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## Multifactorial clinical analysis of factors affecting necrosis of nasal septal mucosal flap after salvage surgery for recurrent nasopharyngeal carcinoma

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To investigate the associated risk factors affecting necrosis of the nasal septal mucosal flap (NSF) after salvage surgery for recurrent nasopharyngeal carcinoma (NPC). A retrospective analysis was conducted on patients with recurrent NPC who underwent endoscopic salvage surgery and NSF repair. Factors analyzed included second-course radiotherapy history, recurrence T stage, recurrence time, and postoperative packing time. Logistic regression identified independent risk factors. Second-course radiotherapy, advanced T stage recurrence, longer recurrence time, and shorter postoperative packing time were identified as independent risk factors for NSF necrosis. Patients with second-course radiotherapy had an 8.338 times higher risk of flap necrosis. Advanced T stage and longer recurrence times were also associated with increased risk. Nasal packing for less than 5 days presented a higher risk of flap necrosis compared to packing for 5 days or more. The predictive model demonstrated good predictive ability. The second-course radiotherapy history, the recurrence T stage, the recurrence time, and the postoperative packing time are independent risk factors for necrosis of the nasal septal mucosal flap after salvage surgery for recurrent nasopharyngeal carcinoma.

**Keywords** Recurrent nasopharyngeal carcinoma, Salvage surgery, Nasalseptal flap, Flap necrosis, Multifactorial analysis

Nasopharyngeal carcinoma (NPC) is a malignant tumor occurring in the nasopharynx, classified as a type of head and neck tumor. Radiotherapy is the preferred treatment for NPC, with approximately 90% of early-stage disease patients being curable through radiotherapy<sup>1</sup>. However, due to the concealed anatomical location and non-specific early symptoms, more than 70% of NPC patients are diagnosed at stage III or IV<sup>2</sup>. Approximately 20–30% of patients with advanced NPC are incurable due to recurrence and/or metastasis<sup>3</sup>.

Treating recurrent NPC is challenging due to its complex anatomy and the effects of previous radiotherapy. Endoscopic surgery, as a minimally invasive technique, has been increasingly used to treat recurrent NPC. Postoperative wounds require the use of autologous tissue flaps, such as nasal septum mucosal flaps or temporal muscle flaps, for repair. Flap necrosis is a significant complication, impacting surgical outcomes, prolonging healing time, increasing infection risk, and necessitating further surgical interventions. This study aims to explore and identify risk factors for flap necrosis following endoscopic nasopharyngeal tumor resection and nasal septum mucosal flap repair in patients with recurrent NPC. By analyzing these factors, we hope to provide clinicians with information to optimize surgical strategies, reduce complications, and improve overall patient outcomes.

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## Methods

A retrospective analysis was conducted on 137 patients who underwent endoscopic nasopharyngeal tumor resection and nasal septum mucosal flap (or combined nasal floor mucosal flap) repair for recurrent NPC at Fujian Cancer Hospital from January 2017 to April 2024. Inclusion criteria: (1) diagnosed with recurrent NPC after admission; (2) initial treatment with standard radiotherapy; (3) received endoscopic nasopharyngeal tumor resection and nasal septum mucosal flap (or combined nasal floor mucosal flap) repair; (4) surgeries performed by the same surgical team at the institution. Exclusion criteria: (1) preoperative systemic infectious diseases or incomplete clinical data. (2) Negative intraoperative frozen section margins but positive postoperative pathological margins. Collected variables included age, gender, preoperative history of second-course radiotherapy, preoperative EB virus levels, preoperative neutrophil-lymphocyte ratio, albumin, recurrence time, preoperative T stage, recurrence T stage, BMI, etc. Second-course radiotherapy is defined as radiotherapy administered after tumor recurrence following an initial course of radiotherapy (more than 90 days apart).

**Surgical Technique:** After intubation and general anesthesia, the surgeon performs endoscopic surgery through the unilateral or bilateral nasal cavities using Electrosurgical Unit. Depending on the exposure of the lesion, the middle and inferior turbinates may be resected. For tumors confined to the nasopharyngeal cavity (rT1), posterior choana, nasal septum (rT2a), or the floor of the sphenoid sinus (rT3), the nasopharynx, posterior choana, posterior part of the nasal septum, and floor of the sphenoid sinus are resected with the tumor along safe margins. In patients with involvement of the parapharyngeal space, medial pterygoid, and lateral pterygoid (rT2), the resection extends to include the cartilaginous portion of the eustachian tube, parapharyngeal space, and medial part of the petroclival region. For tumors invading the skull base, sinuses, pterygopalatine fossa, and pterygoid structures (rT3), additional resection involves grinding the foramen lacerum, clivus, parts of the C1 vertebra, portions of the medial pterygoid plate, and the root of the pterygoid process, along with clearing the sinuses. For tumors invading the orbit, intracranial structures, or cranial nerves (rT4), surgical resection becomes highly challenging. In these cases, careful evaluation is necessary, and if R0 resection is not feasible, second-course radiotherapy is recommended. During surgery, attention is given to preserving the posterior septal artery. After tumor resection, a posterior septal artery-based nasal septum mucosal flap (or combined nasal floor mucosal flap) is prepared on the affected side or contralateral side to cover the surgical defect. A single 90 cm iodoform gauze strip is used to pack the affected nasal cavity. Preoperative MRI is used to assess the distance between the lesion and the internal carotid artery to determine if preoperative embolization or placement of a covered stent is required for protection. For patients with lymph node metastasis or recurrence, unilateral or bilateral neck dissection is routinely performed. A safe surgical margin is defined as 5–10 mm of peripheral mucosal margin and 2–3 mm of the basal margin from the tumor-affected area. When the basal margin is near the bone, part of the bone is resected. Frozen section pathological examination is performed intraoperatively to ensure negative margins. If positive margins are found, resection continues until negative margins are achieved. If the intraoperative frozen section pathology shows negative margins but the postoperative pathological examination of the surgical margins reveals positive results, a second surgery or a second course of radiotherapy is encouraged.

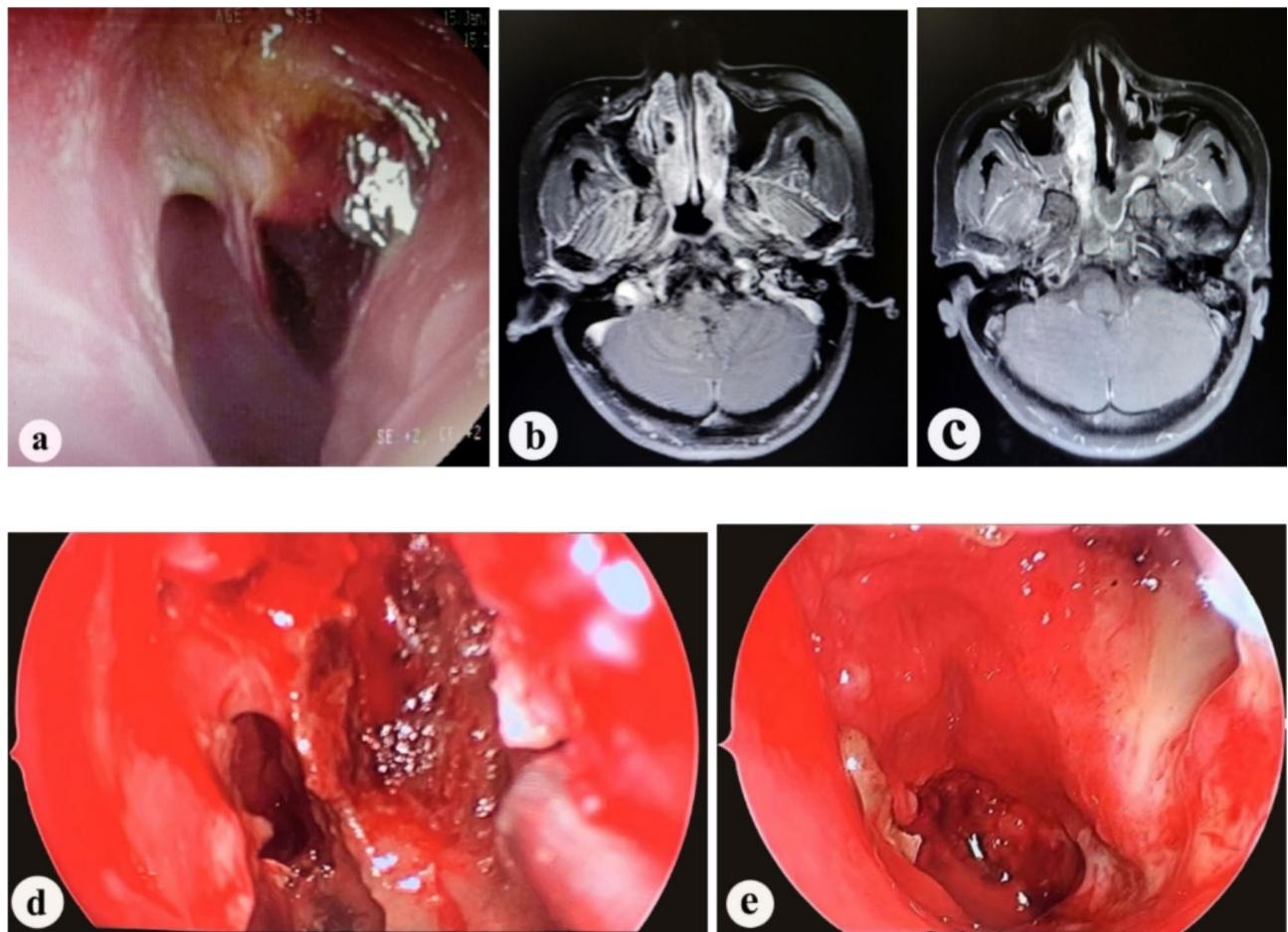
On postoperative day 3, an MRI scan with contrast enhancement of the nasopharynx and skull base is performed to assess the blood supply to the mucosal flap. The blood supply is re-evaluated during the removal of nasal packing under endoscopy. A final assessment of flap viability (survival or necrosis) is conducted at 1 month postoperatively through nasal endoscopic examination. Diagnosis criteria for postoperative flap necrosis: (1) Enhanced MRI suggests poor flap blood supply; (2) Flap color turns pale, dark purple, or black during endoscopic examination; (3) Confirmed absence of normal blood flow by cutting open part of the flap under endoscopy (Fig. 1). This study was approved by the institutional ethics committee of Fujian Cancer Hospital and informed consent was obtained from all patients or their designated proxies. All research was performed in accordance with relevant guidelines/regulations.

Quantitative data with normal distribution are expressed as mean  $\pm$  standard deviation ( $\pm$ s), analyzed using independent sample t-tests; categorical data are expressed as n (%), analyzed using chi-square tests or Fisher's exact tests. Univariate analysis was first conducted on factors affecting flap prognosis, including age, gender (0=female, 1=male), preoperative history of second-course radiotherapy (0=no, 1=yes), preoperative EB virus levels, preoperative neutrophil-lymphocyte ratio, albumin, recurrence time (0 = “T < 5 years”, 1 = “T  $\geq$  5 years”), preoperative T stage, recurrence T stage, BMI. Multivariate logistic regression analysis included variables with statistically significant differences from univariate analysis. A P-value  $< 0.05$  was considered statistically significant. SPSS Statistics (version 26.0) and R software (version 4.2.0) were used for analysis.

## Results

**Clinical Baseline Data:** A total of 137 patients were included, with 99 males and 38 females, average age  $49.72 \pm 9.987$  years. Flap survival was observed in 118 cases, with necrosis in 19 cases, resulting in a necrosis rate of 16.1%. Significant differences were found between groups in terms of second-course radiotherapy, initial T stage, recurrence T stage, recurrence time, and postoperative packing time ( $P < 0.05$ ). No significant differences were observed in age, gender, EB virus levels, BMI, neutrophil-lymphocyte ratio, and albumin levels ( $P > 0.05$ ) (detailed information in Table 1).

**Independent Risk Factors for Flap Necrosis:** Univariate analysis identified five potential predictive risk factors: second-course radiotherapy, initial T stage, recurrence T stage, recurrence time, and postoperative packing time. Multivariate logistic regression analysis showed that second-course radiotherapy, recurrence T stage, recurrence time, and postoperative packing time were independent risk factors for nasal septum mucosal flap necrosis after salvage surgery for recurrent NPC ( $P < 0.05$ ) (Table 2).



**Fig. 1.** (a) Preoperative nasopharyngeal endoscopy shows a mass in the left nasopharynx; (b) Preoperative enhanced MRI shows enhancement of the mass in the left nasopharynx; (c) Enhanced MRI on the third day post-operation shows good blood supply to the nasal septal mucosal flap. Iodoform gauze packing is visible on the surface of the mucosal flap; (d) On the fifth day post-operation, after removing the packing, nasal endoscopy shows good blood supply to the nasal septal mucosal flap; (e) One month post-operation, nasal endoscopy shows good blood supply to the nasal septal mucosal flap, which is closely attached to the nasopharynx.

## Discussion

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the epithelial cells of the nasopharynx mucosa, predominantly found in southern China and Southeast Asia. Due to its high sensitivity to radiotherapy, radiotherapy is the preferred treatment for NPC. However, approximately 10.0–36.0% of patients experience disease recurrence after initial treatment<sup>4</sup>. For these recurrent NPC patients, second-course radiotherapy and salvage surgery are the available treatment strategies. Despite second-course radiotherapy offering treatment opportunities for some patients, it is associated with numerous complications and significantly reduced efficacy compared to initial radiotherapy<sup>5</sup>. According to the NCCN guidelines, endoscopic salvage surgery has become the preferred treatment option for all locally recurrent resectable NPC (rNPC) patients<sup>6</sup>.

Due to the proximity of the nasopharyngeal lesions to the skull base and the surrounding major blood vessels such as the internal carotid artery, the repair of the surgical wound post-endoscopic salvage surgery for recurrent NPC is crucial to promote healing and protect the surrounding vital vessels. The nasal septal flap (NSF), based on the posterior septal artery branch of the sphenopalatine artery, has been considered an effective and reliable method for repairing postoperative nasopharyngeal wounds<sup>7</sup> and radiation necrosis wounds<sup>8,9</sup>. However, necrosis of the NSF is a significant complication during surgery. This study conducted a detailed analysis of patients with recurrent NPC undergoing endoscopic tumor resection and NSF (alone or in combination with nasal floor mucosal flap) repair, finding an 86.13% survival rate for the NSF, consistent with other studies<sup>10,11</sup>. Additionally, we found that second-course radiotherapy, tumor T stage, and nasal packing time are independent risk factors for NSF necrosis.

Patients undergoing second-course radiotherapy exhibited a significantly higher risk of flap necrosis. Our study found that the probability of NSF necrosis in patients who had undergone second-course radiotherapy was 8.338 times higher than in those who had not. Radiation therapy-induced nasopharyngeal tissue necrosis progresses in three stages: the early stage mainly involves the mucosa, presenting with local degeneration and

Factor	NSF survival group	NSF necrosis group	X <sup>2</sup> (t)	P
Age				
<60 years old	104	14	2.861	0.91
≥ 60 years old	14	5		
Gender				
Female	29	9	4.241	0.039
Male	89	10		
Reirradiation				
None	115	13	15.698	0.000
Have	3	6		
EB virus levels				
Normal range	99	14	1.182	0.277
Rising range	19	5		
Initial T stage				
T1	5	3	8.741	0.033
T2	18	6		
T3	72	6		
T4	23	4		
Recurrent T stage				
T1	56	2	9.473	0.024
T2	20	5		
T3	32	6		
T4	10	6		
Recurrence time				
<5 years	99	10	9.839	0.002
≥ 5 years	19	9		
BMI				
<22	43	9	0.830	0.362
≥ 22	75	10		
Postoperative packing time				
<5 days	39	15	8.694	0.003
≥ 5 days	79	4		
Neutrophil to lymphocyte ratio	5.60 ± 0.57	5.44 ± 1.07	0.119	0.905
Albumin levels	40.37 ± 0.36	39.07 ± 1.05	1.312	0.192

**Table 1.** Univariate analysis of factors influencing NSF after salvage surgery for recurrent NPC.

Factor	β	Standard error	Wald	P	OR	95%CI
Reirradiation	2.121	0.895	5.613	0.018	8.338	1.442–48.197
Initial T stage	-0.440	0.351	1.570	0.210	0.644	0.324–1.282
Recurrent T stage	0.746	0.296	6.328	0.012	2.108	1.179–3.768
Recurrence time	1.479	0.606	5.958	0.015	4.386	1.338–14.378
Postoperative packing time	-1.691	0.667	6.438	0.011	0.184	0.050–0.681
Constant	-2.196	1.184	3.440	0.064	0.111	-

**Table 2.** Multivariable logistic regression analysis of factors influencing NSF after salvage surgery for recurrent NPC.

necrosis; the second stage affects the mucosa and muscles, extending to the nasopharyngeal muscles and causing significant defects in the parapharyngeal space; the third stage manifests as skull base radiation osteonecrosis<sup>12</sup>. Most recurrent NPC patients who undergo radiation therapy experience at least the early stage of nasopharyngeal necrosis, affecting blood perfusion in the nasopharyngeal area. Second-course radiotherapy exacerbates this condition. After flap transplantation, in addition to the blood supply from the pedicle vessels, the flap also requires the establishment of new capillary networks with the surrounding tissue or base for nourishment, increasing the complexity of this process in the presence of nasopharyngeal disease. The nasal septal flap (NSF) based on the posterior septal artery, located in the radiation target area for NPC, may suffer from radiation-induced changes in blood flow and tissue degeneration, reducing flap survival. Studies indicate that second-course radiotherapy is

an independent risk factor for post-radiation nasopharyngeal necrosis (PRNN) in recurrent NPC patients<sup>13</sup> and an independent risk factor for the non-epithelialization of the nasopharyngeal area after NSF repair<sup>9</sup>. Therefore, stricter evaluations are warranted when using NSF for repair in patients who have undergone second-course radiotherapy.

Our study indicates an association between later T stage recurrence and flap necrosis. Advanced T stage tumors usually involve more extensive local invasion, necessitating wider tissue resection and flap repair. As the flap size increases, the distance between the distal part of the flap and the pedicle vessels lengthens, challenging blood supply to the distal flap. Researchers have found that advanced T stage is a risk factor for poor healing of the nasal septal flap<sup>14</sup>, and flap size is an independent risk factor for complications after reconstructive surgery<sup>15</sup>. Therefore, tumor staging must be considered when planning surgery and selecting flaps. While the NSF can provide blood supply within the range of the nasal septum and nasal floor mucosa, its coverage area is limited, which may be insufficient for large defects, especially when distal blood supply is compromised. For advanced T stage patients, NSF might not be the best choice for postoperative defects. Instead, the temporalis muscle flap, offering a larger tissue volume and located outside the radiation target area for NPC, could provide better coverage and blood supply for large defects after advanced T stage tumor surgery<sup>16</sup>.

Our study reveals that the time of NPC recurrence is a high-risk factor affecting flap survival. Patients with longer recurrence times have a higher risk of NSF necrosis compared to those with shorter recurrence times. This could be related to the effects of radiotherapy. Radiotherapy causes both acute and late toxic reactions, with late toxic reactions including radiation-induced oral mucositis, xerostomia, dysphagia, radiation caries, radiation-induced osteonecrosis of the jaw, cranial nerve damage, temporal lobe necrosis, hypothyroidism, carotid atherosclerosis, muscle fibrosis, and radiation skin reactions. Although symptoms like xerostomia may gradually alleviate over time, issues such as hearing loss, nutritional deficiencies, tissue fibrosis, and neurological damage may worsen with time<sup>17</sup>. Therefore, radiotherapy may cause vascular and microcirculatory damage to the nasopharynx and nasal septum mucosa in recurrent NPC patients, which could gradually worsen over time. Surgical intervention may further reduce tissue tolerance and healing ability, leading to insufficient blood supply to the nasopharynx and NSF, increasing the risk of necrosis. Studies show that a short interval between radiotherapy and salvage pharyngolaryngeal surgery may increase the risk of complications in microvascular free tissue transfer<sup>18</sup>. Therefore, in patients with long-term NPC recurrence, special attention should be paid to evaluating the long-term effects of radiotherapy and taking measures to reduce the risk of necrosis during flap repair surgery.

The duration of nasal packing affects flap survival. Nasal packing for less than 5 days presents a higher risk of NSF necrosis compared to packing for 5 days or more. The fit between the NSF and the nasopharyngeal defect is a crucial factor affecting NSF survival<sup>19</sup>. Shorter nasal packing times may result in poor NSF adherence, leading to NSF necrosis. While longer packing times may improve NSF adherence, they could also cause poor local blood circulation, adversely affecting flap blood supply and healing. Therefore, reasonable control of nasal packing time during surgery is essential to improve flap survival and reduce the risk of complications, finding a balance between ensuring good flap adherence and maintaining adequate local blood circulation. Our experience suggests that 5 days is an ideal nasal packing time for NSF post-surgery.

For patients with flap necrosis, the relationship between the lesion and the internal carotid artery should be assessed. If the lesion is close to the internal carotid artery, there is a risk of delayed massive hemorrhage, and it is strongly recommended that the patient undergo a second surgery with a temporalis muscle flap repair. For patients assessed to have a low risk of delayed massive hemorrhage and who are unwilling to undergo a second surgery, regular nasal irrigation, nasal endoscopic cleaning and dressing changes, as well as MRI monitoring, are recommended. Some patients with flap necrosis may experience headache symptoms, which can be treated with oral analgesics for symptomatic relief.

In conclusion, the second-course radiotherapy, the recurrence T stage, the recurrence time, and the postoperative packing time are identified as independent risk factors for NSF necrosis following salvage surgery for recurrent NPC. Clinically, identifying these independent risk factors can help in screening high-risk patients, allowing for more targeted treatment strategies and monitoring plans, ultimately reducing the risk of flap necrosis, improving surgical success rates, and enhancing patients' quality of life.

## Conclusion

The second-course radiotherapy history, the recurrence T stage, the recurrence time, and the postoperative packing time are independent risk factors for necrosis of the nasal septal mucosal flap after salvage surgery for recurrent nasopharyngeal carcinoma. Although our findings require further validation in subsequent studies, these results may assist in the clinical identification of high-risk patients for necrosis of the nasal septal mucosal flap after salvage surgery for recurrent nasopharyngeal carcinoma, enabling the implementation of more targeted treatment strategies to improve surgical success rates and enhance patients' quality of life.

## Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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## Author contributions

Youyuan Shi conceived and designed the research; Qilin Gong and Huaying Li analyzed and wrote the manuscript; Hui Liu collected and analyzed the data; All authors reviewed the manuscript.

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## Declarations

### Competing interests

The authors declare no competing interests.

### Additional information

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