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Surgical salvage of recurrent T3 nasopharyngeal carcinoma: Prognostic significance of clivus, maxillary, temporal and sphenoid bone invasion

Jimmy Yu Wai Chan*, Stanley Thian Sze Wong, William Ignace Wei

Division of Head and Neck Surgery, Department of Surgery, University of Hong Kong Li Ka Shing Faculty of Medicine, Queen Mary Hospital, China

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ABSTRACT

Background: To study the efficacy of surgery for recurrent T3 nasopharyngeal carcinoma (NPC) and to determine the prognostic significance of various skull base bone invasion.

Method: Retrospective view of the surgical outcome for recurrent T3 NPC. Kaplan Meier and log rank tests were used to determine the 5-year overall and disease specific survival. Multivariate analysis was used to identify significant independent prognostic factors that affect the surgical outcome.

Results: Between 1990 and 2017, 208 patients with recurrent T3 NPC were recruited. Salvage surgery was performed via the endoscopic endonasal approach (n = 22, 10.6%), endoscopic transpterygoid approach (n = 63, 30.3%) and the maxillary swing approach (n = 123, 59.1%). Thirty-eight (18.3%) patients required vascular bypass. The skull base bone involved by the tumours included: maxillary sinus (n = 13), clivus (n = 36), pterygoid process (n = 61), sphenoid sinus (n = 30), petrous part of the temporal bone (n = 42) and a combination of the above (n = 26). The mean follow-up duration was 41.7 months. Multivariate analysis identified tumours involving with both cortexes of the clivus and the lateral wall of the sphenoid sinus, as well as positive bone resection margins as the significant independent prognostic factors for surgical outcome.

Conclusion: Outcome of surgical salvage is significantly worse for tumours that involve multiple bones at the skull base, particularly when both cortexes of the clivus and the lateral wall of the sphenoid sinus are invaded. Indication of aggressive surgery in such circumstances is controversial.

Introduction

The undifferentiated, non-keratinizing type of nasopharyngeal carcinoma (NPC) is unique among other head and neck malignancies with regard to its epidemiology, pathology and treatment outcome [1,2]. The highest reported incidence is found in the southern part of China (including Hong Kong), with the annual incidence up to 50 per 100,000 populations [3]. Majority of the tumours were associated Epstein-Barr virus (EBV) infection.

Recurrent tumours arising from the nasopharyngeal mucosa, if not detected and treated early, can invade the surrounding bones, which are classified as T3 and at least Stage III disease, according to the American Joint Committee on Cancer (AJCC) seventh edition (2009). The bones that are commonly involved by the recurrent cancer include the maxillary sinus, clivus, petrous part of the temporal bone and the body of the sphenoid bone. Salvage surgery for recurrent T3 nasopharyngeal cancer is challenging, due to the risk of injuring the various neurovascular structures and breaching the underlying dura mater. The objective of this study is to investigate and compare the incidence, characteristics and prognostic significance of recurrent NPC with invasion of various bones of the skull base.

Patients and methods

The study was approved by the ethics committee of the Institutional Review Board of the University of Hong Kong. From January 1990 to December 2017, we had performed salvage surgery for 542 patients with recurrent NPC after previous radiotherapy. Among them, 208 (38.4%) patients had recurrent NPC invading bones of the skull base, as demonstrated by pre-operative magnetic resonance imaging (MRI) or computer tomography (CT). All tumours belonged to the non-keratinizing, undifferentiated sub-type, and all patients had previously underwent either external radiotherapy alone or combined chemoradiotherapy, depending on the stage of the tumour on presentation.

After the completion of radiotherapy, patients received interval assessments regularly and indefinitely. The nasopharynx was examined

* Corresponding author at: Division of Head and Neck Surgery, Department of Surgery, University of Hong Kong Li Ka Shing Faculty of Medicine, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR, China.
E-mail address: chanjyw@gmail.com (J.Y.W. Chan).

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by rhinoscopy and biopsy was taken if necessary. MRI from the skull base to the neck was performed 3 months after the completion of radiotherapy and then yearly afterwards to detect the presence of local and regional tumour recurrence. Plasma Epstein Barr Virus (EBV) DNA level was checked every 6 months. Blood (5 mL) was collected and stored in EDTA bottles. The blood samples were then centrifuged, after which the plasma portion was removed and stored at −20 °C. Plasma EBV DNA copy numbers were measured with real-time quantitative PCR. This was used to identify the *Bam* HI-W fragment region of the EBV genome [4].

Once the patients were diagnosed to have tumour recurrence, whole body positron emission tomography (PET) scan was performed for metastatic work-up. Bone scintigraphy and contrast CT scan of thorax and abdomen were performed instead if PET scan was unavailable. All the patients were discussed in the multidisciplinary meeting in the presence of surgeons, radiation and medical oncologists, and diagnostic radiologists. As it is impossible to perform intra-operative frozen section examination of the bone resection margins, the extent of resection of the bony structure is pre-determined after accurate assessment of the areas of tumour invasion together with the radiologists during the multidisciplinary meeting. Exclusion criteria for the study subjects of the current study include tumours with pathology other than undifferentiated, non-keratinizing type, tumours that were negative for Epstein Barr virus encoded small RNAs (EBER), those with intracranial invasion (ie. Recurrent T4 disease), as well as patients with cytological and histological diagnosis of metastatic lymphadenopathy and radiological diagnosis of distant metastasis.

The surgical approach depends on the location and extent of tumour involvement. For tumours that invaded the posterior maxillary sinus (Fig. 1), pterygoid process and sphenoid sinuses (Fig. 2) and the clivus, endoscopic endonasal approach [5,6] or the maxillary swing [7–9] operation was adopted. For tumours that extended to the parapharyngeal space, endoscopic transpterygoid approach or the open method was utilized to improve tumour exposure and extirpation. For tumours that abutted the internal carotid artery (ICA) (Figs. 3 and 4), the maxillary approach was used to ensure safe and en-bloc removal of tumour from the surface of the artery. After removal of the tumour bearing part of the skull base bone together with a bony resection as planned pre-operatively, the bone resection margins around the area were obtained by rounger and sent for histopathological examination. Irrespective of the approach of tumour resection, exposed ICA, bone and dura was covered using the free vastus lateralis muscle flap. The vascular pedicle of the flap was tunneled to the neck medial to the body of the mandible, where microvascular anastomosis to suitable recipient vessels was performed under microscopic magnification.

For patients with tumour encasement of the cervical, petrous or lacerum segment of the ICA, a two-staged operation would be performed as described previously [10]. A high-flow extra-cranial intracranial (EC-IC) vascular bypass was created during the first-stage surgery. An interposition graft, using the autologous radial artery, was anastomosed between the ipsilateral external carotid artery (ECA) in the neck and the M2 segment of the middle cerebral artery (MCA). The patency of the bypass was ascertained by CT angiogram, before the second stage operation that was performed 7 – 10 days afterwards. The tumour was resected using either open or endoscopic approach, with the underlying bone and ICA as planned pre-operatively. The raw area after tumour resection was covered by free vastus lateralis muscle flap as described before.

All resected specimens were sent to dedicated pathologists specialized in head and neck pathology for detailed histopathological examination. The resection margins specimens at frozen section were examined by Haematoxylin and Eosin staining. These, together with the main specimen, were further examined subsequently by paraffin sectioning and immuno-histochemical staining, if necessary. Positive resection margins were defined by the presence of microscopic tumour cells at the cauterized border. Close resection margins were those with tumour cells within 5 mm from the border. Clear margins were defined as those with tumour cells more than 5 mm from the cut edge. For practical purpose, frozen section examination for specimens that comprised of bone or cartilages were not feasible. As a result, all bone margins were sent separately for de-calcification and subsequent paraffin sectioning and histopathological examination.

All patients were nursed in the intensive care unit after surgery. They were subsequently transferred to the general ward if stable. Speech and swallowing rehabilitation were started and nasal douching techniques were taught. Once available, the final pathology results of the resected specimens were discussed with the oncologists at the multidisciplinary meeting. Patients' with resection margins that were involved by tumour, their previous radiation plan were reviewed and further chemoradiotherapy were given, if feasible. Patients with clear and close resection margins underwent regular surveillance for tumour recurrence after surgery. After discharge from the hospital, the patients were followed up regularly with endoscopic examination at 1 month's interval for the first post-operative year, which was progressively spaced out during the subsequent years. Plasma EBV-DNA was checked every 3 months as the tumour marker, and MRI was performed every 6 months for the first year and then yearly afterwards. 18F-FDG PET scan was performed when there was suspicion of tumour recurrence.

The data forming the basis of the current study were collected prospectively and entered in the head and neck cancer database. They were retrieved for a retrospective analysis in this study. Data were analyzed with Statistical package for social sciences version 18.0 (SPSS, Inc., Chicago IL). A *p*-value of 0.05 or less was considered as significant.

Results

During the study period, 208 patients who received salvage surgery for recurrent T3 nasopharyngeal tumours were recruited. The demographic data and their tumour characteristics were shown in Table 1. The initial T-classification on presentation before radiotherapy was: T1

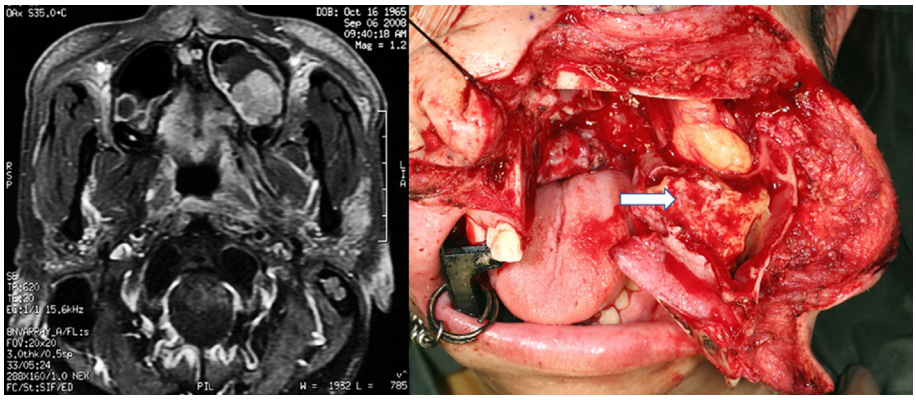

Fig. 1. (*Left*) Recurrent NPC on the left side with MRI showing tumour involvement of the left pterygopalatine fossa and the left maxillary sinus. (*Right*) Tumour resected via the left maxillary swing approach. Posterior part of the maxilla was removed together with the tumour (white arrow). Histopathological examination of the bone resection margins showed no evidence of tumour involvement. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

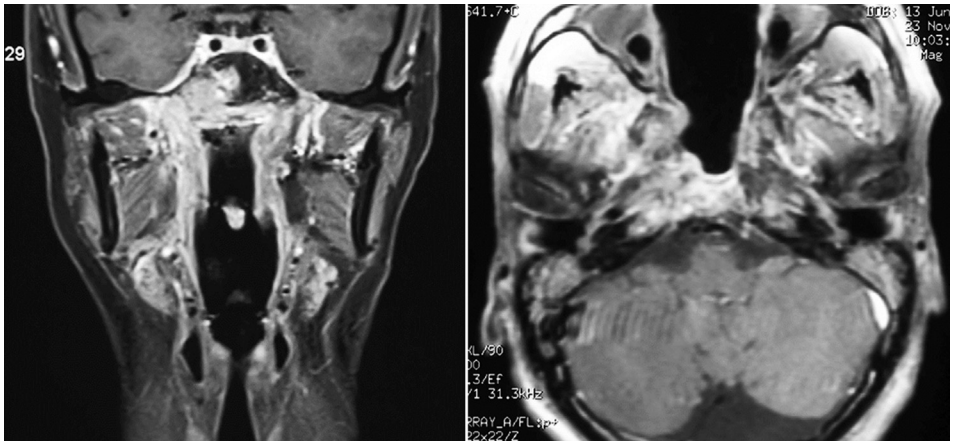

Fig. 2. (*Left*) Coronal view of MRI showing recurrent NPC involving the lateral wall of the right sphenoid sinus abutting the septum. (*Right*) Axial cut of another patient with recurrent NPC invading both the anterior and posterior cortex of the clivus.

(26/208, 12.5%), T2 (49/208, 23.5%), T3 (105/208, 50.5%), and T4 (28/208, 13.5%). The initial N-classification was N0 (12/208, 5.8%), N1 (75/208, 36.1%), N2 (102/208, 49.0%) and N3 (19/208, 9.1%). Concurrent chemoradiation was given in 137 (65.9%) patients, while rest received radiotherapy alone. Induction chemotherapy was given in 32 (15.4%) patients, and adjuvant chemotherapy was required in 26 (12.5%) patients. Routine reassessment MRI was performed for all patients 10 weeks after the completion of radiotherapy. Upon comparison with the pre-treatment MRI, complete radiological response (for both primary tumour and nodal metastasis) was achieved in all patients. Plasma EBV DNA after radiotherapy was checked in 168 patients and all of them demonstrated complete serological response. The mean interval between the completion of radiotherapy and the diagnosis of tumour recurrence was 26.2 months (median: 28.6 months; range: 18.4 – 33.8 months). The mean plasma EBV DNA level before radiotherapy was 564 copies/ml and the mean value at the diagnosis of recurrence was 711 copies/ml.

Endoscopic endonasal approach was performed in 22 (10.6%) patients. Transpterygoid approach was required in 63 (30.3%) patients. For the rest of the patients (n = 123, 59.1%), the maxillary swing approach was adopted. Thirty-eight (18.3%) patients required vascular bypass, as a result of tumour encasement of the cervical segment (n = 18, 47.4%) or petrous/lacerum segment (n = 20, 52.6%) of the ICA. The area of the skull base bone involved by the tumours included: maxillary sinus (n = 13, 6.3%), clivus (n = 36, 17.3%), pterygoid process (n = 61, 29.3%), sphenoid sinus (n = 30, 14.4%), petrous part of the temporal bone (n = 42, 20.2%) and a combination of the above (n = 26, 12.5%). Table 2 showed the tumour and operative characteristics of these patients. Soft tissue resection margins were negative in 189 (90.9%) patients after salvage surgery. There were no significant differences in the risk of microscopically involved final soft tissue resection margins among the various regions of the skull base bone that were invaded by the tumour. The commonest soft tissue margins that were found positive for malignancy during frozen section examination were the maxillary division (V2) of the trigeminal nerve (n = 18, 8.7%) and the mandibular division (V3) of the trigeminal nerve (n = 6, 2.9%). After removing the bone around the foramen rotundum and foramen ovale followed by further resection of the nerve stumps, the final resection margins were positive at the V2 in 2 patients. None of the patients had positive final margin at the resection stump of V3. Among the 38 patients with tumour encasement of the ICA necessitating vascular bypass, histological examination showed frank tumour invasion of the arterial wall in 3/18 (16.7%) of the patients with cervical ICA encasement, and 16/20 (80.0%) of those with petrous ICA encasement. The resection margins at the resected arterial stumps of these patients were all negative for malignancy.

Concerning the bone resection margins, positive margins were present in 1 (7.7%) patient with maxillary sinus invasion, 12 (33.3%) patients with clivus invasion, 9 (14.8%) patients with pterygoid process involvement, 9 (30.0%) patients with sphenoid sinus extension, 8 (19.0%) patients with petrous part of temporal bone involvement, and 17 (65.4%) patients with multiple bone invasion by the tumour. For tumours that invaded the clivus, those with both cortexes involved had significantly higher chance of positive margins compared to those that involved the anterior cortex only (71.4% vs. 9.1%, p = 0.01). Tumours that invaded the lateral wall of the sphenoid sinuses had significantly

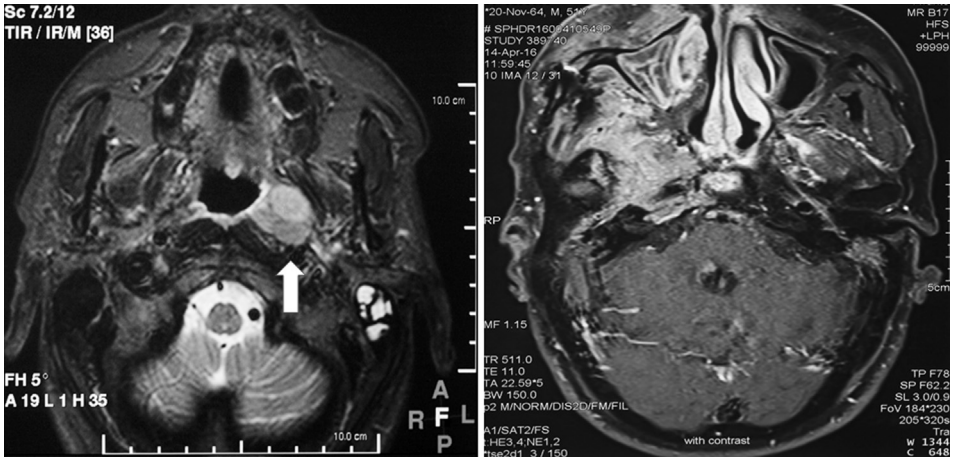

Fig. 3. (*Left*) Axial view of MRI showing recurrent NPC on the left side with invasion of the ipsilateral parapharyngeal space, abutting the left cervical segment of the ICA (white arrow). The left lateral pterygoid muscle is intact and spared from tumour invasion. (*Right*) Axial view of MRI showing extensive tumour invasion of the right infratemporal fossa.

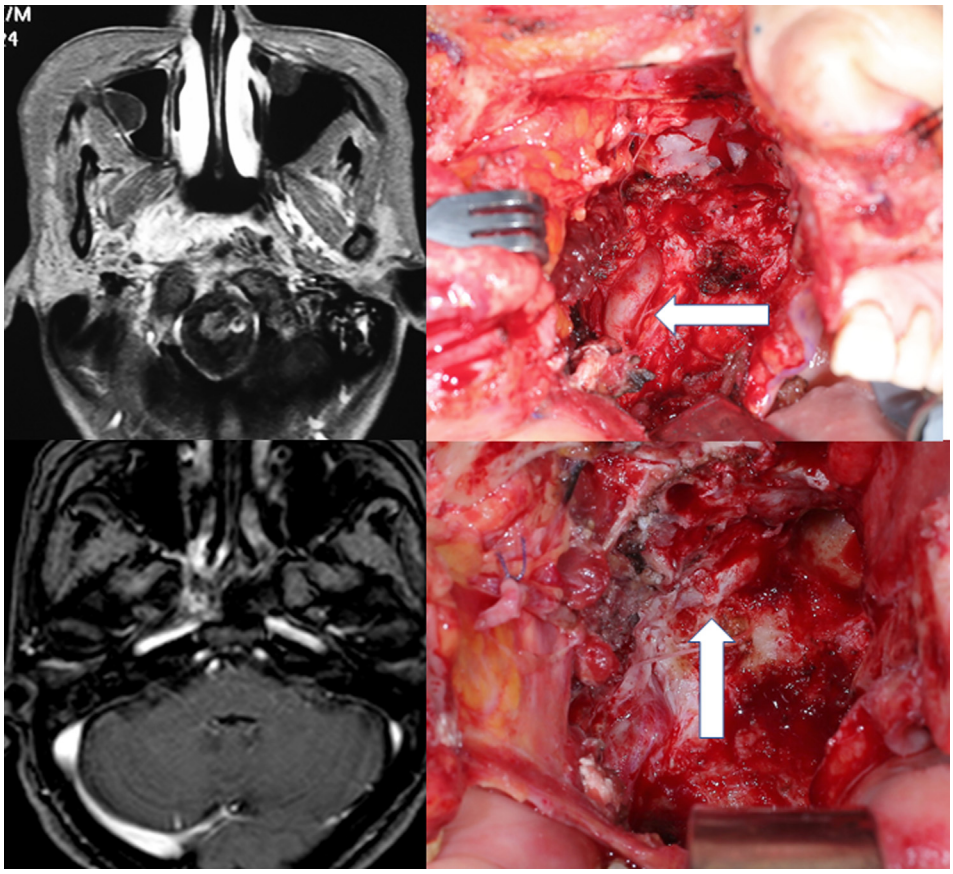

Fig. 4. (*Left, above*) Recurrent tumour arising from the right nasopharynx with invasion of the parapharyngeal space abutting the right cervical segment of the ICA. (*Right, above*) Tumour resected via the right maxillary swing approach, which provided a wide access to the region, allowing en-bloc resection of the tumour down to the surface of the cervical ICA (white horizontal arrow). (*Left, below*) Recurrent tumour with invasion of the right petrous apex abutting the petrous segment of the ICA. (*Right, below*) Tumour exposed and excised via the maxillary swing approach, resulting in the exposure of the petrous and lacerum segment of ICA (white vertical arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Demographic data and the corresponding tumour characteristics for patients with recurrent T3 nasopharyngeal cancer.

	Study subjects (n = 208)
Mean age (yrs.)	52.4
Gender (%)	
Male	175 (84.1)
Female	33 (15.9)
Smoking status (%)	
Smoker	76 (36.5)
Non-smoker	132 (63.5)
Initial tumour stage (%) *	
Stage I	18 (8.7)
Stage II	46 (22.1)
Stage III	112 (53.8)
Stage IV	32 (15.4)
Initial treatment strategy (%)	
Radiotherapy	71 (34.1)
Concurrent chemoradiotherapy	137 (65.9)
Mean time of tumour recurrence after initial treatment (months)	26.2
Mean plasma EBV DNA level (copies/ml)	
- Before radiotherapy	564
- Before surgical salvage of recurrence	711
- 1 month after surgery	0

* American Joint Committee On Cancer (AJCC) seventh edition (2009) staging system for nasopharyngeal carcinoma.

higher chance of positive margins than those that involved the anterior wall only (80.0% vs 5.0%, p = 0.004). The chance of achieving overall negative resection margins (soft tissue and bone combined) by surgical salvage was 63.9%.

The mean hospital stay was significantly longer for patients who required vascular bypass and second stage tumour resection (20.4 days after the second stage surgery). There was no hospital mortality. None of the patients developed carotid artery blowout after surgery. Postoperative complications included 1 patient with vasospasm of the vascular bypass graft with clinical evidence of ischaemia on day 9 after second stage surgery, requiring endovascular stenting. He has full recovery of the ischaemic symptoms immediately after stenting. In addition, 2 patients developed cerebral spinal fluid (CSF) leakage after surgery, among whom, one required reoperation for repair and extraventricular drainage (EVD), and the remaining patient was treated conservatively with lumbar drainage. Twenty-eight (13.5%) patients were dependent on tracheostomy and tube feeding on discharge. All patients had tracheostomy weaned off after a mean of 4.6 months after discharge, although 8 patients remained dependent on gastrostomy tube feeding because of repeated aspiration despite aggressive swallowing rehabilitation supervised by dedicated speech therapists.

The oncological outcomes of salvage surgery for recurrent T3 NPC were shown in Table 3. The mean follow-up duration was 41.7 months. The rate of local tumour recurrence was significantly higher in patients with tumour invading the lateral wall of the sphenoid sinus and when both cortexes of the clivus were breached, but there was no difference among those whose ICA was encased by tumour or not. Kaplan-Meier survival with log-rank test showed that the 5-year overall survival was significantly worse for tumours that invade the parapharyngeal space, encase the ICA, involve the petrous bone, both anterior and posterior cortexes of the clivus, the lateral wall of the sphenoid sinus, patients with positive bone resection margins and those with pre-operative numbness of the face. Multivariate analysis using the Cox proportional hazards model identified tumours that involved with both cortexes of the clivus (HR = 4.23, 95% CI 3.87 – 4.64, p = 0.01) and the lateral wall of the sphenoid sinus (HR = 3.80, 95% CI 3.22 – 4.14, p = 0.01), as well as patients with microscopic tumour involvement of the bone

Table 2
Operative characteristics and post-operative complications after salvage surgery for tumours involving various areas of the skull base bone.

	Regions of skull base bone involvement by tumour							
	Maxillary sinus (n = 13)	Clivus		Pterygoid process (n = 61)	Sphenoid sinus		Petrous part of temporal bone (n = 42)	Multiple bones involvement (n = 26)
		Anterior cortex only (n = 22)	Anterior and posterior cortex (n = 14)		Anterior wall (n = 20)	Lateral wall (n = 10)		
Mean plasma EBV DNA (copies/ml) before surgery	680	708	712	746	623	648	702	865
Operative approach (%)								
Endonasal	4	10	2	0	6	0	0	0
Transpterygoid	4	2	2	24	0	0	18	13
Maxillary swing	5	10	10	37	14	10	24	13
Need for EC-IC vascular bypass								
Due to cervical ICA encasement	2	4	2	6	2	0	0	4
Due to petrous ICA encasement	0	6	1	0	0	2	11	0
Positive final soft tissue margins	0	3	3	0	2	2	4	5
Positive final bone resection margins	1	2	10	9	1	8	8	17
Post-operative complications								
Vasospasm of bypass graft	0	0	0	0	0	0	1	0
CSF leakage	0	0	0	1	0	0	0	1
Permanent non-oral feeding	0	0	1	4	0	0	2	1

Table 3
Oncological outcomes after salvage surgery for tumour involving various areas of the skull base bone.

	Regions of skull base bone involvement by tumour							
	Maxillary sinus (n = 13)	Clivus		Pterygoid process (n = 61)	Sphenoid sinus		Petrous part of temporal bone (n = 42)	Multiple bones involvement (n = 26)
		Anterior cortex only (n = 22)	Anterior and posterior cortex (n = 14)		Anterior wall (n = 20)	Lateral wall (n = 10)		
Mean follow-up duration (months)	38.4	56.2	34.6	60.8	42.4	36.2	28.6	36.6
Local tumour recurrence after surgery (%)	0 (0)	1 (4.5)	***5 (35.7)***	2 (3.3)	2 (10.0)	***4 (40.0)***	3 (7.1)	***6 (23.1)***
Distant metastasis after surgery (%)	0 (0)	0 (0)	2 (14.3)	1 (1.6)	2 (10.0)	2 (20.0)	0 (0)	3 (11.5)
5 – year overall survival	62.2%	64.8%	***30.2%***	70.1%	58.8%	***33.4%***	64.5%	***22.7%***
5 – year disease specific survival	64.5%	68.2%	***32.5%***	76.2%	60.4%	***36.2%***	64.5%	***23.8%***

Clivus (local recurrence: p = 0.04, overall survival: p = 0.04, DSS: p = 0.05) Sphenoid sinus (local recurrence: p = 0.03; OS: p = 0.04; DSS: p = 0.04) Multiple bones involvement (local recurrence: p = 0.01; OS: p = 0.03; DSS: p = 0.03).

resection margins (HR = 5.26, 95% CI 4.85 – 5.60, p = 0.006) as the significant independent prognostic factors that negatively influence the survival after salvage surgery for recurrent T3 nasopharyngeal cancer.

Discussion

Management of recurrent NPC has been challenging. Apart from the anatomical location of the tumour and the presence of vital structures in the vicinity, radical surgery in a previously irradiated field carries a high risk of serious complications, some of which are potentially fatal. Furthermore, because of the diagnostic difficulties of tumour recurrence and the fact that majority of the recurrent tumours appeared submucosally with invasion of deep structures of the skull base and parapharyngeal space [11], recurrent nasopharyngeal cancers are commonly diagnosed at a late stage. Surgical salvage of locally advanced recurrent NPC required wide resection of the tumour in one hand, and a delicate protection of the dura and neurovascular structures on the other hand. Because of the limited experience and the poor treatment outcome, it is rarely reported systematically in the literature.

You et al. [12] from Guangzhou compared the outcomes of surgical salvage versus re-irradiation in the treatment of recurrent NPC and concluded that surgery is superior in terms of survival, quality of life and the cost of treatment. In their cohort of 144 patients, however, only 18.1% were T3 tumours. Ng et al. [13] from Singapore reported the long-term results after salvage nasopharyngectomy using the partial maxillectomy approach in 20 patients. Despite clear resection margins in all patients, 50% developed local recurrence and the 5-year overall survival was 66.7%. All the patients in the cohort, however, had early (T1 and T2) recurrent tumours. Vlantis et al. [14] from Hong Kong reported their experience of endoscopic nasopharyngectomy in 20 patients and performed pooled analysis of 300 patients from 16 papers in the literature. Again, 56.1% of the tumours were recurrent T1 disease and most of the rest were T2 tumours. Wong et al. [15] from Malaysia published a preliminary report on the use of endoscopic endonasal approach for salvaging rT3 and rT4 nasopharyngeal tumours and the results were promising. However, the sample size is small with only 15 patients recruited within the 13 years of study period, and the follow up duration is also limited to a mean of 28.7 months, with a shortest follow up period of only 9 weeks after surgery. In a meta-analysis of 779 patients from 17 published articles on the role of salvage surgery in the treatment of recurrent NPC [16], only 16.6% of the tumours belong to the rT3 and rT4 category, with the rest being early tumours. In addition, the analysis of independent predictors of outcome did not look into specific tumour characteristics, which is vitally important as the category of T3 classification encompasses a widely heterogenous group of tumours with various area and extent of bone invasion. As expected, the outcomes of surgery is highly variable.

The current study is the first in the literature that focused on the surgical salvage of recurrent T3 nasopharyngeal carcinoma, by investigating the surgical details and treatment outcomes of 208 patients in a single centre. Sixty-four percent of our cohort initially presented with locally advanced tumour before radiotherapy, while the rest (36.0%) presented with T1 and T2 disease. Although immediate post radiotherapy MRI and plasma EBV DNA showed complete response in all patients, they all developed locally advanced tumour recurrence after a mean of 26.2 months after treatment. As mentioned in our previous study, more than 60% of the recurrent disease took the form of submucosal tumour with deep invasion, rather than superficial exophytic tumour from the mucosa. As a result, endoscopic examination is often deceiving and superficial biopsy is frequently non-diagnostic of early tumour recurrence. Furthermore, it is also difficult to differentiate, from MRI, early tumour in the nasopharynx from post-radiation fibrosis, and osteoradionecrosis from bone destruction secondary to tumour invasion. The efficacy of PET scan is notoriously low in the diagnosis of early and small tumour recurrence. Further study is needed desperately to identify a better follow-up protocol, including the use of novel biological markers, that allows early diagnosis so that less traumatic salvage surgery can be performed with better chance of cure and quality of life after treatment.

The choice of surgical approach to salvage recurrent T3 tumours of the nasopharynx depends on the expertise and should be personalized according to the location and extent of the tumour. While centrally located tumours such as those involving the clivus, sphenoid sinus, pterygoid process and petrous apex can be managed by the endoscopic approach, more lateral tumours and those low sitting tumours close to the oropharynx are better exposed and resected via the open approach. Another important consideration is the relationship of the tumour with the ICA. The cervical segment and petrous segment of ICA may be encased by locally advanced tumour, and 18.3% of our cohort required a high-flow vascular bypass that allowed subsequent resection of the tumour together with the diseased ICA, in order to achieve a better tumour clearance of the region. One of the important findings from the current study that is not known before is the histological presence of arterial wall invasion by tumour in patients with radiological evidence of ICA encasement. The thick and tough layer of fascia that covers the cervical segment of ICA acts as a barrier to tumour invasion, so that the chance of actual tumour invasion of the arterial wall is only 16.7%. This is significantly lower than that when the petrous/lacerum segment of the artery is encased, as the fascia that covers the cervical segment is absent inside the carotid canal. Once this part of the ICA is radiologically encased, there is an 80% chance of frank tumour invasion of the arterial wall. EC – IC vascular bypass, despite being technically demanding, allows complete resection of tumour with clear margins when the ICA is being encased by tumour, without disturbing the cerebral perfusion due to resection of the native artery [10]. The surgical procedure is technically challenging with a steep learning curve. Understandably, in order to ensure good outcome of treatment, it is best reserved for dedicated, high volume, tertiary centers.

While it is relatively easier to achieve microscopically clear soft tissue margins (90.9% of our cohort had clear soft tissue margins), it is more difficult to ensure that the bone resection margins are clear. One of the reasons is that it is impossible to perform intra-operative frozen section examination of the bony margins. Osteoradionecrosis often coexists with the recurrent tumours, and it is impossible to accurately distinguish between the two during surgery. We relied on pre-operative imaging to assess the extent of bony invasion by the tumours, which was then used to determine the location of osteotomy and the extent of bone removal that would lead to the highest chance of R0 resection. Despite the detailed planning before surgery, the chance of positive bone margin is still up to 26.9% in our series, the chance of which is significantly higher when the tumour invaded both cortexes of the clivus (71.4%) and the lateral wall of the sphenoid sinus (80.0%). This translates into a significantly higher risk of local tumour recurrence after surgery and a significantly lower 5-year overall and disease specific survival. The same trends are observed for tumours that involved multiple areas of skull base bone simultaneously, as this reflects a more extensive nature of these tumours. Wide removal of the posterior wall of the clivus is limited by the risk of inadvertent damage to the underlying dura, which is notoriously difficult to repair in a water-tight manner in that region. On the other hand, extensive resection of the lateral wall of the sphenoid sinus is limited by the presence of the ICA and optic nerve, and the possibility of injuring the abducens nerve when operating around the cavernous sinus. As confirmed by the results of the multivariate analysis, because of the significantly worse surgical outcome for tumours with multiple bones invasion, particularly when both cortexes of the clivus and the lateral wall of the sphenoid sinus are involved, aggressive surgery for such tumours remain controversial.

Conclusions

Surgical salvage for recurrent T3 nasopharyngeal carcinoma is challenging but feasible. Detailed planning before surgery maximizes

the chance of achieving clear soft tissue and bone resection margins. Surgical outcome is significantly worse for tumours that involve multiple bones at the skull base, particularly when both cortexes of the clivus and the lateral wall of the sphenoid sinus are invaded. Indication of aggressive surgery in such circumstances is controversial.

Conflicts of interest

There is no financial interest in the production of this work and there is no financial relationship or commercial association with the manufacturer that might pose a conflict of interest. Informed consent has been obtained from the patients regarding the surgeries performed as well as photo taking for the purpose of subsequent publication.

Financial disclosure

The authors confirm that there is no financial interest in the production of this work and there is no financial relationship or commercial association with the manufacturer that might pose a conflict of interest.

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