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International Guideline on Dose Prioritization and Acceptance Criteria in Radiation Therapy Planning for Nasopharyngeal Carcinoma

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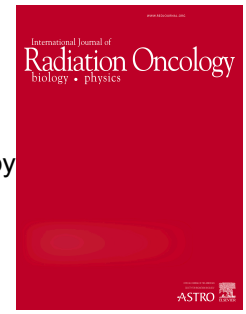

International Guideline on Dose Prioritization and Acceptance Criteria in Radiotherapy Planning for Nasopharyngeal Carcinoma

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Nasopharyngeal carcinoma, clinical target volume (CTV), gross target volume (GTV), guideline, delineation, radiotherapy planning

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Ethical considerations

None to declare

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Conflicts of Interest

Dr. Kevin Harrington reports grants, personal fees and non-financial support from ELEKTA, during the conduct of the study. Dr Langendijk reports that the department of radiation oncology has research agreements with IBA, MIRADA and Raysearch. He has received a fee from IBA for giving a presentation at a symposium and giving consultancy. This had been paid to UMCG research B.V.. Dr. Nancy Lee reports being an Advisory Board/Consultant for Merck, Merck Serono, Pfizer, Sanofi Aventis, and Lily. Dr. Quynh Le reports grants from Redhill, other from BMS advisory board, outside the submitted work. Dr. Yungan Tao reports grants and non-financial support from MSD, non-financial support and other from Merck serono, grants from Debiopharm, grants, non-financial support and other from Onxeo, outside the submitted work. Dr. Sue Yom reports grants from Bristol-Myers Squibb, grants from Merck, grants from Genentech, outside the submitted work.

All the other authors declare no conflicts of interests

Author's contributions

AWL, WTN and JTW conceived of the idea, developed and executed the consensus development. All authors participated in the consensus development. AWL, WTN, JTW, SSP, CLC, HCC and SY were involved in the writing phase of the manuscript. All authors reviewed and approved the final manuscript.

Supplementary Material

Supplementary Table 1: Initial recommendations, % agreement and alternative suggestions.

Supplementary Table 2: Quality of evidence and definitions

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Supplementary Appendix 1: Literature Search Summary

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Summary

This guideline is the result of an international consensus to provide a practical reference for setting dose prioritization and acceptance criteria for tumor volumes and organs at risk for nasopharyngeal carcinoma.

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Abstract

Purpose

The treatment of nasopharyngeal carcinoma (NPC) requires high radiation doses. The balance of the risks of local recurrence due to inadequate tumor coverage versus the potential damage to the adjacent organs at risk (OARs) is of critical importance. With advancements in technology, high target conformality is possible. Nonetheless, to achieve the best possible dose distribution, optimal setting of dose targets and dose prioritization for tumor volumes and various OARs is fundamental. Radiation doses should always be guided by the ALARP (As Low As Reasonably Practicable) principle. There are marked variations in practice. This study aimed to develop a guideline to serve as a global practical reference.

Methods

A literature search on dose tolerances and normal tissue complications following treatment for NPC was conducted. In addition, published guidelines and protocols on dose prioritization and constraints were reviewed. A text document and preliminary set of variants was circulated to a panel of international experts with publications and/or extensive experience in the field. An anonymized voting process was conducted to rank the proposed variants. A summary of the initial voting and different opinions expressed by members were then re-circulated to the whole panel for review and re-consideration. Based on the comments of the panel, a refined second proposal was re-circulated to the same panel. The current guideline was based on majority voting following repeated iteration for final agreement.

Results

Variation in opinion among international experts was repeatedly iterated to develop a guideline describing appropriate dose prioritization and constraints. The percentage of final agreement on the recommended parameters and alternative views is shown. The rationale for the recommendations and the limitations of current evidence are discussed.

Conclusions

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Through this comprehensive review of available evidence and interactive exchange of vast experience by international experts, a guideline was developed to provide a practical reference for setting dose prioritization and acceptance criteria for tumor volumes and OARs. The final decision on the treatment prescription should be based on the individual clinical situation and patient's acceptance of optimal balance of risk.

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Introduction

Radiation therapy (RT) for nasopharyngeal carcinoma (NPC) presents a unique challenge due to the anatomical proximity of target volumes to critical organs at risk (OARs). Although NPC, especially the classical non-keratinizing type, is relatively radiosensitive, high doses are generally needed for eradication of gross tumor and the therapeutic margin for optimal tumor control is notoriously narrow. Even in the contemporary era of intensity-modulated radiotherapy (IMRT) with extensive use of concurrent chemotherapy, dosimetric inadequacy enforced by dose constraints on OARs remains one of the most important independent factors affecting treatment outcome. It is often difficult to achieve the optimal balance and trade-off between risks of local recurrence due to inadequate tumor coverage versus potential serious late complications; this results from the inevitably high doses to OARs in the case of advanced tumors with extensive locoregional infiltration [1]. Decisions on prioritization vary substantially depending on different philosophies.

The advent of newer planning and treatment delivery technologies has led to an evolving capability to maximize dose conformity. Although there is little doubt that IMRT is superior in improving tumour control and reducing toxicities when compared with 2DRT, there is marked variation in the toxicities reported. In the trial by Peng et al. [2], the incidence of temporal lobe necrosis was still as high as 13.1% and optic nerve/chiasm injury was 1.6% in the IMRT arm; in contrast, other studies have shown that it is possible to achieve similar local control with substantially lower rates of neurological toxicity, such as a temporal lobe necrosis rate of 0.2% [3].

Standardizing the appropriate delineation of tumour targets for different dose levels, dose prioritization for tumour targets and the various OARs, and acceptance criteria for each parameter is fundamental for future study and progress. Unfortunately, accurate data on the tolerance doses of critical OARs remain scanty. There is also marked variation in the philosophy and practice amongst different institutions and clinicians with regards to the order of prioritisation and the exact maximum acceptable doses for the different OARs.

Through a process of iterative development amongst international experts, we aimed to provide clinicians with a reference tool for treatment planning for NPC. Twenty-six

contributors from major centres in Asia, Australia, North America, Middle East and Europe previously provided input into the publication of “xxxx” [4]. To address issues that could not be covered in the previous guideline, our goal for this document was to provide a practical reference to assist clinicians in deciding on the optimal RT planning process for NPC and the best possible compromise for difficult cases.

Methodology

The following processes were used for evidence searching and development of the guideline:

Firstly, an initial literature search on NPC-specific late complications was performed on December 2017 in PubMed using the following search terms:
("intensity-modulated radiation therapy" OR "intensity-modulated radiotherapy" OR IMRT) nasopharyngeal ("late toxicity" OR "temporal lobe" OR brainstem OR visual OR optic OR eye OR hearing OR ear)
Published treatment guidelines and dose constraints by various centers were also reviewed. This formed the initial set of planning dose prioritization and acceptance criteria for voting based on a modified Delphi process [5-18]. A preliminary set of proposed variants for planning dose prioritization and acceptance criteria was then drafted. In order to provide a pragmatic reference, both a “goal” OAR constraint and a variation acceptable for treatment in challenging situations (i.e. maximum acceptance criteria (MAC)) were listed.

Secondly, a panel of international experts 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 centres from different parts of the world (including Asia, Middle East/Mediterranean Region, Oceania, Europe and North America).

We used a modified Delphi process for developing the final guideline: the preliminary proposal, together with previously published guidelines and protocols (Table 1), was circulated among international experts for initial voting and comments. The initial percentage of agreement on the proposed criteria and the alternative views are shown in the Appendix

(Supplementary Table 1). The exact votes submitted were anonymized, while summary of this initial voting and different opinions and proposed variants expressed by members were circulated to the whole panel for review and re-consideration. Based on the exchanged comments and supporting data, a refined second proposal was drafted after repeated iteration among the panel members, and circulated for another round of voting. The current, finalized guideline summarized in Table 2 was based on majority views.

In order to identify additional evidence published since the initial manuscript was finalized, a new literature search using the same search terms was conducted in May 2019 to ensure comprehensiveness of this review including the latest published evidence. 256 articles were identified; using the PRISMA checklist approach, 211 were excluded after initial screening of the abstracts. Of the 35 potentially relevant articles reviewed, 11 were excluded as they were found to be irrelevant to the subject of this study. Among the 24 relevant articles, 18 were cited in this manuscript as they provided specific recommendations on OAR dose constraints based on the latest updated data from the institute.

A figure illustrating the literature search summary is added in Supplementary Appendix I.

No major inconsistencies or discrepancies with our recommendations were found except for one very recent article on the dose constraint for the brainstem [19]. This information was circulated to the panel and a brief description of the findings was added to the guideline text, but the unanimous feedback from panel members was that this could not be recommended as practice-changing without further validation.

The strength of the recommendations was rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Supplementary Table 2) [20]. The GRADE level of evidence assigned for each OAR was initially discussed and drafted by the three senior authors; and circulated to all the authors as part of the manuscript review. There were no objections or changes to suggested GRADE assignments. The evidence on dose constraints was largely derived from retrospective studies. 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 2. The alternative constraints suggested by dissenting experts were also shown to illustrate existing variations and the potential range for future consideration.

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Results and Discussion on the Recommendations

Before proceeding to setting dose prioritization and constraints, appropriate contouring of various structures is the first fundamental requirement. An international guideline on contouring of clinical tumour target volumes has been published previously [4]. Many authors in this current guideline also participated in the development of guidelines on contouring of organs at risk specifically for NPC [21] and head and neck cancers [22] which serve as useful references. We recommend that a planning risk volume (PRV) be delineated around critical organs to account for set-up variability. While this set-up variability varies among different institutions, a margin of not less than 2mm was generally recommended based on the study by Van Herk [23].

Prioritisation of dose constraints

A study by Yao et al [24] in a cohort of NPC patients with gross tumour volume exceeding 60 cm^3, showed that the prescribed mean doses to brainstem PRV and optic chiasm PRV were 68.13 Gy (± 4.74 Gy) and 66.54 Gy (± 8.62 Gy), respectively, which were far higher than the usual recommended dose constraints for these OARs. With IMRT treatment planning, setting the appropriate prioritization levels for different structures is fundamental for achieving the desired optimization of dose distribution. The general principle is to achieve full tumoricidal doses to the whole tumour target within the maximum tolerance dose of critical OARs. However, in the frequent situations in which a trade-off must be made, more than 90% of the expert panel agreed that the priority should be given to the critical OAR(s) to avoid potentially lethal or highly morbid sequelae.

When the treatment plan is unable to give adequate tumor target coverage and meet the dose constraints for priority 1 OARs, we suggest either adaptive re-planning or consideration of induction chemotherapy. A recent randomized study by Yang et al suggests that the strategy of restricting full therapeutic dose to the MRI-defined volume that remains after induction chemotherapy, while ensuring that the pre-induction chemotherapy volume receives at least an intermediate dose (64 Gy) appears not to compromise 3-year local, regional and distant control or overall survival but served to reduce late toxicities and overall health status in a

cohort of 212 NPC patients [25]. Whether these results will continue to hold should an even lower dose be used (to meet critical OAR constraints) remains to be seen.

There was unanimous agreement that Priority 1 should include the brainstem, spinal cord and optic chiasm, as damage to these serially arranged structures can result in catastrophic morbidity, and even mortality. Bilateral blindness due to damage to optic chiasm and/or both optic nerves is such a debilitating complication that there is universal agreement that at least the optic nerve on the less involved side should be included as Priority 1 for dose constraint. However, we would consider exceeding the commonly recommended MAC for the ipsilateral optic nerve (lowering to Priority 3) if this is unavoidable to achieve adequate doses to cover the tumour target, provided the patient consents to an increased risk of unilateral partial or complete loss of sight. The latter entails a careful explanation of the relative importance of the different components and trade-offs during the decision process.

There was also unanimous agreement that Priority 2 should include tumour Planning Target Volume (PTV). There was, however, variation as to whether the priority for Gross Tumour Volume (GTV) should be raised to Priority 1 because, although it may still not be feasible to achieve minimum $D_{98\%}$ of the prescribed dose to 100% of the GTV, there would at least be greater attempts to achieve the highest feasible dose. Under such circumstances, the options for the most suitable compromise should be discussed with the patient.

We recommend that the temporal lobes be included under Priority 2 as temporal lobe necrosis (TLN) can lead to serious disability and mortality. The study by Lam et al. [26] showed that 54% of patients progressed to grade 4 severity at 5 years after the diagnosis of TLN (asymptomatic and symptomatic) and 5-year overall survival was only 35%. However, there was variation in the level of priority accorded for this structure.

There was also complete agreement that normal tissues in the oral cavity, post-cricoid pharynx, esophagus and glottic larynx should be assigned to Priority 4. There were variations as to whether the other structures should be set at Priority 3 or Priority 4. We recommend that the brachial plexus, pituitary gland, eyeball and lens be included as Priority 3; while cochlea, mandible and temporo-mandibular joints, thyroid, parotid and submandibular glands should be included under Priority 4.

Readers may wish to familiarize themselves with the DAHANCA Radiotherapy Guidelines 2013 [14]. DAHANCA has a long history of producing RT guidelines, with dose-volume constraints and rules for prioritization. Instead of using two terms for constraints, “Desirable” and “Acceptable”, they distinguish between OAR dose and PRV dose. There are also some differences in the priority listing. In general, DAHANCA ranks PTV coverage lower than critical serial OARs, to allow compromises where the margins are tight.

The desired dose and acceptance criteria for different structures

Brainstem

The QUANTEC review [27] recommended that a small volume of brainstem (1-10 mL) may be irradiated to a maximum dose of 59 Gy using dose fractionation ≤2 Gy and a D_{max} <64 Gy with a point dose <1 cc. Two studies have been reported from Sun Yat-Sen Cancer Center to assess brainstem injury incurred by doses higher than that recommended by QUANTEC. The study (n=1544) by Li et al. [28] showed 59% of patients received a D_{max} ≥54 Gy, and 25% received ≥64 Gy, of whom two developed brainstem necrosis; both had received a D_{max} dose ≥76.4 Gy and a V_{55} ≥3.8 cc. Their most recent analysis by Huang et al. [19] on 6264 NPC patients showed that patients with D_{max} ≥67.4 Gy (equivalent dose in 2-Gy fractions {EQD2}) had significantly higher incidence of brainstem injury (odds ratio = 25.29, 95% CI: 8.63–74.14; P < 0.001) than those with lower dose. D_{max} of 67.4 Gy (EQD2) was recommended as the dose constraint for brainstem, but the authors also concluded that further studies are needed to validate their findings. On the other hand, Yao et al. [29] reported an alarming incidence rate of 2.8% at 5 years in a cohort of 327 NPC patients. Among the 8 patients with brainstem injury, seven (one fatal and one hemiplegic) had D_{max} and $D_{0.1cc}$ ≥ 63.38 Gy and 60.89 Gy, respectively.

Other studies showed that the volume of brainstem with high dose is also important: Uy et al. [30] reported a case of brainstem necrosis with a V_{54} of 4.7 cc.; Debus et al. [31] showed that a V_{50} >5.9 cc, V_{55} >2.7 cc, and V_{60} >0.9 cc were associated with brainstem toxicity. Schoenfeld et al. [32] further recommended to restrict the V_{55} to <0.1 cc.

In view of the potential devastating consequence and risk of serious medico-legal implications by brainstem injury, while a higher dose (D_{max} of 67.4 Gy) may be discussed as an option for patients with tumors encroaching the brainstem, a more conservative dose acceptance criterion was preferred among our panel for this general guideline (26/26 who

responded to this special vote) till more robust validation become available.

Our final recommendation was to aim for a $D_{0.03\ cc}$ PRV dose ≤54 Gy and MAC of 60 Gy.

Level of agreement: 90% (18 of 20 voters) agreed on desirable dose (alternative suggestions ranged from 50-58 Gy); 90% (19 of 21 voters) agreed on MAC (alternative variants proposed ranged from 54-64 Gy).
GRADE of recommendation: High/Moderate

Spinal cord
The QUANTEC review [33] suggests that at 2 Gy per fraction, the probability of myelopathy is 0.03% at 45 Gy and 0.2% at 50 Gy.
Our final recommendation was to aim at a $D_{0.03\ cc}$ PRV dose ≤45 Gy and MAC ≤50 Gy.

Level of agreement: 100% (20 of 20 voters) agreed on desirable dose, 95% (20 of 21 voters) agreed on MAC (alternative variants proposed were up to 55 Gy).
GRADE of recommendation: High

Optic chiasm and optic nerve
The QUANTEC review [34] suggested that the incidence of radiation-induced optic neuropathy (RION) was unusual for a D_{max} <55 Gy, particularly for fraction sizes <2 Gy. The risk increases (3–7%) in the region of 55–60 Gy and becomes more substantial (>7–20%) for doses >60 Gy when fractionation schedules of 1.8–2.0 Gy are used. Similarly, in the study reported by Akagunduz et al. [35], a series of comprehensive visual tests showed that visual field and contrast sensitivity were affected significantly with $V_{55} \geq 50\%$ and $D_{mean} \geq 50$ Gy and visual evoked potential latency was affected significantly with $D_{mean} \geq 50$ Gy, $D_5 \geq 55$ Gy, and $D_{max} \geq 60$ Gy. For the chiasm, a significant detrimental effect of all parameters was observed on visual acuity as well.

We set the same dose criteria for both structures as there were no data to suggest that their radiosensitivities were different. However, we suggest separate considerations for according priority levels as discussed above. Our final recommendation was to aim at a $D_{0.03\ cc}$ PRV

dose ≤54 Gy and MAC of ≤60 Gy, for both structures.

Level of agreement: 93% (14 of 15 voters) agreed on desirable dose for the optic chiasm and optic nerve, respectively (alternative variants proposed was 50 Gy). For the recommended MAC, the agreement level among the panel was 82% (14 of 17 voters) and 95% for optic chiasm (alternative variants proposed ranged from 54-56 Gy) and optic nerve (alternative variants proposed were up to 62 Gy), respectively.
GRADE of recommendation: High / Moderate

Tumour

Gross tumour volume (GTV):

The study by Ng et al. [1], showed that those who received at least 66.5 Gy to primary GTV were less likely to have local failure (odds ratio, 0.289; p = 0.020).

Our final recommendation was to aim for a minimum dose of ≥68.6 Gy (98% dose) and to set a minimum acceptable criterion at 66.5 Gy (95% dose).

Level of agreement: 78% (14 of 18 voters) agreed on desirable dose (alternative variants proposed ranged from 66-70 Gy); 80% (16 of 20 voters) agreed on acceptable dose.
GRADE of recommendation: Moderate

Planning target volume (PTV):

Dose prescription at 3-4 levels at conventional fractionation was agreed upon by 73%, while 18% would prescribe using 2 dose levels only. As discussed in the previous guideline on the contouring of CTVs [4], we recommend three levels of dose prescription in line with the general principles of ICRU: CTV1 for GTV with margin, CTV2 for high-risk structures/regions, and CTV3 for intermediate-low risk structures/regions for microscopic infiltration. Two commonly used prescription schemes are acceptable: either the 35-fraction (2 Gy per fraction) scheme with doses prescribed to 70, 63-60 and 56 Gy; or the 33-fraction (2.12 Gy per fraction) scheme with the doses prescribed to 69.96, 63-59.4, and 54 Gy. It should be pointed out that current NCCN Guidelines recommend restricting the prescribed dose per fraction to ≤2.12 Gy due to concerns about risk of excessive damage to adjacent

neurological structures with larger fraction size. [36]

Our final recommendation is to achieve ≥95% dose of the prescribed dose to 100% PTV or ≥93% dose to ≥99% PTV.

Regarding the issue of dose heterogeneity, we recommend restricting hot-spots ≥75 Gy to <10% PTV70 or ≥77 Gy to ≤5% PTV70 as the preferred criteria; and increased this to ≥75 Gy to <20% PTV70 or ≥77 Gy to ≤10% PTV70 as the acceptable criteria.

We acknowledge that there is an increasing tendency to accept higher dose heterogeneity and "hot spot" doses to ensure better dose conformality as suggested by the ICRU 83 report [37] or even deliberately giving a higher dose (80 Gy) to certain regions of GTV as a means of dose escalation/dose redistribution according to the tumor behavior as visualized on molecular imaging [38]; but 15% of panel members recommended to control the upper limit of the hot spot dose to not exceed 80 Gy. It is important to emphasize that while there is a move towards higher doses within the target volume these areas should be well away from the critical OAR – especially the brain stem to prevent any untoward neurological adverse events from the treatment itself.

Level of agreement:

- PTV dose prescription: 81% (17 of 21 voters) agreed to either the 35-fraction (2 Gy per fraction) scheme with the doses prescribed to 70, 63-60 and 56 Gy; or the 33-fraction (2.12 Gy per fraction) scheme with the doses prescribed to 69.96, 63-59.4, 54 Gy.
- PTV min: 95% (19 of 20 voters) agreed on desirable dose (alternative variants proposed was aim for 100% of the PTV receiving full prescription dose), 90% (18 of 20 voters) agreed on acceptable dose.
- PTV hotspot: 86% (18 of 21 voters) agreed on desirable dose, 90% (18 of 20 voters) agreed on acceptable dose.

GRADE of recommendation: High/Moderate for PTVmin; Moderate for PTV hotspot

Temporal lobe:

The QUANTEC review [39] showed that for conventional fractionation with doses ≤2 Gy, a

5% risk of symptomatic radiation necrosis is predicted to occur at an equivalent dose of 72 Gy (range, 60–84); furthermore, they cautioned that the brain is especially sensitive to fraction sizes >2 Gy. Due to the close proximity of the temporal lobes to the nasopharynx, multiples studies have been reported in the NPC literature to evaluate the dose-volume effects on temporal lobe injury after IMRT. A study by Sun et al. [40] reported that a $D_{0.5cc}$ of 69 Gy may be the dose tolerance of the temporal lobe. However, subsequent studies suggested lower dose equivalents of 60.3 Gy (D_{2cc}) [41], 62.8 Gy (D_{1cc}) [6, 42] and 69 Gy (D_{max}) [42] (at 2 Gy/fraction) for a 5% probability of developing temporal lobe injury at 5 years. These findings concurred with a study reported by Su et al. [43], in which the probability of temporal lobe injury was ≤5% at 5 year if D_{1cc} was less than 58 Gy; and D_{max} was less than 68 Gy. Furthermore, the volume of temporal lobe receiving low to moderate doses is also an important contributing factor for the development of temporal lobe injury.

On the other hand, for patients with a locally advanced tumor, a reasonable balance between adequate tumor coverage and risk of temporal lobe injury is needed; and a dose limit of D_{1cc} ≤ 71.14 Gy [44] and D_{max} ≤72 Gy [1] have been suggested for T4 disease.

The final recommendation of the panel was to aim for a $D_{0.03\ cc}$ PRV dose ≤ 65 Gy for T1-2 tumors and ≤ 70Gy for T3-4 tumors; MAC ≤72 Gy should be confined to T3-4 tumors only. Based on the latest literature findings, we also acknowledge that D_{1cc} may be a better parameter for future studies.

Level of agreement: 85% (17 of 20 voters) agreed on desirable dose (alternative variants proposed ranged from 66-70 Gy irrespective of the tumour stage); 62% (13 of 21 voters) agreed on MAC dose for T3-4 tumors (alternative variants proposed were up to 74 Gy, but 33% would not accept a MAC >70Gy).
GRADE of recommendation: Moderate

Brachial plexus:
Damage to the brachial plexus may have a long latency period of 1 to 17 years (average 8.2 years), but it can lead to significant morbidity of unilateral or bilateral arm or hand paraesthesia, weakness, as well as pain and muscular atrophy [45, 46]. A retrospective study by Cai et al. showed that patients with a therapeutic dose ≥66.8±2.8 Gy to lower cervical lymph node metastasis had a significantly higher incidence of radiation-induced brachial

plexopathy [46]. Chen et al. showed that the incidence of brachial plexopathy increased dramatically when V_{70} exceeds 10% [47]. Thus, the brachial plexus should be outlined as an OAR as a study has shown that a large proportion of patients were exposed to doses exceeding the Radiation Therapy Oncology Group (RTOG) recommended dose constraints when the brachial plexus was not outlined [48]. Placing dose constraints on the brachial plexus can significantly decrease the irradiated volume and dose, without compromising adequate dose delivery to the target volume [49].

In line with the recommendation by RTOG, our final recommendation is to aim at a $D_{0.03\ cc}$ PRV dose ≤66 Gy, and MAC of ≤ 70 Gy.

Level of agreement: 89% (16 of 18 voters) agreed on desirable dose (alternative variants proposed was ≤ 60 Gy); 85% (17 of 20 voters) agreed on acceptable dose (alternative variants proposed was ≤ 66 Gy).
GRADE of recommendation: Moderate

Eyeball and lens:
Jeganathan and colleagues have published an excellent review of ocular risks from orbital and periorbital irradiation [50]. Similar to the considerations for the optic nerve, we would opt to accept exceeding these recommended MACs for ipsilateral structures if necessary, in order to attain adequate tumor dose coverage and the patient has consented to accepting increased risk. The contralateral, less involved side should then be kept within the dose limits.

Our final recommendation of the eyeball was to aim for a mean dose of ≤35 Gy and MAC of $D_{0.03\ cc}$ ≤50 Gy. . For the lens, our final recommendation was to aim for a $D_{0.03\ cc}$ dose <6 Gy and MAC at $D_{0.03\ cc}$ dose ≤15 Gy.

Level of agreement:

- Eyeball: 90% (18 of 20 voters) agreed on desirable dose (alternative variants proposed ranged from 25-45 Gy); 76% (16 of 21 voters) agreed on acceptable dose (alternative variants proposed ranged from 40-60 Gy).

- Lens: 90% (18 of 20 voters) agreed on desirable dose, 82% (18 of 22 voters) agreed on acceptable dose.

GRADE of recommendation: Moderate

Pituitary (and hypothalamus) and thyroid glands:

Even in the IMRT era, it has been reported that a significant number of patients, ranging from 20-50%, develop some element of endocrine deficiency post-RT [51-56]. We recommend including the pituitary gland (and hypothalamus) under Priority 3, while setting the thyroid gland as Priority 4, because damage to the thyroid gland will lead to a deficiency of thyroid hormone alone and replacement is possible. In contrast, damage to the pituitary results in complex dysfunction of multiple hormones including sex hormones, cortisol and thyroid pathways, as well as growth hormones.

For the pituitary, we recommend to aim for a $D_{0.03cc}$ dose ≤60 Gy and MAC of $D_{0.03cc}$ dose ≤65 Gy. However, published data regarding the tolerance of the thyroid gland are scanty. We recommend to aim at V_{50} ≤60%, based on the study by Sachdev et al. (55); and MAC as V_{60} ≤10 cc.

Level of agreement:

- Pituitary: 79% (11 of 14 voters) agreed on desirable dose (alternative variants proposed ranged from 40-54Gy); 87% (13 of 15 voters) agreed on acceptable dose.
- Thyroid: 88% (14 of 16 voters) agreed on desirable dose (alternative variants proposed were $D_{0.03cc}$ ≤45 Gy or D_{mean} ≤50 Gy); 89% (16 of 18 voters) agreed on acceptable dose (alternative variants proposed was $D_{0.03cc}$ dose ≤50 Gy).

GRADE of recommendation: Moderate/Low

Cochlea:

Due to the location and pattern of invasion of NPC, hearing impairment is one of the commonest toxicities in the IMRT era, especially for those who also receive cisplatin-based chemotherapy. QUANTEC [57] recommends that for conventionally fractionated RT, to minimize the risk for sensorineural hearing loss (SNHL), the mean dose to the cochlea should

be limited to ≤45 Gy (or more conservatively ≤35 Gy). Because a threshold for SNHL cannot be determined from the present data, to prevent SNHL the dose to the cochlea should be kept as low as possible. The study by Chan et al. [58] showed that the mean cochlea dose and concurrent cisplatin dose were important determinants of high-frequency SNHL, with an odds ratio of 1.07/Gy increase and 1.008/mg/m^2 increase, respectively; it is thus recommended that the mean MAC to the cochlea should be lowered to ≤47 Gy for patients treated with chemoradiotherapy. Similar findings have been reported by Wang et al. [59], with an accumulative cisplatin dose of ≥200 mg/m2 and radiation dose of 40 Gy to 0.1ml cochlea being predictive factors for the development of SNHL.

Our final recommended dose was to aim for a mean dose of ≤45 Gy and MAC of mean dose ≤55 Gy.

Level of agreement: 90% (18 of 20 voters) agreed on desirable dose (alternative variants proposed ranged from 28-50 Gy), 86% (19 of 22 voters) agreed on acceptable dose (alternative variants proposed ranged from 32-52.5Gy).
GRADE of recommendation: Moderate

Parotid gland:
QUANTEC [60] recommends that severe xerostomia (long-term salivary function <25% of baseline) can usually be avoided if at least one parotid gland has been spared to a mean dose of less than 20 Gy or if both glands have been spared to a mean dose of less than 25 Gy. The study by Lee et al. [61] concurred that with this dose constraint, less than 33% of patients had xerostomia at 3 months and none had it at 12 months. However, this goal might be difficult to achieve, especially with larger tumours and those with gross nodal involvement. A study by Eisbruch et al. [62] reported that partial volume thresholds for prediction of reduced salivary flow were 67%, 45%, and 24% gland volumes receiving more than 15 Gy, 30 Gy, and 45 Gy, respectively, showing substantial preservation of salivary flow rates following RT with continued improvement over time.

Our final recommendation is to aim for a mean dose of <26 Gy and MAC <30 Gy for ≥50% of at least 1 gland.

Level of agreement: 90% (18 of 20 voters) agreed on desirable dose (alternative variants proposed being mean dose <25Gy); 82% (18 of 22 voters) agreed on acceptable dose (alternative variants proposed ranged from mean dose ≤25-35 Gy).
GRADE of recommendation: Moderate

Mandible and temporomandibular joint (TMJ):

The mandible and the TMJ are subject to late effects of radiation, leading to possible osteoradionecrosis (ORN) and joint stiffness of the TMJ. A literature review by Mendenhall et al. [63] found that the incidence of ORN is 5% to 10% with a median latency period of 1 to 2 years or less. The likelihood of ORN depends on a number of factors including primary site and extent of disease, dental status, treatment modality, RT dose, volume of mandible included in the planning target volume, RT fractionation schedule and technique, and dental extractions/root canal work.

In the work of Ben-David et al., half of the patients received at least 70 Gy to ≥ 1% of the mandibular volume; no patients developed ≥ grade 2 ORN [64]. Similarly, Gomez et al. reported that no patients developed ORN using the dose constraint of D_{max} ≤70 Gy. [65] On the other hand, investigators from the MD Anderson Head and Neck Cancer Working Group reported that the volume effect might be more important than maximum dose. It was found that while the mandibular mean dose was significantly higher in the ORN cohort (48.1 vs 43.6 Gy, p<0.0001), the maximum dose was, in fact, not statistically different. Thus, they recommended V_{44} <42% and V_{58} <25% to the mandible as reasonable DVH constraints for IMRT plan acceptability, when tumour coverage was not compromised [66].

Our final recommendation was to aim for a $D_{2\%}$ dose of ≤70 Gy, and MAC ≤75 Gy.

Level of agreement: 95% (18 of 19 voters) agreed on desirable dose, 67% (14 of 21 voters) agreed on acceptable dose (alternative variants proposed ranged narrowly from 73-77 Gy).
GRADE of recommendation: Moderate

Oral cavity:

Excessively high doses to the oral cavity can result in severe mucositis which can lead to

unscheduled treatment breaks or failure to complete treatment. Both radiotherapy and chemotherapy are independent factors for the risk of incurring acute mucosal toxicities. Sanguineti et al. [67] found that concurrent chemoradiotherapy increases the risk of mucosal Grade 3 toxicity approximately 4 times over RT alone, and it is equivalent to an extra of 6.2 Gy to 21 cc of oral mucosa over a 7-week course. For patients receiving induction chemotherapy followed by chemo-radiation for head and neck cancer, Bhide et al. [68] have derived similar dose response curves. Thus, lower doses to the oral cavity (if achievable) should be considered in patients undergoing concurrent chemo-radiotherapy.

Our final recommendation is to aim for a mean dose of ≤40 Gy and MAC of ≤50 Gy.

Level of agreement: 70% (14 of 20 voters) agreed on desirable dose (alternative variants proposed ranged from 35-45 Gy); 77% (17 of 22 voters) agreed on acceptable dose (alternative variants proposed ranged from 30-70 Gy).
GRADE of recommendation: Moderate/Low

Pharynx and constrictor muscles:
Swallowing problems following RT increase with the addition of concomitant chemotherapy and with increased radiation dose to various structures that are part of the swallowing mechanism [69]. While Feng et al. [70] found that all patients who experienced aspiration as a late complication received mean pharyngeal constrictor doses of >60 Gy or more than 50% of the total pharyngeal constrictor volume received more than 65 Gy (V_{65} >50%), multiple series have reported a steeper dose effect relationship starting beyond 45 Gy to the pharyngeal wall. [71-73] Levendag et al. [74] showed that a mean dose of 50 Gy predicted a 20% probability of late dysphagia; this probability increased sharply at mean dose > 55 Gy with the chance of dysphagia increasing by 19% with every additional 10 Gy. QUANTEC [75] recommends that with the limited available data available, minimizing the volume of the pharyngeal constrictors and larynx receiving ≥60 Gy and reducing, when possible, the volume receiving ≥50 Gy is associated with reduced dysphagia/aspiration.

We recommended a D_{mean} ≤45 Gy, and MAC ≤55 Gy.

Level of agreement: 85% (17 of 20 voters) agreed on desirable dose (alternative variants

proposed ranged from 35-50 Gy); 64% (14 of 22 voters) agreed on acceptable dose (alternative variants proposed ranged widely from 45-70 Gy).
GRADE of recommendation: Moderate/Low

Larynx:

The study by Vainshtein et al. [76] on voice and speech outcomes after IMRT to the neck region where the larynx is not a target, showed that amongst patients receiving mean glottic larynx (GL) doses of ≤20 Gy, >20-30 Gy, >30-40 Gy, >40-50 Gy, and >50 Gy; 10%, 32%, 25%, 30%, and 63%, respectively, reported worse voice quality at 12 months compared with pre-treatment status (P=.011); similar results were also observed for speech impairment. A study by Rancati et al. [77] on the incidence of subacute or late laryngeal oedema after RT for head and neck cancers showed a clear volume effect consistent with the parallel architecture of the larynx. The authors recommended an equivalent uniform dose of less than 30-35 Gy to reduce the risk of G2-G3 oedema.

Initial proposals based on existing guidelines were to aim for mean dose of ≤45 Gy and MAC ≤55 Gy to the glottic larynx in order to reduce adverse effects on speech and voice quality, as well as to avoid laryngeal oedema. However the agreement was only 45% (9/20). Among panellists accustomed to lower neck and supraclavicular conventionally planned fields matched to the IMRT fields (which effectively shield the larynx), their recommendation was to restrict the glottic dose to less than 35 Gy. Basing on the literature of other head and neck, a high proportion of panellists feel that attempts should always be made to minimize the laryngeal mean dose to less than 35 Gy, particularly as this was often achievable even for plans utilising a single whole-neck IMRT field. In a study on oropharyngeal cancers not extending to the larynx, a mean dose of 29 Gy was achievable [78].

Level of agreement: the desirable dose finally recommended is 35 Gy and the agreement was 75% (15 of 20 voters).
GRADE of recommendation: Moderate

Submandibular gland:

There are scanty data on the tolerance doses of the submandibular gland. A study by

Murdoch-Kinch et al. [79] showed that with mean doses <39 Gy, submandibular gland salivary flow rates recovered over time at 2.2% per month. The unstimulated salivary flow rates decreased exponentially by 3% per Gy increase in mean dose, and this recovered substantially over time if mean dose was <39 Gy. Similarly, Murthy et al. [80] found that the dose tolerance of submandibular gland leading to a 50% complication risk at 1 year was 36 Gy with a 2-2.5% reduction in the probability of severe xerostomia for every 1 Gy reduction in mean dose. QUANTEC [60] recommends that submandibular gland sparing to modest mean doses (<35 Gy) might reduce xerostomia symptoms.

We recommended a mean dose of <35 Gy. No specific recommendation was set for MAC as there is no supporting data in the literature.

Level of agreement: 81% (17 of 21 voters) agreed on desirable dose (alternative variants proposed included a higher dose of < 39 Gy).
GRADE of recommendation: Moderate

Other structures

Carotid vessels:

Chu et al. [81] carried out a population-based cohort study based on the claims data of the National Health Research Insurance Database of Taiwan and found that ischaemic stroke incidence rates were 2-fold higher in treated NPC patients than in reference populations, with a greater relative risk in younger patients. While the exact dose tolerances for the carotid vessels have not been well established in the literature, a higher risk of carotid artery stenosis following RT for NPC has been reported [82-85]. Although specific recommendations cannot be made in view of the lack of supporting data; the dose to the carotid vessels should be recorded and kept to as low as reasonably achievable.

No specific recommendation could be made as there is no dose tolerance data in the literature.

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Conclusions

This guideline was derived through extensive review of currently available evidence for setting dose prioritization and acceptance criteria to tumour volumes and OARs, supplemented by an iterative process of guideline development from an international expert panel to put forth best practice recommendations for this complex radiotherapy-treated disease.

When initial variants were circulated among the expert panellists, initial levels of agreement were low for some parameters, such as doses for the larynx and the thyroid. There seemed to be a clear dichotomy between practitioners in the East and West, with Asian experts tending to accept higher doses. Although different interpretations of the evidence will always exist, through iterative voting and revisions to the initially controversial parameters, summary final recommendations were able to be issued by the panel.

The guiding principle should always be ALARP (As Low As Reasonably Practicable), as per radiation safety principles. In cases in which there is difficulty in achieving adequate tumor coverage and doses while respecting the recommended dose constraints, consideration of the relative probability of tumor control balanced against the probabilistic likelihood of normal tissue damage should be undertaken. The current guideline provides a practical reference, although the final decision on the optimal balance of risk and best possible compromises should take into consideration the individual clinical situation and the patient's own preferences. Multicentre collaborations to accumulate more accurate data on the radiation planning factors affecting the therapeutic ratio, identification of clinical and molecular/genetic factors for prediction of radiation sensitivity or resistance, and prospective studies to cautiously explore variants in dose constraints are keenly awaited.

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Supplementary Material (Appendix)

Supplementary Table 1: Initial recommendations, % agreement and alternative suggestions.

Supplementary Table 2: Quality of evidence and definitions

Supplementary Appendix 1: Literature search summary.

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	NPC-specific protocol							H&N protocol				
	HKU/ PYNEH (10,11) PYNEH (10,11)		RTOG 0225 (16)	RTOG 0615 (17)	NRG HN001 (18)		China (12)	AIRO (13)		DAHANCA (14)		Ontario (15)
	Goal	Acceptable			Goal	Acceptable		Goal	Acceptable	OAR	PRV	
Brainstem	Max		Max	Max	0.03 cc		Max	Max		Max		Max
	≤54 Gy	≤60 Gy (For T3-4 only)	≤54 Gy or ≤1% vol. >60 Gy	≤54 Gy or ≤1% PRV >60 Gy	<54 Gy	≤60 Gy	≤54 Gy ≤1% PRV >60 Gy	≤54 Gy	≤60 Gy	≤54 Gy	≤60 Gy	≤54 Gy or 0.1cc ≤50 Gy
Spinal cord	Max		Max	Max	0.03 cc		Max	Max		Max		Max
	≤45 Gy	≤50 Gy (For T3-4 only)	45 Gy or ≤1cc vol. >50 Gy	≤45 Gy or ≤1% PRV >50 Gy	<45 Gy	≤50 Gy	≤45 Gy or ≤1% PRV >50 Gy	≤44-45 Gy or PRV ≤44-48 Gy	46 Gy or PRV ≤48-50 Gy	≤45 Gy	≤50 Gy	≤48 Gy or 0.1cc ≤45 Gy
Optical chiasm	Max		Max	Max	0.03 cc		Max	Max (PRV)		Max		Max
	≤54 Gy	≤60 Gy (For T3-4 only)	54 Gy or ≤1% vol. >60 Gy	≤50 Gy or PRV ≤54 Gy	<54 Gy	≤56 Gy	≤50 Gy or PRV ≤55 Gy	≤54 Gy	Max ≤60 Gy	≤54 Gy	≤60 Gy	≤50 Gy
GTV-T & GTV-N	Min		Not stated	Not stated	Not stated		Not stated	Not stated		Not stated		Not stated
	≥68.6 Gy (98% dose)	≥66.5 Gy (95% dose)										
CTV min	Not stated		Not stated	Not stated	CTV6996 - 99 % vol. >65.1 Gy 65.1–60 Gy CTV6270 - 99 % vol.		Not stated	Not stated		CTV1 95%-107% dose CTV2 & CTV3		Not Stated

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					>58.6 Gy; CTV5940 - 99 % vol. >55.2 Gy CTV5412 - 99 % vol >50.2 Gy	58.6–55 Gy 55.2–52 Gy 50.2–45 Gy			95% doses	
CTV Hotspot									≤1.8 cc >107% CTV1	
PTV dose prescription	**PTV70, 63, 56**		**PTV70, 59.4**		**PTV70**	**PTV6996**	**PTV70**			**PTV70, 63, 56**
PTV min	100% PTV ≥95% dose	≥95% PTV 100% dose	≥99% PTV ≥93% dose	95-98% PTV ≥93% dose	≥95% PTV 100% dose	≥95% PTV* 100% dose	≥99% PTV ≥93% dose	Not stated	100% PTV ≥95% dose	≥99 % PTV 100% dose or ≥99 % PTV ≥95% dose
		or ≥99% PTV ≥93% dose			**PTV63, 59.4,54**					
					≥95% PTV 100% dose	≥95% PTV ≥95% dose	≥95% PTV* 100% dose	≥90% PTV* 100% dose		
					≥99% PTV ≥93% dose					
PTV Hotspot	<10% PTV70 ≥75 Gy	<2% PTV70 ≥77 Gy	≤20% PTV70 ≥77 Gy (110% dose) ≤1 cc outside tissue ≥77 Gy		≤20% PTV70 ≥77 Gy ≤5% PTV70 ≥80 Gy Mean dose ≤74 Gy	≤ 40% PTV ≥77 Gy ≤ 20% PTV ≥ 80 Gy	0.03 cc ≤80.5 Gy	0.03 cc 80.5–84 Gy	<20% PTV ≥77 Gy <5% PTV ≥80.5 Gy		<20% PTV1 ≥77 Gy Max mean dose ≤73.5 Gy
Optic nerve	**Max**		**Max**		**Max**		**0.03 cc**		**Max**	**Max (PRV)**	**Max**	**Max**

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	≤54 Gy	≤60-66 Gy	54 Gy* or ≤1% vol. >60 Gy	≤50 Gy or PRV ≤54 Gy	0.03 cc ≤54 Gy	0.03 cc ≤56 Gy	≤ 50 Gy or PRV ≤55 Gy	≤54 Gy	≤60 Gy	≤54 Gy ≤60 Gy	Max ≤50 Gy
Temporal lobes	**1cc**	**Max**	**Max**		**0.03 cc**		**Max**	**Max**		**Max**	
	<65 Gy	≤72-75 Gy	60 Gy or ≤1% vol. >65 Gy	Not stated	<70 Gy	≤72 Gy	≤60 Gy or ≤1% vol. >65 Gy	≤60 Gy	≤65 Gy	≤60 Gy	Not stated
Mandible & TM joint	**≤1cc**		**≤1cc**	**≤1cc**	**0.03 cc**		**≤1cc**	**Max mandible**			**Max 0.1cc**
	>70 Gy	>75 Gy	>75 Gy or Max 70 Gy	>75 Gy or Max 70 Gy	≤70 Gy	≤75 Gy	>75 Gy or Max ≤70 Gy	≤70-73.5 Gy; ≤0.1cc joint > 70 Gy	≤75-77 Gy	Not stated	Joint ≤70 Gy; mandible ≤75 Gy
Brachial plexus	**≤1 cc**			**Max**	**0.03 cc**		**Max**	**Max**			**Max**
	>66 Gy		Not stated	≤66 Gy	<66 Gy	≤70 Gy	≤66 Gy	≤60 Gy	≤66 Gy	Not stated	≤63 Gy
Parotid glands (at least one gland)	**Mean of 1 gland**	**≥50% of 1 gland**	**Mean of 1 gland**	**Mean of 1 gland**	**Mean of 1 gland**		**Mean**	**Mean of 1 gland**	**≥60% of 1 gland**	**Mean**	**Mean of 1 gland**
	<26 Gy	<30 Gy	<26 Gy; ³50% of 1 gland <30 Gy; or ≥20cc of both glands <20 Gy	<26 Gy; or ³50% of 1 gland <30 Gy; or ≥20cc of both glands <20 Gy	<26 Gy	26–33 Gy	one gland: <20 Gy; both glands: <25 Gy	<26 Gy; or ³50% of 1 gland <30 Gy; or ³33% of contralateral gland <40 Gy	. <30 Gy	both glands: ≤26 Gy; contralateral gland: ≤20 Gy	<26 Gy; or ³50% of 1 gland <30 Gy; or ≥20cc of both glands <20 Gy
Parotid Gland (stem cell region)											

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Pituitary	**Max**					**Mean**	**Max**		**Mean**	
	≤60 Gy	≤65 Gy	Not stated	Not stated	Not stated	≤50 Gy	≤50 Gy		≤30 Gy	Not stated
Lens	**Max**			**Max**	**0.03 cc**	**Max**	**Max**			**Max**
	≤6 Gy	≤10 Gy	Not stated	< 25 Gy	<15 Gy	≤25 Gy	<4 Gy	<6 Gy	Not stated	≤5 Gy
Eyeball	**Max**	**Mean**	**Mean**	**Max**	**0.03 cc**	**Max**	**Retina - Max**		**Max**		**Max**
	≤50 Gy	<35 Gy	<35 Gy	<50 Gy	<55 Gy	≤50 Gy	≤54 Gy	≤60 Gy	Retina: ≤45 Gy; Other parts: ≤30 Gy	Retina: ≤50 Gy; Other parts: ≤35 Gy	≤50 Gy
Cochlea	**Mean**		**Mean**	**≤5% vol.**	**0.03 cc**	**Mean**	**Mean**		**Mean**		**Max**
	<50 Gy	≤55 Gy	<50 Gy	≥55 Gy	≤55 Gy	≤45 Gy	<50 Gy	<52.5 Gy	≤45 Gy or ≤5% vol. ≥55 Gy		≤45 Gy
Glottic larynx	**Mean**		**Mean**	**Mean**	**Mean**	**Mean**	**Max**		**Mean**		**Mean**
	<45 Gy		<45 Gy	<45 Gy	<40 Gy	≤45 Gy	supraglottis < 66 Gy; whole larynx: <50 Gy; or ≤25% vol.>50 Gy		≤44 Gy		≤45 Gy or ≤67% vol. >50 Gy
Post-cricoid pharynx, esophagus (within field)	**Mean**		**Mean**	**Mean**	**Mean**	**Mean**	**Max**		**Mean**		**Mean**
	<45 Gy		Not stated	<45 Gy	<50 Gy	≤45 Gy	Esophagus: ≤45 Gy; pharyngeal constrictor muscle: ≤50 Gy	Esophagus: <55 Gy	≤ 30 Gy		Esophagus: ≤45 Gy; pharyngeal constrictor muscle: ≤50 Gy
Oral cavity	**Mean**		**Max**	**Mean**	**Mean**	**Mean**			**Mean**		**Mean**

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(excluding PTV)	<40 Gy	<50 Gy	Tongue: <55 Gy or ≤ 1% vol. >65 Gy	<40 Gy	<40 Gy	Mean ≤40 Gy	Not stated	Not stated	≤30 Gy	≤40 Gy
Submandibular gland	Not stated		Not stated	Not stated	Not stated	Mean <35 Gy	Mean <35 Gy	Not stated	Mean <35 Gy	Not stated
Lips	Not stated		Not stated	Not stated	Not stated	Not stated	Not stated		Mean ≤20 Gy	Not stated
Thyroid										

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Organ at Risk (OAR)				Acceptance Criteria					
					Desirable Dose		Acceptable Dose		
Organ	**Priority**	**% Agree** (of those who voted)	**Disagree** (alternative priority) – Number voting	**Specification**	**Dose**	**% agree** (of those who voted)	**Dose**	**% agree** (of those who voted)	**GRADE of recommendation**
Brainstem	**1**	17/17 100%		**D0.03 cc**	≤54 Gy	18/20 90%	≤60 Gy#	19/21 90%	High/Moderate
Spinal cord	**1**	17/17 100%		**D0.03 cc**	≤45 Gy	20/20 100%	≤50 Gy	20/21 95%	High
Optic chiasm	**1**	16/17 94%	(3) – 1/17	**D0.03 cc**	≤54 Gy	14/15 93%	≤60 Gy	14/17 82%	High/Moderate
GTV-T & GTV-N	**2**	10/16 63%	(1) – 6/16	**Min**	≥68.6 Gy (98% dose)	14/18 78%	66.5 Gy (95% dose)	16/20 80%	Moderate
PTV dose prescription	**2**	15/17 88%	(1) – 1/17 (4) – 1/17	**Prescription dose**	PTV70, 63, 60, 56 = 35# PTV 69.96, 63, 60, 54 = 33#	17/21 81%			
PTV min	**2**	13/15 87%	(1) – 1/15 (4) – 1/15	**Min**	≥95% PTV 100% or ≥99% PTV ≥93% dose	19/20 95%	95% PTV ≥ 95% dose	18/20 90%	High / Moderate
PTV hotspot	**2**	14/15 93%	(4) – 1/15	**Max**	<5% PTV70 ≥ 75 Gy or ≤10% PTV70 ≥77 Gy	18/21 86%	<10% PTV70 ≥75 Gy or ≤20% PTV70 ≥77 Gy	18/20 90%	Moderate
Temporal lobe	**2**	11/17 65%	(1) – 1/17 (3) – 4/17 (5) – 1/17	**D0.03 cc**	≤65 Gy for early stage and ≤70 Gy for late stage	17/20 85%	≤72 Gy	13/21 62%	Moderate
Optic nerve	**3** **Bilateral: 1**	12/17 71%	(1) – 2/17 (2) – 2/17 (3) – 1/17	**D0.03 cc**	≤54 Gy	19/20 95%	≤60 Gy	21/22 95%	High / Moderate
Parotid gland	**4**	12/17 71%	(2) – 2/17 (3) – 2/17 (5) – 1/17	**Mean**	<26 Gy	18/20 90%	<30 Gy (at least one gland)	18/22 82%	Moderate

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Mandible & TM joint	**4**	14/17 82%	(3) – 2/17 (5) – 1/17	**D2%**	≤70 Gy	18/19 95%	≤75 Gy	14/21 67%	Moderate
Brachial plexus	**3**	13/15 87%	(2) – 1/15 (5) – 1/15	**D0.03 cc**	<66 Gy	16/18 89%	≤70 Gy	17/20 85%	Moderate
Pituitary (and hypothalamus)	**4**	11/14 79%	(2) – 1/14 (3) – 1/14 (5) – 1/14	**D0.03 cc**	≤60 Gy	11/14 79%	≤65 Gy	13/15 87%	Moderate / Low
Lens	**3**	12/17 71%	(1) – 1/17 (4) – 2/17 (5) – 2/17	**D0.03 cc**	≤6 Gy	18/20 90%	≤15 Gy	18/22 82%	Moderate
Eyeball	**3**	14/17 82%	(2) – 2/17 (4) – 1/17	**Mean**	<35 Gy	18/20 90%	≤50 Gy (**D0.03 cc**)	16/21 76%	Moderate
Cochlea	**4**	13/17 76%	(2) – 2/17 (3) – 2/17	**Mean**	≤45 Gy	18/20 90%	≤55 Gy	19/22 86%	Moderate
Glottic larynx	**4**	16/17 94%	(3) – 1/17	**Mean**	≤35 Gy	15/20 75%	≤50 Gy (**D2%**)	10/22 45%	Moderate
Post-cricoid pharynx, esophagus (within field)	**4**	13/17 76%	(3) – 2/17 (5) – 2/17	**Mean**	≤45 Gy	17/20 85%	≤55 Gy	14/22 64%	Moderate / Low
Oral cavity (excluding PTV)	**4**	13/17 76%	(3) – 2/17 (5) – 2/17	**Mean**	<40 Gy	14/20 70%	<50 Gy	17/22 77%	Moderate / Low
Submandibular gland	**4**	13/14 93%	(5) – 1/14	**Mean**	<35 Gy	17/21 81%			Moderate
Thyroid	**4**	12/14 86%	(3) – 1/14 (5) – 1/14		V_{50}<70%	14/16 88%	VS_{60}> 10cc	16/18 89%	Moderate / Low

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Table 2. OAR prioritization and Acceptance Criteria - final agreement results.

[#]A recent study by Huang et al [19] suggested D_{max} of 67.4 Gy (equivalent dose in 2-Gy fractions) as the dose constraint for brainstem. While this may be discussed as an option for patients with tumors encroaching the brainstem, a conservative dose acceptance criterion (to aim for a $D_{0.03\ cc}$ PRV dose ≤54 Gy and MAC of 60 Gy) was preferred among our panel (25/25 [100%] of those who responded to this special vote) for this general guideline till more robust validation become available.

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