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EDITORIAL

Retreatment in locally recurrent nasopharyngeal carcinoma: Current status and perspectives

1 | Background

Nasopharyngeal carcinoma (NPC) arises from the epithelial cells that cover and line the nasopharynx. While it is considered a rare cancer globally, it is commonly observed in South China and a few other ethnically distinct racial groups. Due to its propensity to spread early through the submucosal tissue and the highly infiltrative nature of this disease, NPC spreads easily through areas of lesser resistance within the pharyngobasilar fascia with a tendency for neural infiltration [1–3]. Radiation therapy (RT) is the most suitable modality for primary curative treatment and can be complemented with either induction, concurrent, or adjuvant chemotherapy in the more advanced cases.

The overall predominant cause of treatment failure is distant metastases. However, on average, 10% to 20% of NPC patients present with local recurrence after primary curative treatment. The 5-year local failure-free rate decreases depending on the initial stage of the primary tumor. For T1 disease, this can range from 88% to 100%, whereas for T4 disease, this can drop to 55% to 86% [4–8].

For patients with first local failure, the majority of them have only local recurrence without distant metastases [9]. Recurrent disease is defined as a biopsy-proven disease that recurs after a period of remission following completion of initial treatment, occurring more than 3 months post-treatment [10]. Thus, the prospect of offering salvage treatment to these patients is to achieve control of local disease in order to have a chance of cure, as well as alleviate any current and potential symptoms, remains a worthwhile option.

Local recurrence in NPC remains a difficult topic, presenting many challenges in management. As a result of the numerous complex issues arising, recurrent NPC is best treated in an experienced center with expertise in multidisciplinary care.

In this article, we consolidated the available literature on retreatment in cases of locally recurrent NPC, highlighting the role of surgery, patient selection for RT retreatment, RT dose fractionation and constraints, modalities of RT delivery, the role of chemotherapy in re-irradiation cases, and the role of immunotherapeutic advances in re-irradiation cases.

Abbreviations: NPC, nasopharyngeal carcinoma; RT, radiation therapy; OS, overall survival; DFI, disease-free interval; LRRFS, locoregional recurrence-free survival; PFS, progression-free survival; IMRT, intensity-modulated radiation therapy; VMAT, volumetric arc radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy; OAR, organ at risk; KPS, Karnofsky performance status; GTV, gross tumor volume; WHO, World Health Organization; EBV, Epstein Barr virus; BED, Biological Equivalent Dose; EQD2, Equivalent dose in 2 Gray fractions; SBRT, stereotactic body radiation therapy; MRI, magnetic resonance imaging

2 | THE ROLE OF SURGERY IN LOCALLY RECURRENT NPC

Initial RT at first presentation involves extensive coverage of the nasopharyngeal and parapharyngeal tissues, as well as the skull base and its foramina to a high dose, due to the high tissue-infiltrative and neural-infiltrative nature of NPC [2-3, 11]. Thus, for cases of locally recurrent NPC, nasopharyngectomy is the preferred modality of treatment if amenable, either via an open approach, or more commonly, an endoscopic approach. The primary goal is to achieve negative margins with minimal postoperative morbidity.

However, surgery remains feasible only for smaller recurrent tumors in an accessible location. Contraindications to surgery include [1] extensive indurated invasion, [2] cavernous sinus involvement, [3] pharyngobasilar fasciae invasion, [4] extensive skull base involvement, especially with the involvement of neural foramina, [5] perineural involvement, and [6] dural or intracranial involvement [12–14]. Thus, recurrences amenable to surgery with favorable outcomes and a high likelihood of negative margins include the majority of recurrent T1 (rT1;

based on the 8th TNM staging edition of the American Joint Committee on Cancer) and early rT2 disease, and a very selected group of rT3 disease with small disease volume and minimal skull base involvement [12–14].

Studies on the local failure patterns of NPC after initial treatment with intensity-modulated radiation therapy (IMRT) showed that the recurrent disease was rT1 to early rT2 in only approximately 22% to 29% of patients and of the remaining patients, approximately 50% presented as rT3 disease and the other 50% as rT4 disease [15, 16]. A retrospective analysis by Zou et al. [17] showed that only 22.4% out of the 410 patients recruited over a time period of 10 years with local NPC recurrence were eligible for surgery.

There have also been conflicting results regarding the addition of adjuvant radiotherapy after nasopharyngectomy with resultant positive margins. King et al. [18] found that there was a significant improvement in survival and tumor control with the addition of postoperative radiotherapy. However, it must be noted that this was a study done many years ago with recruitment completed in the year 1997. In addition, the surgical approaches were all via the open technique, and the sample size was small ($n = 31$ patients). A later study by Willard E Fee et al. [14] found no benefit from adjuvant radiotherapy in this group of post-nasopharyngectomy patients with positive margins, with around 60% of the cases recurring locally but this result was a subset analysis and the details regarding the extent of positive margins, adjuvant radiotherapy coverage, doses and techniques were not elaborated. Thus, the need for adjuvant irradiation after salvage nasopharyngectomy should be taken on a case-by-case basis, with discussion at a multidisciplinary tumor board; bearing in mind that adjuvant irradiation should not be taken as a replacement for careful case selection of eligible surgical candidates.

The 5-year overall survival (OS) rates for patients with locally recurrent NPC who undergo nasopharyngectomy surgery, considering that a proportion of deaths result from distant metastases, especially for those presenting with later stage recurrent disease, may range from 25.9% to 60%, depending on the center where the treatment was offered and the rT stage [9, 14, 19]. The 5-year local control rates similarly show a decreasing trend with increasing rT stage. For instance, Willard E Fee et al. [14] found that the 5-year local control rates for rT1, rT2, rT3, and rT4 diseases were 77%, 40%, 57%, and 0%, respectively. Thus, surgery should be the choice of treatment for cases with early recurrent disease where clear margins can be confidently obtained with minimal morbidity. In cases with inadvertent resultant positive or close margins less than 5 mm, the role of adjuvant treatment should be evaluated on a case-by-case basis in a multidisciplinary tumor board.

3 | REIRRADIATION IN LOCALLY RECURRENT NPC

For the majority of patients with local recurrence not amenable to surgery, re-treatment with radiotherapy remains the only option available to offer the patient another chance of cure. Compared to primary RT treatment for initially diagnosed NPC, which can lead to 5-year local control rates of 80% to >90% [7–9], re-irradiation, even with IMRT, may lead to considerably lower short-term local control and survival rates. Both Qiu et al. [20] and Chua et al. [21] observed an average 1- to 2-year local progression-free rates of approximately 56% and OS rates of 63%. A meta-analysis looking at the 5-year outcomes after NPC re-irradiation, pooling together 12 studies, also found a trend towards similar outcomes, with a 5-year local progression-free survival (PFS) rate of 72% (95% confidence interval [CI], 66%-78%), and a 5-year OS rate of 41% (95% CI, 36%-47%) [22]. However, putting a patient through a second round of high-dose irradiation can result in severe acute and long-term toxicities, as well as potentially exacerbating any resultant complications from the initial course of radiotherapy.

For optimal outcomes, proper patient selection, as well as appropriate re-RT dose prescription and fractionation are key. Equally crucial is the accurate determination and setting of dose constraints for organs at risk (OARs). Here, we will briefly discuss the different modalities of RT delivery, as well as the role of chemotherapy in re-RT cases.

3.1 | Patient selection

Appropriate patient selection is the first critical step for ensuring good outcomes in re-irradiation cases. Table 1 summarizes postulated and known patient factors which may determine prognosis and outcomes from available published literature [23–31].

Factors found to be significant in influencing treatment outcomes include age at recurrence, with an OS difference found between patients of younger and older than 46 to 50 years old and hazard ratio ranging from 1.02-1.48, depending on the source paper [23–31]. Another important factor is the patient's Karnofsky performance status (KPS), with a hazard ratio of 2.65 for those with KPS ≤70 compared to those with KPS >70 [23–31]. Whether the patient suffered from any grade 3 or higher late toxicities from initial RT was also found to be a significant factor, with a hazard ratio ranging from 1.90 to 2.36 [23–31]. This may be correlated with their performance status, nutritional status, and overall fitness and health status during treatment, which may reflect their ability to tolerate and complete re-irradiation with minimal unscheduled breaks.

TABLE 1 Prognostic factors for OS in NPC re-irradiation cases

Factors	Hazard ratio	Positive prognostic factor	5-year OS rate (%)	Negative prognostic factor	5-year OS rate (%)
Age at recurrence	1.02-1.48	≤46 years old	43.3-53.5	>50 years old	33.5-37.5
Karnofsky performance status (KPS)	2.65	> 70	42.3	≤70	14.4
rT stage	1.96	rT0 to rT2	73.2-75.8	rT3 to rT4	32.4-35.1
Tumor volume	1.57	≤38 cm^3	48.7-55.9	>38 cm3	15.2-30.1
Prior RT-induced > G3 toxicities	1.90-2.36	Absent	46.1	Present	15.4
Tumor histology	-	WHO Type III	-	WHO Type I/II	-
Time to recurrence	1.05 (0.77-1.43)	> 25 months	42.7-48.9	≤ 25 months	39.5-42.3
EBV DNA viral load at recurrence	-	Low	-	High	-
Prior treatment OAR doses	-	Lower previous doses to critical structures	-	Higher previous doses to critical structures	-

Abbreviations: KPS: Karnofsky performance status, G3: Grade 3 and above toxicities as per Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, EBV DNA: Epstein Barr virus DNA quantitative measurement, OAR: Organs at Risk

Disease characteristics at recurrence are similarly important in influencing prognosis. Patients with early recurrent rT0 to rT2 disease show a 5-year OS rate range of 73.2%-75.8% with re-RT treatment. However, this can decrease to 32.4%-35.1% for rT3 to rT4 disease. Tumor volume of the recurrent disease is another important factor influencing prognosis. Various studies have used different volume cut-offs, ranging from 30 cm^3 to 38 cm^3, with the hazard ratio for larger volumes of recurrent disease ranging from 1.57 to 1.96. For example, taking the higher volume cut-off of 38 cm^3, the 5-year OS rate range for tumor volume ≤38 cm^3 was found to be 48.7%-55.9%, whereas for tumors >38 cm^3, it can decrease to 15.2%-30.1%. Furthermore, patients with rT3-4 tumors or gross tumor volume (GTV) >30 cm^3 may exhibit a significantly higher rate of mucosa necrosis than patients with rT1-2 stage tumors (36.8% vs. 26.1%, $P = 0.04$) or with GTV >30 cm^3 (38.7% vs. 23.0%, $P < 0.01$) [26]. NPC tumor histology classification also plays a role in prognostication, with WHO type III tumors generally having a better prognosis with retreatment compared to types I and II, due to their more radiosensitive tumor biology.

Other factors that influence outcomes for re-treatment cases include the disease-free interval (DFI) before recurrence, with a hazard ratio of 1.05 for patients whose disease recurred within 25 months. This is likely to be a reflection of the biology of the tumor, suggesting increased radioresistance. High plasma EBV DNA titer at recurrence is another negative prognostic factor. A recent study found that patients with advanced clinical T and N stage locally recurrent NPC had higher levels of pre-retreatment plasma EBV DNA, and this was further shown to be significant in locoregional recurrence-free survival (LRRFS) (54.2% vs. 75%, $P < 0.001$), implying such patients were at greater risk of subsequent relapses [31]. Lastly, high previous RT doses delivered to critical OARs could also lead to poorer outcomes after retreatment, likely secondary to limitations on retreatment dose deliverable.

There have been a number of prognostic models published that aimed to correlate the above patient characteristics with survival outcomes and treatment-related morbidity and mortality, in order to more objectively ensure appropriate patient selection [25, 32]. These models used weighted hazard ratios of various parameters to stratify the patients into 2 to 3 risk subgroups, with re-irradiation recommended for the low- to intermediate-risk groups, but more clinical evaluation and caution are needed before offering re-irradiation for the high-risk groups. These prognostic tools can be applied clinically to aid in offering suitable treatment recommendations.

3.2 | Re-irradiation doses and fractionation

Currently, there is still no established definitive gold standard dose and fractionation for NPC re-irradiation cases. The available studies are highly variable in terms of timing, technique, and radiation doses; as well as in their use of concurrent chemotherapy and drugs used, and many are retrospective or single-arm, making comparison across different studies difficult. However, available literature largely points to the need for a total EQD2 (Equivalent dose in 2 Gray fractions) dose of at least 60 Gy or more to achieve adequate local control [21, 33-36]. Lee et al. [34] found that the hazard of local failure increased by 1.7% per Gy_{10} biological effective dose (BED) drop during re-irradiation (assuming an alpha/beta ratio of 10). For rT1

to rT2 recurrences, the 5-year local control rate for patients given >70 Gy_{10}, 60 Gy_{10}-70 Gy_{10}, and <60 Gy_{10} doses were 40%, 35%, and 14%, respectively. When compared with the group given 60 Gy_{10}-70 Gy_{10} doses, the local salvage rate in those given <60 Gy was significantly inferior ($P = 0.001$), but the superiority in local control of those given >70 Gy failed to reach statistical significance ($P = 0.229$). A similar trend was also observed for patients with rT3 disease [34].

On the other hand, total EQD2 doses greater than 70 Gy (assuming an alpha/beta ratio of 3) could be associated with increased late toxicities, most commonly mucosal necrosis (30.8% to 50%), trismus and dysphagia (~17.3% to 18.9%), temporal lobe necrosis (17.3% to 22%), and hemorrhage (11.5% to 31%) [34, 36, 37]. Thus, it appears that the optimal EQD2 dose range should lie within a range of 60 Gy to 70 Gy.

The other issue to consider is the optimal fractionation for dose delivery. For most irradiation treatments, including that of initial de-novo NPC treatment, the standard of care is dose delivery at 2 Gy to 2.2 Gy per fraction. In recent years, attention has turned to the consideration of hyperfractionated dose delivery in head and neck re-irradiation cases, including NPC. Hyperfractionated regimens involve delivering a small fraction size of 1.1 Gy to 1.5 Gy, given twice a day with a break of at least 6 hours. This is radiobiologically advantageous for late responding organs such as the spinal cord, brain, mucosa, and other OARs, thus reducing late toxicities of re-irradiation, while still allowing sufficiently high curative doses to be delivered. There have been a number of clinical studies using hyperfractionated radiation doses in head and neck malignancies demonstrating the feasibility of this approach, with no differences in local disease control and acceptable acute and late adverse effects [38–45]. In addition, there are a number of studies looking at locoregional control and late sequelae using hyperfractionation in recurrent head and neck cancers [46–48]. In these studies, a median dose of 60 Gy to 68 Gy was delivered in fractions of 1.2 Gy to 1.5 Gy twice a day, with grade 3 and above toxicities ranging from 14% to 29%.

Lee et al. [49] conducted a non-randomized prospective study comparing hyperfractionation with standard fractionation in locally advanced recurrent NPC. All patients in the study received induction chemotherapy with cisplatin and gemcitabine, as well as weekly cisplatin during the concurrent phase. The hyperfractionated dose delivered was 64.5 Gy at 1.2 Gy per fraction twice a day, while the historical cohort received a standard dose of 60 Gy at 2 Gy per fraction daily. The median local failure-free survival (LFFS) showed a trend in favor of hyperfractionation (28.2 vs. 16.6 months, $P = 0.164$), though there was no significant difference in overall survival. Grade 3 and above late toxicities were similar, with treatment-related hemorrhage showing a marginally significant reduction in the group receiving hyperfractionated irradiation. Another retrospective review by Karam et al. [50] also showed that re-irradiation for recurrent NPC, delivered mostly with hyperfractionated IMRT, resulted in durable local disease control of 46% with acceptable Grade 3 and above late toxicity of 37%. Even with the use of 3-dimensional conformal RT (3D-CRT), Cho et al. [51] showed in their small case series study that they were able to deliver doses of 59.4 Gy to 69.2 Gy in 1.1 Gy to 1.2 Gy per fraction doses twice daily, achieving good local control with minimal late sequelae.

Another novel approach is the use of stereotactic body radiotherapy (SBRT) to target recurrences with high doses of hypofractionated irradiation. SBRT is usually only suitable for small recurrent tumors, where high doses can be delivered safely without compromising the nearby critical organs. This has the theoretical radiobiological advantage of being more able to overcome clones of radioresistant tumor cells compared to conventional fractionation, which is thought to be one cause of local disease recurrence. Doses used in the literature range from single fractions of 11 Gy to 14 Gy, 18 Gy in 3 fractions, 30 Gy in 5 fractions, to 48 Gy in 6 fractions. In general, most studies had small patient numbers and short follow-up periods of 1 to 3 years. Reported 3-year local control rates ranged from 52% to 89.4% with generally acceptable late toxicity rates [52–56]. However, a number of late toxicities were severe, with some study patients developing fatal hemorrhage and brainstem necrosis.

In conclusion, the optimal EQD2 dose range delivered in NPC re-irradiation should lie within a range of 60 Gy to 70 Gy, preferably with hyperfractionated doses of 1.1 to 1.5 Gy delivered twice a day at least 6 hours apart. SBRT remains a promising option, with more studies needed to determine the ideal re-treatment volumes and OAR doses at retreatment, in order to reduce significant late toxicities.

3.3 | Normal tissue dose constraints

The head and neck region contains a large number of radiosensitive organs which can couple with high doses of radiation required to treat de-novo and recurrent NPC and may lead to debilitating normal tissue complications after re-irradiation. Thus, it is particularly important to determine suitable dose constraints to apply to these OARs, focusing especially on vital structures that may result in severe morbidity if damaged. These include the brainstem, cord, optic chiasm, optic nerve, internal carotid arteries, and the temporal lobes.

For late toxicity endpoints, tissues vary considerably in their capacity to recover from radiation damage. Organs such as the skin, mucosa, spinal cord, and nerves have the ability to partially recover from subclinical injury to a

TABLE 2 OAR dose constraints from literature review

Dose Constraint Criteria	OAR	Assumptions	Dose limits	Reference
Absolute dose limits	Cord	Assuming 50% recovery if retreatment ≥12 months	Keep cumulative BED 135 Gy_2	[57–59]
	Brainstem	Assuming 50% recovery if retreatment ≥12 months	Cumulative Dmax <79 GyCumulative D1% ≤78 Gy	[57–59]
	Chiasm	Assuming 50% recovery if retreatment ≥12 months	Cumulative Dmax ≤78 Gy	[57–59]
Desirable dose limits	Optic nerve	Assuming 50% recovery if retreatment ≥12 months	Cumulative Dmax ≤78 Gy To consent for loss of vision with patient	[57–59]
	Carotid	Cumulative EQD2 ≤120 Gy	Avoid 1.5 Gy b.i.d if CCRT	[59, 62, 63]
	Temporal lobe		Cumulative D1cc ≤84.5 Gy	[57, 59, 61]

Abbreviations: EQD2: Equivalent dose in 2 Gray fractions, Dmax: Maximum dose received by an organ at risk, BED: Biological Equivalent Dose, D1%: Highest dose received by 1% of the organ at risk, D1cc: Highest dose received by 1cc of the organ at risk, b.i.d: Twice daily

magnitude dependent on the organ type, size of the initial dose, as well as the interval between irradiation courses [57]. Table 2 summarizes the recommendations from literature for critical head and neck OARs. The brainstem, spinal cord, and optic chiasm were designated as strict constraints while the optic nerves, internal carotids, and temporal lobes were designated as desirable dose constraints [57–63]. A detailed discussion of dose constraints is beyond the scope of this paper.

Re-irradiation for NPC presents unique challenges pertaining to OAR toxicities. Due to the narrow therapeutic dose range in head and neck retreatment, both acute and late toxicities may be more severe and require careful anticipation and management. Reviewing available literature, we found that re-irradiation was associated with a 7.9% to 16.6% of grade 3 and above acute toxicities, most commonly mucositis, with a smaller proportion of patients experiencing severe xerostomia [23-25, 28]. Also, the most common acute adverse effects were grade 1-2 mucositis and xerostomia, as well as otitis media.

The data concerning late toxicities are more sobering in comparison to the acute toxicity data [4, 21, 23-25, 28, 34, 64]. The common late toxicities were hearing loss (7.5% to 22.2%), significant trismus (8.6% to 22.2%), and xerostomia (9% to 43.2%). Radiation-induced brain damages such as temporal lobe necrosis or other brain changes seen on magnetic resonance imaging (MRI) ranged from 3.1% to 28.5%, and the presentation in such patients varied from asymptomatic to headaches and encephalopathy. Among the more debilitating late toxicities were persistent mucosal necrosis (ranging from 16% to 40.6%), cranial neuropathies (3.4% to 12.6%), and repeated epistaxis from atrophic mucosa. On average, a range of 16% to 40.1% of retreatment patients was found to have developed one or more of these late toxicities. The most common cause of death resulting from retreatment-induced toxicity was massive hemorrhage which ranged from 2% to 23.2% and could be a reflection of case selection and early preemptive measures.

3.4 | Modalities of RT delivery

Depending on machine availability at each center, RT can be delivered via 3D-CRT or through more advanced photon treatments such as IMRT, volumetric arc therapy (VMAT) or tomotherapy, or via proton therapy. Regardless of the planning method, it is crucial to ensure that an experienced dosimetrist and planning team are on board, as well as stringent quality assurance checks before dose delivery.

For cases of NPC re-irradiation, the principle should be to achieve the most conformal plan, thus allowing desired dose coverage to the target volume while achieving good OAR sparing. In this aspect, the current advanced photon delivery techniques are superior to 3D-CRT techniques and should be the method of choice in such retreatment cases. The trade-off is increased integral dose, especially with VMAT techniques, as compared with 3D-CRT.

Proton therapy and heavy ion therapy, which both exhibit sharp dose fall-off beyond the penetration range, may be used to further reduce OAR dose without compromising target coverage, potentially reducing complications caused by re-irradiation and improving patients' quality of life [65]. There have been a few retrospective reviews investigating the outcomes and toxicities of these techniques in head and neck re-irradiation over that of IMRT, with encouraging results [66–69]. For example, Hu et al. [70] achieved 1-year OS and PFS rates of 98.1% with carbon ion therapy with aggregate late grade 3 and 4 toxicities of <10%. Longer follow-up periods and larger sample sizes would further establish the role of these irradiation modalities in NPC retreatment.

3.5 | The role of chemotherapy in re-irradiation

In cases of NPC re-irradiation, the role of chemotherapy remains to be clearly defined. As with initial radical treatment, possible timings of chemotherapy would be as induction, concurrent with irradiation, or less frequently, as adjuvant treatment.

The main role of concurrent chemotherapy with irradiation is to act as a radiosensitizer. In general, a review of the literature shows that there is uncertainty with regards to its utility in NPC re-irradiation cases. The chemotherapeutic regimen used was largely platinum-based, utilizing either cisplatin or carboplatin alone, or combined with 5-fluorouracil and/or docetaxel. A number of retrospective studies have shown that the use of concurrent chemotherapy together with re-irradiation either showed no benefit or conversely exhibited poorer local control than those on RT alone [71, 72]. Hua et al. [24] showed that chemotherapy, administered either as induction or concurrent, had prognostic significance in univariate analysis, but not in multivariate analysis. However, a caveat in interpreting these studies would be that a majority of these studies are retrospective in nature and exhibit some degree of selection bias. Most of the patients who received chemotherapy had more adverse prognostic factors, more advanced rT stage, or bulky tumors.

Chemotherapy may however have a role as induction treatment before re-irradiation for selected patients. It can be used to downstage tumor recurrences, allowing RT to be delivered more safely, to reduce high dose volume or to decrease the dose delivered to critical OARs. It can also serve as a bridge to RT treatment for patients with tumor recurrences occurring within 9 months to 1 year; where OAR recovery from the initial irradiation may not be sufficient for a second round of RT to be given. A number of studies looking at induction chemotherapy before re-irradiation have generally shown good response rates, especially with the combination of cisplatin and gemcitabine. Chua et al. [73] observed a 75% partial response (PR) rate with 3 cycles of cisplatin and gemcitabine, while Lee et al. [49] observed a PR rate of 70% with cisplatin/gemcitabine and 40% with cisplatin or carboplatin with 5-fluorouracil. The addition of chemotherapy at any timepoint, however, is associated with significant toxicities [28, 35, 74, 75]. Incidence of grade 3 and 4 toxicities such as temporal lobe necrosis, endocrine toxicities, mucosal necrosis, cranial nerve toxicities, and swallowing dysfunction necessitating long-term enteral feeding were all increased compared to re-RT alone, regardless of retreatment with 3D techniques or with IMRT, thus careful patient selection is paramount.

3.6 | The role of immunotherapeutic advances in re-irradiation

There has also been great interest recently in the role of immunotherapy in NPC, with promising outcomes [76]. In the recurrent and metastatic settings, the use of immune checkpoint inhibitors alone [77, 78], or combined with chemotherapy [79], have shown good objective response rates of 20%-25% and promising antitumor activity in early phase trials, with tolerable toxicities.

Of relevance to the topic of immunotherapy in locally recurrent cases for retreatment, the National Cancer Institute (NCI) held a clinical trial planning meeting in Arizona, USA in 2018, where a randomized phase II trial of adjuvant immunotherapy following salvage treatment for locally recurrent NPC was proposed [80]. The implementation and outcomes of this proposed trial are eagerly awaited and may represent a shift in how we manage these challenging patients.

4 | CONCLUSIONS

Re-irradiation, especially with the use of more conformal irradiation techniques, such as IMRT and VMAT, can result in long-term disease control and survival for a proportion of patients with recurrent NPC. Evidence from the literature shows that the optimal dose received by the recurrent tumor should lie within a range of 60 Gy to 70 Gy EQD2, with an advantage shown for hyperfractionated dose delivery, especially in terms of acute and late effects on OARs such as the spinal cord, brain, temporal lobes, and others. The use of chemotherapy in re-irradiation cases needs to be carefully considered in view of the significantly increased toxicities. Concurrent chemotherapy with re-irradiation should not be routinely undertaken unless in very selected cases after thorough discussion at multidisciplinary tumor boards. Induction chemotherapy may however have a role to downstage tumor recurrences so RT can be delivered more safely to reduce the high dose volume, to decrease the dose delivered to critical OARs, or to act as bridging treatment between courses of RT. Immunotherapy in these cases appears to hold promise, and further trials incorporating immunotherapy treatment in retreatment cases should be encouraged. There are a number of international consensus guidelines bringing together the opinions of key head and neck experts addressing this very pertinent and critical topic, which are eagerly awaited. High-quality prospective studies are also needed to further understand the outcomes of using different dose and fractionations, treatment modalities, and optimal OAR constraints.

AUTHORSHIP

Conceptualization: SSP, YLS, CML, JTSW. Manuscript writing: SSP. Manuscript review and editing: SSP, YLS, KS, CML, KWF, TWKT, MLKC, HJ, JTSW

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Sharon Shuxian Poh[1,2]
Yoke Lim Soong[1,2]
Kiattisa Sommat[1,2]
Chwee Ming Lim[3,4]
Kam Weng Fong[1,2]
Terence WK Tan[1,2]
Melvin LK Chua[1,2]
Fu Qiang Wang[1,2]
Jing Hu[1,2]
Joseph TS Wee[1,2]

[1] *Division of Radiation Oncology, National Cancer Centre Singapore, Singapore 169610*
[2] *Oncology Academic Clinical Programme, Duke-NUS Graduate Medical School, Singapore 169857*
[3] *Department of Otorhinolaryngology-Head and Neck Surgery, Singapore General Hospital, Singapore 169608*
[4] *Surgery Academic Clinical Programme, Duke-NUS Graduate Medical School, Singapore 169857*

Correspondence
Sharon Shuxian POH, Associate Consultant, Division of Radiation Oncology, National Cancer Centre Singapore, Duke-NUS Graduate Medical School, Tel: +65 64368000
Email: sharon.poh.s.x@singhealth.com.sg

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ORCID

Sharon Shuxian Poh https://orcid.org/0000-0003-2504-7414
Melvin LK Chua https://orcid.org/0000-0002-1648-1473
Joseph TS Wee https://orcid.org/0000-0001-6123-1257

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