Minimally Invasive Surgery for Early-Stage Nasopharyngeal Carcinoma

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Abstract: According to the National Comprehensive Cancer Network guidelines, the preferred treatment for early-stage nasopharyngeal carcinoma (NPC) is radiotherapy, however, the toxic effects associated with radiotherapy have been a nuisance for patients. Minimally invasive surgery for recurrent NPC has been widely recognized as an effective way to completely remove the tumor and free the patient from or mitigate the toxicity of radiotherapy. Therefore, some researchers hope that minimally invasive surgery can be used to treat early-stage NPC. It is a bold and controversial attempt, and the researchers’ efforts have achieved initial results. This article reviews the preliminary results of minimally invasive surgery for NPC, especially the feasibility and challenges of minimally invasive surgery for early-stage NPC.

Key Words: Endoscopic nasopharyngectomy, endoscopic surgery, minimally invasive surgery, nasopharyngeal carcinoma, robot-assisted surgery

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy originating from the mucosal epithelium of the nasopharynx. According to the World Health Organization, NPC is divided into 3 pathological subtypes: squamous cell carcinoma, nonkeratinized carcinoma, and basal-like squamous cell carcinoma. Because of its sensitivity to radiotherapy, intensity-modulated radiation therapy (IMRT) has become the preferred treatment of NPC. However, the acute and chronic toxic reactions caused by radiotherapy, such as mucositis, dry mouth, tooth loss, acquired posterior nostril stenosis, radioactive encephalopathy, and radioactive osteonecrosis, have seriously reduced the quality of life of patients and even affected the survival rate of patients.1,2 In a 15-year follow-up study,2 almost all patients with early-stage NPC who received IMRT suffered from grades 1 to 3 acute toxicity, including mucositis (100%), radiodermatitis (99.5%), and xerostomia (96.3%). Subcutaneous fibrosis (89.8%) and deafness or otitis (72.2%) were the most common late toxicities. In addition, even after reducing the radiation therapy clinical target volume and dose, 54.4% of patients still suffered grade 2 or more radiotherapy toxicity.3

As a minimally invasive surgical technique, endoscopic surgery can make use of natural or artificial tract such as nasal cavity, throat, digestive tract, and thoracic cavity to perform delicate surgical operations, and remove lesions without external incision or with only a small incision.4,5 It not only can avoid the huge trauma caused by open surgery, reduces the pain of the patients, and accelerates the recovery of the patients after surgery,6 but also can avoid or alleviate patients suffering from radiation therapy toxicity.7 The nasopharynx is located behind the nasal cavity and can be reached through a nasal endoscopy. However, NPC usually occurs in the center of the skull base region and is adjacent to important nerves and blood vessels such as carotid artery, brain stem, and optic nerve. The difficulty of operation restricts the development of endoscopic application in the surgical treatment of NPC. In recent years, with the in-depth understanding of anatomy and the continuous improvement of surgical skills, endoscopic surgery has been gradually applied in the surgical treatment of NPC as an auxiliary or main surgical method, which can avoid or alleviate patients suffering from radiation therapy toxicity while completely removing tumor.

REVIEW OF ENDOSCOPIC SURGERY IN LOCALLY RECURRENT NASOPHARYNGEAL CARCINOMA

According to the published literature, 10.0% to 36.0% of patients with NPC recur after initial treatment,8 and the National Comprehensive Cancer Network guidelines recommend that salvage surgery should be the treatment of choice for all locally recurrent nasopharyngeal carcinoma (rNPC), when possible. A recent meta-analysis included 22 studies of 1186 patients with rNPC or residual NPC,9 showed that the patients with locally rNPC or residual NPC who underwent endoscopic surgery had significantly improved survival compared with open surgery. In addition, patients who accepted open surgery were also more
prone to serious complications, such as trismus, palatal fistula, cleft palate, nerve injury, osteonecrosis, flap necrosis, cerebrospinal fluid rhinorrhea, dysphagia, etc. The 2 most common complications were trismus and palatal fistula, accounted for 40.3% and 36.4% of all complications. The top 2 complications in patients underwent endoscopic surgery were otitis media and osteonecrosis, accounted for 45.0% and 11.2% of all complications, and fatal complications were rare.

In a multicenter randomized-controlled clinical trial comparing the efficacy and safety of endoscopic salvage surgery and IMRT in patients with locally rNPC,7 200 patients were randomly divided into endoscopic nasopharyngectomy (ENPG) group or IMRT group (1:1). A total of 96 of 100 patients in the ENPG group received ENPG, and all patients in the IMRT group received IMRT. The results showed that during the follow-up period of 42 to 69 months, a total of 74 patients died, of which 29 in the ENPG group were lower than 45 in the IMRT group. The 3-year overall survival rate in the ENPG group was 85.8%, which was significantly higher than that in the IMRT group (68.0%), and the 3-year disease-free survival and local recurrence survival were also better. This suggests that endoscopic surgery significantly improves overall survival compared with IMRT in patients with resectable locally rNPC.

The successful application of endoscopic surgery in locally rNPC has also led surgeons to further consider whether it is possible to apply these successful experiences in the treatment of early-stage NPC, which is a bold and innovative idea, and some researchers have put this idea into practice.

**APPLICATION OF ENDOscopic SURGERY IN EARLY-STAGE NPC**

There are few publications on endoscopic surgery in the treatment of early-stage NPC (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/SCS/E220). The scholars have used single endoscopic surgery or endoscopic surgery combined with chemotherapy or chemoradiotherapy to explore the efficacy and safety of endoscopic surgery in the treatment of early-stage NPC.

Huang and Qiu10 applied endoscopic surgery for the first time in the treatment of 10 patients with early-stage NPC. All patients received 4 courses of cisplatin, paclitaxel and 5-fluorouracil chemotherapy after endoscopic surgery and were followed up for 9 to 128 months, with a 2-year survival rate of 100%, local recurrence occurred in 1 patient, and no postoperative complications such as dry mouth and sticky saliva occurred.

Chen et al11 introduced a novel ENPG and described it in details,12 including: defined the tumor invasion regions and surgical margins for high-risk microinvasion regions. The area of tumor invasion plus an additional 0.5 to 1.0 cm of peripheral mucosal margin and 2 to 3 mm of basal margin of the sphenoid bone surface and cranial base ramp were defined as the surgical margins, which the surgeons need to strictly follow to remove the tumor during dissection. The team successfully used the technology to treat rNPC.13,14 Based on the above foundation, Liu et al15 collected 339 patients with stage I NPC from 2007 to 2017, and performed ENPG alone for 10 patients who refused radiotherapy, the remaining 329 patients received IMRT. All patients undergoing surgery must meet the following conditions: first, the primary tumor or tumor base is <1.5 cm. Second, the tumor is at least 0.5 cm away from the internal carotid artery. Third, the retropharyngeal lymph node is <0.4 cm, and the cervical lymph node is <0.6 cm. The results showed that after a median follow-up of 59 months, none of the 10 patients who received ENPG had died or had local recurrence or metastasis, with a 5-year overall survival rate of 100%, local recurrence-free survival rate of 100%, regional recurrence-free survival rate of 100%, and the distant metastasis-free survival rate of 100%, which were similar to the IMRT group (99.1%, 97.7%, 99.0%, 97.4%). However, compared with IMRT group, the ENPG group had less cost of hospitalization and improved quality of life scores such as pain, swallowing, dry mouth, and thick saliva.

Zhang et al16 explored the feasibility and safety of ENPG combined with low-dose radiotherapy (LDRT) in the treatment of early NPC by referring to the above surgical methods.12,15 A total of 37 patients with localized T1-2 NPC in the experimental group were treated with ENPG+LDRT program (ENPG +LDRT group), meanwhile, they recruited 132 T1-2 NPC patients in the control group treated with IMRT (IMRT group). With a mean follow-up time of 54 months, only 1 patient in the ENPG+LDRT group died of hepatic metastases. There were no significant differences in 5-year overall survival, distant metastasis-free survival, local recurrence-free survival, and regional recurrence-free survival in the ENPG group compared with IMRT group (97.3% versus 97.7%, 97.3% versus 90.2%, 100% versus 95.5%, 100% versus 97.0%, all P > 0.05), but patients’ quality of life and the incidence of late radiotherapy-related sequelae were lower.

Weng et al17 reported the short-term and long-term prognostic effects of ENPG combined with chemoradiotherapy of early-stage NPC. Fifty-eight patients with ENPG combined with chemoradiotherapy (surgery group) and 98 patients with conventional chemoradiotherapy (nonsurgery group) were matched by a propensity score of 1:2. The results showed that the 5-year overall survival rate, disease-free survival rate, and relapse-free survival rate in the surgery group were higher than those in the nonsurgery group (98.3% versus 91.7%, 98.3% versus 81.4%, 100% versus 90.1%). At the end of therapy, there were no cancer residues in the surgical group compared with 14 in the nonsurgical group, and the surgery group also had a lower incidence of severe oral mucositis.

**A NEWLY MINIMALLY INVASIVE SURGERY: ROBOT-ASSISTED SURGERY**

With the rapid development of artificial intelligence, robot-assisted surgery (RAS) has also been gradually applied in otolaryngology head and neck surgery.18–20 Ozer and Waltonen21 first described a robotic-assisted transoral soft palate incision for NPC resection in a cadaveric model to achieve full exposure of the nasopharynx and localize and dissect the internal carotid artery without making an external incision, then stitched with the help of a robot. Tsang et al22 performed nasopharyngectomy for 12 patients with rNPC using the da Vinci surgical robot. The results showed that the operative time was comparable to that of open surgery, with a median operative time of 225 minutes. The survival rate was 83.0%, and the disease-free survival rate was 61.0%. Ding et al19 applied transoral robotic surgery (TORS) retropharyngeal lymph node dissection in NPC patients with retropharyngeal lymph node recurrence, negative margins were obtained in all patients, en bloc resection was achieved in 8 of 10, and only 1 patient experienced recurrence at 19-month follow-up. RAS makes minimally invasive surgery for head and neck cancers safer and more feasible by providing intraoperative flexible robotic arms and 3-dimensional views. We conjecture that RAS may also be used in the treatment of early-stage NPC in the future.
CHALLENGES AND PROSPECTS OF MINIMALLY INVASIVE SURGERY FOR EARLY-STAGE NPC

Although endoscopic surgery for rNPC has been accepted by the public and has achieved good results, there are still few studies on endoscopic surgery for early-stage NPC. It may due to the more practical clinical problems; first, radiotherapy is still the first-line therapy for early-stage NPC, and its high cure rate cannot be ignored; second, the anatomical position of the nasopharynx is hidden and adjacent to important blood vessels and nerves, so the anatomical theory and surgical skills of the operator are highly required. Third, in the existing reports, the sample size of endoscopic surgery for early-stage NPC is small, and there is no convincing big data or multicenter clinical trials to confirm its reliability. In addition, some researchers pointed out that most of the cases reported in the current literature were carefully selected, and the screening process was very complicated, especially for the specific requirements of lymph node size, which might not be universally applicable.

Although some researchers are skeptical or even negative about the efficacy of endoscopic surgery in the treatment of early-stage NPC, it does not mean that this treatment option is completely unfeasible. First of all, with the improvement of people’s health awareness and the application of screening technologies such as Epstein-Barr Virus liquid biopsy, magnetic resonance imaging, and artificial intelligence screening, about 41.7% of early NPC limited nasopharyngeal cavity have been found, which provides the possibility of complete resection of tumors by endoscopic surgery. Second, the implementation of endoscopic technology training and indepth understanding of anatomy have improved the surgical skills of surgeons. Endoscopic surgery is no longer only used to treat inflammatory diseases of the nasal cavity and sinus, but also gradually applied to the complex nasopharyngeal-skull base anatomy. In addition, artificial intelligence-assisted technology and 3-dimensional navigation technology also guide and help surgeons to perform delicate and accurate dissection. All these factors provide favorable conditions for endoscopic surgery in the treatment of early-stage NPC. However, it is worth noting that the application of minimally invasive surgery to early-stage NPC should be very cautious. Strict selection of cases, superb skills of the operators, ensuring the most negative margins, and accurate postoperative follow-up treatment are all necessary indeed.

CONCLUSION

In summary, the current study indicates that minimally invasive surgery is feasible for the treatment of early-stage NPC, and its short-term efficacy is encouraging, but its long-term efficacy needs further observation, and multicenter and large-sample clinical studies are needed to further verify the reliability of the efficacy. Minimally invasive surgery provides a new option for patients with early-stage NPC, especially those who refuse radiotherapy, and it may become a new direction for the treatment of early-stage NPC in the future.

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Benign Meningioma With Rare Radiological and Behavioral Features

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Background: Meningiomas are usually dura-based primary nonmalignant neoplasms of the central nervous system. It is extremely rare that a meningioma is located at the convexity of the brain, but shows no dura attachment and causes osteolysis of the skull.

Case Presentation: A 57-year-old woman presented with an incidentally discovered scalp lump on the head. Neurological deficits were not found. Radiological examination revealed a localized osteolytic lesion in the right parietal bone, which was initially diagnosed as a bone tumor and was surgically resected. At surgery, a tumor mass was found located at the brain convexity without dura attachment. It was tightly attached to the brain parenchyma and had no distinct boundary from the brain. The mass was rather small, but resulted in significant osteolysis of the skull and destruction of the dura. Simpson grade I resection of the tumor was performed. Histological and immunohistochemical results indicated a meningothelial meningioma.

Conclusions: Both preoperative and intraoperative diagnoses are difficult for this case. Knowledge of this case is crucial for clinicians to be aware of this entity because it can be easily confused with bone tumors. Further research on the relationship between meningioma and bone metabolism is required to investigate the mechanism of osteolysis.

Key Words: Dura destruction, intraparenchymal meningioma, osteolytic meningioma, subcortical meningioma

Meningiomas are considered the most common primary neoplasms of the central nervous system, accounting for 54.5% of nonmalignant tumors in adults.† These are generally extra-axial dura-based masses with typical radiological features and therefore easily diagnosed preoperatively. We present a case of meningioma with very special radiological and behavioral features, making preoperative and intraoperative diagnoses rather difficult. Radiological examination revealed a localized osteolytic lesion in the right parietal bone. During the operation, the skull and dura were discovered to be destroyed. A small sized tumor mass was found located at the brain convexity, which traversed a dual defect, but had no dura attachment and no contact with the destructed inner table of the skull bone. Histological and immunohistochemical results indicated a meningothelial meningioma. As far as we know, osteolytic meningioma associated with this type of clinical phenotype has not yet been reported.

CASE PRESENTATION

A 57-year-old woman came to our outpatient clinic because she discovered an accidental scalp lump in the right parietal region of the head. She did not complain about headaches, limb weakness, convulsions, or any other discomfort. Physical examination revealed a painless subcutaneous mass, ~5 cm in diameter, which was hard in nature, clear and stationary through which fluid leakage was noticed (Fig. 2A). After the fluid leakage was noticed, an extra-axial fluid collection was removed through a small incision (Fig. 2B). The patient underwent surgical resection of the lesion with a typical U-shaped incision under general anesthesia. The right parietal bone was disrupted prominently in the inner table and the outer table was as thin as an eggshell with small defects through which fluid leakage was noticed (Fig. 2A). After the outer table was partially opened, no intraosseous tumor mass was observed, but the underlying dura mater was abnormally thin and translucent with several small defects. A small soft papillary mass attached to the brain traversed one of the defects.