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Tumour Review

# Management of locally recurrent nasopharyngeal carcinoma☆

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ABSTRACT

As a consequence of the current excellent loco-regional control rates attained using the generally accepted treatment paradigms involving intensity-modulated radiotherapy for nasopharyngeal carcinoma (NPC), only 10–20% of patients will suffer from local and/or nodal recurrence after primary treatment. Early detection of recurrence is important as localized recurrent disease is still potentially salvageable, but this treatment often incurs a high risk of major toxicities. Due to the possibility of radio-resistance of tumors which persist or recur despite adequate prior irradiation and the limited tolerance of adjacent normal tissues to sustain further additional treatment, the management of local failures remains one of the greatest challenges in this disease. Both surgical approaches for radical resection and specialized re-irradiation modalities have been explored. Unfortunately, available data are based on retrospective studies, and the majority of them are based on a small number of patients or relatively short follow-up. In this article, we will review the different salvage treatment options and associated prognostic factors for each of them. We will also propose a treatment algorithm based on the latest available evidence and discuss the future directions of treatment for locally recurrent NPC.

## Introduction

The previous review by the International Head and Neck Scientific Group (IHNSG) on recurrent nasopharyngeal carcinoma (NPC) summarized the available data that had emerged over the past decade prior to 2010 to identify the scope of the problem [1]. With the adoption of intensity-modulated radiotherapy (IMRT) ± stereotactic radiotherapy (SRT) for the primary management of NPC in the contemporary era, a renewed review of strategies is needed for the management of recurrent NPC as most failures are now likely to be related to radioresistance.

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Furthermore, most of the adjacent normal tissues have already endured varying degrees of damage from the previous course of high-dose radiotherapy (RT). This poses additional complexity and challenges in the salvage treatment. In this article, we will focus on the different salvage options reported in the recent decade and their associated prognostic factors. A treatment algorithm based on the latest evidence is proposed and we will also explore the various ways of the future direction of various approaches that might be useful in tackling this challenging condition.

## Scope of the problem

Using IMRT in the primary setting, excellent loco-regional control rates have been consistently achieved in the treatment of NPC [2,3]. A study by the Hong Kong Nasopharyngeal Cancer Study Group (HKNPCSG-1301 study) recently reported eight-year survival outcomes for NPC patients receiving primary treatment by IMRT with/without chemotherapy at public oncology centers in Hong Kong [4]. Amongst the 3328 patients included, 14% of them developed local recurrence or persistent disease, while 21% had concomitant distant metastasis at the time of local relapse. The median time from the diagnosis of primary NPC to local recurrence was approximately 30 months. Among the patients with recurrence, 41% had local recurrence detected within the first two years, 44% in the second to fifth year and 15% of the recurrences were detected more than five years later.

The majority of the local recurrences were noted to be in the high dose zone [5,6]; while marginal failure ($\leq$2.1%) and geographical miss (0–1%) were uncommon. Hence, it is obvious that most of the recurrences result from radio-resistance [7]. In addition, these radiation resistant tumors are surrounded by critical organs at risk (OAR) that have already absorbed near tolerance radiation dose.

## Detection of local recurrence

Vigilant follow-up by physical and endoscopic examination, surveillance monitoring by magnetic resonance imaging (MRI) and determination of plasma Epstein-Barr virus deoxyribonucleic acid (EBV DNA) level at regular intervals are recommended for all NPC patients following primary treatment. As subsequently illustrated in this manuscript, the importance of early detection cannot be over-emphasized as this is associated not only with a higher chance of survival, but also with better salvage options with lower toxicities.

### Endoscopy

Periodic endoscopic examination is the one of the main modalities for follow-up assessment [8]. The emerging development of narrow-band imaging endoscopy offers a diagnostic advantage. Wang et al. reported that narrow-band imaging endoscopy could enhance the detection rate of mucosal recurrent lesions (88% for both sensitivity and specificity) [9], and also noted that post-radiation effects may give rise to false-positive results. However, neither method could detect deep seated or skull base recurrence.

### MRI

MRI is another main modality for follow-up assessment, but interpretation still remains challenging [10]. Both recurrent tumor and post-therapeutic inflammatory changes may display hyperintensity with intense enhancement on T2-weighted (T2W) images on conventional MRI, leading to equivocal distinction between the two differential diagnoses [11]. Similarly, post-RT induced scar tissue and bony changes also pose diagnostic difficulty in differentiating from the highly variable appearance of recurrent tumors [12]. Diffusion-weighted imaging is now increasingly used as distinction can be improved by the differences in intravoxel incoherent motion-diffusion and perfusion morphology patterns [13,14].

### Positron emission tomography-computed tomography (PET-CT)

PET-CT at the time of local recurrence is valuable as up to ~20% of patients have been reported to have concomitant distant metastasis at the time of local recurrence [15,16]. Furthermore, Yen et al. reported that FDG-PET was superior to MRI in detecting residual/recurrent NPC, showing improvement in sensitivity (100% vs. 62%), specificity (93% vs. 44%) and accuracy (96% vs. 49%) [17].

Another recent meta-analysis revealed that both PET-CT and single-photon emission computed tomography (SPECT) facilitated accurate detection of residual/locally recurrent NPC. Superiority to MRI in the distinction between recurrent disease versus post-RT changes was demonstrated: the pooled specificity estimates for PET-CT (93%) and SPECT (81%) were higher than for MRI (76%) [18]. However, it should be noted that PET-CT may give false-positive results arising from post-RT mucosal inflammatory changes/mucositis or osteonecrosis.

### EBV DNA

Despite the lack of prospective data and the need of standardization of the test, monitoring of plasma EBV DNA is found to be useful for follow-up assessment, especially for the detection of distant failures [19,20]. However, its sensitivity in the detection of local recurrences is relatively low. Elevated plasma EBV DNA level was seen in 55% to 96% of patients with distant metastases, but varied from 0% to 67% in patients with local and/or nodal recurrence [20–24]. Nonetheless, plasma EBV DNA level is still useful, as a high pre-operative level may identify those at a higher risk of distant failure after attempt at salvage surgery [25].

The use of trans-oral nasopharyngeal brush biopsy for EBV DNA in the detection of local NPC recurrence has also been reported [26]. In a series by Hao et al., nasopharyngeal swab testing for PCR-based latent membrane protein (LMP)-1 gene and Epstein-Barr nuclear antigen (EBNA)-1 gene was used to monitor local recurrence in 84 NPC patients [27]. Of the 12 patients who were tested positive for both LMP1 and EBNA1, 11 developed local recurrence (sensitivity 91.7%, specificity 98.6%). This method is convenient and simple but its reliability for detecting deep-seated lesions may be limited.

## Surgical approach

There is as yet no randomized controlled trial offering a head to head comparison of surgery versus re-irradiation or systemic therapy in the management of recurrent NPC. Retrospective comparisons are hindered by various confounding factors: eligible surgical candidates usually exhibit more clinically favorable profiles with lower disease volume, earlier r-T category, better performance status and fewer medical co-morbidities.

Retrospective studies have suggested that the local salvage rates were similar between surgery and re-irradiation [28], but a recent case-matched study by You et al. demonstrated that endoscopic nasopharyngectomy offered more optimal treatment outcomes, better quality of life (QOL) and a significantly lower rate of treatment-related complications as compared with salvage IMRT [29].

In view of the high incidence of severe late toxicities associated with re-irradiation [30], surgical salvage should be considered in resectable cases. Various surgical techniques (including endoscopic resection ± robotic assistance [31] and open nasopharyngectomy via various approaches [32]) could be adopted depending on the disease extent and location.

The resectability of the recurrent diseases can be broadly categorized as follows:

- Easily resectable: rT1 disease, rT2–3 with limited parapharyngeal space involvement or disease confined to the base of sphenoid sinus.
- Potentially resectable (definition could vary depending on availability of expertise) [33]: involvement of the internal carotid artery (ICA), limited invasion to the clivus, posterior maxillary sinus,

**Table 1**
Comparison between open surgery and endoscopic resection.

| | Open surgery | Endoscopic resection |
|---|---|---|
| Advantages | Better macroscopic exposure to the operating field<br>Most suitable for more locally advanced tumors close to internal carotid artery | Less invasive<br>Avoids the morbidities inherent with open procedure<br>Most suitable for centrally located tumors, especially rT1–T2 with limited parapharyngeal involvement |
| Procedure-specific complications | Cosmesis, facial numbness, trismus, palatal fistula formation, nasal blockage, ectropion, epiphora | Flap necrosis with flap coverage of the NP defect |
| Other complications in common | Skull base osteonecrosis, inadvertent damage to the carotid vessel, velopharyngeal insufficiency, eustachian tube dysfunction causing otitis media with effusion | |

pterygoid process and petrous apex.
- Unresectable: tumor invading both cortexes of the clivus (difficult to repair the dura in a water-tight manner if inadvertently damaged), significant involvement of the lateral wall of the sphenoid sinus (due to the presence of internal carotid artery, optic nerve and abducens nerve), frank cavernous sinus or intracranial invasion, and multiple areas of skull base involvement [33].

The advantages and disadvantages of open surgery vs. endoscopic resection for early resectable recurrences are delineated in the Table 1. Irrespective of the operative approach, exposed ICA, bone and dura should be covered by a muscle flap. One approach is to use the vastus lateralis muscle free flap tunneled medial to the body of the mandible to the neck, where a microvascular anastomosis will be carried out [34].

Special surgical techniques are also needed for recurrent disease with carotid artery involvement. A two-stage operation has been described: an extra-to-intracranial vascular bypass using the autologous radial artery or long saphenous vein is performed during the first-stage. After ascertaining the patency of the bypass by CT angiogram, the tumor including the involved bone and ICA will be removed en-bloc in the second operation [35].

The treatment outcomes of open surgery and endoscopic resection are summarized in Table 2 [36–46]. Irrespective of treatment methods, local control exceeding 50% has been consistently reported in modern series. Peri-operative mortality rate seems low and late complications appear to be significantly less common than after re-irradiation, particularly if an endoscopic approach has been used. Furthermore, global quality of life (QOL) after salvage nasopharyngectomy has been reported as generally good; only palatal fistula and osteoradionecrosis might potentially affect the social life of the patients [47]. The results of removal of recurrent nasopharyngeal carcinomas after radiotherapy failure are encouraging for rT1–T2 and select T3 tumors, and even for T4 tumors with extracranial extension. On the other hand, patients with rT4 tumors with intracranial involvement generally recur locally or die due to development of metastatic disease. Although some authors report encouraging results in the case of intracavernous involvement, surgical salvage of NPC recurrence with significant intracranial extension is usually not justified.

While the role of surgical treatment is increasingly recognized if expertise is available, the role of adjunctive RT and/or chemotherapy remains unclear, except that most would agree to consider post-operative RT for patients with positive resection margins [48].

### *Re-irradiation approach*

Various studies conducted in recent years have advocated IMRT, SRT or intensity-modulated proton therapy (IMPT) for re-irradiation. These techniques have surpassed the roles of brachytherapy, 3D-conformal RT and other older techniques [1]. Various radiobiological factors including total dose, dose/fraction, altered fractionation, dose tolerance of OAR (especially the nasopharyngeal mucosa, carotid vessels and neurological structures) and their prior dose exposure should be carefully considered. Furthermore, the best quality control of RT technique and precision set-up should be adopted for maximal sparing of the neighboring uninvolved normal tissues.

IMRT is universally the most used modality at present, and most protocols aim to deliver a radiation dose of $\geq 60$ Gy to the recurrent gross tumor volume (rGTV), to achieve a promising local control rate of 52–86% [49–55]. Table 3 summarizes the recent studies based on IMRT [7,16,49–51,53–61] and provides an in-depth analysis of the effect of re-irradiation on overall survival. Such studies can be broadly divided into two groups based on the reirradiation dose ($\leq 60$ Gy vs. $> 60$ Gy). The reported five-year survival rates range from 28 to 60%, with rT3–T4 disease at the lower end of the survival spectrum. Fatal

**Table 2**
Efficacy and major complications of selected series of nasopharyngectomy for recurrent nasopharyngeal carcinoma.

| Author | No. | rT1 (%) | Post-operative RT (%) | Salvage rate (5 year) | | Severe complications | |
|---|---|---|---|---|---|---|---|
| | | | | LC (%) | OS (%) | Carotid injury/Massive bleeding (acute or late) (%) | Hospital mortality (%) |
| *Open surgery* | | | | | | | |
| King et al. [36] | 31 | 65 | 77 | 43 | 47 | 3 | 0 |
| Fee et al. [37] | 37 | 59 | 22 | 67 | 60 | 3 | 3 |
| Hao et al. [38] | 53 | 51 | 39 | 54 | 49 | 4 | 0 |
| Vlantis et al. [39] | 97 | 55 | 73 | 47 | 52 | 3 | 0 |
| Wei et al. [40] | 246 | NS | NS | 74 | 56 | 1 | 0 |
| Bian et al. [41] | 71 | 38 | NS | 54 | 42 | 0 | 0 |
| Ng et al. [42] | 20 | 90 | NS | 70 | 67 | 0 | 0 |
| *Endoscopic surgery* | | | | | | | |
| Chen et al. [43] | 37 | 46 | 0 | 86* | 84* | 0 | 0 |
| Ko et al. [44] | 28 | 43 | 7 | T1 – 100*<br>T2 – 42* | 59* | 4 | 0 |
| Zou et al. [45] | 92 | 50 | NS | NS | 78 | NS | NS |
| Liu et al. [46] | 91 | 33 | NS | NS | 38 | 10 | 0 |

Abbreviation: LC – local control, NS – not stated, OS – overall survival.
* 2 year outcomes.

**Table 3**
Cross-study comparisons for selected series of recurrent nasopharyngeal carcinoma treated with intensity modulated radiotherapy.

| Author | No. of patients | % rT3–4 | Dose (Gy) | Median FU (months) | Endpoint (year) | Local control (%) | OS (%) | Severe complications (%) | Fatal complication (%) |
|---|---|---|---|---|---|---|---|---|---|
| *Planned total radiation dose > 60 Gy* | | | | | | | | | |
| Qiu et al. [51] | 70 | 57 | 50–77.4 (median 70) | 25 | 3 | 49 (LRRFS) | 52 | mucosal necrosis – 16<br>CN palsy – 24<br>TLN – NR<br>massive epistaxis – 9 | massive epistaxis – 9 |
| Han et al. [49] | 239 | 75 | 61.7–78.7 (mean 69.9) | 29 | 5 | 86 (LRFS) | 45 | mucosal necrosis – 41<br>brain injury – 29 | overall – 35 |
| Chen et al. [54] | 54 | 80 | 49.8–76.6 (mean 70) | 17 | 2 | 64 (LPFS) | 44 | mucosal necrosis – 32<br>dysphagia – 20<br>TLN – 19<br>massive epistaxis – 11 | overall – 25 |
| Hua et al. [50] | 151 | 81 | 62.1–77.6 (mean 70.4) | 40 | 3 | 83 (LCR) | 46 | mucosal necrosis – 20<br>CN palsy – 13<br>brain injury – 22 | massive epistaxis – 19<br>brain injury – 17 |
| Tian et al. [55] | 117 | 79 | 65.4–73.1 | 25 | 3 | 64-71[b] (LFFS) | 48 | mucosal necrosis – 39<br>CN palsy – 13<br>TLN – 21 | overall – 32 including mucosal necrosis / bleeding – 20<br>TLN – 4 |
| Tian et al. [56] | 245 | 100 | 60.1–78.7 (median 70) | 24 | 5 | 61 (LRFFS) | 28 | mucosal necrosis – 27<br>CN palsy – 14<br>TLN – 22<br>massive epistaxis – 16 | overall – 29 including mucosal necrosis / bleeding – 13<br>TLN – 7 |
| Kong et al. [7] | 77 | 39 | 46.2–70 (median 66) | 26 | 3 | 67 (LPFS) | 52 | mucosal necrosis – 40<br>CN palsy – 26<br>TLN – 9 | overall – 53 including mucosal necrosis / bleeding – 22 |
| Kong et al. [57] | 184 | 65 | 42–77 (median 66.7) | 33 | 3 | 85 (LRFS) | 46 | mucosal necrosis – 30<br>CN palsy – 11 | mucosal necrosis – 24 |
| *Planned total radiation dose ≤60 Gy* | | | | | | | | | |
| Chua et al. [53] | 31 | 75 | 50-60[a] (median 54) | 11 | 1 | 65 (LPFS) | 63 | CN palsy – 10<br>brain necrosis – 7 | NR |
| Koutcher et al. [e] [58] | 29 | 45 | (median 45–59.4)[a] | 45 | 5 | 52 (LCR) | 60 | CN palsy – 7<br>TLN – 14 | NR |
| Karam et al. [59] | 27 | 23 | 44–59.4 (mean 51) | 36 | 3 | 53 (LCR) | [49][c] | mucosal necrosis – 0<br>CN palsy – 7<br>TLN – 0 | 0 |
| Chan et al. [16] | 38 | 100 | 50–64.8[d] | 48 | 3 | 44 (LCR) | 47 | mucosal necrosis – 23<br>TLN – 24<br>dysphagia – 24<br>massive epistaxis – 20 | massive epistaxis – 8 |
| Lee et al. [60] | 20 | 100 | 60–64.8[d] | 45 | 3 | [ < 26%][c] (LFFS) | [35][c] | brain necrosis – 20<br>aspiration – 30<br>massive epistaxis – 15 | massive epistaxis – 15 |
| Ng et al. [61] | 32 | 100 | 60 | 29 | 3 | 45 (LCR) | 64 | mucosal necrosis – 15<br>TLN – 31<br>CN palsy – 31<br>dysphagia – 15<br>massive epistaxis – 12 | massive epistaxis – 8<br>TLN – 1 |

Abbreviations: LCR – local control rate, LFFS – local failure free survival, LPFS – local progression free survival, LRFFS – locoregional failure free survival, LRFS – local recurrence free survival, LRRFS – locoregional recurrence free survival, NR – not reported, OS – overall survival.

[a] Some patients had additional stereotactic radiotherapy or brachytherapy boosting.
[b] 5 year.
[c] Estimated figure.
[d] 1.2 Gy per fraction, twice daily.
[e] 83% IMRT.

complications are not uncommon, especially in series delivering a high total dose (≥70 Gy) for the second course of RT. The commonest catastrophic toxicities include carotid blowout, temporal lobe necrosis, mucosal necrosis and aspiration pneumonia. Given the narrow therapeutic margin, it is important to note that a higher radiation dose may not lead to higher chance of survival as fatal complications negate the benefit of higher tumor control rates.

Due attention should also be paid to the allowable maximal tolerated dose for neurologic OARs in the second course of radiotherapy. Several models have been proposed based on the partial recovery from the first course of treatment by approximately 50% (provided that the first course was delivered more than 1 year ago) [62,63], total cumulative radiation dose [64,65] and the time interval between the two courses of radiotherapy [66,67]. However, all of these models are based on rather scanty clinical information, and details of dose distribution within the OARs are largely unknown. Hence the OARs tolerance in the second course of treatment should always be guided by the "As Low As Reasonably Practicable" principles. Similar consideration also apply to the design of re-irradiation volume, and elective treatment (such as the uninvolved regional nodal basin or the subclinical disease in the vicinity of rGTV) is generally not recommended as reported in other locally recurrent head-and-neck squamous cell carcinoma (SCCHN) [68], and the treatment targets usually consist of the rGTV with tight margin only.

**Table 4**
Recent reports on stereotactic radiotherapy for recurrent nasopharyngeal carcinoma.

| Author | No. of patients | % rT3–4 | Dose | Median FU (months) | Endpoint (year) | Local control (%) | OS (%) | Severe complications | Fatal complication |
|---|---|---|---|---|---|---|---|---|---|
| Dizman et al. [69] | 24* | 42% | 5–6 Gy/fr, 5 fr | 20 | 3 | 21 | 31 | 4% TLN | 4% |
| Ozyigit et al. [70] | 24 | 71% | 6 Gy/fr, 5 fr | 23 | 2 | 82 | NR | 12% cranial neuropathies, 4% TLN, 17% carotid blowout | 12.5% |
| Seo et al. [71] | 35** | 43% | 7.5–12 Gy/fr, 3–5 fr | 25 | 5 | 79 | 60 | 6% mucosal necrosis, 9% NP hemorrhage | 6% |
| Leung et al. [72] | 30 | 30% | 2.5–4.5 Gy/fr, 8–22 fr | 47 | 5 | 57 | 40 | 23% cranial neuropathies, 20% TLN | 3% |
| Chua et al. [73] | 43*** | 30% | 8–18 Gy in single fr | 40 | 3 | 51 | 66 | 16% brain necrosis 2% NP hemorrhage | 0% |
| | 43*** | 30% | 20–49 Gy in 4–6 fr | 24 | 3 | 83 | 61 | 12% brain necrosis 4% NP hemorrhage | 7% |

Abbreviations: fr – fraction, NP – nasopharyngeal, TLN – temporal lobe necrosis.
* 29% had metastatic disease.
** 9% – no records for the evaluation of the toxicity data.
*** 44% – persistent disease.

Another commonly employed precision treatment technique for locally recurrent NPC is SRT. Table 4 summarizes the published series reported since our last review [1,69–73]. The number of patients treated with this technique is too small for robust comparisons with IMRT [69–75]. This is still considered a technical approach that remains under development.

The availability of IMPT in recent years, a technique which is characterized by its unique beam properties of a Bragg peak followed by a rapid distal fall-off, has optimized the physical dose distribution and OAR sparing [76]. A study by Lin et al. [77], using IMPT to doses of 59.4–70.2 cobalt gray equivalent in 16 patients with recurrent NPC (12 of whom had rT4 disease), reported 50% OS and loco-regional PFS at 2 years, with low doses (0–22 Gy) given to the critical OARs resulting in minimal side effects to central nervous system structures. On the other hand, Feehan et al., using heavy charged particles to a median dose of 50 Gy equivalent in 11 patients with recurrent T3–4 NPC, reported less remarkable results [78]: at a median follow up of 28 months, the local control rate was 45%, but temporal lobe necrosis (TLN) and serious aneurysmal bleeding were observed in 36% and 9% of patients, respectively. No long-term outcomes and side effects were subsequently reported for these two series. The study by Hu et al., using carbon ions to doses of 50–66 Gy equivalent in 75 patients with recurrent NPC [79], reported an encouraging 87% local recurrence-free survival at one year, but the median follow-up was only 15 months and longer observation seems warranted. Furthermore, mucosal necrosis and TLN were observed in 9.3% and 1.3% of patients respectively, demonstrating that the NP mucosa will be a key dose limiting factor with particle beam therapy.

One of the most important considerations associated with re-irradiation is the risk and the severity of RT-related toxicities. According to a recent meta-analysis [30], grade 5 toxicities were observed in 33% of patients, with the most common severe effects being mucosal necrosis and massive hemorrhage, followed by feeding difficulties and radiation encephalopathy [30,56].

Carotid blowout is one of the major causes of treatment-related deaths. A literature-based systematic review by McDonald et al. on 1554 patients reported a crude incidence rate of 2.6% following re-irradiation to the head and neck region, and the mortality rate was 76% [80]. The reported rate of hemorrhage after re-irradiation for NPC has varied widely: the incidence after IMRT or SRT ranges from 0 to 25%. [54,70,71,81] Apart from the dose to the carotid artery [82], the total re-irradiation dose is also an important factor. In a phase 2 randomized study by Tian et al. in which two IMRT dose regimens in recurrent NPC were compared [55], the massive hemorrhage rate at a median follow-up of 25 months was 19% in the group given 60 Gy in 27 fractions as compared with 31% in the group given 68 Gy in 34 fractions; the prior radiotherapy dose was the same in the two groups.

Mucosal and adjacent soft tissue/bone necrosis is frequently observed after re-irradiation, causing foul odor, intense headache, and/or profuse bleeding. Endoscopic examination showed extensive areas of crusting, necrotic tissue and even exposed bone. This can also give rise to massive nasal bleeding similar to the carotid blowout syndrome. The reported incidence ranged from 6.3% to 40.6% [49,51,54,55]. In the study reported by Yu et al. on 204 patients [83], lethal nasopharyngeal necrosis (LNN) was observed in 31 patients (15.2%). Logistic regression analysis revealed several independent risk factors for LNN: including the female sex, presence of necrosis before re-irradiation, accumulated total prescription dose to GTV $\geq$ 145.5 Gy, and recurrent tumor volume $\geq$ 25.38 $cm^3$. A curative-intent endoscopic necrectomy followed by reconstruction using the posterior pedicle nasal septum and floor mucoperiosteum flap was recently described as a safe and effective treatment for post-radiation nasopharyngeal necrosis [84].

Dysphagia is another common RT-related toxicity. The cause of dysphagia can be related to trismus, pharyngeal constrictor muscle dysfunction and/or cranial nerve (IX-XII) injury. Chen et al. reported that 20% of patients required long term feeding tube insertion or gastrostomy due to severe dysphagia after re-irradiation [54]. Other series have reported severe trismus rates of around 15% [51,55,58].

Last but not least, TLN is another serious late toxicity that is potentially life-threatening. While some patients may be asymptomatic especially at the early stage, others progressively develop debilitating symptoms including headache, dizziness, memory loss, epilepsy, pressure symptoms, changes in consciousness and/or occasional intracranial hemorrhage [85]. The incidence of TLN is much higher in the re-irradiation cohort than that of single-course RT, ranging from 7% to 35%. [49,53–55,58,86] Risk factors for TLN include the fractional dose, the cumulative dose, the technique of RT and the time interval between the 2 RT courses [87–90]. The study by Liu et al. on over 200 recurrent NPC patients re-irradiated to around 70 Gy revealed a 31% risk of TLN with a median latency period of only 15 months [91]; a maximum cumulative dose of less than 125 Gy (calculated as equivalent dose in 2 Gy fractions (EQD2)) and an intervening treatment interval of at least 2 years from prior radiation were recommended.

*Role of systemic treatment*

Despite the lack of high-level evidence, induction and/or concurrent chemotherapy is often given with re-irradiation. Induction chemotherapy is especially considered in patients with rT3–4 diseases because this may down-size the recurrent tumor bulk facilitating easier

**Table 5**
Adverse prognostic factors affecting the outcomes of recurrent nasopharyngeal carcinoma after re-irradiation.

| | Han et al. [49] | Li et al. [107] | Leong et al. [30]* | Tian et al. [108] | Yue et al. [109] |
|---|---|---|---|---|---|
| Gender | NR | NR | NR | NR | No association |
| Age | Age > 46 | Increasing age | NR | Age > 50 | No association |
| Performance status | NR | NR | NR | KPS ≤ 70 | NR |
| Time to recur | NR | NR | < 36 months | NR | No association |
| rT category | Increasing rT | rT3–4 | rT3–4 | rT3–4 | Increasing rT |
| rGTV | > 38 cc | Increasing rGTV | NR | > 30 cc | Increasing rGTV |
| rN + | rN + | NR | High nodal burden | rN + | No association |
| 2nd course RT dose | NR | ≥ 68 Gy | NR | NR | No association |
| Mean fractional dose | < 2.3 Gy | NR | NR | NR | NR |
| Prior RT complications | NR | Presence of ≥ G3 toxicities | NR | Presence of late complications | NR |
| Addition of chemotherapy | NR | NR | No association | NR | No association |

Abbreviations: GTV – gross tumor volume, KPS – Karnofsky performance status, NR – not reported, RT – radiotherapy.
* Reirradiaton dose ≥ 70 Gy to rGTV was not associated with improved survival.

sparing of adjacent OARs and eradicate micro-metastases. Concurrent chemotherapy may improve radio-sensitivity leading to improved local tumor control. However, the potential aggravating effect of chemotherapy related to increased late toxicities should also be addressed. It is also unclear whether chemotherapy can be safely sequenced or combined with stereotactic or other hypofractionated or accelerated forms of re-irradiation.

Various chemotherapy agents and their combinations have been investigated in the locally recurrent setting, including cisplatin [58,92], 5-fluorouracil [92], gemcitabine [93] and taxanes [61]. Targeted agents such as anti-epidermal growth factor receptor agents [61,94] have also been tried, though no study has been reported with anti-angiogenic agents due to the underlying risk of hemorrhagic complications for locally recurrent tumors. In fact, in the study reported by Hui et al. on thirteen NPC patients who were treated with sunitinib and had previously been given high-dose radiation to upper aerodigestive tract, a high incidence (64%) of hemorrhagic events was found, and it appeared that direct vascular invasion by tumors (which is not uncommon in the locally recurrent setting) further increased the risk of serious bleeding [95]. Hence, the study of anti-angiogenic agents is now mainly confined to use in the distant metastatic setting [96]. On the other hand, the HKNPCSG has reported a study aiming to evaluate the effect of induction docetaxel, cisplatin, and fluorouracil (TPF) followed by weekly docetaxel and cetuximab given concurrently with IMRT on the overall treatment outcomes among a group of rT3–4 patients without distant metastasis. While the proposed regimen achieved a superior treatment outcome (3-year PFS and OS rates of 36% and 64%, respectively) compared with results seen in previous studies, the poor tolerability of induction TPF and the high rate of TLN (31%) will impose limitations on its applicability [61].

Another proposed approach suggests treatment of advanced recurrent disease with chemotherapy alone [97]. A case-control study on 88 rT3–4 N0-1 NPC patients treated with chemotherapy with or without re-RT reported no statistical significance in the 5-year survival rates between the two groups (27.5% vs 23.4%), suggesting the possibility of sole use of chemotherapy in conservative settings.

No ongoing studies focus on the emerging role of immunotherapy in locally recurrent NPC. Promising results have been reported with pembrolizumab, nivolumab, and camrelizumab in the second-line setting (overall response rate 20–34%) [98–100] or in combination with chemotherapy (overall response rate 91%) [100]. However, all of these studies comprise small series of mixed groups with distant metastases and/or local-regional recurrence. Therefore, the exact role of immunotherapy in the management of locally recurrent NPC remains yet to be evaluated. The observed long-term disease control in some patients with recurrent or metastatic SCCHN [101,102] warrants investigation of immunotherapy as a single modality or in combination with radiation therapy in the treatment of locally recurrent disease. Studies are currently combining re-irradiation with immune check point inhibitors in the treatment of recurrent SCCHN including NPC (NCT03521570). Other novel strategies including adoptive immunotherapy [103] and therapeutic vaccine [104] are also under active investigation.

## *Prognostic factors*

### *Surgery*

Several important adverse prognostic factors have been identified in patients receiving surgery. These include advanced T category, large tumor size, positive resection margins, presence of gross tumor in the sphenoid sinus, cavernous sinus invasion and synchronous cervical nodal metastasis [48,105]. Further modifications based on resectability have been proposed regarding T category [106]. Specifically, resectable rT2 and resectable rT3 were defined as tumor being confined to the superficial parapharyngeal space, and tumor confined to the base of sphenoid sinus.

A meta-analysis in 2014 involving 779 patients with locally recurrent NPC showed that endoscopic surgery was superior to open surgery in selected patients with T3/4 disease. In addition, this study showed that adjuvant re-irradiation achieved additional survival advantages when compared with surgery alone [48].

### *Radiotherapy*

In a prognostic model proposed by Li et al. [107], five significant prognostic factors for OS in patients with locally recurrent NPC were identified: age, T-category of the recurrence (rT3–4), size of rGTV, presence of prior RT-induced grade 3 or above toxicities, and the dose of re-irradiation by IMRT (EQD2 of ≥ 68 Gy). A prognostic index (PI) was constructed based on these five factors. A PI score of 252 consistently categorizes patients into good vs poor risk for OS and grade five toxicities. This may serve as a useful model to guide clinicians and patients making decisions about re-irradiation. Table 5 summarizes other factors that influence the outcomes of recurrent NPC as reported by various studies [30,49,107–109]. Recurrent T category and tumor size are the most consistent prognostic risk factors.

## *Treatment outcomes*

The management strategy outlined above is the most commonly adopted practice in Hong Kong, as shown in a recent Patterns of Care study reported by the HKNPCSG [110]. The study included 272 locally recurrent non-metastatic NPC patients who were treated with a primary course of IMRT: their rT stage distribution was 30.5%, 9.6%, 25.4% and 34.6% for rT1, rT2, rT3 and rT4, respectively. Among these patients, 30.9% were treated with radical surgery ± adjuvant RT or chemotherapy, 35.7% with re-RT ± induction or concurrent chemotherapy, 23.2% with palliative chemotherapy alone, and 10.3% were managed with palliative intent with no active treatment given.

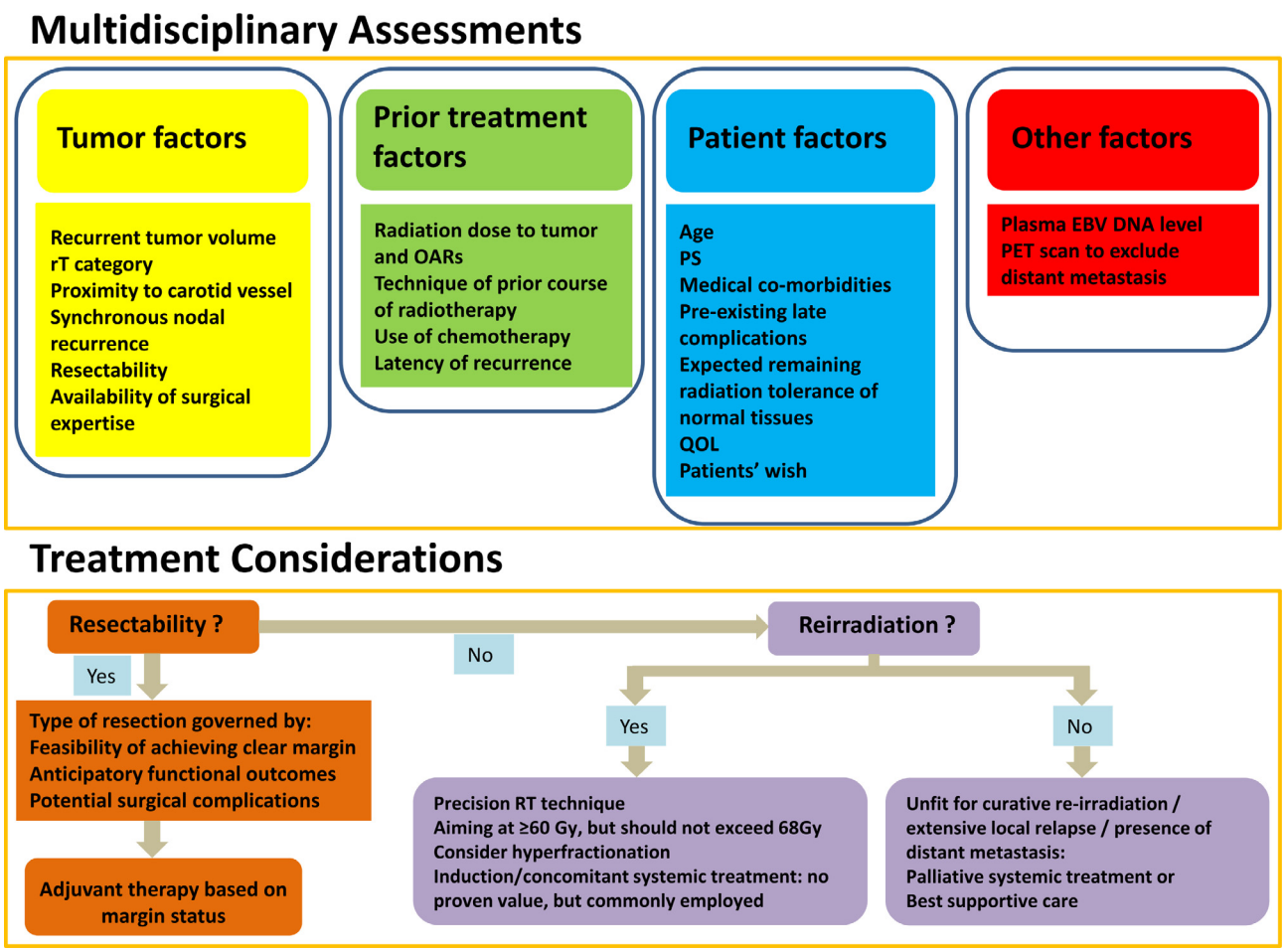


**Fig. 1.** Treatment algorithm for locally recurrent nasopharyngeal carcinoma. Abbreviations: EBV DNA – Epstein-Barr virus deoxyribonucleic acid, OARs – organs at risk, PET – positron emission tomography, PS – performance status, QOL – quality of life.

The most common treatment modality for recurrent stage I, II, III and IV diseases was surgery (82.3%), surgery (38.1%) or re-RT (38.1%), re-RT (52.1%), and chemotherapy alone (42.3%), respectively. The 5-year OS for the whole series was 30.2%, and the corresponding 5-year OS for patients who received surgery, re-RT, chemotherapy or no active treatment was 56.3%, 21.8%, 11.6% and 11.1%, respectively. Our results indicate favorable long-term outcomes with surgery for a resectable recurrence, while re-RT will achieve a two-fold OS improvement compared against chemotherapy or no active treatment.

*Treatment algorithm and follow up*

The appropriate treatment algorithm for patients with locally recurrent NPC is described in detail in Fig. 1. Multidisciplinary assessment with comprehensive consideration of all factors (including recurrent tumor factors, prior treatment factors and patient factors), and an in-depth discussion with the affected patient are important for treatment decisions. Salvage surgery should be considered whenever feasible, while re-irradiation should be considered for patients with unresectable disease, or those who are unsuitable or reluctant for surgery. For patients with extensive recurrences, it is impossible to attain adequate therapeutic dose coverage using re-irradiation due to the limited remaining tolerance of critical OARs; treatment by chemotherapy and/or immunotherapy is an alternative option.

After radical salvage treatment, follow-up is similar to that recommended by the NCCN [111] and ESMO [8] guidelines as in the setting of primary treatment. This consists of a combination of periodic clinical and radiological assessment. Clinical examination of the nasopharynx and neck, cranial nerve function, fiberoptic endoscopy, and evaluation for the presence of systemic symptoms are performed at approximately every 3 months in the first 2 years, half-yearly at 3–5 years after treatment, and annually thereafter. MRI should also be performed every 6–12 months not only for surveillance of the local disease but also the detection of late complications. Patients are also regularly reviewed by nurse specialists and relevant allied health professionals for supportive care, rehabilitation of speech, hearing, swallowing function, and monitoring of nutritional status.

*Future directions*

Recent advances in robotic surgery and 3D-endoscopic visualization have enhanced surgical feasibility and accessibility. The Da Vinci robotic surgical system provides a magnified, three-dimensional view of the surgical field, and thus facilitates more precise surgical dissection with the possibility of three-handed manipulation. The next-generation flexible robotic surgical systems further improve the access to the nasopharynx, avoiding the need to split the soft palate and enabling simultaneous manipulation of four instruments (three surgical instruments and a camera) into the NP without collision or restriction of the surgeons' joint movement [112]. Furthermore, anecdotal series on photodynamic therapy suggest that this form of treatment may also play a role in the salvage of superficial NP recurrence [113–115].

Integration of RT with immunotherapy has been proposed with promising preclinical data of radiosensitization by immune checkpoint blockade therapies [116]. The newly launched HKNPCSG trial will examine this concept in further scope, by combining re-irradiation with

avelumab for unresectable localized recurrent NPC. Better understanding of the tolerance of key OARs is obviously important for optimizing dose-fractionation schedules for re-irradiation. Previous publications by Yu et al. and IHNSG have provided useful summary data for both mucosal [49] and carotid artery tolerances [117]. Photobiomodulation therapy using light therapy (lasers or LEDs) [118] has shown promising potential to promote mucosal healing through biostimulation of cellular repair, angiogenesis, and its anti-inflammatory effects. Preliminary evidence suggests that this can potentiate a clinically effective treatment for post-irradiation mucosal necrosis. Other strategies including hyperbaric oxygen [119] and tissue grafting [84] have been described and further studies are warranted.

## Conclusion

The evolution of the management of NPC has been very impressive. High rates of local disease control have been achieved though both technological improvements and oncological research. Paradoxically this success has now made treatment of local recurrences extremely challenging. This review summarizes the current clinical options, with ongoing research targeting radioresistance and further technological advances awaited.

## Declaration of Competing Interest

The authors declare that there is no conflict of interest related to this review.

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