



Clinical advances in nasopharyngeal carcinoma surgery and a video demonstration

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Abstract – Nasopharyngeal carcinoma (NPC) is highly radiosensitive, and radiotherapy is recommended for newly diagnosed NPC. Because of the poor visual surgical field, narrow operating space, difficulty protecting the internal carotid artery (ICA) and poor wound healing, the development of NPC surgery has been severely limited. For recurrent NPC, some open surgical approaches, such as the maxillary swing, successfully solve the above major problems. However, these operations are traumatic and lead to many postoperative complications. With the development of minimally invasive surgery, two concepts, the “third-hand technique” and “dumpling making technique”, have been proposed, combining with the intraoperative navigation systems and multiple anatomical landmarks for identifying ICA. Endoscopic nasopharyngectomy (ENPG) can also break through the above restrictions and has become a first-line treatment for locally recurrent NPC. Moreover, a new surgical staging system for recurrent NPC was devised to aid clinicians in choosing the most suitable treatment for these patients. A current study on ENPG alone for newly diagnosed stage I NPC shows that the long-term survival outcomes after ENPG are similar to those after IMRT. ENPG was associated with low medical costs and satisfactory QOL and might be an alternative strategy for treating newly diagnosed localized stage I NPC patients who refuse radiotherapy.

Key words: Nasopharyngeal carcinoma, Recurrent, Surgery, Endoscopic nasopharyngectomy

Introduction

Nasopharyngeal carcinoma (NPC) has an obvious geographical pattern of incidence and is endemic in Southern China and Southeast Asia with an annual incidence of 10–40/100,000 [1]. Radiotherapy is the first choice for newly diagnosed NPC. However, surgery, the classical treatment to cure malignant tumors, has not been recommended for newly diagnosed NPC for the following reasons: (1) undifferentiated nonkeratinizing squamous cell carcinoma (NKSCC) accounts for approximately 95% of Chinese NPC patients. NKSCC is highly malignant–prone to infiltration into the skull base and metastasis to the cervical lymph nodes–making it difficult to achieve radical resection of the nasopharyngeal primary tumors, cervical lymph nodes, and communicating lymphatic vessels. However, this tumor is highly radiosensitive, and radiation exposure can cover the above lesions simultaneously. The efficacy of radiotherapy can be further improved after combined chemotherapy.

The 5-year OS rates of stage I-IV patients were 96.3%–100%, 91.2%–95.1%, 87.5%–88.3%, and 78.6%–80%, respectively [2–5]. (2) The nasopharynx is located in the center of the skull base, and the surrounding tissues and organs do not move, which makes it possible to position for radiotherapy repeatably and precisely, but inaccessible to resect for surgery. Furthermore, the surrounding radiosensitive structures can tolerate radiation well and are suitable for high-dose radiotherapy. (3) Intensity-modulated radiotherapy (IMRT) can achieve excellent local control with a high dose of radiation to the tumors and results in few radiotherapy complications by limiting the dose to normal tissues. In addition, IMRT has been shown to reduce long-term toxicity in the salivary glands, temporal lobes, connective tissue, and auditory and optic structures [6] and has become the first choice for newly diagnosed NPC.

Approximately 10–36% of patients relapse after radiotherapy. Recurrent lesions are radiation-resistant; thus, the efficacy of reirradiation is poor, and the 5-year Overall Survival (OS) rate of recurrent NPC is only 26%–45% [7–9]. Furthermore, the radiation-related complications were severe, and the

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incidence of late radiation-induced injury above grade III in rT1-2 and rT3-4 patients was 45.8% and 78.3%, respectively. Moreover, 28.5% and 40.6% of patients developed new radiation encephalopathy and nasopharyngeal necrosis, respectively, which seriously affected the patient quality of life [8].

Compared with salvage IMRT, salvage surgery has obvious advantages for locally recurrent NPC: surgery can directly remove lesions insensitive to radiotherapy while avoiding reirradiation damage, and the related complications are relatively mild. In addition to killing the visible primary tumor and metastatic lymph nodes, the first cycle of radiotherapy also seals the lymph channels. Therefore, for recurrent NPC or regional lymph nodes, only the isolated lesions need radical resection without the need for radical surgery for primary nasopharyngeal lesions, neck lymph nodes, and communications with lymphatic vessels. However, in clinical practice, more recurrent NPCs are treated with reirradiation rather than salvage surgery. According to the NCCN guidelines (version 1.2019), surgery is not the only choice even for “resectable” recurrent NPC, and systemic therapy or radiotherapy is also recommended. The root cause is that traditional nasopharyngectomy is very invasive, difficult to perform, and not widely popular. The majority of traditional open surgical approaches require a facial incision to expose the nasopharyngeal cavity. The nasopharynx is adjacent to many important organs, especially the internal carotid artery (ICA) located in the parapharyngeal space, which can lead to fatal hemorrhage if accidentally injured. Therefore, only a few cancer centers can carry out such operations, while most patients with local recurrence still need to receive reirradiation.

The development of NPC surgery technology has faced three major problems: (1) the limited visual field and narrow operation space make it difficult to achieve radical resection; (2) recognition of the ICA is not easy, and the consequences of accidental injury are serious; and (3) the postoperative nasopharyngeal incision heals poorly, which affects patient quality of life.

Salvage surgery for locally recurrent nasopharyngeal cancer

Traditional open surgery

Access to the nasopharynx varies with different directions, such as the anterior approach (the midfacial degloving procedure), anterior-lateral approach (maxillary swing), lateral approach (infratemporal fossa approach and trans-mandibular-pterygoid approach), inferior approach (transpalatal approach), and transcervical approach with widespread exposure. Among these approaches, the maxillary swing successfully solved the above three major problems [10]: First, it provides complete exposure of the ipsilateral nasopharynx down to the oropharynx inferiorly and the parapharyngeal space posterolaterally. With the removal of the posterior part of the nasal septum, the contralateral nasopharynx can also be exposed. Safe resection of tumors invading the parapharyngeal space and those with retropharyngeal lymph node metastasis can be performed. Second, the ICA can be identified and safeguarded

by intraoperative palpation, ultrasound, or CT navigation. Finally, the maxillary osteo-cutaneous flap can maintain the blood supply when swung out. The temporalis muscle flap or microvascular free flap can be employed to protect exposed arteries to avoid blow-out bleeding; thus, the incidence of post-operative maxillary osteonecrosis and massive hemorrhage is low (0–1%), and wound healing occurs more easily than with the other approaches [11, 12]. Therefore, the maxillary swing has become one of the most influential open surgical approaches with the largest number of reported cases. In the largest series involving 338 patients (72% rT1-2) who received the maxillary swing for recurrent NPC, 78.4% of patients had microscopically clear resection margins, and the 5-year disease-free survival (DFS) rate was 63% for patients with negative margins and 37% for those with positive margins. However, traumatic resection can lead to a higher incidence of long-term procedure-related complications. Overall, 40.8% of patients developed middle ear effusion, and 11.2%, 10.9%, 9.5% and 7.1% had trismus, palatal fistula, osteoradionecrosis, and facial numbness, respectively [11].

Endoscopic nasopharyngectomy (ENPG)

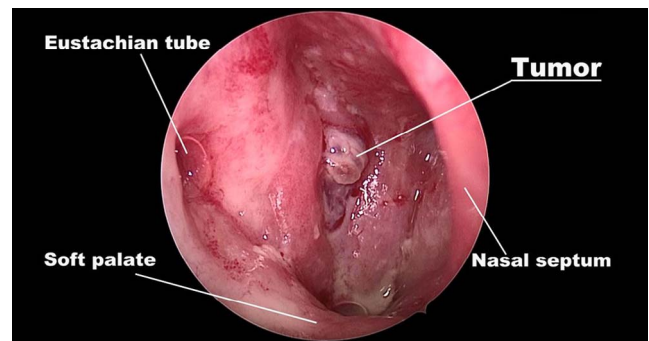
In the late 1990s, with the development of nasal endoscopic instruments and the maturation of functional endoscopic surgical techniques, minimally invasive surgery applied for the treatment of sinonasal malignancies began to emerge. In the early 2000s, the application of ENPG for locally recurrent NPC also started and gradually became mainstream. The first reported article on ENPG for recurrent NPC was reported by MY Chen in 2007 [13]. Among 25 patients (rT1-3), only 1 had a positive surgical margin, and no patients received post-operative radiotherapy (the patient with a positive margin refused it). The 1-year OS and local recurrence-free survival (LRFS) rates were 100% and 86%, respectively. No surgical complications or perioperative deaths occurred. In 2009, the authors once again reported 37 patients, including 17, 4, 14, and 2 patients staged as rT1N0M0, rT2aN0M0, rT2bN0M0, and rT3N0M0, respectively. Thirty-five patients achieved en bloc tumor resection with negative surgical margins. In the remaining two cases, the tumors were dissected into pieces, and one patient showed positive surgical margins. No patients received postoperative radiotherapy (the positive-margin patient refused), and no severe complications were observed. The 2-year OS, LRFS, and progression-free survival (PFS) rates were 84.2%, 86.3%, and 82.6%, respectively [14]. These two studies have shown that nasal endoscopic salvage surgery has good prospects for early recurrent NPC.

Moreover, MY Chen and his colleagues proposed eligible solutions to the major problems: (1) Exposure of the nasopharynx and radical resection: the nasopharynx is basically surrounded by bone. In endoscopic surgery, as long as dissection and excision occur along the bone surface, the mucosa of the anterior wall, superior wall, and posterosuperior wall of the nasopharynx can be removed. Furthermore, the “third-hand technique” was promoted to allow an assistant to use one or two straws to pull tissues and aspirate blood and smoke through the bilateral nasal cavities to reduce the inconveniences of the operation. The “dumpling making technique” was developed

to wrap the tumor using surrounding normal nasopharyngeal mucosae so that the surgical instrument could not contact the tumor directly, and the nasopharyngeal tumors could be removed en bloc, rather than in pieces, based on the principles of no-touch and en bloc resection. (2) Wound healing: wound recovery is necessary for NPC patients receiving postoperative radiotherapy. The pedicled middle turbinate mucoperiosteal flap was devised by MY Chen in 2007, and the study showed that 96% of patients achieved complete wound closure [13]. To expand the repair area further, a pedicle nasal septum and floor mucoperiosteal flap was reported among 12 locally recurrent NPC patients, with 2 patients receiving 2 cycles of radiotherapy. Finally, all flaps successfully covered all nasopharyngeal defects and relined the nasopharynx with good functional recovery [15]. (3) Protection of the ICA: because of the inability to expose and directly visualize the ICA during nasal endoscopic surgery, blow-out of ICA has been regarded as the biggest constraint for ENPG. Therefore, MY Chen and his colleagues strictly limited the indications and chose tumors that were ≥ 0.5 cm away from the ICA to ensure en bloc resection without damaging it. At present, multiple anatomical landmarks can be applied to comprehensively locate the ICA, such as the deep part of the eustachian tube, the tensor veli palatini muscle, and canalis pterygoideus [16–18]. Coupled with intraoperative navigation systems and ultrasound positioning, the safety of the ICA can be guaranteed.

Video 1 is a real example demonstrating the ENPG procedure. The patient was diagnosed with recurrent NPC, staged as rT2N0M0 and overall recurrent stage II. Since the tumor was more than 0.5 cm away from the ICA, the patient was treated with ENPG after excluding any surgical contraindications. The operation was performed with the endoscopic endonasal approach. Exploration revealed that the tumor was located in the right pharyngeal recess with a relatively clear margin. Before the operation, boundary marking was conducted, and the tumor was marked with an additional 5–10 mm surrounding normal tissue to ensure a safe margin. The anterior, superior, left and right lateral, inferior and posterior walls were excised in order. After the gross tumor was removed, a pedicle nasal septum and floor mucoperiosteal flap were used to reconstruct the nasopharyngeal defect. Three months later, the endoscopic image demonstrated that no abnormal neoplasm was observed in the nasopharynx, and the nasopharyngeal defect was completely re-epithelialized.

According to surgical practices for recurrent NPC patients, Chen et al. pioneered the specific definition of “resectable area” for ENPG in 2009 to include rNPC with tumors confined to the following locations: 1) the nasopharyngeal cavity (rT1); 2) the postnasal or nasal septum (rT2a); 3) the superficial parapharyngeal space (rT2b); or 4) the base wall of the sphenoid sinus (T3); in contrast, all rT4 diseases were unresectable by ENPG according to the 2002 clinical staging system of the UICC/AJCC. To promote the application of ENPG as salvage nasopharyngectomy, MY Chen and his colleagues established a new surgical staging system for patients with recurrent NPC with the largest series ($n = 894$) based on the UICC/AJCC rTNM staging system [19]. In detail, all UICC/AJCC clinical recurrent T1-4 and recurrent N0-3 tumors were stratified as resectable and unresectable based on the imaging data of the



Video 1. Procedure of endoscopic nasopharyngectomy and reconstruction of nasopharyngeal mucosa for recurrent NPC. The video presents an endoscopic nasopharyngectomy, followed by resurfacing the nasopharyngeal with a pedicle nasal septum and floor mucoperiosteal flap for a 31-year-old man with rT2N0M0 and overall recurrent stage II (American Joint Committee on Cancer seventh edition classification) non-keratinizing squamous cell carcinoma of right nasopharynx at 2018. <https://vcmedsciences.org/10.1051/vcm/2021001#V1>

head and neck according to the above definitions, and there were 8 subgroups in the rT stage and 7 subgroups in the rN stage. These stages were further subdivided into surgical T stages and surgical N stages with similar clinical characteristics and death risks and were reintegrated into 4 new “surgical” stages using a Cox proportional hazards model, which are minimal (stage I), limited (stage II), extensive (stage III), and disseminated recurrence (stage IV). For “surgical” stage I (sI) patients, ENPG was associated with a better OS than 2D-CRT and IMRT (5-year OS rates: 93.4%, 26.8%, and 71.1%, respectively; $P < 0.001$); therefore, ENPG is preferred. In “surgical” stage II, the 5-year OS rates of ENPG and IMRT were 61.8% and 53.8% ($P = 0.14$), respectively. Although there was no statistical significance between the two treatments, ENPG was probably related to fewer complications and lower risk. In “surgical” stage III, the lesion is “unresectable”, and IMRT was associated with a better OS than 2D-CRT and chemotherapy alone for sT3 patients (5-year OS rates: 27.7%, 15.9%, and 16.2%, respectively; $P = 0.022$); thus, IMRT is the first choice. In “surgical” stage IV, a combination of aggressive treatment (surgery or reirradiation) and palliative chemotherapy showed an improved 5-year OS compared with palliative chemotherapy alone and no treatment; however, the differences did not achieve statistical significance (OS rates: 16.4%, 8.1%, and 0%, respectively; $P = 0.482$). In short, compared with the recurrent TNM staging system, the “surgical” staging system exhibited improved prognostic value for predicting recurrent NPC patient survival and could aid clinicians in choosing the most suitable treatment for recurrent NPC patients. Moreover, a well-balanced cohort of 144 limited recurrent NPC patients was created by matching each patient who underwent ENPG with one who received IMRT [20]. The results indicated that ENPG was associated with a relatively good 5-year OS rate (77.1% vs. 55.5%, $P = 0.003$), QOL conservation (mean global health status score, 57.6 vs. 29.8, $P < 0.001$), and significant reduction in post-treatment complications (12.5% vs. 65.3%, $P < 0.001$) and medical costs compared with IMRT. The corresponding prospective study has been completed, and the results will be reported soon.

Currently, the Chinese *Expert consensus on the treatment of recurrent nasopharyngeal carcinoma* notes that for patients with locally recurrent NPC, ENPG is more suitable for the resectable rT1-2 stage, and radiotherapy should be supplemented for patients with a positive margin. For the rT3-4 phase, precise radiotherapy is the main treatment. Moreover, surgery is the first choice for regionally recurrent NPC. The *Nasopharyngeal carcinoma: United Kingdom National Multidisciplinary Guidelines* note that surgery is the first choice for locally recurrent NPC, and radiotherapy is only used as a second-line treatment.

Minimally invasive surgery alone for newly diagnosed NPC

Considering that ENPG has been successfully promoted and applied in recurrent NPC, some early malignant tumors, such as early esophageal cancer, early gastric cancer, and early glottic cancer, can currently be cured by endoscopic surgery. In addition, recent studies have reported that early screening technology for NPC can find 17.3%–47% of patients with stage I disease at the time of first diagnosis [21, 22], which provides a good research background for endoscopic salvage surgery.

Under the premise of ensuring a similar efficacy to IMRT and not violating the principles of surgical treatment for malignant tumors, we reported 10 newly diagnosed localized stage I NPC patients who voluntarily underwent ENPG alone [23]. Simultaneously, the data of 329 stage I NPC patients treated with IMRT were collected and used as a reference cohort. The indication criteria for ENPG were very strict: (1) stage T1 with a maximum primary tumor diameter ≤ 1.5 cm for radical resection and to reduce local recurrence and distant metastasis; (2) distance from the tumor margin to the ICA was ≥ 0.5 cm to avoid accidental injury; and (3) the minimal axial diameter on magnetic resonance imaging (MRI) was no more than 0.4 cm for the retropharyngeal lymph nodes (RPLNs) and 0.6 cm for the cervical lymph node (CLNs) – smaller than the radiographic diagnostic criteria for lymph node metastasis (0.5 cm for RPLNs and 1 cm for CLNs). Based on the fact if the size of the nasopharyngeal tumor, RPLNs, and CLNs are less than the above strict thresholds, the risk of sub-clinical lesions before surgery and recurrence and metastasis after surgery will be significantly reduced [24–27]. Therefore, there is no need for auxiliary treatment such as preventive neck dissection or neck radiotherapy after surgery to achieve the effect of radical resection for early NPC. The results showed that the 5-year OS, LRFS, regional relapse-free survival, and distant metastasis-free survival rates of the ENPG-treated patients were similar to those of the IMRT-treated patients (100% vs. 99.1%, 100% vs. 97.7%, 100% vs. 99.0%, 100% vs. 97.4%, respectively, $P > 0.05$). In addition, compared with IMRT, ENPG was associated with reduced total medical costs and improved QOL scores, including for dry mouth, sticky saliva, pain, and swallowing.

Therefore, we think ENPG might be an alternative strategy for treating newly diagnosed localized stage I NPC patients who refuse radiotherapy. While it must be emphasized that this cohort has been strictly selected for, and it remains to be seen if

the quality were repeatable by other centers of different levels. The contemporaneous review by Melvin et al. from the National Cancer Centre Singapore [28] stated that the results are impressive with regard to the possibility of replacing IMRT with ENPG in early-stage NPC patients without compromising the excellent prognosis, but the generalized application of ENPG for low-risk NPC should still be approached prudently, and prospective clinical trials are needed to further verify the results.

Conclusion

With deep insight into the biological characteristics of NPC and evolving treatment technologies, the treatment methods for NPC have been gradually enriched and updated. At present, radiotherapy is still the first choice for newly diagnosed NPC, and ENPG has become the first-line therapy for sI-II local recurrent NPC. Given the iterative upgrades of early screening technology, an increasing number of early patients can be found. By strictly restricting the indication criteria, this prudent radical surgical treatment for “very early” stage NPC is expected to become an alternative to radiotherapy for patients who are unwilling to experience radiotherapy toxicity. However, more studies and patients are needed in the future to validate these results.

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Competing interests

The authors declare that they have no conflicts of interest.

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