A Novel Endoscopic Nasopharyngectomy Technique Using Low-Temperature Plasma Radiofrequency Ablation with Piece Resection In Resectable Locally Recurrent Nasopharyngeal Carcinoma: Operative Video and Technical Nuances

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Research Article
Abstract

Objectives: Endoscopic nasopharyngectomy (ENPG) with en bloc resection has been well accepted in resectable locally recurrent nasopharyngeal carcinoma (rNPC), but it is difficult to master the technique and disseminate. We designed a novel method using low-temperature plasma radiofrequency ablation (LPRA) with piece resection and evaluated the survival benefit.

Materials and Methods: A total of 56 resectable rNPC patients were retrospectively analyzed, and the following factors were assessed: ratio of R0 margin, overall survival rate (OS), local relapse-free survival rate (LRFS), and progression-free survival rate (PFS).

Results: All surgeries were successfully performed without any severe postoperative complications or deaths. The median operation time was 130 minutes (range, 32–280 minutes), with little blood loss (median, 30 ml; range, 5–500 ml). The average number of hospital days postoperation was 3 days (range, 2–5 days). All cases (100.0%) had R0 margins. The nasopharyngeal defects were completely re-epithelialized in 53 (94.6%) patients. The 2-year OS, LRFS, and PFS rates of the entire cohort were 100%, 90.7% and 88.6%, respectively. Multivariate Cox proportional hazards model analysis indicated that cycles of radiotherapy were independent risk factors for LRFS (hazard ratio [HR], 16.607; 95% CI 1.638–168.417; P = 0.017) and PFS (HR, 7.424; 95% CI 1.190–46.320; P = 0.032).

Conclusions: Radical endoscopic nasopharyngectomy is a novel, safe and relatively easier method for treating resectable rNPC by using low-temperature plasma radiofrequency ablation with piece resection. However, further data and longer follow-up time are needed to prove its efficacy.

Introduction

Nasopharyngeal carcinoma (NPC) is a frequent malignancy in Southeast Asia, especially in Guangdong Province of China. Radiotherapy is a fundamental treatment for NPC, with a 5-year overall survival (OS) rate of 68.2%-87.4% for nonmetastatic NPC.[1–3] However, 5–15% of patients develop residual or recurrent disease at the primary site.[4–6] Surgery can directly resect recurrent nasopharyngeal carcinoma (rNPC) and avoid sequelae caused by second-stage radiotherapy and chemotherapy. Theoretically, it is the best treatment method for rNPC.[7–9]

We designed a novel endoscopic nasopharyngectomy (ENPG) with en bloc resection that was applied in patients with rNPC; the approach could radically remove the primary tumor with minimal invasiveness. [10–12] Moreover, we performed a randomized, controlled trial to prove that ENPG significantly improved OS compared with IMRT in patients with resectable rNPC.[13] To date, ENPG has become the first choice for resectable rNPC, and the results have been accepted for Class I recommendation (2A Evidence) according to the Chinese Society of Clinical Oncology guidelines.[2] However, the techniques are difficult to master for most otorhinolaryngology head and neck surgeons, and only a few medical centers have applied them to more rNPC patients.
Ablation surgery is a new and relatively easier method to remove tumors that is performed by piece resection with a security boundary instead of en bloc resection. Ablation surgery has been successfully used in the treatment of liver cancer and liver metastases.\[14, 15\] Mai et al.\[16\] reported that endoscopic microwave coagulation therapy (MCT) achieved significant survival and tumor control without severe complications in selective rT1 NPC; the average operative time was 20 minutes (range: 15–30 minutes), and there was almost no intraoperative bleeding.\[16\] However, the technique was only suitable in selective stage I rNPC patients.

The rapid development of low-temperature plasma radiofrequency ablation (LPRA) in recent decades has seen the technique mature gradually in various applications of the medical field because of its low-temperature, minimally invasive, hemostatic, precise cutting, and ablation characteristics.\[17\] LPRA has been successfully applied in early laryngeal carcinoma and some maxillary sinus carcinomas.\[17\] However, to the best of our knowledge, there has been no previous report concerning the use of LPRA in rNPC.

Thus, we design a novel endoscopic nasopharyngectomy technique using LPRA with piece resection in resectable rNPC, and report the evaluation of the safety and efficacy.

**Materials And Methods**

**Patient selection**

rNPC patients who had undergone radical endoscopic nasopharyngectomy with piece resection using LRPA from May 2019 to July 2020 were enrolled in this study.

The enrollment criteria were as follows: 1) biopsy-proven recurrent undifferentiated nonkeratinizing carcinoma (World Health Organization [WHO] III), differentiated nonkeratinizing carcinoma (WHO II), and keratinizing squamous cell carcinoma (WHO I). 2) The disease was staged sT1–2N0M0 according to the new surgical staging system based on the International Union Against Cancer/American Joint Committee on Cancer TNM classification.\[12\]

The exclusion criteria for this study were as follows: 1) the tumor was beyond the sT1–2 range, 2) distant metastases were confirmed before surgery, and 3) the patient presented with physical conditions unsuitable for surgery, such as heart failure, severe cardiac tamponade, unstable hemodynamics, severe nervous system abnormalities, clinically apparent malperfusion including lower limb, cerebral, coronary and renal malperfusion, and visceral ischemia or severe hepatic and renal abnormalities. This study was approved by the ethical committee of Sun Yat-Sen University Cancer Center. Written informed consent was obtained from all patients.

**Preoperative preparation**
Before the operation, we designed the surgical tumor volume (STV), which was determined with magnetic resonance imaging (MRI) as well as position emission tomography-CT (PET-CT) imaging, and endoscopic findings plus an additional 0.5 to 1.0 cm peripheral mucosa margin and a 2–3-mm basal margin on the surface of the sphenoid bone and the clivus in the skull base. The surgeon strictly followed the planned surgical boundary to remove the tumor during the dissection. When the distance of the tumor to the internal carotid artery (ICA) was not enough to remain safe during the operation (<3–5 mm), a balloon occlusion test (BOT) was performed, which determined whether the ICA could be safely occluded without cerebral ischemia.

**Surgery method**

1) All operations were performed under systemic anesthesia guided by a 4-mm rigid endoscope (0 and 30°) (Karl-Storz, Tuttlingen, Germany). Nasal shrinkage was performed using 1:10,000 epinephrine to expose the nasopharyngeal cavity and tumor adequately.

2) Before excision, the tumor was marked by the bilateral nasal cavity according to the planned STV using low-temperature plasma (EIC8898-01) (Smith & Nephew, London, England). The first step was ablated from the surroundings to the center of the tumor using piece method in the superior wall of the nasopharynx, during which the soft tissue was gasified by LPRA and cleaned up by suction. The second step was ablation of the posterior parietal wall of the nasopharynx from the superior wall to the distal incision margin. The third step was ablation of the lateral margin of the tumor along the anterior side of the eustachian tube toward the pharyngeal space until no obvious mucosa of the lateral margin was observed by the naked eye (Supplementary material: Video 1 and 2). When the coblation head could not reach the deep pharyngeal space, the head could be mildly bent to adjust the distance of the pharyngeal space. When the tumor is low and cannot be resected through the nose, the head be inserted in the mouth and enter the nasopharynx through the oropharynx for surgical resection. When seeing obvious arterial pulsation during resection of the pharyngeal space, the lateral margin should be quickly ablated to avoid a massive ICA (Fig. 1A and B).

3) After washing the operative lumen on the wound surface, frozen pathology from the suspicious surgical margin surrounding the tumor was retained to determine whether the surgical resection scope was sufficient. If not, the resection scope should be further expanded.

4) When we resected deeper margins in the parapharyngeal space or exposed a broad skull base or the patient underwent second-stage radiotherapy, a posterior pedicle nasal septum and floor mucoperiosteum flap (nasal septum and floor flap, NSFF) were harvested to repair the defect, as reported in our previous study[7, 11, 18] (Fig. 1C).

5) Some absorbable gelatin sponges were gently placed into the nasopharynx to reduce hemorrhage and prevent turbinate synechiae. Absorbable fibrin glue (Shanghai RAAS, Shanghai, China) was used to pack the nasopharynx and avoid the discomfort and hemorrhage of extraction after surgery.

6) Contrast-enhanced MRI of the nasopharynx was performed within 1 week after the operation to evaluate excision extension, which was consistent with the planned STV. Endoscopic nasal clean-up was performed every 2–4 weeks until the defect was completely epithelialized (Fig. 2).
Follow-up

All patients were followed up to assess the surgical outcomes, disease and performance status every 3 months in the first 3 years after the operation, every 6 months in the fourth and fifth years, and annually thereafter. Follow-up examinations included complete physical examinations, chest X-ray, abdominal ultrasonography, MRI of the head and neck and/or whole-body bone scan.

Statistical analysis

The ratio of the R0 margin was defined as complete macroscopic resection with a negative microscopic margin. The following endpoints were assessed: ratio of the R0 margin, overall survival rate (OS), local relapse-free survival rate (LRFS), and progression-free survival rate (PFS). OS was measured from the date of treatment to the date of the first observation of death due to any cause. LRFS was measured from the date of treatment to the date of the first observation of local recurrence. PFS was measured from the date of treatment to the date of the first observation of local or regional recurrence or distant metastasis. For all cohorts, data for patient characteristics were described as numbers and percentages, and continuous data are presented as medians. We used the nonparametric Spearman rank correlation to determine links between re-epithelialization with or without NSFF. The Wilcoxon rank-sum test was conducted for ranked data. Survival results were calculated using the Kaplan–Meier method, and differences were compared using the log-rank test. Covariates significantly associated with prognosis detected in univariate analysis ($P < 0.1$) were included in the multivariate Cox proportional hazards model to identify the independent prognostic factors. All analyses were performed using SPSS software (version 22.0, SPSS, Chicago, IL, USA), and a two-tailed $P$ value less than 0.05 was considered statistically significant.

Results

Patient characteristics and surgical outcomes

A total of 56 resectable nasopharyngeal tumor patients, including 44 males and 12 females, with a median age of 46 years (range, 23–68 years), were enrolled in the present study. Based on these imaging data, 32 patients were classified as sT1, and the remaining 24 patients were classified as sT2 (Table 1)
## Table 1
Clinical characteristics and treatment outcomes by LPRA with piece resection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NO.</th>
<th>%</th>
<th>2-y LRFS</th>
<th>P</th>
<th>2-y PFS</th>
<th>P</th>
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<tr>
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<td>23–68</td>
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</tr>
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</tr>
<tr>
<td>Female</td>
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</tr>
<tr>
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<tr>
<td>One</td>
<td>43</td>
<td>76.8</td>
<td>97.6</td>
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<td>95.3</td>
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<tr>
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<td>41.5</td>
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<td>1</td>
<td>32</td>
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<td>89.8</td>
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<tr>
<td>2</td>
<td>24</td>
<td>42.9</td>
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<tr>
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<tr>
<td>&gt; 5 mm</td>
<td>53</td>
<td>94.6</td>
<td>90.1</td>
<td></td>
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<td>3–5 mm</td>
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<td>5.4</td>
<td>100</td>
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<td>100</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
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<td>94.6</td>
<td>90.6</td>
<td></td>
<td>88.4</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>5.4</td>
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<td></td>
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<tr>
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<tr>
<td>LPRA without NSFF</td>
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<td>R0 margin</td>
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<td></td>
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<tr>
<td>All patients</td>
<td>56</td>
<td>90.7</td>
<td>88.6</td>
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Abbreviation: ICA, internal carotid artery; NSFF, nasal septum and floor mucoperiosteum flap; LPRA, low-temperature plasma radiofrequency ablation; LRFS, local relapse-free survival rate; PFS, progression-free survival rate.
All endoscopic nasopharyngectomy using LPRA with piece resection were successfully performed, and no patients experienced any severe postoperative complications or death. The median operation time was 130 minutes (range, 32–280 minutes), with little blood loss (median, 30 ml; range, 5–500 ml). The average number of hospital days postoperation was 3 days (range, 2–5 days). No patients required a blood transfusion. All cases (100.0%) had radical resection with R0 margins. Forty-three patients simultaneously harvested NSFF in one operation. The nasopharyngeal defects were completely re-epithelialized in 53 (94.6%) patients, and the median re-epithelialization time was 1.9 months (range, 0.5–10.8 months). There was no significant difference in the ratio of re-epithelialized cells with or without NSFF (100% vs. 93.0%, P=0.328). Three patients with a 3–5 mm distance to the ICA successfully underwent LPRA with piece resection (Table 1).

During the follow-up period (median, 20 months; range, 7–28 months), four patients were diagnosed with primary recurrence, and 1 patient was diagnosed with cervical lymph node recurrence. The 2-year OS, LRFS, and PFS rates of the entire cohort were 100%, 90.7% and 88.6%, respectively. From the univariate Cox proportional hazards model, gender, sT classification, distance to ICA, re-epithelialization and surgical method were nonsignificantly associated with LRFS and PFS. Cycles of radiotherapy were a prognostic factor for LRFS and PFS (P=0.018 and 0.031). Multivariate Cox proportional hazards model analysis indicated that cycles of radiotherapy were independent risk factors for LRFS (hazard ratio [HR], 16.607; 95% CI 1.638–168.417; P = 0.017 ) and PFS (HR, 7.424; 95% CI 1.190–46.320; P = 0.032) (Table 2, 3 and Fig. 3).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age (≤46 vs. &gt;46y)</td>
<td>1.261 (0.177-8.955)</td>
<td>0.817</td>
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<td>Gender (Male vs. Female)</td>
<td>0.034 (0.000-962.415)</td>
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<td>Cycles of radiotherapy (1 vs. 2)</td>
<td>16.614 (1.635-168.771)</td>
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<td>sT classification (1 vs. 2)</td>
<td>1.307 (0.184-9.279)</td>
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<td>Distance to ICA (&gt; 5 mm vs. 3–5 mm)</td>
<td>0.045 (0.000-2.84E+5)</td>
<td>0.735</td>
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<td>Re-epithelialized (Yes vs. No)</td>
<td>0.046 (0.000-1.092E+13)</td>
<td>0.856</td>
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<tr>
<td>Surgical method (NSFF vs. without NSFF)</td>
<td>0.032 (0.000-545.213)</td>
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Abbreviation: ICA, internal carotid artery; NSFF, nasal septum and floor mucoperiosteum flap; CI, confidence interval
Table 3
Univariate and multivariate analyses of variables correlated with progression-free survival rate

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>Hazard ratio (95% CI)</td>
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<tr>
<td>Age (≤46 vs. &gt;46y)</td>
<td>0.837 (0.149-5.013)</td>
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<td>Cycles of radiotherapy (1 vs. 2)</td>
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<td>Surgical method (NSFF vs. without NSFF)</td>
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<td>0.433</td>
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Abbreviation: ICA, internal carotid artery; NSFF, nasal septum and oor mucoperiosteum flap; CI, confidence interval

Discussion

This is the first report that LPRA with piece resection has been used to treat rNPC. In this retrospective study, our research showed satisfactory safety and survival results without any severe postoperative complications or deaths. All cases (100%) had radical resection with R0 margins. The 2-year OS, LRFS, and PFS rates of the entire cohort were 100%, 90.7% and 88.6%, respectively. Cycles of radiotherapy were independent risk factors for LRFS (hazard ratio [HR], 16.607; 95% CI 1.638–168.417; P = 0.017) and PFS (HR, 7.424; 95% CI 1.190–46.320; P = 0.032)

In the late 19th century, Halsted found that the high recurrence rate of breast cancer after surgery was mainly due to the insufficient excision range of surrounding tissue. He designed the first radical mastectomy for breast cancer and proposed the concept of en bloc resection. Then, in 1954, Coled proposed the concept of "tumor-free surgery" in colon cancer surgery. Halsted and Coled proposed en bloc surgical operation, which is the main surgical principle at present and is respected as the classical surgical principle of oncology.[19, 20]

The nasopharynx site is deep and has complex adjacency of the nasopharynx, which is difficult to expose and adjacent to the ICA. Therefore, salvage surgery for primary failure can be challenging, with potentially severe morbidities.[6, 9, 10] Traditional open approaches have demonstrated not only marginal efficacy
but also many complications, such as facial numbness, trismus, and palatal fistula. ENPG with en bloc resection has significantly improved the prognosis of survival and is accepted in resectable rNPC, but it is difficult for most otorhinolaryngology head and neck surgeons to master the technique to ensure an adequate safe margin of parapharyngeal space, and only a few medical centers have applied the techniques to more rNPC patients.

ENPG was mainly performed using high-frequency electrocautery pens (HFEPs). HFEPs can cause extensive tissue damage, carbonization of soft tissue of the wound surface, and unclear division at the anatomical level. Moreover, because of the nasopharyngeal site adjacent to the ICA, it is difficult to ensure an adequate safe margin of the parapharyngeal space. Some studies have shown that the recurrence of parapharyngeal space is the main cause of postoperative residual disease and recurrence, with a ratio of up to 60%. At present, most hospitals still choose intense-modulated radiotherapy. The technology needs an experienced surgeon, and a method to reduce the difficulty of the process is urgently needed.

Low-temperature plasma radiofrequency ablation is a new ablation method that has a soft tissue cutting function similar to that of traditional electrosurgery. Approved by the US Food and Drug Administration in 2000, the technique has been used in clinical practice for more than 10 years and has achieved good results in orthopedics, neurosurgery and urology. In recent years, it has been gradually expanded to benign lesions such as those in the nose, nasopharynx and larynx, and even in treating head and neck malignancies. The working principle of LPRA is that when performing electrode plasma surgery using a high-frequency, high-voltage electric current electrode plasma layer formed in 0.9% sodium chloride, a plasma layer with sufficient energy can destroy organic molecular chains within tissue organization, and the tissue organization is decomposed into simple molecules, atoms or low-molecular-weight gases, realizing multiple functions such as cutting, hemostasis, and ablation. Compared with electrosurgical surgery, LPRA has similar efficacy, shorter operation time, less tissue trauma, less intraoperative bleeding and other advantages. Gong et al. also reported an observational study on the efficacy of low-temperature plasma in the treatment of early laryngeal cancer, and the results showed that the ablation of low-temperature plasma has advantages such as short operation time, less tissue trauma and less intraoperative bleeding. By vaporizing and immediately removing tumors, there is theoretically no risk of implantation metastasis. At present, radiofrequency ablation with piece resection is extensively used in the treatment of liver cancer and liver metastases, and the results show that piece resection is possible. Therefore, we designed a novel endoscopic nasopharyngectomy technique using low-temperature plasma radiofrequency ablation with piece resection to the treatment of resectable rNPC.

Our research results showed that piece resection was successfully performed without any severe postoperative complications or deaths, and no patients experienced implantation metastasis with R0 resection. We also had a shortened operation time (median: 130 minutes) and less intraoperative bleeding (median: 30 ml) compared with our previous studies. Meanwhile, we found that the method has a lower compliance for first assistant, which only involves cleaning up the vaporized tumor and the 0.9% sodium chloride. We think that the method is easier than our previous endoscopic nasopharyngectomy technique. Low-temperature plasma radiofrequency ablation has the function of
transporting 0.9% sodium chloride, which reaches the tissue and further reduces the temperature. After tissue resection, the injury to surrounding tissues and the pain and edema in the operative area can be significantly reduced, which may be beneficial to wound healing. Our research results showed that 94.6% of patients achieved re-epithelialization, which was higher than in our previous studies. Moreover, we found that all patients without NSFF achieved re-epithelialization, but the patients were after a course of radiation. In addition, LPRA has a higher operation accuracy, performs at a resection depth of 1–2 mm, does not cause carbonization of the wound, and more clearly observes the structure of parapharyngeal tissue, which gives surgeons the confidence to attempt resection of the deep parapharyngeal space. We treated 3 patients with a distance of 3–5 mm to the internal carotid artery who were not suitable for surgical treatment according to previous research, they were successfully completed radical endoscopic nasopharyngectomy, and did not suffer from internal carotid artery rupture or hemorrhage according to our own research.

Despite the promising results of this study, there are several potential limitations worth mentioning. First, the data were prospectively collected, and the results were retrospectively analyzed, which is less reliable than prospective analysis. Second, the number of cases in our study was limited, and all of them were enrolled from a single cancer center. Third, the median follow-up time was relatively short. Finally, a randomized controlled clinical trial is needed to prove this phenomenon.

**Conclusion**

Radical endoscopic nasopharyngectomy is a novel, safe and relatively easier method for treating resectable rNPC by using low-temperature plasma radiofrequency ablation with piece resection. However, further data and longer follow-up time are needed to prove its efficacy.

**Abbreviations**


**Declarations**

**Ethics approval and consent to participate:**
This study was approved by the ethical committee of Sun Yat-Sen University Cancer Center. Written informed consent was obtained from all patients. All the experiment protocol for involving human data was in accordance with the guidelines of China and Declaration of Helsinki in the manuscript.

**Consent for publication:**

All authors are agreed to be published.

**Availability of data and material:**

The authenticity of this article will be uploading the key raw data onto the Research Data Deposit (RDD) public platform. (www.researchdata.org.cn)

**Competing interests:**

None declared.

**Authors' contributions:**

All authors have read and approved the manuscript.

- **Study concepts:** Xiong Zou, Yi-Jun Hua, You-Ping Liu, Yu-Long Xie
- **Study design:** Xiong Zou, Yi-Jun Hua, Ming-Yuan Chen
- **Data acquisition:** Xiong Zou, You-Ping Liu, Ming-Yuan Chen
- **Quality control of data and algorithms:** Xiong Zou, Yan-Feng Ouyang, Yong-Long Liu
- **Data analysis and interpretation:** Xiong Zou, Ming-Yuan Chen, Zhi-Qiang Wang, Rui You
- **Statistical analysis:** Ming-Yuan Chen, Yu-Long Xie, Xi Ding, Qi Yang
- **Manuscript preparation:** Xiong Zou, Yi-Jun Hua, Ming-Yuan Chen
- **Manuscript editing:** Xiong Zou, Yu-Long Xie, Ming-Yuan Chen, Zi-Kun Yu

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References


Figures

Figure 1

The radical endoscopic nasopharyngectomy using low-temperature plasma radiofrequency ablation (LPRA) with piece resection and reconstruction using posterior pedicle nasal septum and floor mucoperiosteum flap to resurface nasopharyngeal defects in resectable recurrent nasopharyngeal carcinoma (rNPC) in a 51-year-old man. A-C displayed the anterior views of the nasal and nasopharyngeal cavity. (A) After full exposure of the nasopharyngeal cavity, the recurrent primary (indicated by red arrow) was located in the left lateral pharyngeal fossa of the nasopharyngeal cavity. (B) After radical endoscopic nasopharyngectomy, the skull base and normal tissues were exposed, they were clearly observes the structure of parapharyngeal tissue. (C) the flap (indicated by yellow arrow) recovered the nasopharyngeal defect one month after the surgery. ET, Eustachian tube.
Figure 2

The radical endoscopic nasopharyngectomy using low-temperature plasma radiofrequency ablation (LPRA) with piece resection and reconstruction using posterior pedicle nasal septum and floor mucoperiosteum flap to resurface nasopharyngeal defects in a 50-year-old man with recurrent nasopharyngeal carcinoma (rNPC). Contrast-enhanced magnetic resonance imaging (MRI) of the transverse section and coronal section of a patient before and after surgery. (A and D) rNPCs were located in the left roof of the posterior wall and left lateral pharyngeal fossa of the nasopharyngeal cavity. (B and E) The patient underwent low-temperature plasma radiofrequency ablation with piece resection, and the flap resurfaced the defect with good blood supply at 2 weeks after surgery. (C and F) The flap completely relined the nasopharyngeal mucosa at 5 weeks after surgery.
**Figure 3**

Kaplan–Meier curves of the progression-free survival rate (PFS, A) and the local relapse-free survival rate (LRFS, B) for all patients. Patients were stratified by the cycles of radiotherapy in PFS (C) and LRFS (D).

**Supplementary Files**

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- Video1.mp4
- Video2.mp4