Endoscopic Debridement of Post-Radiation Nasopharyngeal Necrosis: Effects of Resurfacing with Vascularized Flap

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Running title: Coverage with vascularized flap for radionecrosis
CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: SDH. Investigation: BS, CHB, MKC. Data curation: HYK, YGJ. Formal analysis: BS, SDH. Methodology: CHB, MKC. Writing – original draft: BS. Writing – review & editing: HYK, YGJ, SDH

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Abstract

Objectives. Post-radiation nasopharyngeal necrosis (PRNN) is a serious complication and severely impacts on the quality of life and survival of nasopharyngeal carcinoma patients. Endoscopic debridement is considered the first-line treatment for PRNN. This study aims to analyze clinical outcomes focusing on the mucosal resurfacing status and the effectiveness of salvage operation.

Methods. 27 patients who underwent endoscopic debridement were retrospectively analyzed. The patients were divided into two groups according to initial surgery, debridement with nasoseptal flap (NSF; n=21) and debridement only (no NSF; n=6). Clinical features, post-operative mucosal status, internal carotid artery (ICA) rupture, survival, and final mucosal status were evaluated. Furthermore, the NSF group was categorized according to flap viability for risk factor analysis of flap failure.

Results. Regardless of the initial modality, most patients experienced symptom improvement (96.0% for headache and 100% for foul odor); however, complete cranial nerve palsy didn’t improve in anyone. In the NSF group, complete healing was observed in 66.7%, while all of no NSF group underwent salvage surgery because none maintained complete healing. Within the NSF group, 19.0% of patients required salvage surgery. After the last surgery, favorable symptom improvement was noted (100% for headache and 90.0% for foul odor), and 77.8% had completely healed mucosa, whereas only 14.8% and 7.4% had partial healing and persistent necrotic mucosal status. The NSF necrotic or uncovered subgroup showed a tendency for old age, advanced necrosis stage, advanced T stage, ICA involvement, high frequency and dose of radiation therapy, DM, and underlying comorbidities, though there were no statistically significant differences. Two ICA ruptures and three deaths occurred.
Conclusion. Resurfacing the nasopharynx with NSF after endoscopic debridement showed better outcome than debridement only for PRNN treatment. Although initial NSF failure occurs, additional resurfacing reconstructive surgery offers advantages in terms of symptom mitigation, quality of life, and survival.

Keywords: Free Flaps, Nasopharyngeal Carcinoma, Osteoradionecrosis, Pedicled Flap, Radiation, Reconstructive Surgery
HIGHLIGHTS

- In the surgical treatment of post-radiation nasopharyngeal necrosis (PRNN), resurfacing the nasopharynx with nasoseptal flap (NSF) after endoscopic debridement showed a better outcome than debridement alone. As a result, endoscopic debridement with mucosal resurfacing with NSF as the initial operation is crucial.

- Even if the initial mucosal resurfacing with NSF did not cover the entire defect area or had been necrotized, subsequent resurfacing reconstruction surgery provides benefits in terms of symptom relief, quality of life, and survival.

- If mucosal resurfacing was initially not done or was done improperly, resurfacing salvage surgery option with vascularized flap, as well as free flap reconstruction, should be implemented for a better clinical outcome.
INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one of the most common malignancies in the head and neck area, especially in Southeast Asia [1,2]. Radiation therapy (RT) either with or without chemotherapy (CT) is the mainstay treatment for NPC, and 5-year overall survival (OS) rates vary from 63.0 to 87.4% due to advancements in RT technique and application of adjuvant CT in locoregionally advanced NPC patients [3-6]. Although RT has a high response rate and shows favorable survival, it can induce several severe complications, such as post-radiation nasopharyngeal necrosis (PRNN) [7-9]. Not yet known as a common complication, with an incidence rate of 0.8 ~ 1.1% [8,10], PRNN can affect the nasopharyngeal mucosa, parapharyngeal tissues, or skull base, thereby inducing severe headache, foul odor, cranial nerve palsy (CNP), and even massive bleeding due to internal carotid artery (ICA) rupture, which can seriously impact patient quality of life and survival [8,9,11-13].

Therefore, timely diagnosis and proper management of PRNN are essential, and endoscopic debridement has shown favorable outcomes with low morbidity [7,8]. A vascularized flap is needed to cover the exposed ICA or dura to reduce the risk of catastrophic events like carotid blow-out or meningitis. Alongside our previous study [12], several recent studies have reported promising outcomes regarding the use of nasoseptal flap (NSF) for resurfacing the defect site, showing improved functional outcome and better OS [10,14,15,16]. Though there have been promising results using NSF, there are still failures and incomplete resolutions of PRNN. There is nonetheless little explanation on the mechanism of this complication and a lack of research on how to treat such intractable cases after failed NSF reconstruction. Thus, focusing on mucosal resurfacing status of nasopharyngeal wounds, our study aims to analyze the clinical outcome of flap reconstruction after endoscopic debridement based on its mucosal resurfacing status and to investigate the
effectiveness of salvage operation.

MATERIAL AND METHODS

Patients
We retrospectively reviewed the medical records of NPC patients who were surgically treated for PRNN at our institution between April 2013 and March 2021. We selected patients for surgical treatment based on radiation history for NPC, clinical features (including headache, foul odor, and CNP), endoscopic findings, and radiologic studies (such as computed tomography [CT] and magnetic resonance imaging [MRI]). A total of 31 patients underwent endoscopic debridement for PRNN. Among them, four patients with pathologically confirmed recurrent tumor were excluded. Finally, 27 patients were analyzed in the present study. This study was approved by the Institutional Review Board (IRB) of our institution, and the need for informed consent was waived (IRB No. 2022-04-039).

According to the method of initial surgery, patients were divided into two groups, debridement with NSF (NSF; n=21) and debridement only (no NSF; n=6). The patients with continuous or relapsed symptoms along with persistently necrotic surgical bed were considered candidates for salvage surgery. ICA involvement, defined as necrotic tissue surrounding the ICA, no healthy tissues above the necrotic tissue over the ICA, and evidence of a narrowing of the ICA lumen in comparison to the contralateral ICA, even after surgery for radionecrosis was also considered for salvage surgery.

Ultimately, salvage surgery was performed in 10 patients with reconstruction using an NSF (n=5), anterolateral thigh free flap (ALTFF, n=4), and inferior turbinate (IT) mucosal free graft followed by middle turbinate rotation flap (MTF, n=1). All patients were regularly followed up at 3- to 6-month intervals until at least 5 years after the initial surgery.
Nasopharyngeal endoscopic evaluation, contrast-enhanced CT scans, and MRI were performed as follow-up evaluations.

**Surgical techniques**

*Initial surgery*

If the ICA was surrounded with necrotic tissue, we performed the balloon occlusion test (BOT) for potential risk of ICA injury and sacrifice. All patients underwent endoscopic debridement with image-guided surgery. After performing frozen biopsy to exclude recurrent tumor, wide debridement was performed using curettes, a microdebrider or Coblator (Coblator II, Smith & Nephew, Memphis, TN). After debriding the devitalized soft tissue, an endoscopic drill was used to remove the necrotic portion of the skull base bone. Careful attention was paid when debriding on the posterolateral side to avoid carotid artery rupture using Doppler ultrasound. If the carotid artery was surrounded by necrotic tissue, the necrotic tissue was intentionally left in place. After debridement, we performed massive povidone-iodine irrigation.

In the NSF group, we covered the defect with NSF based on the septal branch of sphenopalatine artery. NSF was usually harvested from the contralateral side of the main lesion to avoid potential pedicle injury during debridement around the eustachian tube. The NSF was elevated from the mucocutaneous junction (caudal septal margin), including the nasal floor for a wider width. Gelfoam (Pfizer Inc, New York, NY) pledgets and Merocel (Medtronics Xomed, Jacksonville, FL) nasal packing were used to bolster the area and deter flap detachment. The nasopharynx was packed for 7 to 10 days. Following the removal of the packing, the patients started irrigating the lesion with normal saline solution. Supplementary Video 1 is an example of intra-operative video clip of above endoscopic debridement with NSF reconstruction procedure.
Salvage surgery

When performing salvage surgery, we collected necrotic tissue and remaining deep tissue for frozen biopsy to exclude tumor recurrence. The following debridement procedure was similar to that of the initial surgery. For reconstruction using ALTFF, we used two approaches, the maxillary swing approach for three patients and the transcervical approach for one patient.

Regarding the maxillary swing approach, a Weber–Ferguson–Longmire facial incision was performed to allow a view for further wide debridement and adequate space for transferring the ALTFF. Proper ALTFF donor size and shape were based on defect size and the need for adequate coverage of the ICA. Then, a linear skin incision was created from the anterior superior iliac spine to the lateral border of the patella in the non-dominant leg of the patient.

To identify the perforator of the descending branch of the lateral circumflex femoral artery, which is a feeding artery to the ALTFF, we performed dissection through the level of the rectus femoris and vastus lateralis. After identifying the muscular perforators entering the vastus lateralis, the designed fasciomuscular flap was harvested with the perforators. The flap was then transferred to the nasopharyngeal area and sutured to the nasopharyngeal wall with vicryl suture. This procedure was conducted using the transcervical approach for one patient, where a transverse skin incision was performed on the neck level II area along the skin crease. Arterial anastomoses were performed to the facial artery for three and transverse cervical artery for one, and venous anastomoses to the facial vein for two and external jugular vein and transverse cervical vein each in one patient. Two patients required tracheostomy, while nasopharyngeal airway was inserted in addition to nasal packing and endotracheal tube was maintained till extubation on one day post-operation each in one patient. All procedures described above were performed by ENT surgeons. For one patient who received MTF for a second salvage operation, a posterior lateral nasal artery pedicled posterior-based MTF was
designed. An incision was made anterior to the middle turbinate, afterwards mucoperiosteum was elevated from the front aspect, and the middle turbinate bone was removed. It is critical to avoid damaging the vascular pedicle as it enters at its lateral attachment. After the flap was harvested, it was gently rotated to the nasopharynx and bolstered for 7–10 days using Gelfoam and Merocel.

**Outcome measurements**

Pre- and post-operative symptoms of headache and foul odor, CNP, post-operative mucosal status, and salvage operation rate were evaluated to compare outcomes according to initial surgical method. Post-operative mucosal status was classified as complete healing, partial healing, or persistent necrosis (Fig. 1).

Within the NSF group, patients were subcategorized into the NSF viable subgroup (NSF-V) and the NSF necrotic or uncovered subgroup (NSF-U) according to flap viability after initial surgery for risk factor analysis of flap failure. The risk of flap failure was analyzed according to age, diabetes mellitus (DM), underlying comorbidity, necrosis stage, T stage, ICA involvement, and RT frequency and dose. Based on the clinical features of patient’ symptom, endoscopic examination and radiological findings, necrosis stage was classified as early, middle, or late, as described in previous studies (Fig. 2) [8,12]. Symptoms of headache and foul odor, CNP, final mucosal status, and ICA rupture, along with mortality rates were evaluated for final outcome measurement.

**Statistical analysis**

Statistical analysis was performed with SPSS 27.0 (IBM/SPSS, Armonk, NY); P-values for each variable were calculated using the Mann-Whitney U test. P-values less than 0.05 were considered to represent statistically significant comparisons.
RESULTS

Patient characteristics

Patient characteristics are summarized in Table 1. The mean age was 59.6 years (SD, 10.1). The median follow-up period was 32 months (range, 1-85 months). The mean number and cumulative dose of RT were 1.6 (range, 1-4) and 9914 cGy (range, 6600-21600 cGy), respectively. The median T stage was 3 (range, 1-4), and all patients underwent concurrent or adjuvant chemotherapy. Regarding symptoms, 25 patients had headaches, 19 had foul odor, and four had CNP (cranial nerve [CN] 10 for one, CN 12 for one, and both CN 10&12 for two patients). On endoscopic examination, 24 patients (88.9%) exhibited late stage necrosis, and three patients showed middle stage necrosis. ICA involvement was detected in 13 patients (48.1%). Detailed characteristics of each patient are provided in Supplementary Table 1.

Outcomes of initial surgery

The initial surgery outcomes are summarized in Table 2. Regardless of the initial surgical modality, most patients experienced improvement of symptoms (96.0% for headache and 100% for foul odor); however, those with CNP did not experience any improvement. On the other hand, 14 patients (51.9%) had completely healed mucosa (Fig. 3), whereas five (18.5%) and eight (29.6%) patients had partially healed and necrotic mucosa after initial surgery, respectively. In the NSF group, 66.7% of patients achieved complete healing, while no patients in the no NSF group maintained complete healing that all patients in the no NSF group had to undergo salvage surgery. On the other hand, even with the higher rate of ICA involvement in the NSF group (57.1% vs. 16.7%, P=0.086), only four patients required
salvage surgery, which was significantly lower surgical failure rate compared no NSF group (19.0% vs. 100%, *P*<0.001). The mean time until salvage surgery was 9.4 months across groups, though it had a tendency to be longer in the no NSF group (13.5 months vs. 3.3 months, *P*=0.257).

**Salvage surgery and final outcomes**

Salvage surgery was performed in 10 patients with recurrent headache and necrotic surgical bed, with reconstruction using the NSF in five, the ALTFF (Fig. 4) in four, and the IT mucosal free graft in one patient who underwent second salvage surgery with MTF. After salvage surgery, no patients complained of foul odor, and 90.0% of patients experienced relief from headaches. Moreover, seven (70.0%) had complete healing, whereas two (20.0%) had partial healing, and one patient (10.0%) had persistent necrosis even after salvage surgery. The only patient (Case 25) who underwent second salvage surgery had relapsed his headache due to progression of partially uncovered mucosal status after the first salvage surgery by IT mucosal free graft, but the pain improved after the second salvage surgery using the MTF with maintenance of fully viable mucosa (the interval between salvage surgeries was 50 months). Patient demographics and clinical features in salvage surgery are summarized in Supplementary Table 2.

After their last operation, 21 patients (77.8%) had completely healed mucosa on their last outpatient clinic visit, whereas four (14.8%) and two (7.4%) patients had partial healing and persistent necrotic mucosal status, respectively. No patients suffered from foul odor, and 13 patients (48.1%) still suffered from headaches, but 11 of them noted improvements compared to their initial condition. 10 patients had persistent CNP; two cases were better than initial, two cases were worse, and six cases were newly developed during follow-up (CN 10 for four; CN 12 for one; both CN 10&12 for four; and all 7, 10, and 12 for one patient). The vagus
nerve and hypoglossal nerve were the most often injured nerves, resulting in voice changes, dysphagia, and articulation problems. Among 13 patients whose ICA was exposed, ICA rupture (one from intra-operative and one after one month post-operation) was reported in two, in whom coil embolization was performed. The survival rate was 88.9%, with one patient dying from stroke and pneumonia after ICA rupture, and two due to tumor recurrence, one of whom refused salvage surgery. The final results and the flow chart of the surgical modalities and mucosal status before and after each surgical step are summarized in Table 3 and Fig. 5.

**Subgroup analysis within the NSF group**

The NSF-V subgroup and NSF-U subgroup comprised 66.7% (n=14) and 33.3% (n=7) of the NSF group, respectively. Age (59.3 vs. 62.7 years, $P=0.443$), necrosis stage (85.7% vs. 100%, $P=0.636$), advanced T stage (50% vs. 85.7%, $P=0.197$), ICA involvement (42.3% vs. 85.7%, $P=0.128$), and number (1.4 vs. 1.6, $P=0.443$) and dose (8651 cGy vs. 10079 cGy, $P=0.799$) of RT tended to be higher in the NSF-U subgroup, but no statistically significant difference existed between the two subgroups. The NSF-U subgroup also had a higher tendency for DM and underlying comorbidities (0.0% vs. 28.6% and 14.3% vs. 42.3%, respectively) without statistically significant difference between the two subgroups ($P=0.322$ and $P=0.322$, respectively). Two ICA ruptures and two deaths were reported in the NSF-U subgroup, and one death was reported in the NSF-V subgroup. The median follow-up period was 13.5 months for the NSF-V subgroup and 16 months for the NSF-U subgroup (range, 1-73 months and 5-54 months, respectively). NSF subgroup analysis is summarized in Table 4.

**DISCUSSION**
Even though PRNN severely impacts on patients’ quality of life and survival, no standard treatment has been established to date. There have been introduced several therapeutic challenges such as conservative management using antibiotics and frequent dressing, hyperbaric oxygen therapy, and endoscopic debridement with or without vascularized flap reconstruction. Among them, endoscopic debridement is widely used method to remove necrotic tissue and replenish fresh tissue, helping to control infection and improve symptoms in the skull base area [7,12]. However, the recovery period is quite long, and necrosis easily relapse, so repetitive surgical debridement might be necessary [8,11,17]. The exact pathophysiology of PRNN is unclear, but hypoxia, hypovascularity, and hypocellularity from RT are thought to be the key factors in its development and resulting inflammation, sequestration, and erosion of the underlying cortex of the nasopharynx [18,19]. Debridement without flap reconstruction seldom achieves complete healing, and failing to resurface defects of the skull base, dura, or ICA that can result in life-threatening complications such as meningitis, ICA blowout, and death [8,10,20]. In fact, ICA involvement has been found to be an independent prognostic factor, and it can increase the risk of death from 41.8-42.9% to 69.2-72.7% [7,8,10,11]. Therefore, resurfacing surgical bed with a vascularized flap and protecting the exposed skull base and ICA are regarded as the most important surgical goals in PRNN treatment. NSF pedicled by the posterior septal artery, a branch of the sphenopalatine artery, has been regarded as an effective and reliable reconstruction method for PRNN considering the advancements in image-guided endoscopic skull base surgery [12,15,21]. There have been some challenges to using free flap reconstruction to cover the extensive defect site either after nasopharyngectomy for recurrent NPC [22,23] or endoscopic debridement for osteoradionecrosis in the head and neck area [24-28]. Although free flap reconstruction is invasive and has some limitations of difficult technique, long operation time, and wound
problems, it can cover more extensive defect, unlike NSF, and has a role in salvage surgery. With its ample size and high vascularity, ALTFF is a good option in extensive PRNN especially involving the ICA, which is a known prognostic factor for symptom aggravation, increased disease extent even after surgery, and death [21,25,26]. A recent study by Zou et al. [15] analyzed 72 PRNN patients treated with NSF. It showed successful outcomes of defect area re-epithelialization (70.8%) and symptom improvement without any surgery-related complications or death, and the 2-year OS rate was 77.9%. They also demonstrated that the viability of NSF reconstruction was a protective factor for re-epithelialization, which could serve as a barrier to protect the ICA.

To our knowledge, outcomes have not been compared according to flap and mucosal status. There is also a lack of study regarding salvage operation using a vascularized flap, especially for free flap reconstruction, after surgical failure in PRNN patients. As such, we not only analyzed data corresponding to initial curative intent endoscopic debridement with or without NSF, but also included the clinical courses of salvage operation using vascularized flap reconstruction and eventually compared the clinical outcomes according to final mucosal resurfacing status. Moreover, based on the flap viability of the initial NSF group, we tried to figure out the risk factors for NSF failure in PRNN patients. Our data showed that resurfacing the defect area with an NSF in initial surgery showed better outcomes than debridement only. Most patients in the NSF group obtained healthy mucosal status, and only four patients underwent salvage surgery even in the setting of more ICA involvement, while all six patients in the no NSF group had to undergo salvage surgery due to recurrent necrosis with recurrent symptoms. Among 10 salvage surgery, free flaps were also performed in four patients with ALTFF (Case 4, 5, 21, 23). Interestingly, although not all of the 10 patients maintained completely healed mucosa after salvage surgery, they also showed good clinical outcomes with relief of their symptoms in most patients. Finally, 21 patients (77.8%) had
completely healed mucosa on final presentation, whereas six patients (22.2%) did not. No patients suffered from foul odor, and headaches were improved in all but two patients compared to their initial condition. Among 13 patients whose ICA was involved, two ruptures (Case 21: one month post-operation, Case 24: intra-operative) were reported and rescued by coil embolization. Only three patients died (Case 5, 21, 22) that survival rate was 88.9%. Our results suggest that endoscopic debridement and mucosal resurfacing with NSF reconstruction are essential for surgical management of PRNN. Even if the initial surgery was ineffective and the NSF had not covered the whole defect area or became necrotized, additional reconstructive resurfacing surgery using another vascularized flap is necessary for better clinical outcomes.

Yang et al. [10] recently reported the clinical outcomes of NPC with PRNN. They demonstrated that osteoradionecrosis, re-irradiation, and ICA involvement affected survival, although only re-irradiation and ICA involvement were independent prognostic factors, with hazard ratios of 1.75 and 1.80, respectively. Additionally, NSF reconstruction was associated with better overall survival compared to conservative management. Among 44 patients with NSF in their study, eight flaps (18.2%) did not show favorable re-epithelialization, though explanation and analysis of risk factors for NSF failure were missing. In our study, by categorizing the NSF group according to flap viability, we found that age, necrosis stage, advanced T stage, ICA involvement, number and dose of RT, and the propensity toward DM and underlying comorbidities tended to be higher in the NSF-U subgroup. Including the variables such as necrosis stage, ICA involvement and re-irradiation that are already known to be related to the survival of PRNN patients, the factors that we investigated in this study might also have a role in NSF failure due to poor vascularization and perfusion of the underlying nasopharyngeal surface, hindering its healing and mucosalization. There should be further studies with larger cohort and enough period, and clear pathophysiology should be
elucidated for validation of this trend.

There were four patients with lower CNP on initial pre-operative examination. Among them, two (Case 23, 24) partially improved their CNP following salvage surgery, allowing the gastrostomy tube to be removed. During the follow-up period, six cases of newly developed CNP, four (Case 4, 11, 17, 18; 19.0%) of which emerged even after final successful flap surgery. One (Case 17) of those four cases developed due to recurrent tumor and another (Case 4) after initial surgery without NSF, so the other two (Case 11, 18; 9.5%) in the complete healing group developed new CNP as a consequence of PRNN. In contrast, two patients (Case 1, 27; 33.3%) in partially or totally necrotic group newly developed CNP. Therefore, even if the vascularized flap might not fully prevent the development of lower CNP, at least it seems to lessen the likelihood. However, we should be cautious that even after successful surgery, necrosis may spread beneath the flap and CNP may develop and get worse over time. Additionally, although statistically insignificant, a larger proportion of ICA involvement was observed in the nasoseptal flap failure group compared to the success group (85.7% vs. 42.3%), which implies that if the necrotic tissue around the ICA was left in order to avoid ICA rupture, there may be a greater chance of flap failure. On the other hand, there is a representative example (Case 8) of completely healed mucosa and a viable flap with persisting necrotic tissue beneath the mucosal layer on follow-up imaging, but without any symptoms, CNP, or ICA rupture (Fig. 6). Nonetheless, the necrotic bed poses a high risk for flap failure that it is the dilemma whether to entirely remove the necrotic tissue around the ICA, or not. In such instance, total removal of necrotic tissue following prophylactic ICA embolization or superficial temporal artery (STA) to middle cerebral artery (MCA) bypass surgery may be an excellent option, as described in a recent publication by Cho et al. [16]. In their study, they presented a strategy for managing ICA involvement in which coil embolization was conducted if BOT followed by brain perfusion single-photon emission
computed tomography revealed no hypoperfusion, while STA to MCA bypass surgery was
performed if hypoperfusion was seen. This approach allowed for extensive sequestrectomy
and successful outcomes, providing a valuable message for the future direction of ICA
handling in PRNN. Nevertheless, more research on this subject is required.

Despite promising advancement from our previous study and some meaningful results
herein, the present study has limitations of retrospective analysis including patient selection
bias for each surgical modality since we only did endoscopic debridement without
vascularized flap as initial operation and free flap for salvage operation in earlier cases that
has changed to current practice pattern of employing NSF as our experience and evidence for
the utility of NSF have gradually been accumulated. Other limitations include the small
number of patients that were treated at a single institute and operated on by a single surgeon,
and a short follow-up period. Hence, further studies with a longer follow-up period and larger
cohort are required to validate our results.

In conclusion, if mucosal resurfacing was initially not done or improper, prognosis was not
good. Reconstruction using an NSF after endoscopic debridement is an effective and reliable
modality in initial surgical management of PRNN. Even if the initial NSF fails, subsequent
resurfacing salvage surgery with vascularized flap, including free flap reconstruction, should
be used to improve clinical outcomes.
REFERENCES


**FIGURE LEGEND**

**Fig. 1.** Post-operative mucosal status. (A) Complete healing (B) Partial healing. (C) Persistent necrosis.

**Fig. 2.** Stage of necrosis. (A) Early: mucosal necrosis alone. (b) Middle: necrosis involving mucosa, muscle, and tendon. (C) Late: osteoradionecrosis.

**Fig. 3.** A representative example of debridement with nasoseptal flap (NSF) as the initial operation (Case 14). (A) Pre-operative endoscopic image of radionecrosis. (B) Pre-operative magnetic resonance image (MRI) shows extensive necrotic lesion on both sides of nasopharynx extending to left internal carotid artery and eroding clivus. (C) 17 months after operation; viable NSF with complete mucosal healing was achieved. (D) MRI shows fully viable nasopharyngeal tissue without any remnant necrotic tissue.

**Fig. 4.** A case of salvage operation with anterolateral thigh free flap (ALTFF) (Case 4). (A) Pre-operative endoscopic image shows extensive necrosis on whole nasopharynx nearly extending to superior margin of oropharyngeal wall. (B) Intra-operative endoscopic image after debridement; resurfacing with flap was not performed. (C) Post-operative examination shows extensive necrotic tissue again. (D) Four months post-salvage operation with repetitive debridement and ALTFF; complete healing was achieved.

**Fig. 5.** Flow chart and treatment outcomes.

**Fig. 6.** An example of the persistent necrosis under completely healed mucosa with free of symptoms (Case 8). (A) Pre-operative endoscopic image of radionecrosis. (B) Intra-operative endoscopic image after debridement of necrotic tissue. (C) 52 months after debridement with nasoseptal flap (NSF); completely healed mucosa with viable NSF is observed. (D) Pre-operative computed tomography (CT) scan shows radionecrosis involving nasopharyngeal deep tissue near the right internal carotid artery (ICA). (E) CT scan on four months post-
operation. (F) CT scan on 52 months post-operation; remaining necrotic tissue near the ICA without any progression compared to pre-operative imaging.
### Table 1. Summary of patients’ initial characteristics

<table>
<thead>
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<th>Characteristic</th>
<th>No. of patients (percentage)</th>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
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</tr>
<tr>
<td>II</td>
<td>3 (11.1%)</td>
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<tr>
<td>III</td>
<td>13 (48.1%)</td>
</tr>
<tr>
<td>IV</td>
<td>10 (37.0%)</td>
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<tr>
<td><strong>T stage</strong></td>
<td></td>
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<tr>
<td>I</td>
<td>3 (11.1%)</td>
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<tr>
<td>II</td>
<td>6 (22.2%)</td>
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<tr>
<td>III</td>
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</tr>
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<tr>
<td><strong>Number of RT</strong></td>
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<td>3</td>
<td>1 (3.7%)</td>
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<td>4</td>
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<td>13 (48.1%)</td>
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<td>19 (70.4%)</td>
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<td>25 (92.6%)</td>
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<td>No</td>
<td>2 (7.4%)</td>
</tr>
</tbody>
</table>

NPC, nasopharynx cancer; RT, radiation therapy; ICA, internal carotid artery.
Table 2. Outcomes of initial surgery between the NSF and no NSF groups

<table>
<thead>
<tr>
<th></th>
<th>NSF (n=21)</th>
<th>No NSF (n=6)</th>
<th>Total (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years (mean ± SD)</strong></td>
<td>60.5 ± 10.5</td>
<td>56.5 ± 8.9</td>
<td>59.6 ± 10.1</td>
</tr>
<tr>
<td><strong>Gender (M:F)</strong></td>
<td>19:2</td>
<td>5:1</td>
<td>24:3</td>
</tr>
<tr>
<td><strong>Pre-operative foul odor</strong></td>
<td>15 (71.4%)</td>
<td>4 (66.7%)</td>
<td>19 (70.4%)</td>
</tr>
<tr>
<td><strong>Pre-operative headache</strong></td>
<td>20 (95.2%)</td>
<td>5 (83.3%)</td>
<td>25 (92.6%)</td>
</tr>
<tr>
<td><strong>Pre-operative lower CNP</strong></td>
<td>4 (19.0%)</td>
<td>0 (0.0%)</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td><strong>Improvement of foul odor</strong></td>
<td>15 (100%)</td>
<td>4 (100%)</td>
<td>19 (100%)</td>
</tr>
<tr>
<td><strong>Improvement of headache</strong></td>
<td>20 (100%)</td>
<td>4 (80%)</td>
<td>24 (96.0%)</td>
</tr>
<tr>
<td><strong>Improvement of lower CNP</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Post-operative mucosal status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete healing</td>
<td>14 (66.7%)</td>
<td>0 (0.0%)</td>
<td>14 (51.9%)</td>
</tr>
<tr>
<td>Partial healing</td>
<td>5 (23.8%)</td>
<td>0 (0.0%)</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Persistent necrosis</td>
<td>2 (9.5%)</td>
<td>6 (100%)</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td><strong>Salvage operation</strong></td>
<td>4 (19.0%)</td>
<td>6 (100%)</td>
<td>10 (37.0%)</td>
</tr>
<tr>
<td><strong>ICA rupture</strong></td>
<td>2 (9.5%)</td>
<td>0 (0.0%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>2 (9.5%)</td>
<td>1 (13.3%)</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td><strong>Follow-up period (months)</strong></td>
<td>25.9</td>
<td>53.3</td>
<td>32.0</td>
</tr>
</tbody>
</table>

SD, standard deviation; CNP, cranial nerve palsy; ICA, internal carotid artery; NSF, nasoseptal flap.
**Table 3.** Final outcomes

<table>
<thead>
<tr>
<th></th>
<th>Complete healing (n=21)</th>
<th>Partial Healing (n=4)</th>
<th>Persistent necrosis (n=2)</th>
<th>Total (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>60.2 ± 10.3</td>
<td>57.5 ± 9.9</td>
<td>57.0 ± 14.1</td>
<td>59.6 ± 10.1</td>
</tr>
<tr>
<td>Number of RT</td>
<td>1.6</td>
<td>1.5</td>
<td>2.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Dose of RT (cGy)</td>
<td>10089</td>
<td>9628</td>
<td>16245</td>
<td>9914</td>
</tr>
<tr>
<td>Reconstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSF</td>
<td>17</td>
<td>3</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>ALTFF</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>IT graft, MTF</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Final foul odor</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Final headache</td>
<td>7 (33.3%)</td>
<td>4 (100%)</td>
<td>2 (100%)</td>
<td>13 (7.4%)</td>
</tr>
<tr>
<td>Final lower CNP</td>
<td>5 (23.8%)</td>
<td>4 (100.0%)</td>
<td>1 (50.0%)</td>
<td>10 (48.1%)</td>
</tr>
<tr>
<td>ICA rupture</td>
<td>1 (4.8%)</td>
<td>1 (25.0%)</td>
<td>0 (0.0%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (9.5%)</td>
<td>0 (0.0%)</td>
<td>1 (50.0%)</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
<td>32.3</td>
<td>26.3</td>
<td>39.5</td>
<td>32.0</td>
</tr>
</tbody>
</table>

RT, radiation therapy; ICA, internal carotid artery; CNP, cranial nerve palsy; NSF, nasoseptal flap; ALTFF, anterolateral thigh free flap; IT, inferior turbinate flap; MTF: middle turbinate flap.
Table 4. Subgroup analysis of the NSF group

<table>
<thead>
<tr>
<th></th>
<th>NSF-V (n=14)</th>
<th>NSF-U (n=7)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>59.4 ± 11.0</td>
<td>62.7 ± 9.7</td>
<td>0.443</td>
</tr>
<tr>
<td>DM</td>
<td>0 (0%)</td>
<td>2 (28.6%)</td>
<td>0.322</td>
</tr>
<tr>
<td>Underlying comorbidity</td>
<td>2 (14.3%)</td>
<td>3 (42.3%)</td>
<td>0.322</td>
</tr>
<tr>
<td>Advanced T stage (3-4)</td>
<td>7 (50.0%)</td>
<td>6 (85.6%)</td>
<td>0.197</td>
</tr>
<tr>
<td>Number of RT</td>
<td>1.4</td>
<td>1.6</td>
<td>0.443</td>
</tr>
<tr>
<td>Dose of RT (cGy)</td>
<td>8651</td>
<td>10079</td>
<td>0.799</td>
</tr>
<tr>
<td>Necrosis stage: Late</td>
<td>12 (85.7%)</td>
<td>7 (100%)</td>
<td>0.636</td>
</tr>
<tr>
<td>ICA involvement</td>
<td>6 (42.3%)</td>
<td>6 (85.7%)</td>
<td>0.128</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; RT, radiation therapy; ICA, internal carotid artery; NSF-V, nasoseptal flap viable subgroup; NSF-U, nasoseptal flap necrotic or uncovered subgroup.
Figure 3
Figure 5

NSF
n=21 (77.8%)

- Complete healing
  n=14 (66.7%)
    - n=3
      - Salvage op.
        n=4 (19.0%)
          - 1 ALTFF
            - Complete healing
              n=1 (25.0%)
                - 1 MTF
                  - Complete healing
                    n=1
        - Partially uncovered
          n=5 (75.0%)
            - n=1
      - 1 NSF
        - 1 ALTFF
          - Complete healing
            n=5 (83.3%)
          - Persistent necrosis
            n=1 (16.7%)
    - n=1
      - Salvage op.
        n=6 (100.0%)
          - 3 NSF
            - 2 ALTFF
              - Complete healing
                n=5 (83.3%)
              - Persistent necrosis
                n=1 (16.7%)

- Partial healing
  n=5 (23.8%)
    - n=1
      - Salvage op.
        n=6 (100.0%)
          - 1 NSF

- Persistent necrosis
  n=2 (9.5%)
    - n=1
      - Debridement only
        n=6 (22.2%)
          - Persistent necrosis
            n=6 (100.0%)
Figure 6