



A 4-year review of surgical and oncological outcomes of endoscopic endonasal transpterygoid nasopharyngectomy in salvaging locally recurrent nasopharyngeal carcinoma

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Abstract

Purpose To study the surgical and oncological outcomes of endoscopic endonasal transpterygoid nasopharyngectomy (EETN) in salvaging locally recurrent nasopharyngeal carcinoma (NPC).

Method This was a retrospective clinical record review study carried out at a tertiary centre from June 2013 until May 2017. A total of 55 locally recurrent NPC patients (rT1–rT4) underwent EETN performed by single skull base surgeon with curative intention with postoperative adjuvant chemotherapy but without postoperative radiotherapy.

Results There were 44 (80.0%) males and 11 (20.0%) females, with mean age of 52.5 years. The mean operating time was 180 min (range 150–280 min). 85% (47/55) of patients achieved en bloc tumour resection. 93% (51/55) of patients obtained negative microscopic margin based on postoperative histopathological evaluation. Intraoperatively, one (1.8%) patient had internal carotid artery injury which was successfully stented and had recovered fully without neurological deficit. There were no major postoperative complications reported. During a mean follow-up period of 18-month (range 12–48 months) postsurgery, five patients (9.1%) had residual or recurrence at the primary site. All five patients underwent re-surgery. One patient at rT3 passed away 6 months after re-surgery due to distant metastasis complicated with septicaemia. The 1-year local disease-free rate was 93% and the 1-year overall survival rate was 98%.

Conclusions EETN is emerging treatment options for locally recurrent NPC, with relatively low morbidity and encouraging short-term outcome. Long-term outcome is yet to be determined with longer follow-up and bigger cohort study. However, a successful surgical outcome required a very experienced team and highly specialised equipment.

Keywords Nasopharyngeal carcinoma · Nasopharyngectomy · Endoscopic surgery · Recurrence · Outcome

Introduction

Nasopharyngeal carcinoma (NPC) is very rare among Caucasian with age standardized incidence rate of 0.5 per 100,000 [1]. However, it has a high prevalence among natives of southern China, Southeast Asia, the Arctic, and the Middle East/North Africa.

According to National Cancer Registry Malaysia 2007–2011, Sarawakians had the highest incidence of nasopharyngeal carcinoma among other states [2]. Beena et al. [3] described Bidayuh group (native people of Sarawak) to have the highest risk of nasopharyngeal carcinoma in the world; about 50% higher than Hong Kong which had the highest record by any population-based registry for the same period. Genetic susceptibility, local dietary habits, environmental factors, and Epstein–Barr virus (EBV) infection were

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the suggested etiological factors in view of distinct racial and geographical distribution of nasopharyngeal cases worldwide [3].

The primary treatment for untreated NPC is radiotherapy alone for early stage lesion and concurrent chemo-radiation for advanced tumour [4]. The reported incidence of local recurrence was approximately 8–58% [5–7]. Local recurrent NPC can be treated with salvage re-irradiation or surgery [8]. Despite the advent of intensity-modulated radiotherapy (IMRT), high-dose re-irradiation may still result in severe complications such as osteoradionecrosis, brain necrosis, radiation induced myelitis, hypopituitarism, and trismus [8–10].

Nasopharyngectomy is a well-established surgical procedure for salvaging locally recurrent NPC, with various surgical approaches, e.g., midfacial degloving, transpalatal, transmaxillary, maxillary swing, or transmandibular. The common complications for open nasopharyngectomy were middle ear effusion, palatal fistula, nasal regurgitation, and trismus [9, 11]. Over the past decade, the evolution of these approaches has incorporated endoscopic endonasal techniques to complement conventional skull base approaches, and in certain patients, as the sole approach. Endoscopic nasopharyngectomy was first reported by Yoshizaki et al. [12]. Endoscopic nasopharyngectomy has then emerged as a viable treatment option for local recurrent NPC with minimal invasiveness, avoiding morbidity from external approaches and the absence of facial scar [13].

This study aimed to describe the surgical and oncological outcomes of endoscopic endonasal transpterygoid nasopharyngectomy (EETN) in treating locally recurrent T1–T4 NPC.

Methods

This was a retrospective study carried out at a tertiary centre from June 2013 until May 2017. During the study period, a total of 55 locally recurrent NPC patients (rT1–rT4) were subjected to EETNs. The surgeries were performed by a single skull base surgeon with curative intention and without postoperative radiotherapy.

Patient selection and preoperative workup

Local recurrent or residual of NPC was confirmed by histopathological biopsy. Distant metastases were excluded with imaging investigation of computed tomography (CT), magnetic resonance imaging (MRI), and bone scan. Patients were restaged based on imaging, using the American Joint Committee on Cancer TNM classification (7th edition, 2010) [14].

A multidisciplinary approach involving surgeons, anaesthetists, oncologists, pathologists, and physicians was carried out to determine patient's eligibility for EETN and meticulous planning was done to optimise patient's condition preoperatively.

Exclusion criteria for EETN were based on disease factors and patient factors. The disease factors included tumour with significant extensive parapharyngeal space involvement, internal carotid artery encasement, cavernous sinus involvement with multiple cranial nerves palsy, brain parenchymal involvement, and presence of distant metastasis. Besides, patients who were medically unfit for surgery or general anaesthesia were excluded for EETN.

Preparation for surgery

The surgery was performed under general anaesthesia with the patient in supine position. The ENT navigation system was applied. The nasal cavities were decongested with Moffet's solution [15] for 30 min to optimise the surgical field. The solution contains 1 ml adrenaline 1:1000, 2 ml of 10% cocaine, 4 ml of 8.4% sodium bicarbonate, and mixed together with 13 ml of water for injection. Subsequently, both middle turbinates and nasal septum were infiltrated with a solution of lidocaine 1% and epinephrine 1/100,000 enhanced haemostasis.

Surgical procedure

EETN was performed using a 4 mm diameter 0° and 30° rod lens endoscope, with two surgeons working concomitantly, using a bimanual, three/four-handed technique via both nostrils and nasal cavities. This facilitated dynamic visualisation as well as bimanual dissection, which was vital for depth perception, traction, and countertraction and for maintenance of a blood-free surgical field. (Fig. 1).

Sinonasal corridor

First, the surgery initiated with enlarging the natural sinonasal corridor ipsilateral to the lesion by removing the inferior half of the right middle turbinate and completing an uncinectomy, large mid-meatal nasomaxillary window, and anterior and posterior ethmoidectomies. This increased the working space and exposed the entire posterior wall of the antrum. A medial maxillectomy was performed to expose the entire height of the posterior wall of the maxillary sinus and allowed an extended dissection of the pterygopalatine fossa. This medial maxillectomy was limited anteriorly by the nasolacrimal duct, which acted like a fulcrum point, preventing free movement of the scope laterally. Endoscopic

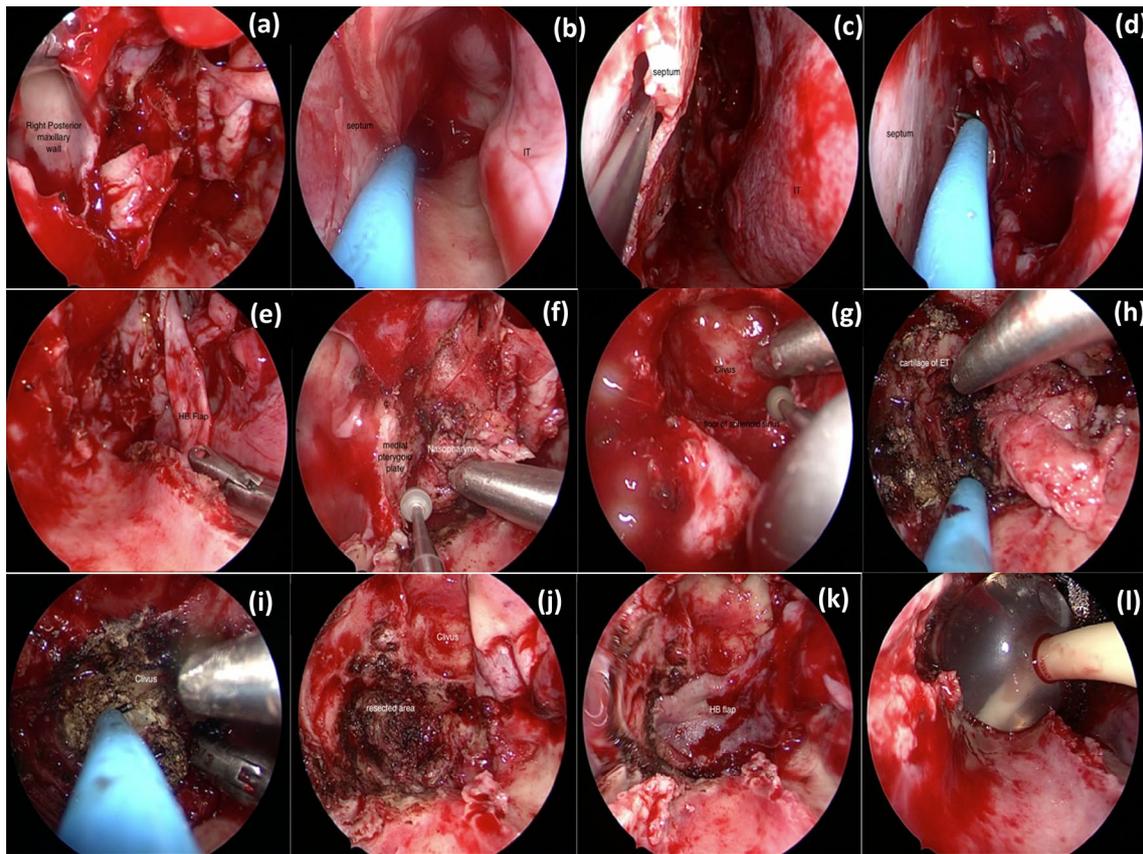


Fig. 1 Series of photographs showing surgical steps for endoscopic endonasal transpterygoid nasopharyngectomy. **a** Right medial maxillectomy performed as part of the transpterygoid approach, **b** creating Hadad–Bassagaisteguy nasoseptal flap, **c** posterior septectomy, **d** creating Caicedo’s flap, **e** two nostrils and four hands technique after removing posterior septum, **f** drilling pterygoid base and medial

pterygoid plate, **g** drilling anterior wall and floor of the sphenoid sinus, **h** resecting cartilage part of eustachian tube, **i** resecting posteriorly at prevertebral muscle, **j** final view after resection of right fossa of rosenmuller of nasopharynx, **k** placing HB flap to the resected area, **l** Catheter tube with balloon to hold the flap in place

Denker’s approach could be performed to further increase the lateral angle of exposure and optimize instrument maneuverability [15]. Endoscopic Denker’s approach was a procedure to remove the piriform aperture, as well as the anterior maxillary wall, until the lateral wall of the antrum was in direct and full view, especially viewing the entire infratemporal fossa.

Additional lateral control was obtained by bringing the instruments from the contralateral side of the nose through a posterior septectomy. The posterior septectomy allowed visualization of the entire posterior wall of the maxillary sinus using a 0° endoscope that crossed over the contralateral side of the nose.

Nasoseptal flap

The pedicled nasoseptal flap (or Hadad–Bassagaisteguy flap) which consisted of mucoperiosteum and mucoperichondrium of nasal septum and supplied by posterior nasoseptal

artery was raised [16]. The Hadad–Bassagaisteguy nasoseptal flap (HBF) was harvested from the contralateral side of the tumour to avoid ipsilateral pedicle blood supply severance due to the transpterygoid dissection. A reverse rotational flap (or Caicedo flap) was raised to line the HBF donor defect to hasten the recovery of nasal mucosa [16].

Inferior sphenoidectomy

The anterior and inferior walls of sphenoid sinus were removed. The sella turcica’s floor, intersinus and intrasinus septations, and the lateral walls of the sphenoid sinus could be visualised with the removal of superior part of the sphenoid crest. After complete removal of the vomer, intersinus septum, and sphenoid sinus floor, the sphenoidectomy was extended superiorly to be in plane with the roof of the nose and laterally to be in plane with the laminae papyracea bilaterally. The removal of the sphenoid sinus floor was completed with the cavity almost flushed with clivus.

Pterygopalatine fossa dissection

The sphenopalatine and posterior nasal arteries were divided at the level of the sphenopalatine foramen. Posterior wall of the antrum and the ascending process of the palatine bone were removed to expose the pterygopalatine fossa with its intrinsic and bordering foramina and fissures. Dissection of the soft-tissue contents of the pterygopalatine fossa was then performed.

Transpterygoid dissection

Several landmarks were identified during the transpterygoid approach before tumour extirpation. The vidian nerve was identified proximal to the pterygopalatine ganglion, as it exited from the vidian canal. The maxillary nerve was identified in its canal coursing the lateral wall of the sphenoid sinus. The pharyngeal end of the Eustachian tube or torus tubarius was located posterior to the pterygoid process. Cartilaginous eustachian tube was exposed with the removal of the pterygoid process. The parapharyngeal segment of the ICA was posterior to the Eustachian tube in most of the patients.

Tumour extirpation

After a proper exposure, 0.5–1 cm margin around tumour was outlined with needle point electrocautery which helped with hemostasis. The superior and posterior dissections were done by elevating the mucoperiosteum from the floor of the sphenoid sinus and the clivus posteriorly. The dissection proceeded inferiorly to the level of the soft palate, where the prevertebral musculature (deep to the pharyngobasilar fascia) and prevertebral fascia were encountered. The prevertebral muscle and fascia were quite resilient, but could be effectively resected with electrocautery or Kerrison rongeurs.

Laterally, the medial pterygoid plate and pterygoid process were exposed, above which lied the sinus of Morgagni, through which Eustachian tube and tensor veli palatine muscle passed through. These structures were excised along with the levator palatini muscle to expose the parapharyngeal tissues. The mucosa was elevated off the base of foramen lacerum and continued anteriorly towards the posterior aspect of fossa of Rosenmüller. The eustachian tube cartilage was identified laterally and included in the specimen. The Doppler probe was used to map out the internal carotid artery as the dissection proceeded laterally, to reduce the likelihood of inadvertent injury.

Nasopharyngeal reconstruction

The tumour margins (circumferential and deep margins) were sent for frozen section. Once the margins were cleared,

the reconstruction was done by placing the pedicle nasoseptal flap. The vascularised pedicle flap aimed to facilitate the healing of the defect, resist irradiation, and protect the ICA against exposure and blowout. The flap was held in place with Surgicel[®] held on by balloon-inflated Foley's catheter at the nasopharynx. Meroce[®] was placed in both nostrils each, to support the Foley's catheter and also as nasal packing for hemostasis.

Postoperative care

Following reversal from general anaesthesia, patients were kept in the ward with nasal packing and covered with intravenous antibiotics for 3–5 days. Removal of nasal packing depends on any active bleeding from the surgical site. Most of the patients would keep the nasal packing for 3 days. Once the nasal packing was removed, the intravenous antibiotics would be converted to oral antibiotics to complete a total of a week duration upon discharged. Meantime, patients were educated with comprehensive instruction regarding nasal hygiene, nasal douching (sodium bicarbonate mixed with mupirocin nasal rinses three-to-four times per day), and sign of possible hazardous complications such as cerebrospinal fluid (CSF) leak. Patients were generally reviewed in clinic every 2–3 weeks for endoscopic examination, during which nasal decrusting was performed carefully without disrupting the nasoseptal flap.

Results

From June 2013 until May 2017, there were 983 newly diagnosed NPC cases; Bidayuh 485 (49.3%), Chinese 236 (24.0%), Malay 141 (14.3%), Iban 69 (7.0%), and others 52 (5.3%). A total of 55 locally recurrent NPC patients (rT1–rT4) underwent EETN performed by single skull base surgeon with curative intention with postoperative adjuvant chemotherapy but without postoperative radiotherapy. Among the 55 patients with locally recurrent or residual NPC who underwent EETN, there were 44 (80.0%) males and 11 (20.0%) females. The mean age of patients was 52.5 years (range 21–69 years). The distribution of cases according to ethnic and race was as follows: Bidayuh 22 (40%), Chinese 16 (29.1%), Malay 10 (18.2%), Iban 5 (9.1%), Kayan 1 (1.8%), and Lumbawang 1 (1.8%) (Table 1).

All 55 patients had completed primary treatment of 70 Gy fractionated radiotherapy and concurrent chemotherapy with cisplatin and 5-fluorouracil. The duration of time from treatment completion to detection of local recurrence or residual ranged from 4 to 120 months (mean 28 months). With the restaging, most patients, 25 (45.5%) were classified with rT1N0M0, 20 (36.4%) patients with rT2N0M0, 9 (16.3%)

Table 1 Demographic data and clinicopathological characteristics of 55 patients who underwent endoscopic endonasal transpterygoid nasopharyngectomy (EETN)

Parameter	No. (%)
Sex	
Male	44 (80.0%)
Female	11 (20.0%)
Ethnicity	
Bidayuh	22 (40.0%)
Chinese	16 (29.1%)
Malay	10 (18.2%)
Iban	5 (9.1%)
Kayan	1 (1.8%)
Lumbawang	1 (1.8%)
rT classification	
rT1	25 (45.5%)
rT2	20 (36.4%)
rT3	9 (16.3%)
rT4	1 (1.8%)
Microscopic surgical margin	
Negative	51 (92.7%)
Positive	4 (7.3%)
En bloc tumour resection	
Yes	47 (85.5%)
No	8 (14.5%)
Major complication	
Intraoperative (internal carotid artery injury)	1 (1.8%)
Residual/local recurrence post operation (mean follow-up period of 18 months)	
rT1	0/25 (0.0%)
rT2	3/20 (15.0%)
rT3	2/9 (22.2%)
rT4	0/1 (0.0%)

patients with rT3N0M0, and 1 (1.8%) patient with rT4N0M0 (Table 1).

The mean operating time was achieved at 180 min, with a range of 150–280 min. 93% (51/55) of patients obtained negative microscopic margin based on postoperative histopathological evaluation. 85% (47/55) of patients achieved en bloc tumour resection.

Intraoperatively, 1 (1.8%) patient had internal carotid artery injury which was treated with stenting and had recovered fully without neurological deficit. There were no major postoperative complications reported. Postoperatively, all patients experienced nasal crusting in the first week, which had gradually decreased from 6 to 12 weeks with meticulous douching with mupirocin. There were eight (14.5%) patients who complained of neck pain post operatively, of which all resolved within 4 weeks. The average stay in hospital was 4 days (1-day preoperative admission and 3-day postoperative).

93% of the nasoseptal flap uptake was successful with good epithelization. There were four patients who suffered from osteitis at basisphenoid due to partial migration of nasoseptal flap-causing bony exposure. All patients were treated with 6 weeks of ciprofloxacin and symptoms resolved.

At the end of this review, only one patient with rT4N0M0 with involvement of Meckel's cave underwent EETN together with the excision of tumour at Meckel's cave. She underwent six cycles of chemotherapy without re-radiotherapy postoperatively. She still remained disease-free 2-year postsurgery at the time of this review (Fig. 2).

During a mean follow-up period of 18-month (range 12–48 months) postsurgery, five patients (9.1%) were noted to have residual/recurrence at the primary site. Three were seen at rT2 at 11, 12, and 20 months, respectively, and two patients were seen at rT3 at 6 and 7 months, respectively. All five patients underwent for re-surgery. One patient at rT3 passed away 6 months after re-surgery due to distant metastasis complicated with septicaemia. The 1-year local disease survival free (LDFS) rate was 93% and the 1-year overall survival (OS) rate was 98%.

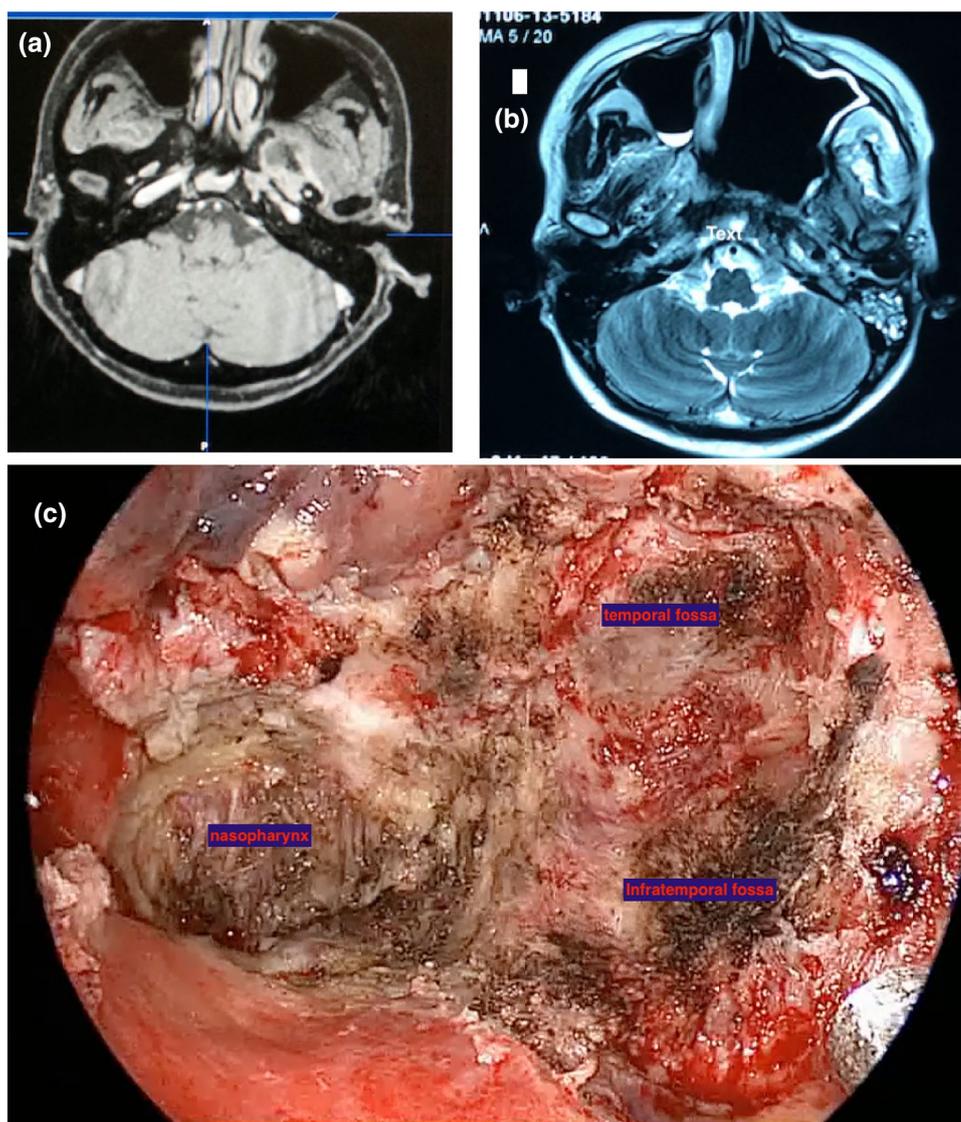
Discussion

In NPC, despite being radiosensitive and adequate primary treatment, local recurrence still poses an important problem. Various treatment modalities were practised in the cases of local recurrent NPC, including re-irradiation and surgery.

A case-matched comparison study involving 144 patients by You et al. reported that salvage endoscopic nasopharyngectomy is superior to IMRT for treating local recurrent rT1–T3 NPC; with better survival rates and quality of life, lower treatment-related complications, and lower overall medical cost [8]. Ridge et al. recommended that locally discrete recurrent NPC should be resected unless the patient is not fit for operation [17]. Tumours that persist or recur after primary radiotherapy (RT) are agreed by most people to be significantly resistant to radiotherapy. Therefore, surgical treatment shall be considered for patients with residual or recurrent tumour after radiotherapy or chemoradiotherapy and for patients with glandular or mesenchymal differentiation tumours that are poorly responsive to radiotherapy [18].

Nasopharyngectomy is a well-established surgical procedure for managing locally recurrent NPC. However, external nasopharyngectomy may lead to severe and fatal complications, e.g., massive haemorrhage from the injury of internal carotid artery, intracranial complications such as meningitis and osteoradionecrosis, and functional disabilities such as severe trismus, oronasal fistula, and palatal dehiscence, leading to poor quality of life and severe disfiguring cosmetically [13].

Fig. 2 rT4N0M0 patient with involvement of Meckel's cave underwent EETN together with the excision of tumour at Meckel's cave. Pre- (a) and postsurgery (b) MRI scan axial view. Final endoscopic view after resection of nasopharynx and Meckel's cave (c)



An ideal surgical approach to nasopharynx shall include the ability to provide adequate visualisation of the tumour margins, allow a complete resection with negative margin, allow extension of resection margin if necessary, and allow the identification and preservation of important neurovascular structures [18]. Moreover, the surgery shall preserve neurologic and masticatory functions, facilitate the reconstruction of the surgical defect, and avoid facial scarring or deformity. Over the past decade, endoscopic endonasal techniques have been incorporated to complement conventional skull base approaches for nasopharyngectomy or as the sole approach in certain patients.

Salvage endoscopic nasopharyngectomy is a minimally invasive procedure. As compared to external approaches, endoscopic nasopharyngectomy showed favourable local control and survival outcomes and was indeed a good surgical approach taking postoperative morbidity, patient's

quality of life, and hospitalization time into consideration [13, 19, 20]. Endoscopic method provides a better cosmetic outcome with the absence of facial scar [13].

The advancements in endoscope technologies together with high definition imaging systems and navigation systems enable surgical field to be clearly magnified for better visualisation. In the hands of an experienced surgeon on endoscopic skills, removal of the pterygoid base endoscopically can provide a good window into parapharyngeal space. This makes tumour (rT2 onwards) invading the parapharyngeal space accessible and resectable and easier identification of the parapharyngeal internal carotid artery. A literature review by Emanuelli et al. reported that endoscopic method attained a higher negative surgical margin of 93.75% than external approach (71.6%) [13]. The margin clearance rate for endoscopic nasopharyngeal resection ranged from 78.9 to 100% in various studies [13, 19–23].

From our patient series, the 1-year LDFS rate was 93% and the 1-year OS rate was 98%. Other studies reported 2-year OS and DFS rate ranging from 84.2 to 100% and 69.2 to 88.9%, respectively [13, 19, 23]. Ko et al. demonstrated a significantly higher 2-year OS (rT1 90.9%; rT2 38.5%) and LDFS (rT1 100%; rT2 41.7%) rate in rT1 patient as compared to rT2 patients.

EETN is a relatively safe procedure with no treatment-related mortality reported from journals. The possible intraoperative complications were similar to other endoscopic sinus surgery, including major vessels (internal carotid artery) injury, skull base injury with cerebrospinal fluid leak, and orbital injury. Good preoperative planning, adequate surgical field exposure, and meticulous surgical skills are crucial to minimize surgical complications and to handle intraoperative complications should any problems arise. The common postoperative complications were nasal crusting, postoperative headache, and serous otitis media [14, 24]. Both nasal crusting and postoperative headache improved with nasoseptal flap and frequent nasal douching with mupirocin. Serous otitis media can be managed with myringotomy with tympanostomy tube insertion or amplification with hearing aids and depends on surgeon's and patient's preferences.

Conclusion

EETN is a minimally invasive treatment modality for locally recurrent NPC, especially in rT1–rT3 patients, with encouraging short-term outcome. However, an excellent outcome warrants expert knowledge of the surgical field by the expertise with the aid of highly specialised equipment. Nevertheless, a long-term follow-up with bigger cohort is needed to provide a more promising data on 5-year local disease-free and overall survival rates.

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Compliance with ethical standards

Conflict of interest Author and all the co-authors declare that all of them have no conflict of interest.

Ethical approval All procedures performed in studies involved human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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