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Review

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Surgical treatment of nasopharyngeal carcinoma

Feng Pang[1,2,3], Yu Guo[1,2,3], Tian-Run Liu[1,2,3]

[1]Department of Otorhinolaryngology Head and Neck Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou 510655, Guangdong, China.
[2]Department of Thyroid Center/Thyroid Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou 510655, Guangdong, China.
[3]Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong, China.

Correspondence to: Dr. Tian-Run Liu, Department of Thyroid Center/Thyroid Surgery, Otorinolaryngology Head and Neck Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou 510655, Guangdong, China. E-mail: liutrun@mail.sysu.edu.cn

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Abstract

Nasopharyngeal carcinoma (NPC) is a relatively rare cancer, primarily prevalent in China and other parts of Asia. Radiotherapy is the preferred treatment for primary NPC and has proven to be highly effective. However, approximately 10% of patients experience recurrence after treatment. Surgical intervention serves as a key treatment option for locally recurrent NPC and selected primary cases, aiming to completely remove the tumor while preserving normal tissues and functions as much as possible. This review provides a comprehensive overview of surgical treatment options for NPC discussing the advantages, disadvantages, appropriate indications, and outcomes of various surgical techniques, thus offering guidance for selecting the most suitable treatment approaches.

Keywords: Nasopharyngeal carcinoma, surgery, nasopharyngectomy

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is defined as malignant neoplasms situated in the nasopharynx. The International Agency for Research on Cancer reports that the global incidence of nasopharyngeal cancer is relatively low, with approximately four cases per million people[1]. Nevertheless, there is significant geographical variance, with East and Southeast Asia accounting for over 70% of new diagnoses. In China,

the incidence rate is around three cases per 100,000 individuals[2]. The development of NPC is influenced by both genetic and environmental factors[3]. Nasopharyngeal squamous cell carcinoma is the predominant subtype in these regions. Radiotherapy remains the cornerstone of treatment[4,5], with intensity-modulated radiation therapy (IMRT) emerging as the preferred method. IMRT has led to impressive outcomes, with a 5-year local recurrence-free survival rate of 94.6% for cases without distant metastasis[6]. Despite these advancements, recurrence remains a challenge, afflicting 10%-40% of patients[6]. Additionally, many patients experience side effects from radiotherapy, such as dry mouth and mucositis, which significantly affect their quality of life[7]. For those with recurrent NPC, treatment options typically include surgery and re-irradiation. Although re-irradiation carries a high risk of complications, salvage surgery often provides a safer and more effective alternative[4,5,8]. Surgical approaches are also important in the management of nasopharyngeal adenocarcinoma and early-stage NPC[9,10]. This review systematically outlines the surgical treatment methods for NPC and assesses their therapeutic efficacy.

Pathological features

NPC encompasses a range of pathological variants, including keratinizing squamous cell carcinoma (K-NPC), non-keratinizing squamous cell carcinoma (NK-NPC), undifferentiated carcinoma, adenocarcinoma, and lymphoma[11]. NK-NPC is the predominant subtype, accounting for approximately 95% of all NPC cases in regions such as China[12]. Additionally, nasopharyngeal adenocarcinoma, often considered a "low-grade" malignancy due to its relatively less aggressive nature, warrants attention. In contrast, nasopharyngeal lymphoma makes up about 15% of all head and neck lymphoma diagnoses.

Anatomical considerations

The intricate anatomy of the nasopharynx presents significant challenges for surgical interventions targeting malignancies in this region. Positioned posterior to the nasal cavity and above the soft palate, the nasopharynx occupies a confined space by critical anatomical structures. It is supported by an osseous framework consisting mainly of the sphenoid bone, the basilar segment of the occipital bone, and the petrous facets of the temporal bones. This complex structure requires careful surgical navigation to avoid damage to adjacent vital structures[13]. The proximity of key neurovascular structures, such as the internal carotid artery, jugular vein, and multiple cranial nerves, necessitates a precise surgical approach to prevent severe bleeding or neurological injury. Additionally, the dense lymphatic network of the nasopharynx increases the risk of early lymphatic spread of malignancies. Thus, a thorough understanding of lymphatic drainage pathways is crucial for achieving effective surgical excision and performing appropriate cervical dissection.

The challenges of surgery in the nasopharynx are amplified by its complex anatomy, posterior location, and restricted access, which significantly limit surgical reach. Traditional surgical techniques are often insufficient, necessitating the use of advanced methods such as endoscopic or transnasal approaches[14]. The primary goal remains to preserve key functions - such as hearing, eustachian tube function, and cranial nerve integrity - while achieving effective cancer control. This balance highlights the complexity of surgical procedures for NPC. The close proximity of critical structures increases the risk of complications, including cranial nerve damage, vascular traumas, and cerebrospinal fluid leaks, as well as the potential for locoregional relapse due to residual microscopic disease. However, advances in surgical techniques and improved imaging techniques offer promising solutions, paving the way for more effective and minimally invasive approaches to managing NPC[15].

COMMON SURGICAL METHODS

Overview of surgical treatment

Surgical resection of the nasopharynx is inherently challenging due to its complex anatomy. In 1951, Wilson made a significant breakthrough in addressing this complexity by introducing three surgical approaches for nasopharyngeal resection: transnasal, transmaxillary, and transoral routes[14]. Over time, technological advancements have led to the development of additional techniques to manage NPC, including the temporal fossa approach, inferior/transpalatal approach, maxillary swing approach, endoscopic nasopharyngectomy, and robot-assisted resection. A landmark prospective randomized controlled study by Liu *et al.* revealed that endoscopic nasopharyngectomy provides superior patient survival compared to re-irradiation, with a 3-year overall survival rate of 85.8% *vs.* 68.0%. Additionally, this technique resulted in fewer postoperative complications and significantly improved patients' quality of life[16]. Similarly, Teo *et al.* found that nasopharyngeal resection is more effective than local re-irradiation in the treatment of NPC[17].

Surgery is preferred over re-irradiation in specific situations where it becomes the first-line treatment. This includes cases where patients experience severe radiation-induced complications, such as osteoradionecrosis, making additional radiation risky. Surgery is also favored for localized, resectable recurrences (e.g., rT1-rT2) without distant metastasis, as it can achieve better local control. When patients have reached the maximum safe radiation dose yet still experience recurrence, surgery can offer effective management with fewer severe side effects. Additionally, in tumors located near critical structures or those less responsive to radiation (e.g., nasopharyngeal adenocarcinoma), surgery allows for precise removal and minimizes damage to surrounding tissues.

Surgical intervention remains instrumental in managing NPC. According to the guidelines set forth by the National Comprehensive Cancer Network (NCCN), surgical resection is the preferred treatment for locally recurrent NPC. The indications for surgery encompass a range of clinical scenarios: primary well-differentiated squamous cell carcinoma (stages T1-T3, and selectively, T4), nasopharyngeal adenocarcinoma, locally recurrent resectable NPC (rT1-rT3, and select rT4 cases), and recurrent neck lymph nodes[5,9]. Notably, Liu *et al.* suggested that for early-stage primary NPC (T1), minimally invasive surgical resection alone can rival radiotherapy in terms of survival outcomes while inflicting fewer adverse effects[10]. However, these findings should be interpreted with caution due to the lack of a prospective randomized control in the study. The applicability of surgical intervention in early undifferentiated squamous cell carcinoma remains a subject of ongoing research. For patients suffering from skull base osteonecrosis after nasopharyngeal radiotherapy, endoscopic debridement has been identified as an efficacious management strategy[14]. Table 1 summarizes the options for various surgical modalities.

Endoscopic nasopharyngectomy

Introduced in 2005, Endoscopic nasopharyngectomy has emerged as a primary technique for nasopharyngeal cancer treatment[18-21]. This procedure focuses on the precise removal of tumors within the nasopharynx, behind the nasal septum, and within the sphenoid sinus, using the accuracy afforded by nasal endoscopy. Castelnuovo *et al.* outlined three specific resection techniques: Type 1 targets the posterior nasopharyngeal wall; Type 2 expands upward to the sphenoid, and Type 3 adopts a trans-pterygoid strategy focusing on the postero-lateral nasopharynx, necessitating the extraction of both the pterygoid plates and the Eustachian tube, all executed while safeguarding the parapharyngeal-petrous-cavernous segments of the internal carotid artery[22]. These procedures can leave the exposed internal carotid artery in the neck vulnerable, posing risks of severe complications such as rupture and bleeding. As a result, an intricate mucosal repair of the nasopharynx is essential. Yet, for patients who have previously undergone radiation therapy for recurrent NPC, effective repair can be challenging due to compromised mucosal regeneration and heightened necrosis risk. In these cases, using a nasal septal mucosal flap, as highlighted by Chen *et al.*,

Table 1. Decision-making for selecting surgical approach based on tumor characteristics

Surgical technique	Indication	Advantages	Limitations
Endoscopic nasopharyngectomy	Early-stage NPC (T1-T2), localized and resectable recurrence	Minimally invasive, better visualization, fewer cosmetic concerns	Limited for tumors near the internal carotid artery
Maxillary swing approach	Larger tumors with parapharyngeal involvement	Provides extensive exposure to the nasopharynx and parapharyngeal space	More invasive, potential complications such as facial numbness
TORS	Small, localized recurrent tumors (rT1-rT2)	High precision, minimal invasiveness, enhanced recovery	Lacks tactile feedback, limited to smaller tumors
Hard palate approach	Small nasopharyngeal tumors; avoids external incisions	Improved cosmetic outcome, reduced postoperative discomfort	Risk of oronasal fistulas, not suitable for complex or large tumors
Pterygopalatine fossa approach	Tumors located within the pterygopalatine fossa	No external incisions, direct access to the target area	Not suitable for tumors outside the pterygopalatine fossa
Infratemporal fossa approach	Tumors in the ipsilateral nasopharynx	Access to complex anatomical areas such as the skull base	Limited exposure for contralateral tumors, potential nerve damage

NPC: Nasopharyngeal carcinoma; TORS: transoral robotic surgery.

has proven advantageous, significantly enhancing the post-operative flap survival rates[23].

Endoscopic nasopharyngectomy is particularly suitable for patients with early-stage recurrent NPC (rT1-rT2) and primary NPC (T1-T2) that are confined to the nasopharynx or parapharyngeal space without invasion of critical structures such as the skull base or internal carotid artery. It is also recommended for patients with nasopharyngeal adenocarcinoma who are not ideal candidates for radiotherapy due to contraindications or preference for a less invasive approach[16,23,24]. In cases where radiation therapy has failed or is associated with severe side effects, endoscopic resection offers an alternative with reduced surgical trauma and better preservation of adjacent tissues[14]. Some experts suggest that surgical excision may be considered for tumors with lateral extension that does not exceed the foramen ovale or with localized involvement of the pterygomaxillary fissure, provided that the upper boundary does not extend into the anterior cranial fossa[25-27].

Compared to traditional open surgical techniques, endoscopic nasopharyngectomy proffers an array of advantages, including reduced invasiveness, no facial cosmetic concerns, a lower risk of damage to critical vascular and neural structures, improved accuracy in identifying tumor margins, and better patient survival outcomes[28-31]. Research by Liu *et al.* underscores that, for cases of locally recurrent NPC suitable for resection, endoscopic procedures manifest superior survival outcomes and fewer post-operative complications compared to intensified radiotherapy regimens[16]. Nonetheless, the method has its limitations. It might not be ideal for tumors that are close to or involve the internal carotid artery due to the risk of flap necrosis. Liu *et al.* suggest that significant skull base involvement or proximity (< 0.5 cm) to the internal carotid artery of the neck, coupled with non-resectable neck lymph nodes, is a contraindication for endoscopic resection[16]. While consensus on these contraindications is still lacking, advancements in surgical techniques and instrumentation may expand the applicability of endoscopic resections in the future.

Open surgery

Open surgery is indicated for patients with locally advanced or recurrent NPC where endoscopic approaches are not feasible, such as when the tumor involves the carotid artery, the cavernous sinus, or extensive soft tissue structures. It is particularly recommended for patients with rT3-rT4 tumors or when there is significant involvement of the skull base that requires more extensive resection. Open surgery is also suitable for cases where a clear surgical margin cannot be achieved with minimally invasive techniques,

providing direct access to the tumor and allowing for thorough excision. Compared to endoscopic surgeries, open surgery offers enhanced visualization of the operative site, facilitating meticulous tumor excision. It is particularly efficacious for tumors located near the carotid artery or those that invade a section of the artery. However, it is paramount to recognize potential complications associated with open surgery, including cosmetic challenges, facial numbness, trismus, formation of palatal fistulas, nasal obstructions, and eyelid ectropion.

Maxillary swing approach

The maxillary swing approach is a leading open surgical procedure for the resection of NPC. This procedure involves making an incision and performing osteotomies on the ipsilateral maxilla, which is then delicately swung outwards, providing access to the tumor. A nasopharyngectomy is then executed under direct view, allowing for en bloc tumor removal. The resection typically encompasses the medial pterygoid muscles, the posterior portion of the nasal septum, and the entire posterior wall of the nasopharynx up to the medial edge of the contralateral fossa of Rosenmüller. The extent of the excision is directed by intraoperative frozen section findings, proceeding until all margins are devoid of tumor or when no further resection is viable. Finally, the maxillary osteocutaneous unit is realigned and affixed with titanium miniplates and screws[32,33].

The maxillary swing approach is ideal for patients with recurrent NPC that extends to the parapharyngeal or retropharyngeal space, especially when the tumor invades structures such as the medial pterygoid muscles or the posterior wall of the nasopharynx. This approach is indicated for cases where precise control over tumor margins is needed due to its ability to provide extensive exposure of the nasopharyngeal region and internal carotid artery. It is best suited for patients with rT3 or select rT4 tumors where other less invasive techniques are not adequate.

This approach provides direct access to the nasopharynx and unrivaled exposure of the internal carotid artery in the neck, making it particularly advantageous for tumors localized in the parapharyngeal space. Documented postoperative complications are facial numbness (7.4%), ectropion (1.8%), epiphora (6.5%), trismus (9.2%), palatal fistula (4.3%), and middle ear effusion (37.8%)[32]. A study by Chan *et al.* involving 312 patients subjected to this procedure reported full macroscopic tumor resections in all instances[34]. The average postoperative hospital stay was 12 days, with a 74% five-year local tumor control rate. Notably, tumor size and margin status emerged as pivotal influencers of postoperative survival rates.

Despite its invasive nature, this method is characterized by a minimal incision, reduced tissue trauma, lesser postoperative pain, and shorter recovery times[35,36]. It is an excellent choice for complex NPC cases, especially those with associated parapharyngeal and retropharyngeal lymph node metastases. The main contraindications for this approach are tumor encroachments into the sphenoid sinus and comprehensive encirclement of the internal carotid artery in the neck. Further findings by Chan *et al.* intimate that patients undergoing maxillary swing nasopharyngeal cancer resection maintain a laudable postoperative quality of life, with negligible alterations in the average Global Health System score[35]. However, factors such as palatal fistula and skull base osteonecrosis can notably impact the postoperative quality of life.

Hard palate approach

The hard palate approach is an operative technique used for resecting nasopharyngeal tumors. This procedure provides access to the nasopharynx through an incision in the hard palate of the oral cavity, facilitating excision of tumors localized in this area[37]. Generally, this approach is designated for smaller nasopharyngeal neoplasms and is less suitable for those involving complex anatomical areas, such as the skull base. A salient advantage of the hard palate approach is its favorable cosmetic outcome; as it avoids external incisions, offering improved aesthetic results for patients. Additionally, the technique minimizes

tissue disruption and postoperative distress, resulting in accelerated recovery durations compared to alternative surgical procedures. However, potential complications, such as oronasal fistulas - abnormal connections between the oral and nasal cavities - should be carefully considered, as they may require additional treatment. The appropriateness of the hard palate approach primarily hinges upon the tumor's size and spatial orientation, being optimally suited for superficial tumors not extensively invading intricate anatomical landmarks. It remains incumbent upon the surgeon to judiciously assess the individualized case, factoring in the tumor's unique attributes and the patient's holistic health profile.

Pterygopalatine fossa approach

The pterygopalatine fossa approach is a surgical strategy invoked for the excision of nasopharyngeal tumors. This approach accesses the nasopharynx via the maxillary sinus, obviating the necessity for external incisions and offering a direct conduit for tumor excision[37]. It exhibits particular efficacy against NPC located within the pterygopalatine fossa. The suitability of this approach depends on the specific characteristics and location of the tumor. Predominantly, it is tailored for neoplasms anchored within the pterygopalatine fossa, rendering it less fitting for tumors ensconced in other nasopharyngeal sectors. A meticulous patient assessment, along with a case-centric evaluation, is imperative to ascertain whether the pterygopalatine fossa approach is appropriate for a given case of nasopharyngeal tumor resection.

Infratemporal fossa approach

The infratemporal fossa approach is a surgical technique devised for the resection of nasopharyngeal tumors. This method provides access to the nasopharynx by navigating through the infratemporal fossa, a complex anatomical region located beneath the skull base, bordered by the maxilla and temporal bone. It allows surgeons to remove tumors affecting the ipsilateral nasopharynx. While the infratemporal fossa approach is adept at addressing specific tumor presentations, it may be less suitable for tumors extending into the contralateral nasopharynx. The exposure afforded by this methodology may fall short for all-encompassing tumor resection in such scenarios, potentially engendering complications such as conductive hearing impairment and trigeminal nerve anomalies[38].

Lymph node dissection

For patients with locally recurrent neck lymph node metastasis of NPC following radiotherapy, surgical intervention becomes a viable consideration. This approach is generally considered for individuals who are not candidates for additional radiotherapy or chemotherapy, especially when distant metastases are absent.

Historically, radical neck lymph node dissection stood as the favored approach to treat neck lymph node recurrence in nasopharyngeal cancer. However, recent studies suggest a negligible difference in postoperative survival and recurrence rates between selective neck lymph node dissection and its comprehensive counterpart[39,40]. Research by Wang *et al.* posits that salvage neck lymph node dissection for recurrent NPC yields a local control rate nearing 86.3%[41]. Earlier scholarly publications estimated the postoperative survival rate at a range of 54%-57%[41,42]. Investigations by Li *et al.* discerned adverse prognostic markers, such as extranodal extension, the presence of over two pathologically positive lymph nodes, and afflictions of the lower neck, notably at levels IV and Vb[43,44]. For patients with isolated retropharyngeal lymph node recurrence, selective neck lymph node removal remains feasible. Chan *et al.* reported a 5-year control rate of 76% and a 5-year disease-free survival rate of 59% for this approach[44]. The choice of the optimal surgical approach is heavily influenced by these factors. An emerging surgical frontier is the incorporation of robot-assisted transoral retropharyngeal and parapharyngeal lymph node dissection, hailed for its precision and potential recovery advantages[45].

Robot-assisted resection

The evolution of head and neck surgery has been markedly influenced by robot-assisted resection, especially with the integration of transoral robotic surgery (TORS) for salvage nasopharyngectomies in recurrent NPC cases. Robot-assisted nasopharyngectomy is mainly applicable to patients with small recurrent NPC (rT1-rT2) that is localized and has minimal invasion into surrounding structures. Ozer *et al.* blazed the trail in 2008 by pioneering transoral robotic nasopharyngectomy as a therapeutic avenue for NPC[46]. This was soon followed by the proposition and validation of combined transnasal and transoral robotic nasopharyngectomy through cadaveric anatomical evaluations[47-49]. Tsang *et al.* reported that robotic-assisted nasopharyngectomy for recurrent NPC achieved a five-year local control rate of 85.1%, an overall survival rate of 55.7%, and a disease-free survival rate of 69.1%[50].

The distinguishing features of TORS nasopharyngectomy include exceptional tumor visualization provided by a 3D camera and the enhanced dexterity of the robotic wrist design, which is especially valuable for navigating the tight spaces of the nasopharynx. When the tumor's extent mandates a sphenoid bone resection, a synergistic approach combining transnasal endoscopy and transoral robot assistance proves effective[45,51]. Nonetheless, TORS nasopharyngectomy has its limitations, particularly the lack of the tactile feedback intrinsic to open surgeries. While TORS can be utilized for retropharyngeal lymph node recurrence, its current application remains circumscribed to diminutive recurrent tumors manifesting local parapharyngeal invasion.

Endoscopic microwave coagulation therapy

In addition to traditional endoscopic approaches, novel techniques such as endoscopic microwave coagulation therapy have been explored for managing early recurrent T1 NPC. Mai *et al.* demonstrated that this technique offers a promising alternative for local tumor control with reduced complications and improved patient outcomes[52].

Indications for different surgical methods

Endoscopic nasopharyngectomy

This approach is particularly suitable for early-stage (T1-T2) or recurrent (rT1-rT2) NPC confined to the nasopharynx or parapharyngeal space, with no involvement of critical structures such as the skull base or internal carotid artery. It is ideal for patients who cannot undergo radiotherapy or who experience significant side effects from prior radiation.

Robot-assisted nasopharyngectomy

Recommended for small, localized tumors requiring precise dissection, this method provides enhanced visualization and dexterity, making it suitable for early-stage NPC where detailed excision is necessary.

Maxillary swing approach

Indicated for cases where early-stage NPC extends into the parapharyngeal space or when greater access is required to ensure complete resection. This approach is beneficial when endoscopic methods may not achieve clear surgical margins.

SURVIVAL AND PROGNOSIS

Surgical treatment of locally recurrent NPC has shown promising outcomes, with 5-year survival rates generally ranging from 63% to 77.1%. For nasopharyngeal adenocarcinoma, the 5-year survival rate is around 57.1%[16,32,53-56]. Notably, about 30% of patients who receive salvage nasopharyngectomy for recurrent NPC eventually succumb to the disease, with distant metastasis being the predominant cause of

mortality[57]. Current literature underscores that variables such as expansive tumor volume, advanced-stage recurrence, and positive surgical margins stand out as independent detrimental prognostic markers influencing both local control and the overall survival rate post salvage nasopharyngectomy[58,59].

NON-SURGICAL ADVANCEMENTS IN NPC TREATMENT

While surgical interventions have historically played a pivotal role in managing NPC[60], the treatment landscape has been significantly shaped by non-surgical modalities. Advances in both radiotherapy and chemotherapy reflect the ongoing efforts of the medical community in improving NPC outcomes.

One of the landmark developments in this domain has been the advent and adoption of IMRT[61]. IMRT offers the advantage of delivering radiation doses with precision, targeting the tumor while preserving adjacent normal tissues. This approach not only diminishes treatment-related side effects but also results in enhanced local control and overall survival. Parallel to this, the refinement of chemotherapy regimens, including induction, concurrent, and adjuvant strategies, has further revolutionized the NPC treatment paradigm[62].

Furthermore, the treatment arsenal for NPC has been enriched with the introduction of immune checkpoint therapies[63]. Agents targeting checkpoints such as PD-1/PD-L1 and CTLA-4 have shown exceptional efficacy, rejuvenating the immune system's ability to recognize and combat NPC cells[64,65].

Given these technological and pharmacological strides, there is an air of optimism surrounding the future treatment prospects for NPC[2]. The crux of this optimism lies in integrating radiotherapy, chemotherapy, and the nascent immunotherapies. This holistic approach not only aims to improve survival rates but also prioritizes patients' quality of life by reducing treatment-induced complications.

In sum, while surgical techniques are invaluable in the management of NPC, the leaps in non-surgical modalities, ranging from IMRT to immune checkpoint therapies, paint a hopeful picture for comprehensive NPC treatment in the future.

CONCLUSION AND FUTURE DIRECTIONS

In the management of recurrent nasopharyngeal neoplasms, surgical resection is increasingly favored when practicable. This preference is due to its potential for greater efficacy and reduced side effects compared to radiotherapy. Modern surgical paradigms are steadily gravitating towards minimally invasive techniques in nasopharyngectomy, emphasizing approaches such as TORS and 3D high-definition endoscopic nasopharyngectomy.

Looking ahead, the evolution of nasopharyngectomy is expected to be significantly shaped by technological advancements. Promising opportunities include exploring the therapeutic potential of immunotherapy and integrating strategies such as concurrent radiotherapy and chemotherapy or combining surgery with chemotherapy. These approaches aim to provide a more comprehensive and effective management of nasopharyngeal malignancies.

DECLARATIONS

Authors' contributions

Conceived the study design, undertook the methodology, collected and analyzed data, and edited the manuscript: Pang F, Guo Y, Liu TR

Reviewed and approved the final manuscript to be published: Pang F, Guo Y, Liu TR

Availability of data and materials
Not applicable.

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Not applicable.

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