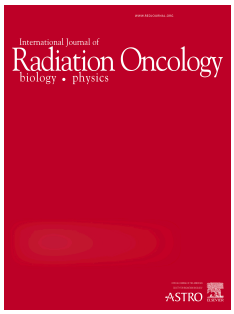

International Recommendations on Re-irradiation by Intensity-modulated Radiotherapy for Locally Recurrent Nasopharyngeal Carcinoma

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Ethical considerations

None to declare.

Summary

This guideline is the result of an international consensus to provide a practical reference for re-irradiation by intensity-modulated radiotherapy for locally recurrent nasopharyngeal carcinoma.

International Recommendations on Re-irradiation by Intensity-modulated Radiotherapy for Locally Recurrent Nasopharyngeal Carcinoma

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Summary

This guideline is the result of an international consensus to provide a practical reference for re-irradiation by intensity-modulated radiotherapy for locally recurrent nasopharyngeal carcinoma.

Abstract

Purpose:

Re-irradiation for locally recurrent nasopharyngeal carcinoma (NPC) is challenging as prior radiation dose delivered in the first course is often close to the tolerance limit of surrounding normal structures. A delicate balance between achieving local salvage and minimizing treatment toxicities is needed. However, high-level evidence is lacking as available reports are mostly retrospective studies on small series of patients. Pragmatic consensus guidelines, based on an extensive literature search and the pooling of opinions by leading specialists, will provide a useful reference to assist decision-making for these difficult decisions.

Methods and Materials:

A thorough review of available literature on recurrent NPC was conducted. A set of questions and preliminary draft guideline was circulated to a panel of international specialists with extensive experience in this field for voting on controversial areas and comments.
A refined second proposal, based on a summary of the initial voting and different opinions expressed, was re-circulated to the whole panel for review and reconsideration. The current guideline was based on majority voting following repeated iteration for final agreement.

Results:

The initial round of questions showed variations in clinical practice even among the specialists, reflecting the lack of high-quality supporting data and the difficulties in formulating clinical decisions. Through exchange of comments and iterative revisions, recommendations with high-to-moderate agreement were formulated on general treatment strategies and details of re-irradiation (including patient selection, targets contouring, dose prescription and constraints).

Conclusion:

This paper provides useful reference on radical salvage treatment strategies for recurrent NPC and optimization of re-irradiation through review of published evidence and consensus building. However, the final decision by the attending clinician must include full consideration of an individual patient's conditions, understanding of the delicate balance between risk and benefits, and acceptance of risk of complications.

Introduction

Management of recurrent nasopharyngeal carcinoma (NPC) is one of the most difficult challenges. With complex problems related to the radiation doses to various organs at risk (OAR) by the primary course of treatment, individual intrinsic radio-biologic characteristics, extent and location of the recurrent tumor, there is no 'one-size-fits-all' treatment. The decision on trade-off between the chance of salvage and the risk of serious toxicity is a daunting dilemma both to the oncologist and the affected patient [1,2]. Unfortunately, because high-quality data on optimal treatment are lacking, it is almost impossible to come-up with a good evidence-based guideline. Amidst all the uncertainties, it is especially valuable to provide a pragmatic reference for clinical consideration by gathering the views from experienced specialists to build a consensus 'recommendation'.

This guideline is a continuation of our efforts to develop international guidelines on the delineation of the clinical target volumes (CTV) [3] and on dose prioritization and acceptance criteria in radiotherapy planning for primary treatment of NPC [4]. The panel consists of top opinion leaders from major centres in Asia, Australia, North America, Middle East and Europe. Our objective is to provide a practical reference through a comprehensive review of existing literatures and sharing of different views on controversial areas in re-irradiation.

Methodology

The following processes were used for evidence searching and development of the guideline: First, an initial literature search (conducted by XX) on clinical outcomes of recurrent NPC treated with re-irradiation (re-RT) was performed on 9 June 2020 in PubMed, Scopus and EMBASE using the following search terms: "nasopharyngeal carcinoma" OR "npc" OR nasopharyngeal cancer" AND "intensity-modulated radiation therapy" OR "imrt" OR "intensity-modulated radiotherapy" AND "re-irradiation" AND "local recurrence" (Supplementary Figure 1 & Supplementary Table 1). Articles from January 2000 to June 2020 were reviewed by YY and ZZ independently; we included both prospective studies and retrospective studies with reported survival and/or toxicity outcomes and articles written in English for synthesizing the evidence on specific issues relating to treatment strategy, target delineation, dose prescription and OAR dose constraint criteria. We then summarized these issues into a preliminary list of questions, which

was then circulated to international specialists for initial voting and exchange of comments based on a modified Delphi process [5,6]. Next, a panel of international specialists was convened to develop the guideline. To ensure appropriate recommendations with international representation, criteria were set to include only members with publications on treatment outcome (tumour control and toxicity), and/or extensive experience specific to NPC in major academic centers from different parts of the world (including Asia, Middle East/Mediterranean Region, Oceania, Europe and North America).

Based on the summary of feedback through repeated iterations, a list of questions on controversial issues was re-circulated for a second round of voting if the agreement was below 85%. The respective degree of agreement on each discussed item was defined as high (≥85% agreement), moderate (75-84%) or low (<75%), as in our previous consensus guideline [3], to reflect the strength of each recommendation. This process is adopted as the consensus-building form the fundamental bases for the recommendations given the scarcity of high-quality, level 1, published data on this clinical problem [5,7].

The strength of the recommendations was rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Supplementary Table 2) [8]. The GRADE level of evidence assigned for each question was initially discussed and drafted by the three senior authors (XX, YY, ZZ); and circulated to all the authors as part of the manuscript review. There were no objections or changes to the suggested GRADE assignments. The percentages of agreement among the panel members in the final vote (together with the exact number of votes) were listed in the manuscript and Table 1-2.

Results (Table 1) and Discussion on the Recommendations

General principles in primary treatment modality for resectable recurrence

1. *The preferred option is surgical resection, provided that expertise is available and clear margin is likely to be achievable, to avoid the added morbidities associated with second course radiotherapy [Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: High];*
2. *For patients who are salvaged by surgery, re-RT should be considered for positive resection*

margin [Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: High];

3. *For patients who are salvaged by surgery, re-RT should be considered for resection margin less than 2-5mm [Consensus: moderate (19 of 24 voters, 79%); GRADE of recommendation: Moderate]*.

Upon the diagnosis of local recurrence, thorough assessment of physical condition and re-staging are needed. In addition to magnetic resonance imaging (MRI) ± computed tomography (CT) scanning of the head and neck region, full metastatic work-up, preferably by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)-CT scan, is needed to exclude concomitant nodal and/or distant metastases [9]. The role of plasma Epstein Barr Virus (EBV) DNA for the detection of local recurrence is less well defined as only about 50% of cases have detectable levels [10].

The interval from the primary course and details of the treatment [both radiotherapy (RT) and chemotherapy] given should be reviewed. It will be useful to retrieve the original RT plan to assess whether the recurrence is likely to represent a geographical miss or failure within the high dose zone, which would be suggestive of radio-resistance. Furthermore, it is important to know the doses given to the OARs and the late toxicities already incurred by the primary course. All patients with local recurrence should ideally be managed by a multi-disciplinary team. Other important factors including age, performance status, co-morbidities and patient's preference should also be considered in decision-making. Discussion with the patient and family about the trade-offs on benefit/risk is always crucial. The final decision on trade-off depends on what the patient accepts rather than what the clinician considers as 'acceptable'.

While our panel unanimously agrees that surgery is the treatment of choice for resectable recurrence [1,11-14], the availability of surgical expertise is a serious consideration. In the study by Ng et al. [2] on the patterns of care and treatment outcomes for local recurrence of NPC in Hong Kong, where experienced surgical expertise is available, only 31% of recurrent NPC had surgical salvage. Among the patients treated by surgery, the outcomes were encouraging with 5-year post-recurrence survival of 56% and peri-operative treatment mortality of 2.4%. Hence, surgical option should be discussed with patient should expertise be available.

Due to the anatomical location of the nasopharynx, open surgical approach is always challenging, given the need to dissect through substantial normal tissue, much of which may

have been previously irradiated, in order to access the diseased area [15]. It is thus preferable that the surgical procedure is performed by someone with vast experience in skull base surgery. With the advancement in endoscopic instruments, contemporary case series based on endoscopic approach have reported comparable local control with significantly fewer morbidities compared with re-RT [12,16,17]. Irrespective of which surgical approach is adopted, patient selection is of utmost importance. Careful preoperative assessment and planning are needed in order to maximize the chance of achieving clear resection margin.

With regards to the indication for post-operative RT, there is little controversy that R1 resection mandates additional treatment [18], but it is controversial in the situation of 'close margin'. Opinions vary widely from liberal use of postoperative radiotherapy irrespective of margin status, margin less than 2 to 5 mm, or withholding re-RT so long as the final resection margin is negative regardless of the proximity of microscopic tumor. The reasons for such discrepancies include concerns about different surgical approaches (open vs endoscopic), accuracy of margin assessment (especially when *en bloc* resection might not be easily performed with endoscopic resection), patient's performance status, and toxicities due to prior RT. While no specific study for NPC has been reported, a randomized study on patients with salvage surgery for other head and neck cancers showed that addition of postoperative re-RT combined with chemotherapy resulted in significantly increase of both acute and late toxicity (39% *vs* 10% at 2 years post-treatment) without any OS benefit when compared with salvage surgery alone [19]. Clearly, a comprehensive multi-disciplinary discussion with the operating surgeon, diagnostic radiologist and pathologist is needed.

It should be noted that re-RT (including the use of brachytherapy [20] and stereotactic radiotherapy [21]) have been shown to be a highly effective treatment for small and potentially resectable recurrences. Though there were concerns about increased risks of late toxicities from two courses of treatment, re-RT remains a valuable option especially in areas where surgical expertise is limited or unavailable.

Consideration for avoiding radical re-irradiation

Multiple factors are known to affect the efficacy/morbidities of re-RT [22-26]. These include age, performance status, latency of recurrence, recurrent T-category, size of the recurrent tumor

and the presence of prior radiation complications. Here, we highlight the key factors for treatment decision-making.

4. *Short latency of less than 6-12 months following completion of primary RT [Consensus: high (23 of 24 voters, 96%); GRADE of recommendation: Moderate]*

After exclusion of geographical miss or persistent tumor that is potentially salvageable by RT boost, most specialists believe that an early local recurrence within the high dose target volume reflects intrinsic radio-resistance, making re-RT unlikely to be effective. In addition, there are concerns that there is inadequate time for partial recovery of normal tissues. 96% of the panel would not give radical re-RT for patients with latency ≤6 months (63% even preferred to use 1 year as the cut-off). However, a more flexible minimum latency time could be considered if there are no alternative options and the patient understands the risks.

5. *Existing major RT-induced late toxicity [based on Common Terminology Criteria for Adverse Events (CTCAE)]:*

≥ G1 toxicity at brainstem, spinal cord or optic chiasm [Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: High];

≥ G3 toxicity for temporal lobe, optic nerve or brachial plexus [Consensus: high (23 of 24 voters, 96%); GRADE of recommendation: High];

≥ G3 toxicity for soft tissue or bone [Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: High]

While late toxicities do occur in a substantial proportion of patients following their first course of RT, there are concerns that patients who have already developed debilitating toxicities (except xerostomia or endocrine dysfunction) may not be able to tolerate another course of RT. Furthermore, individuals with severe toxicities of multiple OARs, especially after a course of RT with acceptable normal tissue dosimetry, may have intrinsic sensitivity leading to extra risks of excessive toxicities. On the other hand, the decision on re-RT should also take into consideration the type of toxicity, the location of the specific OAR in relation to the recurrence, and the estimated dose to the affected OAR if re-RT is given. For instance, re-RT may still be

recommended for patients with grade 4 hearing loss as additional dose to the damaged cochlea would not lead to further detrimental effect. Thorough assessment of existing damage and individual consideration is always required.

6. *Bulky recurrent tumor is not a factor for exclusion from re-RT [Consensus: moderate (19 of 24 voters, 79%); GRADE of recommendation: Moderate]*

Multiple series have shown that size of the recurrent tumor is a significant factor affecting local control [27]. The studies by Tian et al. [25] and Han et al. [23] showed that recurrent tumor volumes exceeding 30 cc and 38 cc, respectively, were negative prognostic factors; the study by Hong Kong NPC Study Group (HKNPCSG) further demonstrated that the local control rate decreased rapidly to <10% if the gross tumor volume (rGTV) exceeded 80 cc [27]. However, the panel believes that any cut-off criterion for volume is likely to be arbitrary, and 79% would not consider bulkiness of the recurrent tumor alone as an exclusion factor. Other factors including rT-category, extent of intracranial extension, and the degree of tumor shrinkage following induction systemic treatment may also be important considerations.

Li et al. [24] have jointly developed a prognostic index, PRANCIS (Predicting RAdioresistant Nasopharyngeal CarcInoma Survival [www.PRANCIS.Medlever.com]), basing on a training cohort of 251 patients and a validation cohort of 307 patients from two academic institutions. Five parameters (rGTV; rT-category; age; previous RT toxicity and planned RT dose) were included in the formulation to stratify patients into different prognostic groups. The study showed that high PRANCIS score predicts not only poor survival outcome, but also a high risk of re-treatment mortality. This tool may help the clinician and the patients in decision-making on re-RT.

Integration with systemic therapy

7. *Systemic therapy (irrespective of sequence) should be integrated with second course radiotherapy [Consensus: high for rT3-4N0 (23 of 24 voters, 96%); GRADE of recommendation: Moderate; high for rT1-4N+ (23 of 24 voters, 96%); GRADE of recommendation: Moderate; low for rT1-2N0 (9 of 24 voters, 37%); GRADE of recommendation: Moderate]*

Despite the lack of concrete evidence of benefit for systemic therapy in the treatment of recurrent NPC, the majority of the panel (96%) would recommend the incorporation of systemic therapy, based on extrapolation of data from primary treatment, to address the needs for eradication of micro-metastases and potentiation of RT efficacy. However, 63% of the panel believe that small rT1-2N0 recurrence can be adequately treated with re-RT alone.

When chemotherapy is to be recommended, all the specialists preferred the sequence of induction with or without concurrent chemotherapy [23,28-37]; 67% recommended induction-concurrent chemotherapy based on extrapolation from trials showing survival benefit for locoregionally advanced primary tumors [38,39]. Perceived benefits with induction therapy include buying more time for recovery, especially if the latency of recurrence is less than 12 months, down-sizing the recurrent tumor bulk and facilitating better sparing of adjacent OARs.

So far, only one prospective phase 2 trial conducted by the HKNPCSG has been reported on combining re-RT with systemic therapy [40]. This study consisted of 33 rT3-4 NPC patients. Three cycles of induction docetaxel, cisplatin, and fluorouracil (TPF) were given followed by 60 Gy IMRT with concurrent weekly docetaxel and cetuximab. While this regimen achieved promising outcomes with 3-year progression free survival (PFS) and overall survival (OS) rates of 36% and 64%, respectively; the tolerability to induction TPF was poor (with 18% of the patients failing to complete the induction phase) and there was also a high incidence of temporal lobe necrosis (31%).

No “one-size-fits-all” recommendation could be made in choosing the optimal systemic agent. Prior exposure to systemic agents, latency of recurrence and previous chemotherapy-related treatment toxicity from the initial course should be considered collectively. The majority of the panel would use cisplatin in combination with other drugs including gemcitabine, taxane and/or 5-fluorouracil as induction chemotherapy. However, if cisplatin is contraindicated or if recurrence occurs shortly after cisplatin-based chemoradiotherapy in the primary course, agent(s) with non-overlapping toxicity or anti-tumor activity of action should be considered. Thus far, data on the use of targeted therapy (including anti-epidermal growth factor receptor agents) have been disappointing. However, there is emerging interest in the use of immunotherapy based on encouraging data in the palliative setting for metastatic/recurrent NPC [41-43] and other head

and neck squamous cell carcinomas [44]. The potential role of combining immunotherapy with optimal local salvage treatment warrants further exploration [45].

Radical Re-irradiation

8. *Choice on the mode of radiotherapy delivery [Consensus - IMRT/VMAT: high (23 of 24 voters, 96%); GRADE of recommendation: High]*

There is little controversy that the most conformal technique should be used, the final choice depends on the availability of equipment and expertise in individual institution. As Intensity-modulated Radiotherapy (IMRT) / Volumetric Modulated Arc Therapy (VMAT), with dosimetric advantages compared with 2-dimensional (2D) or 3D-conformal RT, is now widely available in most parts of the world, this is the mode most commonly recommended.

The development and increasing availability of proton/heavy ion therapy can potentially lead to further improvement in dose conformity. Heavy ion therapy [46], with its higher linear energy transfer (LET), leading to a higher relative biological effectiveness, is especially appealing. The high LET radiation can potentially circumvent radioresistance due to tumor hypoxia [47]. However, it must be cautioned that this enhanced biological effect may also increase the damage of normal tissues. It is important to avoid having critical structures at the end of a particle range, as there are still dosimetric uncertainties about particle ranges and the biological effects at the end of the particle track [48]. This concern is particularly relevant for recurrent NPC as the recurrent tumor is often closely surrounded by critical organs like the brainstem, temporal lobes, and optic apparatus. More data are needed to properly assess the benefit in therapeutic ratio for particle therapy in the treatment of recurrent NPC [46,49-52]. To date, the largest series consisted of 206 patients treated with carbon ion therapy at a single institution, with a median follow-up of 23 months, reported a promising 2-year overall survival of 84% [46]. They showed that acute and late toxicity rates were low, with the exception of delayed mucosal necrosis (16%). Based on the available evidence, the majority of the panel (82%) would suggest considering proton/heavy ion if a facility is available, but 36% of the panel recommend performing comparative treatment planning with IMRT versus protons/heavy ions before deciding on the RT modality [53] since, depending on the location and the extent of

invasion by recurrence, protons/heavy ions may not always achieve a superior sparing of critical OARs.

Stereotactic radiosurgery (SRS) or fractionated RT (SRT) with its characteristic dose conformity and precision set-up, is a potentially advantageous modality. Effective tumor control for low volume recurrence has been reported [21,54-57]. However, serious toxicities (including damage to the central nervous system, fatal carotid blowout syndrome, or massive hemorrhage from mucosal/tissue necrosis) were incurred, and the authors cautioned against using this mode for recurrent tumor close to neural tissues [56] or the carotid vessel [21]. Whether the toxicities are related to the use of a very high dose per fraction is yet uncertain. Further studies are needed to explore the optimal dose fractionation, especially if there may be a potential benefit in combination with immunotherapy [58].

Since the main purpose of this manuscript is to provide a useful guideline on the most commonly used RT technique, the subsequent sections on target contouring, dose and fractionation and OAR constraints hence focus solely on IMRT/VMAT.

Contouring of targets

9. *Principle of delineation of Clinical Target Volume (CTV): geometric expansion +/- anatomical editing [Consensus: high (23 of 24 voters, 96%); GRADE of recommendation: Moderate];*
10. *Expansion margin for CTV:* ≤5 mm *[Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: Moderate];*
11. *Expansion margin for Planning Target Volume (PTV): rCTV + 2-3 mm [Consensus: high (23 of 24 voters, 96%); GRADE of recommendation: Moderate];*
12. *Elective nodal treatment is not indicated [Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: High]*

In general, the veracity of rGTV definition relies heavily on the imaging quality at the time of recurrence, and thus co-registration with MRI images with or without PET-CT is always recommended. Differentiation between tumor and post-radiation changes related to the first

course of treatment could be difficult [59,60], seeking opinions from experienced head and neck diagnostic radiologists is crucial.

The evidence to support adding a margin from rGTV to rCTV is based on the surgico-pathological series on recurrent NPC reported by Chan et al. [61]. In this study, the mean diameters of tumor measured by histological examination were approximately 3-4 mm larger than those measured by MRI. Hence, 96% of the panel would recommend adding a margin where feasible, 79% advocate a geographical expansion of rGTV by 5 mm with anatomical editing of natural barrier (e.g. air), while others suggest a tighter margin and accept 0 mm when the tumor is adjacent to critical OARs. All panel members agree not to give elective nodal irradiation to clinically negative nodal basins.

The margin for PTV should be based on the type of immobilization and the set-up variation of individual institutes. Image-guidance (if available) should be used, and the majority (96%) recommends 2-3 mm expansion from rCTV if the treatment is carried out under image-guidance.

Radiation dose and fractionation

13. Preference on the intended total dose in the second course of IMRT is 60-66 Gy [Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: High]

Supplementary Table 1 summarizes the radiation dose employed and treatment outcomes in contemporary IMRT series [23,25,28-37,40,62,63]. The most commonly used total dose for radical re-RT is ≥60 Gy (equivalent total doses in 2 Gy fractions (EQD2)). This is in line with the study by Lee et al. showing that salvage rate is dose-dependent, and outcome is significantly inferior if the total re-RT dose is below 60 Gy [64]. On the other hand, several studies also revealed that dose ≥68 Gy is detrimental for post-re-RT survival due to excessive fatal toxicities. In the phase II randomized study on 117 patients by Tian et al. [62], the group treated with 68 Gy in 34 fractions had a poorer outcome compared with those given 60 Gy in 27 fractions: 5-year OS of 30% vs 44%, and the difference reached borderline significance ($p = 0.06$). Similarly, in a meta-analysis on 1768 NPC patients treated with re-RT, OS was lower for subgroups treated with ≥70 Gy vs <70 Gy (39 vs 48%) [22]. The PRANCIS prognostic index concurred with this observation, the hazard rate for death was 1.42 ($p = 0.03$) when the total dose exceeded 68 Gy

[24]. However, it should be cautioned that none of these studies accounted for the radiation dose and technique that were employed in the initial course of treatment.

The HKNPCSG has conducted a study on the dose volume effect of re-RT for 91 locally recurrent patients following a more homogeneous primary course of treatment by IMRT to ~70 Gy [27]. Both the local salvage rate and the fatal complication rate increased with the prescribed dose; with a very narrow therapeutic window, the optimal survival rate appeared to peak at around 60 Gy in that study.

14. Ideal fractionation is hyper-fractionation (BID) given twice daily with ≥6-hour interval [Consensus: low (17 of 24 voters, 71%); GRADE of recommendation: Moderate 71%)];

While there are biological rationales supporting the use of lower dose per fraction and hyper-fractionation, the clinical data for such fractionation schedules are sparse in recurrent NPC [34,37]. A small retrospective study on 20 patients reported by Lee et al. showed that hyper-fractionation to a total dose of 64.8 Gy (in 1.2 Gy per fraction, twice daily) achieved similar OS with substantial decrease in hemorrhage (30% vs 0%, p = 0.06) as compared to 60 Gy in 30 fractions [37]. Similarly, the study by Karam et al. showed that hyper-fractionation (1.1 – 1.2 Gy per fraction, twice daily) could achieve iso-effectiveness in tumor control with fewer treatment-related toxicities [34]. It is worth noting that 71% of the panel recommend hyper-fractionation despite the logistic difficulties of arranging twice daily treatment.

For patients treated with standard once daily fractionation, 75% of the panel recommend 1.8 - 2 Gy per fraction. Only 17% of the panel would use fractional dose >2 Gy.

Planning priority and tumor coverage (Table 2)

Preference on dose prioritization are:

15. Priority 1 should be set for brainstem [Consensus: high (19 of 21 voters, 90%); GRADE of recommendation: Moderate], spinal cord [Consensus: high (20 of 21 voters, 95%); GRADE of recommendation: Moderate], optic chiasm [Consensus: high (22 of 24 voters, 92%); GRADE of recommendation: Moderate], bilateral optic nerves [Consensus: high (17 of 19

voters, 89%); GRADE of recommendation: Moderate], rGTV [Consensus: moderate (16 of 21 voters, 76%); GRADE of recommendation: Moderate];

16. *Priority 2 should be set for PTV [Consensus: moderate (20 of 20 voters, 100%); GRADE of recommendation: Moderate], temporal lobe [Consensus: moderate (13 of 17 voters, 76%); GRADE of recommendation: Moderate], unilateral optic nerve [Consensus: low (11 of 19 voters, 58%); GRADE of recommendation: Moderate];*
17. *Priority 3 should be set for carotid artery [Consensus: moderate (15 of 19 voters, 79%); GRADE of recommendation: Moderate]*

Following the principle of giving the maximal permissible dose within the tolerance of critical OAR, ≥90% of the panel recommend setting priority 1 dose constraint for brainstem and spinal cord. Consensus for avoiding bilateral blindness was high (92% and 89% for optic chiasm and bilateral optic nerves as priority 1 structures, respectively), and many accept setting lower priority for unilateral optic nerve or one of the optic nerves if there is a bilateral involvement (Priority 2 by 58% and Priority 3 by 37%, respectively).

Regarding tumor doses, there are moderate consensus (76%) on setting Priority 1 for rGTV and Priority 2 for PTV (Note: the recommendation for GTV in the guideline for primary treatment is Priority 2 with 63% agreement). Ninety-six percent of the panel recommend aiming for ideal isodose coverage ≥95% (within the limitations imposed by critical OAR).

There are moderate agreements for setting Priority 2 for temporal lobe (76%), and Priority 3 for carotid artery (79%). Careful evaluation is also needed to avoid hotspot at OARs, and no more than 5% of PTV should receive ≥107% dose as recommended by ICRU (71%).

Dose constraints for Organs at Risk (Table 2)

18. *Brainstem: Safe cumulative dose is ≤130% [Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: Moderate], maximal acceptable cumulative dose if safe cumulative dose could not be met is 150% [Consensus: high (23 of 24 voters, 96%); GRADE of recommendation: Moderate];*
19. *Spinal Cord: Safe cumulative dose is ≤130% [Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: High], maximal acceptable cumulative dose if safe cumulative*

dose could not be met is 150% [Consensus: high (23 of 24 voters, 96%); GRADE of recommendation: Moderate];

20. *Optic chiasm: Safe cumulative dose is ≤130% [Consensus: moderate (18 of 24 voters, 75%); GRADE of recommendation: Moderate], maximal acceptable cumulative dose if safe cumulative dose could not be met is 150% [Consensus: moderate (18 of 24 voters, 75%); GRADE of recommendation: Moderate];*
21. *Optic nerve: Safe cumulative dose is ≤130% [Consensus: high (24 of 24 voters, 100%); GRADE of recommendation: Moderate], maximal acceptable cumulative dose if safe cumulative dose could not be met for bilateral optic nerves is 150% [Consensus: moderate (19 of 23 voters, 83%); GRADE of recommendation: Moderate]; and no dose limit if patient accept the risk of unilateral blindness [Consensus: high (19 of 20 voters, 95%); GRADE of recommendation: Moderate];*
22. *Temporal lobe: Safe cumulative dose is ≤130% [Consensus: high (23 of 23 voters, 100%); GRADE of recommendation: Moderate], maximal acceptable cumulative dose if safe cumulative dose could not be met is 150% [Consensus: high (23 of 23 voters, 100%); GRADE of recommendation: Moderate];*
23. *Carotid artery: Safe cumulative dose is ≤125Gy [Consensus: low (16 of 24 voters, 67%); GRADE of recommendation: Low], and up to 65% of the panel did not specify a dose constraint for carotid artery [Consensus: low (15 of 23 voters, 65%); GRADE of recommendation: Low]*

Data on re-RT dose constraints for OARs are sparse, and thus far there is only one comprehensive literature review reported [65]. Supplementary Table 3 showed some of the selected constraints reported in the literature [28,31,33,36,51,52,66-68]. For the spinal cord, data from other recurrent head and neck cancers [69] and animal experiments using primate model by Ang et al. [70] suggested a partial recovery from the first course of treatment by approximately 50% (provided that the interval between the two courses is 1 year or more). In addition, a cumulative spinal cord dose of above 75 Gy EQD2 has been suggested to be safe by some of the panel members in a multi-national expert consortium on re-RT of the spinal cord [71]. Furthermore, Mason et al. reported important radiobiological data on re-treatment tolerance of the spinal cord [72], showing that the greater the damage inflicted by the first dose, the lower the

degree of possible recovery - ranging from 100% with low initial doses to 0% when the first dose to tissues already reached ED50.

Lee et al. showed that, while the tumor salvage rate was dependent on the dose at re-RT irrespective of the dose at primary course, the toxicity was dependent on the cumulative dose composite of doses by both courses [64]. They suggested using a maximum lifetime biologically effective dose (BED) of 130% of tolerance dose for primary treatment for NPC, assuming the relevant OAR regions have already received a close to maximum dose in the primary course, which is often the case in nasopharyngeal carcinoma. The lifetime BED (with α/ß ratio = 2.5 Gy) of spinal cord, brainstem and optic chiasm are 100 $Gy_{2.5}$, 130 $Gy_{2.5}$ and 130 $Gy_{2.5}$, respectively [73]. This is basically equivalent to partial recovery from the first course of treatment by 30% if maximal limit had been reached in the first course of treatment. Using this dose restriction, no adverse effects were observed in the studies reported by the HKNPCSG and Chan et al. [36,40]; the authors further suggested that lifetime BED_{1cc} of 150 Gy might be safe for the temporal lobes [36]. Qiu et al. used more generous dose constraints (40 Gy for spinal cord, 50 Gy for the brainstem and temporal lobes, and 54 Gy for the optic nerve and optic chiasm) regardless of the dose delivered in the first course of radiotherapy [30]. More long-term data on toxicities are needed to confirm the safety of these dose levels.

In the published series of proton/heavy-ion therapy treatment on recurrent NPC, Dionisi et al. used a maximum 64 Gy for brainstem and assumed a 30-50% brainstem recovery [51]. They did not assume any recovery in the optic structures and applied a maximum cumulative dose of 64 Gy, and a maximum 120 Gy cumulative dose for the carotid artery. On the other hand, Hu et al. assumed OARs had a 70% recovery from the primary radiotherapy course, the reported incidence of temporal lobe necrosis was 13% after a median follow-up of 23 months. Furthermore, a high incidence of massive hemorrhage (16%) secondary to mucosal necrosis was observed leading to a 5% treatment mortality [46,52].

Massive hemorrhage is one of the most catastrophic sequelae of re-irradiation. The majority are due to RT-induced carotid blowout, while some cases are due to mucosal ulceration with superimposed chronic infection. In the literature review by Dionisi et al. [65] on the tolerance and dose limits of OARs for the re-RT of head and neck cancers, a significantly higher incidence of the carotid blowout was observed if the maximum cumulative dose to the carotid

artery exceeds 126 Gy. The current recommendation of setting safe maximum cumulative dose at ≤ 125Gy is agreed by 67% of the panel. However, due to its anatomic relationship with the nasopharynx, avoidance of the artery is seldom feasible without significantly under-dosing the rGTV, up to 65% of the panel did not specify a dose constraint for carotid artery, but all advocate avoiding a hotspot directly within the vessel. Another observation is the relationship of high incidence to total dose and fractional dose as shown in the trial by Tian et al [62]: the incidence of carotid blowout was as high as 31% in the Group given 68 Gy (2 Gy/fraction) and 19% in the Group given 60 Gy (2.2 Gy/fraction).

The guiding principle should always be ALARA (As Low As Reasonably Achievable), as per radiation safety principles. Amidst all the uncertainties and difficulties, we have reached a consensus on the principle of recommending 130% cumulative dose as goal-setting with an agreement that 150% can be used for estimating the maximal permissible cumulative dose for critical OARs and important neurological structures. However, less stringent dose constraints with acceptance of potential sacrifice of less critical OAR with the patient's consent may be considered to minimize salvage failure due to inadequate dose at rGTV.

Summary

All locally recurrent NPC patients should have detailed work up to exclude co-existing nodal and/or distant metastases. For patients with isolated local recurrence, a multi-disciplinary review is mandatory to select the treatment option with the best possible therapeutic ratio. To avoid the risk of excessive morbidities with a second course of RT, surgical resection is preferred for resectable recurrence if expertise is available and clear margin is likely to be achievable. For patients treated with re-RT, the most conformal technique should be used. IMRT/VMAT is most often employed; while proton/heavy ion therapy (if available) may potentially be beneficial, comparative evaluation against IMRT/VMAT treatment plans is advised for the selection of modality. A tight margin of ≤5 mm from the gross tumor is recommended to account for the microscopic disease, with further anatomical editing for natural barriers and critical OARs. An additional margin of 2-3 mm is needed to account for set-up error under image-guidance. Prophylactic treatment to the regional lymph nodes is not indicated. Re-RT dose of 60 Gy to 66 Gy EQD2 is recommended. Hyper-fractionation at 1.1-1.2 Gy per fraction, twice per day (with at least ≥6-hour inter-fraction interval) is desirable. Although there is no concrete evidence of

therapeutic benefit, cisplatin-based induction chemotherapy with or without concurrent chemotherapy is reasonable for maximizing the chance of disease control. While studies showed that the spinal cord could tolerate a cumulative dose of 130-150% from both courses of radiotherapy, the tolerance of other neurologic structures (especially the optic chiasm) and carotid artery to re-RT were less well understood. Meticulous attention is, therefore, necessary to minimize the dose to the OARs to observe the ALARA principle, and patients should be duly informed of the risk-benefit trade-offs and possible treatment sequelae.

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Table 1. Consensus Recommendation for Radical Salvage Treatment for Recurrent Nasopharyngeal Cancer

Questions	Recommendation	Results of final voting
Option for resectable local recurrence	First preferred option – surgical resection (if expertise available and clear margin achievable)	First preferred option is surgical resection, if expertise is available and clear margin likely to be achievable 1) Agree: 24/24,100% 2) Disagree: 0
For patients salvaged by surgery, re-RT should be considered for positive resection margin	Indication for Re-RT after surgery positive resection margin or close margin < 2 mm	Re-RT if positive margin 1) Agree: 24/24,100% 2) Disagree: 0
For patients salvaged by surgery, re-RT should be considered for close resection margin less than 2mm after surgery		Re-RT if close margin 1) < 2 mm: 16/24, 67% 2) < 5 mm: 3/24, 12.5% 3) Other: 5/24, 21% [gross residual only; 0 mm; depends on multiple factors including site of close margin, past toxicity]
Exclude patients with short latency of recurrence from completion of primary RT	Re-RT not recommended if latency ≤ 12 months	Exclusion if shortest interval between two courses of RT (especially for recurrence within high dose zone) 1) ≤ 6 months: 8/24, 33% 1) ≤ 12 months: 15/24, 63% 1) Other: 1/24, 4% [no exclusion]
Exclude patients with existing major RT-toxicity	Re-RT not recommended if toxicity Grade ≥1 at brainstem, spinal cord or optic chiasm Grade ≥3 at temporal lobe, optic nerve, brachial plexus, soft tissue or bone	Xerostomia, hearing or endocrine toxicity: No exclusion 1) Agree: 24/24, 100% 2) Other: 0% Toxicity at critical OAR (brainstem, spinal cord or

		optic chiasm): Exclusion if Grade ≥1 1) Agree: 24/24, 100% 2) Other: 0% Toxicity at other neurological structures (temporal lobe, optic nerve or brachial plexus): Exclusion if 1) Grade ≥3: 23/24, 96% 2) Grade ≥4: 1/24, 4% Toxicity at Soft tissue or bone: Exclusion if 1) Grade ≥3: 18/24, 75% 2) Grade ≥4: 6/24, 25%
Exclude patients with bulky recurrent tumor	No exclusion of re-RT based on tumor bulk alone	Bulkiness is NOT a factor for exclusion 1) Agree: 19/24, 79% 2) Disagree: 5/24, 21%
Additional of systemic therapy	Addition of systemic therapy if rT3-4N0 or rT1-4N+	Adding systemic therapy for rT1-2N0 1) Agree: 9/24, 37% 2) Disagree: 15/24, 63% rT3-4N0 1) Agree: 23/24, 96% 2) Disagree: 1/24, 4% rT1-4N+ 1) Agree: 23/24, 96% 2) Disagree: 1/24, 4%
Choice of time-sequence	Induction with or without concurrent	First choice of chemotherapy sequence for bulky or T3-4 recurrence abutting critical OAR:

		1) IC: 8/24, 33% 2) IC-CC: 16/24, 67% 3) CC alone: 0%
Choice of cytotoxic drugs	Induction – cisplatin-based combination Concurrent - cisplatin	For patients with more than 6-month interval from previous radiotherapy ± chemotherapy and good renal function: For Concurrent phase The core cytotoxic drug is 1) Cisplatin alone: 23/24, 96% 2) Other: 1/24, 4% For Induction phase The preferred cytotoxic drug combination is 1) Cisplatin-Gemcitabine: 17/27, 63% 2) Cisplatin-doxetaxel-5FU: 4/27, 15% 3) Cisplatin-capecitabine: 1/27, 4% 4) Cisplatin-5FU: 2/27, 7% 5) Other: 3/27, 11% [carboplatin-gemcitabine if prior ≥3 cycles of cisplatin; cisplatin + docetaxel]
Addition of immunotherapy	No	Adjuvant phase 1) Yes – Adjuvant phase: 7/25, 28% 2) Yes – Induction+/- concurrent phase: 1/25, 4% 3) No: 13/25, 52% 4) Other: 4/25, 16% [only on trial]
Choice of RT mode	Choice of RT mode: IMRT/VMAT	Choice of RT mode (can choose more than 1 option) 1. IMRT/VMAT: [23 / 24, 96%] 2. SRT/SRS: [9 / 24, 38%]

	Consider proton if available, but preferable to have comparative plans vs IMRT for final selection	3. Proton/heavy ion: [15 / 24, 63%] 4. Others (such as brachytherapy): [5 / 24, 21%] Additional details First choice if proton is available: 1) Proton: 13/28, 46% 2) Alternative plan with IMRT/VMAT for comparison before decision: 10/28, 36% 3) IMRT/VMAT: 5/28, 18%
Principle for delineation of rCTV	Geometric expansion ± anatomical editing (e.g. air, skull base)	1) No expansion from rGTV: 1/24, 4% 2) Geometric expansion ± anatomical editing (e.g. air, skull base): 23/24, 96%
Margin for rCTV	≤5mm expansion margin	Expansion margin from rGTV to rCTV (by IMRT/VMAT) 5 mm with differential curtailing for critical OAR 1) Agree: 19/24, 79% 2) Other: 5/24, 21% [0mm; 2-3mm; 2-5mm; ≤3 mm]
Margin for PTV	2-3 mm (with image guidance)	Margin from rCTV to rPTV (RT under image guidance) 1) 2-3 mm: 23/24, 96% 2) Other: 1/24, 4% [specification by physicist]
Aimed total dose (equivalent dose by 2 Gy/Fr)	60-66 Gy	Aimed total dose by daily fractionation schedule 1) 60-66 Gy: 24/24, 100% 2) Other: 0%
Fractionation	1st choice: Hyper-fractionation (if can be arranged) Dose/fraction for BID schedule: 1.1-1.2 Gy/Fr	Ideal fractionation – 1) QD: 7/24, 29% 2) BID with ≥6-hr interval: 17/24, 71%

	(≥6 hours inter-fraction interval) If conventional daily fraction is used: Dose/fraction for QD schedule: 1.8-2 Gy/Fr	Dose/fraction for QD schedule: 1) 1.8-2 Gy/Fr: 18/24, 75% 2) 2.12 Gy/Fr: 2/24, 8% 3) Other: 4/24, 17% [always BID (2); 3.0 Gy/Fr if target is >5 mm away from critical neural structures; otherwise 2.5 Gy/Fr; Not <2 Gy/Fr and overall time not >6 weeks] Dose/fraction for BID schedule: 1) 1.1-1.2 Gy/Fr: 22/24, 92% 2) Other: 2/24, 8% [1.8Gy/Fr BID]

Table 2. Consensus Recommendation on Dose Prioritization and Acceptance Criteria for Radical Re-irradiation by IMRT/VMAT for Recurrent Nasopharyngeal Cancer

	Priority			Reference tolerance dose for 1 course	Acceptance criteria (Cumulative dose of both primary and 2nd courses)[#]			
Critical OAR		Agree	Disagree		Desirable		Acceptable	
Organ	Priority	n/N (%)[a]	Alternative priority: n (%)[a]		Cumulative dose (EQD2)	n/N (%)[a]	Cumulative dose (EQD2)	n/N (%)[a]
Brainstem	1	19/21 (90%)	2: 1 (5%) 3: 1 (5%)	D0.03 cc 54 Gy	≤70.2 Gy[b]	24/24 (100%)	81 Gy[b]	23/24 (96%)
Spinal cord	1	20/21 (95%)	3: 1 (5%)	D0.03 cc 45 Gy	≤58.5 Gy[b]	24/24 (100%)	67.5 Gy[b]	23/24 (96%)
Optic chiasma	1	23/24 (96%)	3: 1 (4%)	D0.03 cc 54 Gy	≤70.2 Gy[b]	18/24 (75%)	81 Gy[b]	18/24 (75%)
Optic nerve	Unilateral: 2 Bilateral: 1	11/19 (58%) 17/19 (89%)	1: 1 (5%) 3: 7 (37%) 2: 2 (11%)	D0.03 cc 54 Gy	≤70.2 Gy[b]	24/24 (100%)	Unilateral: No dose constraint if patient accepts Bilateral: 81 Gy[b]	19/20 (95%) 19/23 (83%)
Temporal lobes	2	13/17 (76%)	3: 4 (24%)	D0.03 cc 70 Gy	≤91 Gy[b]	23/23 (100%)	105 Gy[b]	23/23 (100%)
Carotid artery	3	15/19 (79%)	4: 2 (11%) Not specified: 1 (5%) No constraint: 1 (5%)	D0.03 cc 70 Gy	≤125 Gy[c]	16/24 (67%)	No constraint	15/23 (65%)
Tumor target								

GTV-rP	1	16/21 (76%)	2: 5 (24%)	Min	≥98% dose	19/21 (90%)	≥95% dose	23/24 (96%)
PTV	2	20/20 (100%)		<10%	≤5% PTV	15/21 (71%)	<10% PTV	18/23 (78%)

(%)[a]: The percentage among those who voted;
Gy[b]: Equivalent dose in 2 Gy fractions for desirable and acceptable doses are based on desirable tolerable dose for the primary course x 130% and 150%, respectively as stated in the previous guideline on dose prioritization and acceptance criteria in RT planning for NPC [4];
Gy[c]: Based on a literature review by Dionisi et al. [65];
[#]Example of the estimation of the second dose tolerance based on the cumulative dose of both courses: Assuming that the maximal tolerable dose of brainstem in the first course of treatment was 54 Gy (EQD2) [4], the cumulative desirable dose (130%) and acceptable dose (150%) will be 70.2 Gy (EQD2) and 81 Gy (EQD2), respectively. If a patient had already received 50 Gy EQD2 in the first course, the desirable and the acceptable D_{max} by the second course using conventional fractionation of 2 Gy daily to the brainstem will be 20.2 Gy and at 31 Gy, respectively. However, if a patient receives 60 Gy EQD2 in the first course, the corresponding desirable and acceptable tolerance to the brainstem will be 10.2 Gy and 21 Gy D_{max} EQD2, respectively. This is based on the assumption that the same spatial region of the brainstem is re-irradiated, and the patient has received close to the maximal dose in the first course of treatment, which is often the case for nasopharyngeal carcinoma.