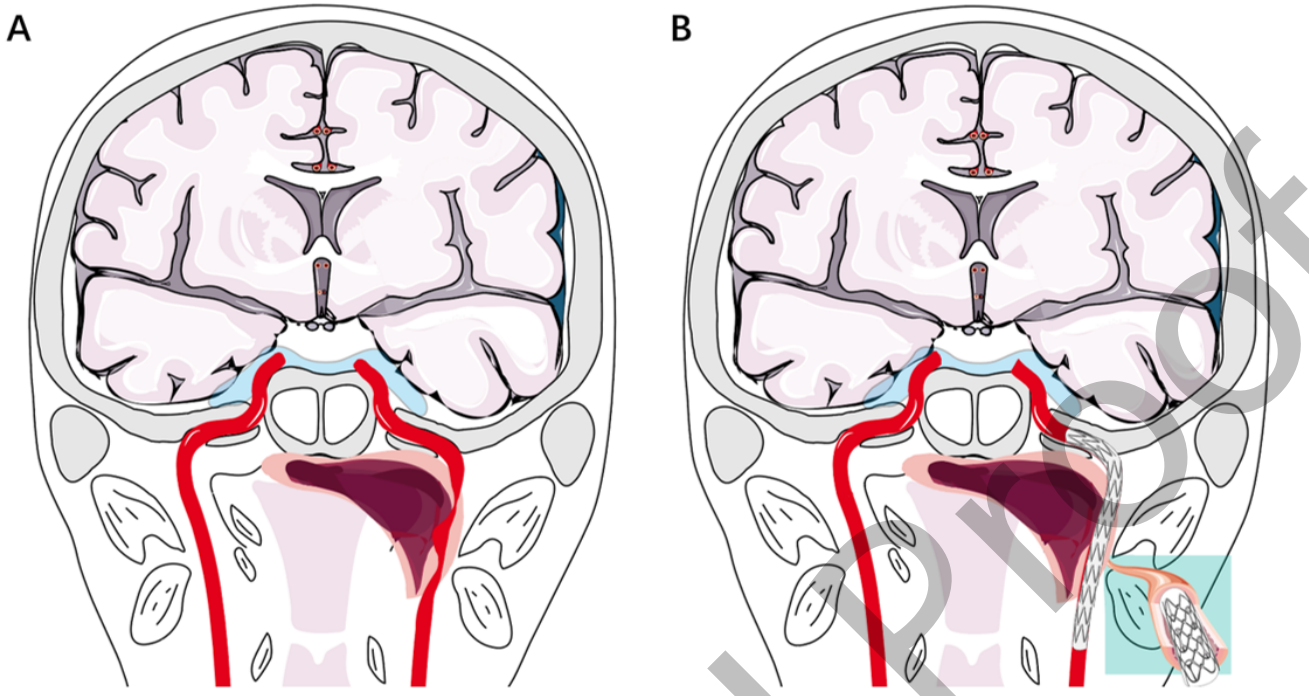

Figure 1. Application of ICA stents in patients with PRNN lesions invading the ICA. (A) The ICA was exposed to PRNN. (B) The stent covered the exposed segment of the ICA.

active bleeding. ENPG could be performed 2 weeks after the stents are placed according to the clinical needs of the patients. The nasopharyngeal necrotic tissue was completely resected until underlying normal fresh tissue was observed. Surgical specimens from the lateral and basal surgical margins, any tissue suspected to be a malignancy, and the necrotic tissues were sent for pathological examination. After the necrotic tissues around was removed, the nasal septum and floor mucosal flaps were often used to recover the nasopharyngeal defect. If the one-side flap was not large enough to cover the defect, the flap on the opposite side of the nasal septum was simultaneously harvested with the inferior turbinate mucoperiosteum being separated to cover the oropharyngeal defect, especially when the necrotic anterior arch of the atlas was removed [7, 13]. Magnetic resonance angiography (MRA) of the nasopharynx and nasopharyngoscope was performed within 1 week after surgery to evaluate the ICA blood supply and flap blood supply.

Evaluation of treatment efficacy

For patients who underwent stent pretreatment after BOT, additional clinical data were collected until the last follow-up. The occurrence of ipsilateral ischemic stroke was recorded as the outcome. The following data were also collected from these patients: timing of symptom onset, infarct location, and medical management of the patient preceding and during the ischemic event. Ipsilateral ischemic stroke was defined as weakness, numbness or paralysis in the face, arm or leg, slurred or garbled speech or difficulty understanding others, blindness in one or both eyes or double vision, vertigo or loss of balance or coordination.

Follow-up

All patients were followed to assess the surgical outcomes, disease status, and performance status every month. Follow-up examinations included complete physical examinations, MRA of the head and neck, and/or whole-body bone scans. All patients in the ENPG group underwent endoscopies to remove nasal secretions and assess wound reconstruction every 2 weeks after surgery until the wound was completely reepithelialized.

Statistical analysis

Categorical variables were compared by Chi-square or Fisher's exact test. A two-tailed P value < 0.05 was considered statistically significant. The Cox proportional-hazards model was used to calculate the HRs and 95% CIs [14]. Overall survival was calculated using the Kaplan–Meier method. Data are presented as mean ± SD unless otherwise stated. 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

Patient characteristics

The demographic, preoperative, and postoperative characteris-

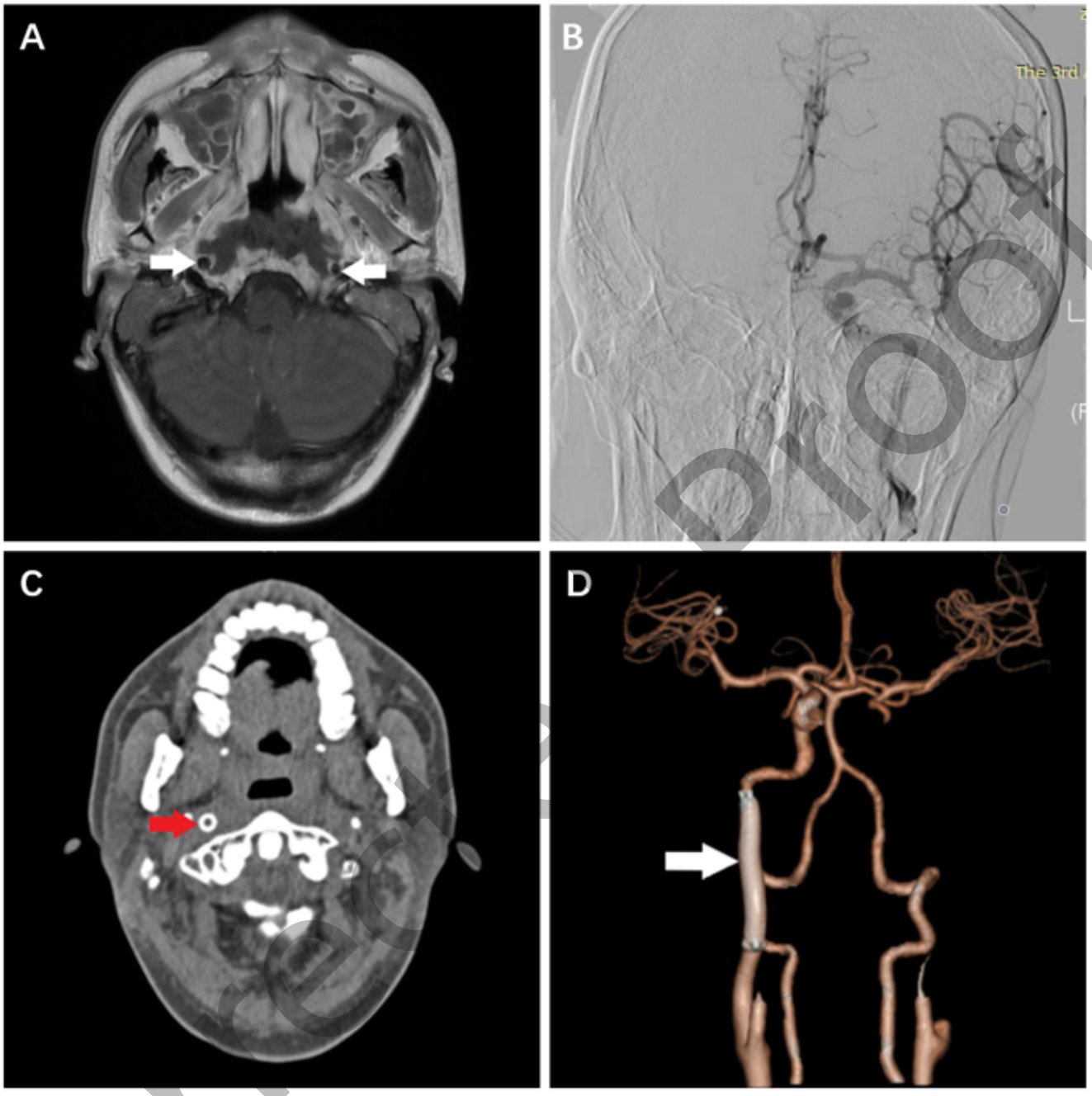

Figure 2. Imaging findings of ICA stents. (A) Horizontal enhanced MRI shows that the ICA was exposed to PRNN. (B) Cerebral angiography shows a positive BOT result. (C) Stents are observed on coronal enhanced CT scans. (D) CT scan with 3D reconstruction showing the location of the ICA stent.

tics of the patients and operations are shown in Table 1. Clinical records of 36 patients, including 30 males and 6 females, with a median age of 53 years (range, 31-78 years) were selected. Concerning the initial diagnosis and therapy, all patients were pathologically diagnosed with NPC and received radical radiotherapy with chemotherapy. All of 36 patients received initial radiotherapy, 19 of them developed recurrence after the primary treatment. 16 of the recurrence were in nasopharynx, 3 were in both nasopharynx and neck. Fifteen of them received reirradiation and 4 received surgery for their recurrence. The initial radiation dose and reirradiation dose to nasopharynx were 69.6 ± 2.3 Gy and 63.4 ± 3.1 Gy, respectively. All 36 patients received initial chemotherapy and 15 patients received chemotherapy for their recurrence. The initial radiation dose to neck was 65.1 ± 4.6 Gy, 3 patients developed both neck and nasopharynx recurrence after primary treatment in our cohort, all of them underwent selective neck dissection followed by ENPG.

Thirty-one patients had pseudoaneurysm, and 17 patients had ICA stenosis. The ICA of all patients was exposed in their necrotic lesions and received stent pretreatment, among which 23

Table 1. Characteristics and clinical data of the patients.

Patient characteristics	Patients (%)
Patients	36
Demographics	
Gender(%male)	30 (83.3%)
Smoking	7 (19.4%)
BMI	20.0 ± 2.9
Age	53.3 ± 12.3
Diabetes	6 (16.7%)
Hypertension	7 (16%)
Initial radiotherapy dose to nasopharynx	69.6 ± 2.3
Initial radiotherapy dose to neck	65.1 ± 4.6
Initial chemotherapy	
Yes	36 (100.0%)
No	0
Treatment of recurrence	19 (52.8%)
Reirradiation	15 (41.6%)
Surgery	4 (13.3%)
Reirradiation dose to nasopharynx	63.4 ± 3.1
Chemotherapy for recurrence	
Yes	15 (41.6%)
No	4 (11.1%)
Endoscopic nasopharyngectomy	14 (38.9%)
Internal carotid artery (ICA) stenosis	16 (44.4%)
Pseudoaneurysm	30 (83.3%)
BOT results	
Positive	23 (63.9%)
Negative	13 (36.1%)
Pretreatment	36 (100.0%)
Unilateral stent implantation	23 (63.9%)
Bilateral stent implantation	6 (16.7%)
ICA embolization and contralateral stent implantation	7 (19.4%)

Table 2. Relevant information of cerebral ischemic patients.

Variables	Cerebral ischemic	Normal	P
Sex			0.899
Male	9	20	
Female	2	5	
Age			0.454
≥53	7	19	
< 53	4	6	
Reirradiation			< 0.001
Yes	7	3	
No	4	22	
Hemoglobin, g			0.017
≥90	5	21	
<90	6	4	
Serum albumin, g			0.531
≥30	9	18	
< 30	2	7	
Intracranial Aneurysm			< 0.001
Yes	5	0	
No	0	31	
ICA Stenosis			0.006
Yes	9	8	
No	2	17	
Body mass index, kg/m^2			0.018
≥20	4	21	
< 20	7	5	

patients underwent unilateral ICA stent implantation, 7 patients underwent unilateral ICA stent implantation and contralateral ICA embolization, and 6 patients underwent bilateral ICA stent implantation. 14 patients experienced ENPG, all of which followed by reconstruction using the posterior pedicle nasal septum and floor mucoperiosteum flap, 2 patients had large defect involved oropharyngeal and had their inferior turbinate mucoperiosteum combined with the flap separated. 22 patients experienced endoscopic cleaning or antibiotic therapy followed by stent pretreatment (Table 1).

Outcomes of the pretreatment

Before surgery, the BOT was performed for every patient (23 with positive results and 13 with negative results). Among the patients with negative BOT results, 7 patients had undergone unilateral ICA embolization before the stent pretreatment, and 6 patients had lesions invading the bilateral ICA. During follow-up, 8 (22.2%) patients developed stroke (6 with positive BOT results and 2 with negative BOT results), and 3 (8.3%) developed TIA (2 with positive BOT results and 1 with negative BOT results). Among these patients, 7 were detected to have stent occlusion. A lower body mass index (BMI) <20 kg/m^2 (P=0.018), hemoglobin level <90 g (P=0.017), reirradiation (P<0.001), pseudoaneurysm (P<0.001), and ICA stenosis (P=0.006) were associated with the increased occurrence of postoperative cerebral ischemic events, but similar associations were not observed for sex, age, or hypoproteinemia (Table 2).

Outcomes of ENPG and conservative treatment:

The median ENPG surgical time was 180 minutes (range 60–300 minutes), with a 30 ml median blood loss (range 20–80 mL). Fourteen patients received ENPG followed by reconstruction using a posterior pedicle nasal septum and floor mucoperiosteum flap. Overall, the flap survived in 13 (92.9%) patients, and 1 (7.1%) patient underwent a reoperation to harvest the flap on the opposite side of the nasal septum because the one-sided flap necrotized after the surgery. The clinical outcomes at the 3-month follow-up examination showed that KPS significantly differ between the ENPG group (81.4 ± 16.1) and non-ENPG group (61.4 ± 23.4) (P=0.012), Numeric Rating Scale (NRS) of headache was significantly lower in the ENPG group (2.8 ± 0.9) than in the non-ENPG group (6.3 ± 1.6) (P<0.001). The remaining 22 patients received irrigation and antibiotic therapy, among which 3 (13.6%) recovered, 19 (86.4%) patients did not recover,

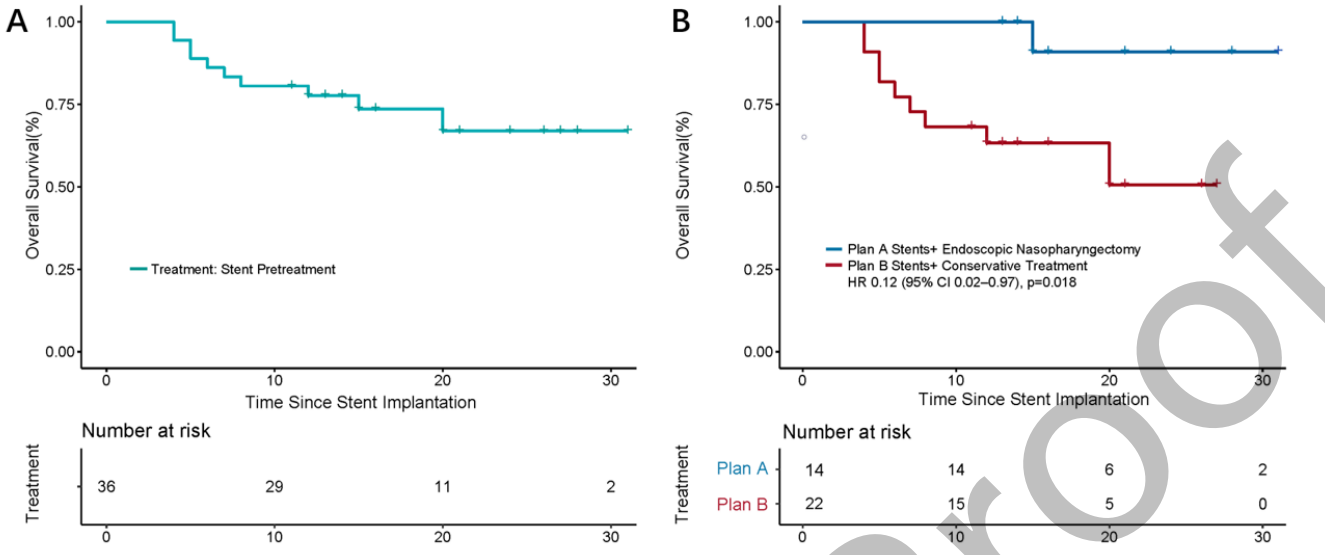

Figure 3. Overall survival. (A) Overall survival of patients with PRNN pretreated with stents. (B) Kaplan-Meier curves showing the survival of patients with PRNN in the stents + ENPG and stents + conservative treatment groups. Plan A = stents+ endoscopic nasopharyngectomy and Plan B= conservative treatment.

and their headache was not relieved.

Survival

Among the 36 patients enrolled in this study, 3 (8.3%) patients in the conservative treatment group died due to massive nasopharyngeal bleeding (2 with contralateral ICA ruptured, 1 with ipsilateral ICA beyond the coverage of the stent ruptured). Among which, 1 case experienced massive bleeding in the contralateral ICA 1 month after stent implantation. Nasal endoscopy showed that the range of nasopharyngeal necrosis was enlarged. The patient refused ENPG and received stent implantation in the contralateral ICA and died of repeated massive bleeding after 5 months. The other two patients died of a severe bleeding at 8 and 12 months respectively. Four (11.1%) died of pulmonary infection, 2 (5.6%) died of stroke, and 1 (2.8%) died of asphyxia due to aspiration. The Kaplan-Meier estimates of overall survival were higher in the ENPG group than in the conservative treatment group ((HR 0.12 95% CI 0.02–0.97, log-rank P=0.018) (Figure 3).

Discussion

To our knowledge, this study is the first to report stent pretreatment in patients with PRNN followed the ENPG or conservative treatment.

Stent pretreatment might be an effective measure in patients with PRNN invading the ICA. Compared with conservative treatment, stent pretreatment followed by ENPG produced a promising overall survival rate and quality of life.

ENPG is considered the standard treatment option for PRNN. However, performing endoscopic surgery is still a challenge in patients with lesions invading the ICA. In patients with PRNN invading the ICA, the exposure of the ICA and the pretreatment for ICA invasion before or during surgery must be determined because ICA rupture may cause intraoperative bleeding, which is deadly. As a method address these matters, Wei et al. performed extracranial intracranial vascular bypass before the craniofacial approach to treat patients with rNPC lesions adjacent to the ICA and achieved a clear resection margin in 13 patients (46.4%) [15]. Although this approach provides new hope for patients with lesions invaded ICA, it may result in severe complications, and this surgery can only be performed in a few cancer centers. Thus, lesion invasion of the ICA has been considered a restricted indication for nasopharyngeal endoscopic surgery, which is an important limit on options for these patients. Some novel techniques, such as vascular intervention, are needed to enlarge the resectable area to enable ENPG to be suitable for more patients with PRNN.

Over the years, we have been working with interventional surgeons to provide surgical treatment for patients with PRNN invading the ICA. We proposed the application of ICA embolization followed by radical endoscopic necrectomy to treat PRNN involving the ICA [8, 10].

However, some patients who have experienced unilateral ICA embolization or with positive BOT results are not suitable for ICA embolization. Moreover, the rate of ischemic stroke following carotid sacrifice in patients who have passed a BOT protocol of intraprocedural neurological assessment and angiographic testing remains significant. Whisenant and colleagues summarized their experience in ICA embolization; 150 BOTs were performed during the study period, after which 37 patients (25%) had permanent occlusion of the tested ICA. 6 of the 37 patients ex-

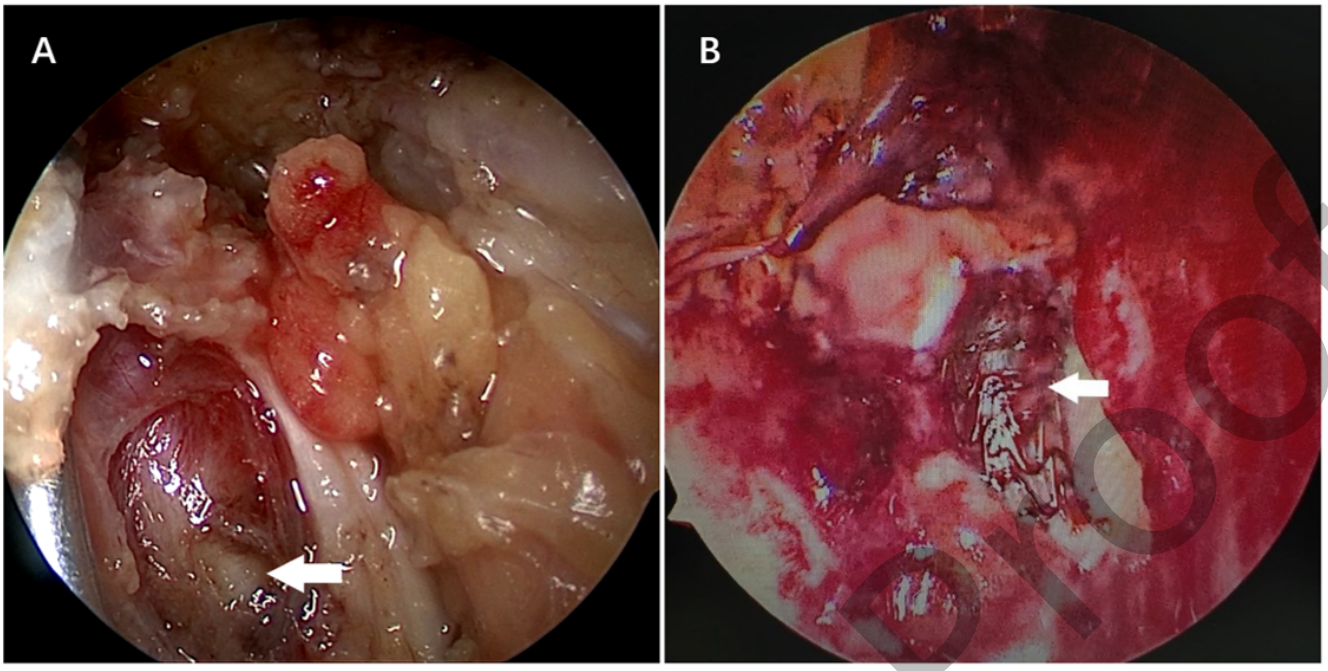

Figure 4. ENPG after ICA stent pretreatment. (A) The ICA was exposed. (B) The stent was exposed after rupture of the carotid wall.

perienced ipsilateral stroke (16.2%), and 3 experienced transient ischemia attack (TIA) (8.1%) [16]. Other treatment options must be considered. Currently, endovascular stent grafting has been used for artery pretreatment before tumor resection, which was originally indicated for endovascular repair of ICA aneurysms in patients who could not undergo a radical operation [17].

We proposed ICA stent pretreatment before ENPG as a procedure to expand the extent of surgical resection (Figure 1). When the preoperative pathological result showed necrosis and the distance between the necrotic lesion and ICA was 0 mm, ICA pretreatment was needed to ensure that the lesions invading the ICA could be completely excised to promote nasopharyngeal tissue healing. We divided these patients into 3 categories according to the BOT results and invasion pattern of lesions into the ICA: 1. the BOT result was positive; 2. the lesions invaded both the left and right ICA, and 3. when patients had undergone unilateral ICA embolization, ICA stenting was used regardless of whether the BOT result was positive or negative. In these cases, extracranial intracranial vascular bypass might also be a choice if the center was able to perform this surgery. We used stents as an ICA pretreatment before ENPG, and all the procedures were performed safely without ICA bleeding (Figure 4). With a median follow-up of 15 months, 3 (8.3%) patients died of massive nasopharyngeal bleeding, 4 (11.1%) died of pulmonary infection, 2 (5.6%) died of stroke, and 1 (2.8%) died of asphyxia due to aspiration, which was obviously decreased compared with the rate in historic cohort. A retrospective study by Chen et al. showed that PRNN invading the ICA contributed to the death of 69.2–72.7% of patients with PRNN because of massive nasopharyngeal bleeding [6, 7]. Stent pretreatment for those lesions invading the ICA might improve survival rates. After the operation, 7 (19.4%) patients developed ipsilateral stroke, and 3 (8.3%) developed TIA. Our findings indicate that preoperative nutrition may reduce the incidence of stroke, and ICA pseudoaneurysm and ICA stenosis may suggest a high probability of postoperative stroke. We suggest that nutritional deficiencies, anemia and hypoalbuminemia should be actively treated before surgery to reduce the incidence of postoperative stroke. Clinicians should be more vigilant when the patient is observed to have ICA stenosis or aneurysm through imaging.

Compared with conservative treatment, ENPG was reported as a more effective traditional treatment for PRNN (70.8% of these patients were cured vs. 13.4–28.6% undergoing endoscopic debridement) [6-8, 18-20]. ENPG was considered the standard treatment option for improving the quality of life and for curing PRNN [2, 8]. In our study, the necrotic lesions invading the ICA were completely excised in 14 patients to promote nasopharyngeal tissue healing and prolong survival. Compared with conservative treatment, ENPG improved the overall survival rate and quality of life of patients with PRNN invading the ICA and significantly reduced the pain caused by necrosis. We also suggest posterior pedicle nasal septum and floor mucoperiosteum flap construction followed by PRNN resection. A retrospective study by Zou et al. showed that ENPG followed by construction using the posterior pedicle nasal septum and floor mucoperiosteum flap is a safe and effective treatment for PRNN [8]. In our study, we used a floor mucoperiosteum flap to reconstruct the nasopharyngeal mucosa and relined the nasopharyngeal

mucosa in most cases.

Limitations and challenges associated with ICA stent pretreatment before ENPG still exist. Our findings should also be considered in the context of the limitations of this retrospective study. Although ICA stenting can effectively prevent intraoperative bleeding, a risk of stent thrombosis persists after surgery. Based on the results of the present study, when the result of BOT is positive, PRNN invading the ICA, which was considered inoperable in the past, may be feasibly treated, but the number of patients was relatively small and the follow-up time was short. In our study, a considerable proportion of patients developed cerebral ischemia following pretreatment, and the main cause of death in our case series was secondary to pulmonary infection, stroke and asphyxia, which raised the concern regarding the need for multidisciplinary therapy after surgery. More prospective studies are needed to refine the regimens and reduce the risks of hemorrhagic and thromboembolic complications.

Conclusion

The innovative application of ICA stents is effective at preventing massive nasopharyngeal bleeding of the ICA exposed to PRNN. Therefore, this treatment may be an effective method with the potential to improve outcomes in patients with PRNN invading the ICA. Multidisciplinary therapy is needed to reduce cerebral ischemia after pretreatment. Compared with conservative treatment, stent pretreatment followed by endoscopic surgery resulted in a promising increase in the overall survival rate and quality of life of patients with PRNN invading the ICA.

Authorship contribution

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

Acknowledgement

Not applicable

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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