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

Keywords

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

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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 setting dose prioritization and acceptance criteria for tumor volumes and organs at risk for Nasopharyngeal Carcinoma.

Abstract

Purpose

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

Methods

A literature search on doses and normal tissue complications following treatment for NPC was conducted. In addition, published guidelines/protocols on dose prioritization and constraints were reviewed. A preliminary proposal was circulated to a panel of international experts with publications and/or extensive experience in the field. Summary of the initial voting and different opinions expressed by members were circulated to the whole panel for review and re-consideration. Based on the comments exchanged, a refined second proposal was crafted and re-circulated to the same panel. The current consensus guideline was based on majority views following repeated iteration for final agreement.

Results

Variation in opinion among international experts were summarized and discussed to build a consensus guideline on appropriate dose prioritization and constraints. The percentage of final agreement on the recommended parameters and alternative views are shown. The rationale for the recommendations and the limitations of current evidence are discussed.

Conclusions

Through this comprehensive review of available evidence and interactive exchange of vast experience by international experts, this guideline is developed to provide a practical

reference for setting dose prioritization and acceptance criteria for tumor volumes and OAR. The final decision on the treatment prescription should be based on individual clinical situations and patient's acceptance for optimal balance of risk and benefit.

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 radio-sensitive, 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].

Enhancing our knowledge on the appropriate delineation of tumour targets for different dose levels; setting dose prioritization for tumour targets and the various OARs; and setting the acceptance criteria for each parameter are fundamental. 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 this sharing of experience and building of consensus amongst international experts, we hope to provide clinicians with a reference tool in the treatment planning for NPC.

Twenty-six contributors from major centres in Asia, Australia, North America, Middle East and Europe have resulted in the publication of "xxxx" [4]. Continuing with this concerted effort, we propose this guideline for setting dose prioritisation and acceptance criteria for tumour targets and various OARs. Our goal is to provide a practical reference to assist clinicians in deciding on the optimal RT plan for NPC and the best possible compromise for difficult cases.

Methodology

The following processes were used for evidence searching and consensus building:
Firstly, a literature search was performed via Pubmed (the search terms include IMRT, nasopharyngeal, late toxicity, temporal lobe, brainstem, visual, optic, eye, hearing and ear); and published treatment guidelines / dose constraints by various centres were summarized and compared [5-18]. A preliminary proposal on 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 formed to develop the guideline. To ensure appropriate recommendation with international representation, criteria were set to include only members with publications on treatment outcome (tumour control and toxicity), and/or extensive experience specific on NPC/head and neck cancers 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 consensus building: the preliminary proposal, together with the published guidelines/protocols (Table 1), was circulated among international experts for initial voting and comments. The 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 expressed by members were circulated to the whole panel for review and re-consideration. Based on the exchanged comments, a refined second proposal was drafted and circulated. The

current consensus guideline summarized in Table 2 was based on majority views after repeated iteration among the panel members.

The strength of our recommendations was gauged using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as shown in Table 3 [19]. The evidence on dose constraints was largely based on 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.

Finally, an additional Pubmed search was carried out in preparation of this manuscript to account for latest publications on NPC related late complications. The purpose is to see if it is consistent with the current recommendations.
(Supplementary Appendix 1: New papers reviewed)

Results and Discussion on the Recommendations

Before proceeding to setting dose prioritization and constraints, appropriate contouring of various structures is the first fundamental requirement. International consensus guideline on contouring of clinical tumour target volume has been published by our group [4]. Many authors in the current guideline have also participated in the development of the guideline on contouring of organs at risk specifically for NPC [20] and head and neck cancers [21]. We also recommend that a planning risk volume (PRV) to be delineated around these 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 [22].

Prioritisation of dose constraints

A recent study by Yao et al [23] 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 situation in which a trade-off must be made, more than 90% of the expert panel agree that 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 for induction chemotherapy. A recent randomized study by Yang et al suggests that this strategy of restricting the full therapeutic dose to the post-induction chemotherapy MRI volume, but ensuring that the pre-induction chemotherapy volume will receive at least an intermediate dose (64 Gy) appears not to compromise 3-year local, regional and distant control as well as overall survival but served to reduce late toxicities and overall health status in this cohort of 212 NPC patients [24]. Whether these results will continue to hold should an even lower dose be used (say to meet the 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 in 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 could then 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. [25] 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 might also want to avail themselves to the DAHANCA Radiotherapy Guidelines 2013 [14]. DAHANCA has a long history of 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 is also some difference in their priority listing, and they rank PTV coverage lower than critical serial OAR, to allow compromises where the margins are tight.

The Aimed Dose and the Acceptance Criteria for different structures

Brainstem

The QUANTEC review [26] 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 recent studies have been reported with prescribed brainstem dose higher than that recommended by QUANTEC. The study (n=1544) by Li et al. [27] 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 V55 ≥3.8 cc. In the study reported by Yao et al. [28], an alarming incidence rate of 2.8% at 5 years was noted in a cohort of 327 NPC patients. Among the 8 patients with brainstem injury, seven of them (one fatal and one hemiplegic) had Dmax and D0.1cc ≥ 63.38 Gy and 60.89 Gy, respectively. The volume of brainstem with high dose is important: Uy et al. [29] reported a case of

brainstem necrosis with a V54 of 4.7 cc. Debus et al. [30] showed that a V50 >5.9 cc, V55 >2.7 cc, and V60 >0.9 cc were associated with brainstem toxicity. Schoenfeld et al. [31] further recommended to restrict the V55 to <0.1 cc.

In view of potential medico-legal implication with brainstem injury, a conservative dose acceptance criterion is preferred among our panel. Our final recommendation is to aim for a $D_{0.03\ cc}$ PRV dose ≤54 Gy and MAC of 60 Gy.

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

Spinal cord
The QUANTEC review [32] 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 is to aim at a $D_{0.03\ cc}$ PRV dose ≤45 Gy and MAC ≤50 Gy.

Level of consensus: 100% (20 of 20 voters) agree on desirable dose, 95% (20 of 21 voters) agree on MAC (alternative suggestion up to 55 Gy).
GRADE of recommendation: High

Optic chiasm and optic nerve
The QUANTEC review [33] suggests that the incidence of radiation-induced optic neuropathy (RION) was unusual for a Dmax <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. [34], 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, 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 radio-sensitivities were different. However, we suggest separate considerations for according Priority levels as discussed above. Our final recommendation is to aim at a D0.03 cc PRV dose ≤54 Gy and MAC of ≤60 Gy, for both structures.

Level of consensus: 93% (14 of 15 voters) agree on desirable dose for the optic chiasm and optic nerve, respectively (alternative suggestion is 50 Gy). For the recommended MAC, the agreements among the panel were 82% (14 of 17 voters) and 95% for optic chiasm (alternative suggestion ranging from 54-56 Gy) and optic nerve (alternative suggestion 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 is 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 consensus: 78% (14 of 18 voters) agree on desirable dose (alternative suggestion ranged from 66-70 Gy); 80% (16 of 20 voters) agree on acceptable dose.
GRADE of recommendation: Moderate

Planning target volume (PTV):
Dose prescription at 3-4 levels at conventional fractionation was agreed by 73%, while 18% would prescribe at 2 dose levels only. As discussed in our previous guideline on contouring of CTV [4], we recommend three levels of dose prescription in line with the general principle by 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 fractions (2 Gy per fraction) scheme with

the doses prescribed to 70, 63-60 and 56 Gy; or the 33 fractions (2.12 Gy per fraction) scheme with the doses prescribed to 69.96, 63-60, 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 fractions. [35]

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 also acknowledge that there is an increasing tendency of accepting higher dose heterogeneity and "hot spot" doses to ensure better dose conformality as suggested by the ICRU 83 report [36] or even deliberately giving a higher dose (80 Gy) to certain region of GTV as a means of dose escalation/dose redistribution according to the tumor behavior on molecular imaging [37]; but 15% of panel members recommend 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 consensus:

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

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

Temporal lobe:

The QUANTEC review [38] showed that for conventional fractionation with doses ≤2 Gy, a 5% risk of symptomatic radiation necrosis is predicted to occur at 72 Gy equivalent (range, 60–84); furthermore, they cautioned that the brain is especially sensitive to fraction sizes >2 Gy. Due to the close proximity of temporal lobe 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. [39] reported that a D0.5cc of 69 Gy may be the dose tolerance of the temporal lobe. However, subsequent studies suggested lower dose equivalents of 60.3 Gy (D2cc) [40], 62.8 Gy (D1cc) [6, 41] and 69 Gy (Dmax) [41] (at 2 Gy/fraction) for a 5% probability of developing temporal lobe injury at 5 years. These findings concurred with study reported by Su et al. [42], the probability of temporal lobe injury was ≤5% at 5 years if D1cc was less than 58 Gy; and Dmax was less than 68 Gy. Furthermore, 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 locally advanced tumor, a reasonable balance between adequate tumor coverage and risk of temporal lobe injury is needed; and dose limit of D1cc ≤ 71.14 Gy [43] and Dmax ≤72 Gy [1] have been suggested for T4 disease.

Our final recommendation is 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 D1cc may be a better parameter for future studies.

Level of consensus: 85% (17 of 20 voters) agree on desirable dose (alternative suggestion ranging from 66-70 Gy irrespective of the tumour stage); 62% (13 of 21 voters) agree on MAC dose for T3-4 tumors (alternative suggestion 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 [44, 45]. 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 [45]. Chen et al. showed that the incidence of brachial plexopathy increased dramatically when V70 exceeds 10% [46]. 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 restraints when the brachial plexus was not outlined [47]. Placing dose constraints on the brachial plexus can significantly decrease the irradiated volume and dose, without compromising adequate dose delivery to the target volume [48].

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 consensus: 89% (16 of 18 voters) agree on desirable dose (alternative suggestion ≤ 60 Gy); 85% (17 of 20 voters) agree on acceptable dose (alternative suggestion was ≤ 66 Gy). GRADE of recommendation: Moderate

Eyeball and lens:

Jeganathan and colleagues provide an excellent review of ocular risks from orbital and periorbital irradiation [49].

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

Level of consensus:

- Eyeball: 90% (18 of 20 voters) agree on desirable dose (alternative suggestion ranged from 25-45 Gy); 76% (16 of 21 voters) agree on acceptable dose (alternative suggestion ranged from 40-60 Gy).
- Lens: 90% (18 of 20 voters) agree on desirable dose, 82% (18 of 22 voters) agree on acceptable dose

GRADE of recommendation: Moderate

Pituitary (and hypothalamus) and thyroid glands:

Even in the IMRT era, it had been reported that a significant number of patients, ranging from 20 – 50%, developed some element of endocrine deficiency post-RT [50-55]. 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 relatively easy. 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 V50 ≤60%, based on the study by Sachdev et al. (55); and MAC as V60 ≤10 cc.

Level of consensus:

- Pituitary: 79% (11 of 14 voters) agree on desirable dose (alternative suggestion ranged from 40-54Gy); 87% (13 of 15 voters) agree on acceptable dose
- Thyroid: 88% (14 of 16 voters) agree on desirable dose (alternative suggestion $D_{0.03cc}$ ≤45 Gy or D_{mean} ≤50 Gy); 89% (16 of 18 voters) agree on acceptable dose (alternative suggestion $D_{0.03cc}$ 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 this modern era, and especially for those treated with additional cisplatin-based chemotherapy. QUANTEC review [56] 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. [57] 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 chemo-radiotherapy. Similar findings have been reported by Wang et al. [58], with an accumulative cisplatin dose of ≥ 200mg/m2 and radiation dose of 40Gy to 0.1ml cochlea being predictive factors for the development of SNHL.

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

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

Parotid gland:

QUANTEC [59] 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. [60] concurred that with this dose constraint, less than 33% of patients had xerostomia at 3 months and none 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. [61] reported that partial volume thresholds for prediction of reduced salivary flow were 67%, 45%, and 24% gland volumes receiving more than 15Gy, 30Gy, and 45Gy, 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 <26Gy and MAC <30 Gy for ≥50% of at least 1 gland

Level of consensus: 90% (18 of 20 voters) agree on desirable dose (alternative suggestion being mean dose < 25Gy); 82% (18 of 22 voters) agree on acceptable dose panel (alternative suggestion ranged from mean dose ≤25-35Gy).
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. [62] 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 [63]. Similarly, Gomez et al. reported that no patients developed ORN using the dose constraint of Dmax ≤70 Gy. [64] 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 V44 <42% and V58 <25% to the mandible as reasonable DVH constraints for IMRT plan acceptability, when tumour coverage was not compromised [65].

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

Level of consensus: 95% (18 of 19 voters) agree on desirable dose, 67% (14 of 21 voters) agree on acceptable dose (alternative suggestion ranging narrowly from 73-77Gy).

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. [66] found that concurrent chemo-radiotherapy 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. [67] 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 ≤50Gy.

Level of consensus: 70% (14 of 20 voters) agree on desirable dose (alternative suggestion ranged from 35-45 Gy); 77% (17 of 22 voters) agree on acceptable dose (alternative suggestion 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 [68]. While study by Feng et al. [69] 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 (V65 >50%), multiple series have reported a steeper dose effect relationship starting beyond 45 Gy to the pharyngeal wall. [70-72] Levendag et al. [73] showed a mean dose of 50 Gy predicted a 20% probability of late dysphagia; this probability increased sharply when mean dose > 55 Gy with the chance of dysphagia increase by 19% with every additional 10 Gy. QUANTEC [74] 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 recommend to aim for a D_{mean} ≤45 Gy, and MAC ≤55 Gy,

Level of consensus: 85% (17 of 20 voters) agree on desirable dose (alternative suggestion ranged from 35-50 Gy); 64% (14 of 22 voters) agree on acceptable dose (alternative suggestions ranged widely from 45-70 Gy).
GRADE of recommendation: Moderate/Low

Larynx:
The study by Vainshtein et al. [75] 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. [76] 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.

Initially, we recommended aiming for a 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.

For the panellists who were used to lower neck and supraclavicular fields matched to the IMRT fields (which effectively shielded the larynx), their recommendation was to restrict the glottic dose to less than 35Gy, which they felt was achievable even for plans utilising a single IMRT field. In a study on oropharyngeal cancers not extending to the larynx, a mean dose of 29Gy was achievable [77]. Whilst this was the only OAR that we failed to achieve > 50% consensus, we acknowledge that attempts should always be made to minimize its mean dose to less than 35Gy.

Level of consensus: 45% (9 of 20 voters) agree on desirable dose (alternative suggestion

aiming at a lower dose of ≤40 Gy); 45% (10 of 22 voters) agree on acceptable dose
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. [78] 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. [79] found that the dose tolerance of submandibular gland leading to 50% complication risk at 1 year was 36Gy with a 2-2.5% reduction in the probability of severe xerostomia for every 1 Gy reduction in mean dose. QUANTEC [59] recommends that submandibular gland sparing to modest mean doses (<35 Gy) might reduce xerostomia symptoms.

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

Level of consensus: 81% (17 of 21 voters) agree on desirable dose (alternative suggestion a higher dose of < 39Gy).
GRADE of recommendation: Moderate

Other structures

Carotid vessels:

Chu et al. [80] 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, higher risk of carotid artery stenosis following RT for NPC has been reported [81-84]. 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.

Conclusions

This guideline is derived through extensive review of currently available evidence for setting dose prioritization and acceptance criteria to the tumour volumes and OARs, along with interactive exchange of opinion from an international expert panel on best practice recommendations.

When the initial suggestion was circulated among the expert panellists, the initial agreement was low on some parameters, e.g. the doses for the larynx and the thyroid. There seems to be a clear dichotomy between east and west, with Asian experts tending to accept higher doses. Although differences of opinion always exist, through iterative discussion and revision of the initial controversial parameters, majority views are summarized to come up with a final recommendation 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, the final decision on optimal balance risk and best possible compromise should take into consideration individual clinical situation and the patient's preferences. Multi-center collaboration to accumulate more accurate data on radiation factors affecting therapeutic ratio, identification of clinical and molecular/genetic factors for prediction of sensitivity/resistance, and prospective studies to cautiously explore different dose constraints are keenly awaited.

Supplementary Material (Appendix)

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

Supplementary Appendix 1: New papers reviewed

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