CENTER FOR CLINICAL GUIDELINES | CANCER

Radiotherapy Guidelines 2025
Danish Head and Neck Cancer group

Version 2.0

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Head and neck cancer, radiotherapy, quality assurance

Revisions to previous version (changelog)

An overview of the changes in the different editions of this guideline can be found in appendix 3.

Revisions to version 1.0

Guideline chapter	Description of revisions or additions
Purpose	In the present 2025 guidelines the following issues are included: Constraints for hypofractionation, planning of reirradiation, target definition after induction chemotherapy, planning of complex target, and clarification of the guidelines for elective targets. The chapter of unknown primary tumours are updated and rewritten.

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1. Recommendations English (Quick guide)

Target delineation (GTV)

1. **All steps in immobilisation, scanning, image reconstruction, image transfer and co-registration should be quality assured (D)**

2. **All scans used for target delineation in radical radiotherapy should be less than 3 weeks old (D)**

3. **The responsible oncologist should take part in all parts of the target definition in complex cases (D)**

Planning CT

4. **A planning CT scan of optimal quality with the use of metal artefact reduction should be acquired with a maximal slice thickness of 2 mm (D)**

Recommended MRI sequences for delineation

5. **MRI sequences for target delineation should be T1 with and without contrast + T2 with and without fat suppression (STIR/ Dixon) (D)**

PET-CT

6. **The procedures related to PET/CT should follow EANM guidelines from 2015 (D)**

Pharynx and oral cavity

7. **PET-CT and MRI should be used for target delineation of cancers in the pharynx and oral cavity. Areas of special attention are perineural invasion, bone and skull base invasion (D)**

Larynx

8. **PET-CT and MRI should be used for target delineation of cancers in the larynx (D)**

9. **In case of tumours not visible on the diagnostic scans (e.g. T1N0 larynx cancer), PET and MRI are not indicated (D)**

10. **Examination in general anaesthesia, drawings or photos should be used for the delineation of superficially spreading tumours (D)**

Cancer of nasal cavity, paranasal sinuses and the salivary glands

11. **PET-CT and MRI should be used for target delineation of sinonasal and salivary gland cancers (D)**

Nodal metastases

12. **The choice of imaging modality follows the primary tumour. In case of unknown primary, it follows either the guidelines for post-operative radiotherapy (MRI only) or radical radiotherapy (PET-CT + MRI) (D)**

Post-operative radiotherapy

13. **The indication for postoperative radiotherapy is decided at a multidisciplinary team conference (D)**

14. **All cases of T3/T4, ENE, high risk histology and non-radical surgery, must be discussed at the multidisciplinary team conference (D)**

Target definition

15. **For postoperative radiotherapy, all available information must be used for target delineation (D)**

16. **Optimal naming and marking of the surgical specimen are essential for optimal delineation of e.g. extranodal extension (ENE) or R1 resections (D)**

17. **Complicated targets should be defined with the operating surgeon (D)**

Imaging

18. **MRI should be used for target delineation in post-operative radiotherapy, except when there was no visible pre-operative target and no reconstruction, e.g. T1 glottic larynx (D)**

19. **There is no indication for PET-CT in immediate post-operative radiotherapy, unless macroscopic tumour is suspected, or the neck needs evaluation (D)**

Definition of volumes beyond the GTV

20. **The nomenclature of volumes by the ICRU should be applied, and the definitions of nodal levels according to international consensus guidelines should be followed (D)**

DAHANCA principles for target delineation

21. CTV1 includes GTV with 5 mm geometric margin, modified for natural borders for tumour spread (D)

22. CTV2 includes GTV with 10 mm geometric margin, modified for natural borders for tumour spread (D)

23. CTV3 includes CTV2 and elective areas (D)

GTV and CTV in postoperative radiotherapy

24. CTV1 includes the pre-operative non-radical operated tumour (R1 or R2) with an isotropic margin of 5 mm modified for barriers for tumour spread (D)

25. CTV2 includes preoperative GTV with 10 mm margin modified for barriers for tumour spread (D)

26. CTV3 includes CTV2, surgical bed and elective volumes (D)

GTV and CTV in radiotherapy after induction chemotherapy (nasopharynx, sinonasal cancer)

27. After induction chemotherapy, the actual target may be delineated. It should be considered to include, pre-chemotherapy involved volumes especially concerning bone, skull base and involved sinuses (B)

Normal tissues

28. The nomenclature (D), dose-volume constraints (C), and definition of volumes (D) should follow the guidelines of Table 1 and Appendix 1.

Cumulated treatment plan for evaluation and planning of re-irradiation

29. A cumulated treatment plan, even corrected for recovery and fractionation, may be beneficial for the planning of re-treatment, but physical and biological uncertainties should be considered (D)

Radiotherapy dose planning

30. Dose planning should attempt to comply with the tolerance levels for target-coverage and normal tissue sparing described in Table 2 (D)

Radiotherapy quality assurance

31. Dose planning should strive to achieve the tolerances for target-coverage and normal tissue sparing mentioned in table 2 (D)

2. Introduction

Head and neck cancer is a heterogeneous group of cancers located between the base of scull and the clavicles. The anatomical region is characterized by an abundance of critical normal structures, important for senses, appearance, breathing, communication, and eating. The population of patients with head and neck cancer varies with a large proportion of patients having a smoking-induced cancer, and thus, a high risk of co-morbidity and socio-economic problems. The number of patients with head and neck cancer is slightly increasing due to an increase in the number of HPV-induced oropharyngeal cancers. In 2022, 852 patients received radiotherapy for head and neck cancer with curative intend (annual report 2022of the Danish Head and Neck Cancer Group, DAHANCA). Unfortunately, radiotherapy often leads to severe acute and late side effects. Both side effects and the chance of cure are very dependent on the quality of radiotherapy. DAHANCA has a long-standing tradition for conducting clinical trials as well as establishing national guidelines for radiotherapy for head and neck cancer to improve outcome. DAHANCA guidelines and treatment recommendations have been applied worldwide.

The evidence for the recommendations is scarce and based on indirect conclusions from retrospective studies modelling the risk of side effects and likelihood of loco-regional tumour control, as well as technical studies on the inaccuracies of radiation equipment and uncertainties in treatment setup. Nevertheless, the recommendations for adhering to the guidelines is strong as the possibility to evaluate the treatment quality on a national level depends on the consistency of the treatment. Overall, the guideline is a product of discussions within in the DAHANCA radiotherapy quality assurance group and endorsed by DAHANCA (Level 5 evidence). When nothing else is mentioned, this forms the evidence of the guidelines, and specific literature review is not included in the chapters which may be characterized as a “cookbook”.
Nevertheless, DAHANCA is very concerned about adherence to the guidelines and has evaluated the clinical consequences. DAHANCA has thoroughly analysed and reported on these issues (1-3).
As mentioned, several international groups have evaluated previous editions of the present guidelines and thereby produced new recommendations (4, 5). These guidelines have, in turn, to some extent been incorporated into the present edition.

High quality radiotherapy is to a large extent driven by development in equipment and software technology and is as such a very dynamic field. The need for research, quality assurance, and evaluation of new techniques is therefore a continuous process that continuously must be implemented via endorsed national clinical guidelines to ensure equal and high levels of treatment quality.

Objective

The overall objective of this guideline is to support high quality cancer care across the Danish healthcare system.
The specific objective of the present guidelines is to secure a high and consistent quality of radiotherapy for patients with head and neck cancer. To increase the quality of care, both within and outside of clinical protocols, we strive for a high degree of consistency and adherence to guidelines.

Patient population

Radiotherapy for all patients with head and neck cancer can be planned according to the principles of the guidelines.

Target users

This guideline is developed to support clinical decision-making and quality improvement. Thus, the target users are healthcare professionals working in Danish cancer care. The guidelines are applicable to all treatments in the head and neck area and should serve as a guideline for radiotherapy at all Danish centres treating head and neck cancer patients. They are applicable for the whole process of radiotherapy from scanning, target delineation, dose planning, and evaluation and quality assurance and should therefore guide both physicians and physicists involved in radiotherapy for head and neck cancer.

3. Scientific basis

Target delineation (GTV)

To cure a patient, one must ensure that all clonogenic cells receive a tumoricidal dose. I.e. that the target is covered by a relevant dose. Tumour deposits can be seen far from the bulk of disease, i.e. in lymph nodes or via perineural spread. These deposits will not be covered by the clinical target volumes irrespectively of the GTV to CTV margin size. Utmost care must therefore be put into the delineation of the GTV, and all available information must be used. According to the ICRU 83, the GTV is the gross demonstrable extent and location of the tumour. All examinations and imaging modalities which provide information on the extent and location of the tumour should be used, e.g. clinical examination, anatomic imaging and functional imaging.

1. **All steps in immobilisation, scanning, image reconstruction, image transfer and co-registration should be quality assured (D)**

2. **All scans used for target delineation in radical radiotherapy should be less than 3 weeks old (D)**

3. **The responsible oncologist should take part in all parts of the target definition in complex cases (D)**

The extent of disease outside what is defined as GTV with the available information can be evaluated by four distinctly different methods, that supplement each other: 1) Pathology examination of surgical specimens, e.g. (6-9). 2) evaluating the macroscopic tumour extent on surgical specimens with respect to different imaging modalities e.g. (10-13)3) Evaluating the recurrence pattern with respect to target definition and dosimetry (1, 14-18), and finally 4) Evaluating tumour spread on imaging and from that inferring frequent routes of progression (19, 20) . With the available evidence, it is not obvious that geographical miss is the dominant problem on a population basis. This is important to keep in mind when margins are discussed. Larger treatment volumes may prohibit treatment intensification or reduce compliance due to side effects (1, 21). Nevertheless, optimal GTV definition remains critical for optimal radiotherapy of the individual patient.

In radiotherapy, the planning CT is the reference imaging, as this is the basis for correct dose planning and treatment setup. Information from other scans must therefore be evaluated with respect to anatomical and geographical precision. That is, co-registration must be evaluated regardless of whether it is performed rigidly or deformable.
Imaging acquired in non-treatment position, e.g. diagnostic MRI or PET-CT scans, can be used for target delineation. The scans should not be more than 3 weeks old (consensus), otherwise they must be repeated or used with extreme caution.

Ideally, the same oncologist should be involved in the entire patient trajectory, from staging at the MDT to patient information and discussion of expected and accepted side effects to target definition. This is especially important in case of advanced disease or potentially serious side effects, e.g. double-sided blindness or brainstem injury.

Planning CT

4. A planning CT scan of optimal quality with the use of metal artefact reduction should be acquired with a maximal slice thickness of 2 mm (D)

The optimal scan quality of the CT is important and metal artefact reduction should be used (22). Slice thickness should not be larger than 2 mm. Intra-venous contrast should be used for nodal evaluation, if an MRI in treatment position is not available. Field of view settings and pixel size should be evaluated as these can potentially change margins. On board imaging (CBCT, virtual CT) may be used for replanning in photon radiotherapy, if appropriately validated and continuously quality assured.

Recommended MRI sequences for delineation

5. MRI sequences for target delineation should be T1 with and without contrast + T2 with and without fat suppression (STIR/ Dixon) (D)

The recommended MRI sequences should be optimized to the local hardware such as scanner and coils. Priorities should be geometric stability, image quality, patient convenience and scanning in treatment position i.e. in immobilisation as well as resources. If available, 3D scans should be considered for geometric stability, but it will often be necessary to add axial scans for optimal image quality. Sequences optimized for image quality only, can lead to serious geometric distortions (23).The recommended sequences are T1 with and without contrast + T2 with and without fat suppression (STIR/ Dixon). Adding fat suppression sequences to T1 with contrast is recommended in cases of suspected intracranial or intraorbital spread. Diffusion weighted imaging including ADC maps may be added. The order of sequences should be prioritized so that the most important sequences are done first in case the patient tolerates the scanning poorly (e.g.: T1, T1+contrast, T2, DWI).

PET-CT

6. The procedures related to PET/CT should follow EANM guidelines from 2015 (D)

Whole body PET-CT scans can be used to detect distant metastasis or other primaries. In case the patient has been evaluated with 3D imaging below the clavicles, the PET-CT scan area for treatment planning does not need to be as large. Metal artefact reduction algorithms should be used, especially if the CT is used as the

planning CT and not only for attenuation correction. A flat table couch and an immobilisation mask should ideally be used (24).

A nuclear medicine specialist, a radiologist and an oncologist should participate in the target delineation process, ideally at a multidisciplinary team conference with the purpose of target evaluation.

Nuclear medicine specialists and the radiologist (25-27) create a written description of the target, and this is stored together with the images in RIS/PACS archiving system.

Pharynx and oral cavity

7. **PET-CT and MRI should be used for target delineation of cancers in the pharynx and oral cavity. Areas of special attention are perineural invasion, bone and skull base invasion (D)**

Larynx

8. **PET-CT and MRI should be used for target delineation of cancers in the larynx (D)**

9. **In case of tumours not visible on the diagnostic scans (e.g. T1N0 larynx cancer), PET and MRI are not indicated (D)**

10. **Examination in general anaesthesia, drawings or photos should be used for the delineation of superficially spreading tumours (D)**

Areas of special attention are cartilage invasion and superficially spreading tumours.

Cancer of nasal cavity, paranasal sinuses and the salivary glands

11. **PET-CT and MRI should be used for target delineation of sinonasal and salivary gland cancers (D)**

Areas of special attention are perineural invasion, bone, orbital and skull base invasion

Nodal metastases

12. **The choice of imaging modality follows the primary tumour. In case of unknown primary, it follows either the guidelines for post-operative radiotherapy (MRI only) or radical radiotherapy (PET-CT + MRI) (D)**

The normal anatomical nodal characteristics should be considered: small size, kidney or bean shape, presence of hilus, homogenous cortex and hilar vascularity. Some of these characteristics are superiorly assessed with ultrasound, which should be considered. Deviations from these characteristics should be considered an indication for malignancy.

The malignancy criterion concerning size is measured in the shortest axis (28). The sensitivity, using this criterion alone is not high, and the morphological criteria should be weighted as well (29):

- Neck nodes in general: 10 mm
- Angular nodes (upper jugulo-carotid): 11 mm (30)
- Retropharyngeal nodes: 6 mm.
- Using functional imaging, other malignancy criteria might be used.

Post-operative radiotherapy

13. The indication for postoperative radiotherapy is decided at a multidisciplinary team conference (D)

14. All cases of T3/T4, ENE, high risk histology and non-radical surgery, must be discussed at the multidisciplinary team conference (D)

Tasks to be clarified at the MDT conference

The indication for post-operative radiotherapy should be discussed at the multidisciplinary team (MDT) conference between the operating surgeon and an oncologist as soon as the final pathology report becomes available. Hereafter, the conclusion is presented to and discussed with the patient. Ideally, all post-operative cases should be discussed at the MDT with respect to the indication of postoperative radiotherapy. As a minimum, all cases of T3/T4, ENE, high risk histology and non-radical surgery must be discussed between an oncologist and a surgeon. Lack of information in the pathology report and e.g. ambiguous nomenclature of specimens and large specimens with several nodal levels are other issues that must be clarified at the MDT conference. The target should be described in the medical report from the MDT conference.

Target definition

15. For postoperative radiotherapy, all available information must be used for target delineation (D)

16. Optimal naming and marking of the surgical specimen are essential for optimal delineation of e.g. extranodal extension (ENE) or R1 resections (D)

17. Complicated targets should be defined with the operating surgeon (D)

Except in case of macroscopic non-radical surgery/ debulking surgery, there is no GTV in post-operative radiotherapy. Nevertheless, it is of advantage for accurate target delineation, that a pre-operative tumour volume (pre-operative GTV) can be defined (31). Furthermore, the surgical bed should be defined with optimal accuracy irrespective of any reconstruction. Any area of non-radical surgery should also be defined with optimal precision. With all these considerations in mind, it is strongly recommended that the operating surgeon takes part in the target delineation, as a minimum for complex cases. Post-operative oedema and altered

anatomy are typical issues that need special attention. The oncologist participating in the MDT conference and defining the target should be the same.

Other considerations for postoperative target delineation
To ensure optimal workflow and quality of the target definition, the operating surgeon should take preoperative photographs or make a tumour drawing, and make a thorough description of tumour extension, evaluated with the patient in general anaesthesia. Optimally, areas of anticipated narrow margins or e.g. ENE should be marked with surgical clips. Clips can also be used to mark the entire surgical bed (32).

Imaging

18. MRI should be used for target delineation in post-operative radiotherapy, except when there was no visible pre-operative target and no reconstruction, e.g. T1 glottic larynx (D)

19. There is no indication for PET-CT in immediate post-operative radiotherapy, unless macroscopic tumour is suspected, or the neck needs evaluation (D)

MRI has superior soft-tissue contrast that can be utilized to delineate the surgical bed. Furthermore, MRI for target delineation allows for comparison with pre-operative MRIs.

Literature and evidence review
The evidence is sparse, and the recommendations are based on consensus or other guidelines

Patient values and preferences
Not relevant.

Rationale
Optimal delineation of the target is essential for high quality radiotherapy. All errors in this part of planning will result in systematic errors and therefore inferior-quality radiotherapy.

Comments and considerations
The guidelines for GTV delineation have (January 2020) been discussed among the DAHANACA Radiotherapy Quality Assurance group and imaging specialist from all centres. The present guidelines is the result of these discussions and will provide us with an opportunity to evaluate target delineation on a national level in the future.

Definition of volumes beyond the GTV

20. The nomenclature of volumes by the ICRU should be applied, and the definitions of nodal levels according to international consensus guidelines should be followed (D)

Literature and evidence review

Clinical target volumes (CTVs) and organs at risk (OARs) must be defined in the dose planning system for CT-based radiotherapy. The terminology for these volumes is defined by the ICRU. The relevant editions are ICRU 50 (1993), ICRU 62 (1999) and ICRU 83 (2010). The definitions in ICRU 83 and ICRU 62 are the same, but in the latter edition, the 'Remaining volume at risk' (RVR) – defined as CTV + OAR subtracted from the patient contour – is reported as an important volume for IMRT dose planning in order to avoid high dose areas outside the targets and to avoid unexpected late morbidity, including secondary cancer. The use of an internal margin in head and neck cancer radiotherapy is considered irrelevant according to ICRU 83 as a defined volume, but the internal margin should be included in the CTV.

Definition of volumes according to ICRU

1. GTV = gross tumour volume includes all verified tumour extensions from clinical examinations and all available scanning modalities. Other volumes such as ”GTV_preop”, ”GTV_MR” or ”GTV_PET” may be defined.
2. CTV = clinical target volume includes GTV if present and subclinical tumour extension to the vicinity of the primary or lymph nodes. The CTV should also include a margin for internal changes and uncertainties e.g. shape, size and organ movement (rarely relevant for head and neck radiotherapy).
3. PTV = planning target volume is a geometrical volume defined to secure dose delivery to the CTV. The PTV includes uncertainties related to dose delivery including setup and mechanical uncertainties. The size of the PTV-margin is dependent on systematic and random uncertainties related to a specific treatment technique, local quality assurance and other specific local dependent factors. It should ideally be defined based on local measurements. The size of the PTV is generally defined by adding the square of the single independent uncertainties (ICRU 62). Note: PTV is not used for proton therapy. See the chapter on proton therapy.
4. OAR = organ at risk
5. PRV = planning risk volume = OAR + margin for internal movements and setup margin as described above. The PRV is mainly relevant for serially organized and small OAR volumes (lacrimal glands).
6. RVR = remaining volume at risk = CTV and OAR subtracted from the total patient volume
7. TV = treated volume = the volume receiving the prescribed dose.
8. IV = irradiated volume = volume receiving a dose relevant for normal tissue effects

DAHANCA principles for target delineation

21. CTV1 includes GTV with 5 mm geometric margin, modified for natural borders for tumour spread (D)

22. CTV2 includes GTV with 10 mm geometric margin, modified for natural borders for tumour spread (D)

23. CTV3 includes CTV2 and elective areas (D)

DAHANCA uses the following volumes and definitions for radiotherapy: GTV is delineated based on examinations, imaging, pathology reports, drawings and other information. Elective regions are selected based on estimations of the risk of subclinical spread. There are two elective risk levels: high risk (CTV2) and low risk (CTV3). Low risk is defined as elective nodal regions with a risk for subclinical spread of at least 10%. The risk estimations, and thereby the recommended elective regions, are significantly different between the N0 and N+ neck.
When air is removed from the CTV (see below), it should also be removed from within the CTV, e.g. in the pharynx or paranasal sinuses, in order to improve optimization and reporting of dose.

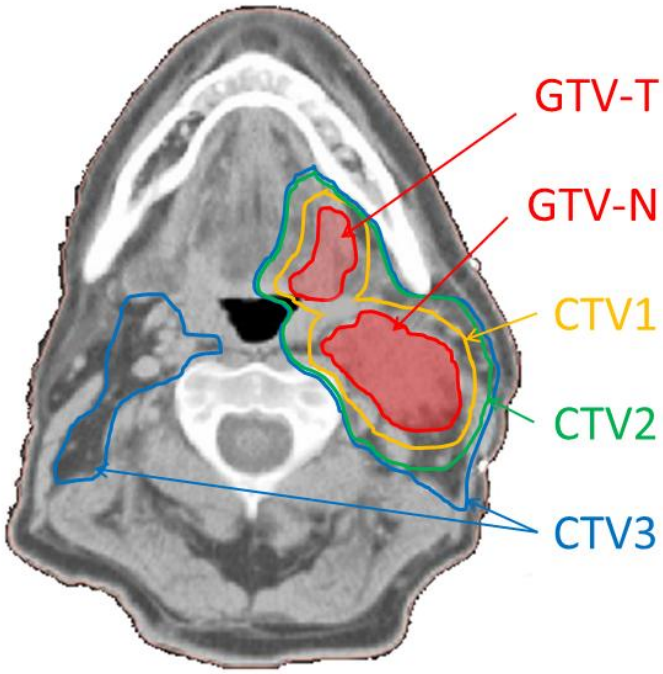


Figure 1. Principles for target delineation and nomenclature

GTV and CTV in radical radiotherapy
GTV: Gross tumour in both T (GTV-T) and N (GTV-N) site evaluated by clinical examination and imaging.

CTV1*:* Includes the primary tumour (GTV-T) and involved nodes (GTV-N) with an isotropic margin of 5 mm, though larger if the tumour is poorly defined and smaller if the margin extends into air, uninvolved bone or other natural borders for tumour spread. That is, uninvolved bone is not included in the CTV1.

CTV2: Includes CTV1 and the surrounding volume outside CTV1 with the highest risk of subclinical tumour extension. It is defined as GTV with an isotropic margin of 10 mm. The margin may be less if it extends into air or surpasses natural borders such as bone. Furthermore, a disease-specific high-risk anatomical region could be added. See the guidelines for the specific regions for details.

CTV3: Contains CTV2 and regional elective lymph nodes without margin. The CTV3 definition is highly dependent on nodal status. N0 and N+ are treated as recommended in Grégoire 2014 (33), respectively. For N+ patients, the elective nodal regions are extended 2 cm cranially and caudally from any pathological lymph nodes (GTV-N). The sternocleidomastoid muscle is included 2 cm above and below any pathological node GTV in case of suspected muscle involvement. In some regions, the Gregoire 2014 guidelines are ambiguous, and we have therefore produced a set of clarifying comments to the guidelines (Appendix 4).

GTV and CTV in postoperative radiotherapy

24. CTV1 includes the pre-operative non-radical operated tumour (R1 or R2) with an isotropic margin of 5 mm modified for barriers for tumour spread (D)

25. CTV2 includes preoperative GTV with 10 mm margin modified for barriers for tumour spread (D)

26. CTV3 includes CTV2, surgical bed and elective volumes (D)

Preoperative-GTV: As defined from pre-operative clinical examination and imaging (See above).
In case of reconstruction with a flap: It is uncertain if the flap should be a part of the target. Recurrences within the flap are rare (34)

CTV1*:* Includes the pre-operative non-radically operated tumour (R1 or R2) with an isotropic margin of 5 mm, though larger if the tumour is poorly defined and smaller if the margin extends into air, uninvolved bone or other natural borders for tumour spread. That is, uninvolved bone is not included in the CTV1.

CTV2: After R0 resection, CTV2 includes the preoperative GTV with an isotropic 10 mm margin. In case of non-radical resection, the CTV2 includes CTV1 with 5 mm margin. The margin may be larger in case of poorly defined tumour and less if it extends into air or surpasses natural borders such as bone. Furthermore, a disease specific high-risk anatomical region could be added. See the guidelines for the specific regions for details.

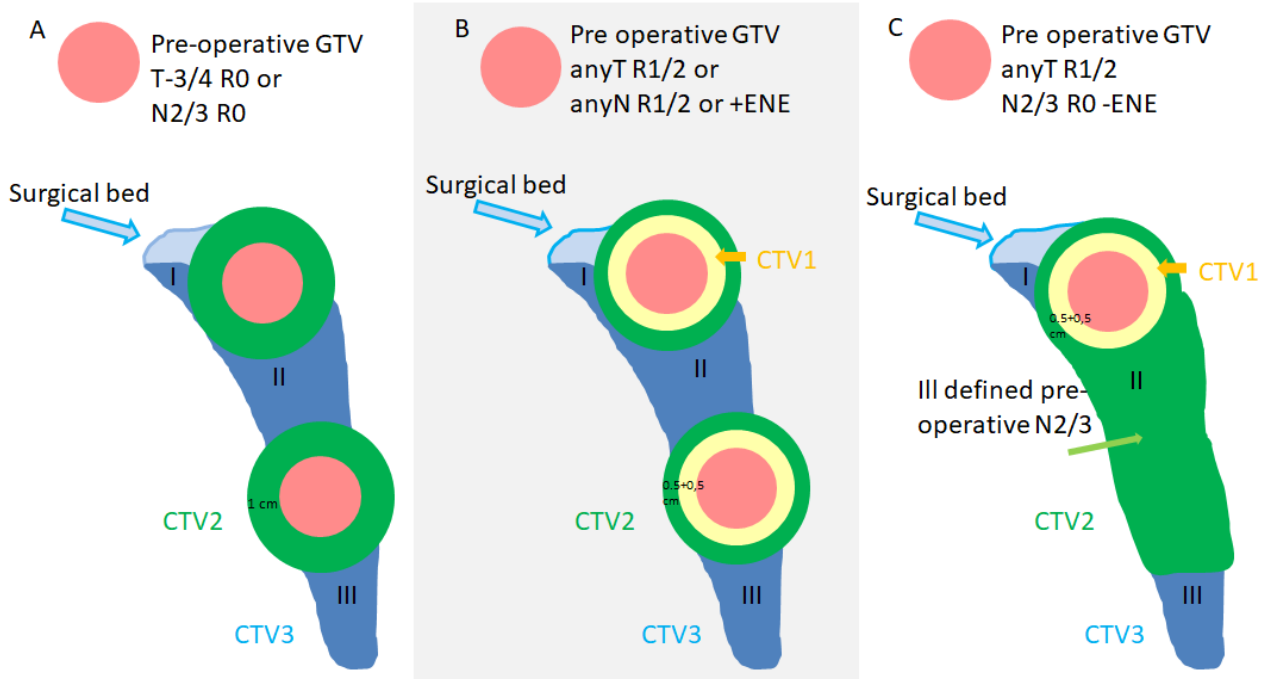


Figure 2: *Examples of postoperative radiotherapy scenarios. I, II and III refer to elective nodal regions. Scenario A: Stage is the only indication for post-operative radiotherapy (R0) and thus, no CTV1 is present. Scenario B: Volumes with*

insufficient margins or ENE are included in CTV1. If there is only indication of post-operative radiotherapy in the T-site, but N0 disease, elective nodal regions are not treated. Scenario C: Well-defined pre-operative primary tumour GTV with R1 or R2 resection. Nodal areas with R0 resection and no ENE, but ill defined, e.g. several smaller positive nodes. In general: In case of well-defined pre-operative volumes, geometrical margins are applied. In case of ill-defined volumes or diffuse soft tissue invasion, entire nodal levels or anatomical regions (e.g. entire tongue) may be used as an anatomical margin.

CTV3: Contains CTV2 and the surgical bed of the primary tumour site outside preoperative GTV + 10 mm + regional elective lymph nodes without margin. The CTV3 definition is highly dependent on nodal status. See references above.

GTV and CTV in radiotherapy after induction chemotherapy (nasopharynx, sinonasal cancer)

27. After induction chemotherapy, the actual target may be delineated. It should be considered to include, pre-chemotherapy involved volumes especially concerning bone, skull base and involved sinuses (B)

If patients are treated with induction chemotherapy, there is a large chance of response (95% had at least partial response) before radiotherapy and improved survival in nasopharynx cancer (35). Pre-induction-chemotherapy-GTV volume has been used for target delineation with unaltered margins (36). A randomized study comparing pre- versus post chemotherapy GTV irradiation showed no detrimental effect of reducing the target volume (37) and the long term results are gaining influence, as post-induction chemotherapy targets are often used (38). Bone or cartilage involved before induction chemotherapy is included in the high dose volume (e.g. skull base or paranasal sinuses). In case of large tumours with good result of induction therapy, the CTV may be further modified to spare critical normal tissue. For involved nodes with visible soft tissue (ENE extension), the GTV-nodal is defined by the pre-ICT involved region.
CTV2 and CTV3 is identical to those of radical RT

PTV
PTV1, PTV2, PTV3: Contains corresponding CTVs with uncertainties, including set-up margins (SM), that may vary with field localisation, patient immobilisation, and the use of image guided adaptive radiotherapy (IGRT). It is recommended that all departments gather data for their respective SM. PTV can be further divided into sub-volumes, e.g. close to surfaces or in case of overlaps with OAR and PRV.
In proton planning, the PTV margin is not used.

Example of workflow

1) When present, GTV-T and GTV-N are delineated on basis of the above-mentioned recommendations

2) CTV1 is generated from GTV by adding an isotropic margin of 0-5 mm.

3) CTV2 is generated from GTV by adding an isotropic margin of 5-10 mm. CTV2 is modified for bone, air, skin, and specific anatomical consideration

4) CTV1 outside CTV2 is erased.

5) CTV3 is delineated according to atlases, available at DAHANCA.oncology.dk.

6) Organs at risk are defined according to the treatment area and delineated according to atlases (defined in Appendix 1). The spinal cord must always be delineated, and the brain stem should be delineated at least in all cases with a defined CTV3.

7) Targets and organs at risk should be visualized in beams eye view to identify target and OAR irregularities and inconsistencies. The CTVs are modified to represent clinically and biologically relevant volumes.

8) The volumes are transferred to the dose planning process and considerations concerning bolus and priorities are discussed with the treatment planner.

9) Target definition and dose prescription used for the dose planning process is formally approved and documented.

Patient values and preferences

Not relevant.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated, and the international literature is closely monitored.

Comments and considerations

Adherence to the guidelines may influence both tumour control and side effects. Data on loco-regional control and side effects are continuously monitored through the clinical DAHANCA database and in clinical protocols.

Normal tissues

28. The nomenclature (D), dose-volume constraints (C), and definition of volumes (D) should follow the guidelines of Table 1 and Appendix 1.

Literature and evidence review

Atlas of relevant normal tissues

Knowledge on normal tissue anatomy in the head and neck area can be acquired from the anatomy/-radiology literature. The definition of organs at risk does not always follow the strict anatomical or functional definition of an organ, but it is aimed for the organs at risk to be defined in a safe and operational manner, e.g. the location of the division from the spinal cord to the brainstem by bony landmarks. See Appendix 1 for delineation guidelines of OAR.

Dose volume constraints

The dose volume constraints relevant for head and neck cancer are listed below in Table 1. Data is mainly acquired from studies of conventional radiotherapy of adults without concomitant chemotherapy. Normal tissue tolerance can be different for other fractionation schedules, and the table is only applicable for curative doses, >30 fractions of ≤2 Gy per fraction and is not applicable for children or hypo-fractionation. For some normal tissues, other models and other parameters are available. For other organs, no or limited data are available, and the dose-volume constraints are products of discussions and consensus among the members of the DAHANCA Radiotherapy Quality Assurance Group. The models and constraints are selected from the available evidence, with emphasis on being operational, simple, and relevant for the dose levels used in head and neck cancer radiotherapy.

For the optimization process, it is important to have in mind that the risk of toxicity is not dependent on a single dose-volume (DVH) parameter, but on a complex dose-volume interplay. All tissues should be spared to doses "as low as reasonable possible", - considering and prioritizing competing organs at risk.

If over-dosage is unavoidable due to prioritization of target coverage, some guidance to over-dosage of critical normal tissues, with low risk of severe side effects, is provided. The violation of these constraints should be discussed with the patient, and consent should be recorded (BrainStem, SpinalCord and optical structures). The nomenclature follows Santanam, when applicable (39). Suffixes for L=left / R=right should be applied. D_{max} means $D_{0,027\ cm^3}$ (3x3x3 mm^3). For delineation guidelines, see Appendix 1.

Table 1: Dose Constraints

	Structure (alphabetically within groups). Nomenclature and explanation	Dose constraint OAR [Gy]	Dose constraint PRV/ wc [Gy]	Comments. Endpoint in bold	References
ABSOLUTE	BrainStem	D_{max} ≤ 54Gy	D_{max} ≤ 60Gy	Treating ≤10 cm^3 of the OAR to a maximum of 59 Gy results in a low risk of **neurological damage.** If over-dosage is unavoidable due to target coverage, it may be done. In the peripheral 3 mm rim of the	Mayo(40) *Weber(41) *Debus(42)

				brain stem, 64 Gy causes a low risk of neurological sequelae *.	
	SpinalCord	D_{max} ≤ 45Gy	D_{max} ≤ 50Gy	Risk of **neurological damage** is estimated to 6 % for doses at 60 Gy. Limited over-dosage may therefore be allowed to achieve target coverage.	Kirkpatrick (43)
MUST	Chiasm OpticNerve_L OpticNerve_R	D_{max} ≤ 54Gy	D_{max}≤ 60Gy	Dmax ≤ 55 Gy leads to a low risk of **visual disturbance**. Doses above 60 Gy leads to an estimated risk of above 7%. Dose constraint can be violated in order to achieve target coverage	Mayo(44)
	EyeBack_L EyeBack_R	D_{max}≤ 45Gy	D_{max}≤ 50Gy	**Retinopathy** is seen after doses as low as 30 Gy, and doses must be kept as low as possible. There is a volume effect and e.g. the lateral retina can be spared separately.	Jeganathan(45)
	EyeFront_L EyeFront_R (cornea, iris, lens)*	D_{max}≤30 Gy	D_{max}≤35 Gy	**Conjunctivitis, dry eye syndrome and cataract.** *The lenses have been removed from the list of OARs since it is contained in the anterior eye OAR and side effects may be treated. Even if constraints are not met for other parts of the optic pathways, the anterior eyes are worth sparing in order to preserve the eye in situ.	Jeganathan (45)
	Lacrimal_L Lacrimal_R (lacrimal gland)	D_{mean}≤25Gy	D_{mean}≤30Gy	**Dry eye syndrome.** Even if constraints are not met for other parts of the optic pathways, lacrimal glands are worth sparing in order to preserve the eye in situ. In case of severe dry eye syndrome, the eye must often be removed.	Jeganathan(45)
SHOULD	Brain	D_{1ccm}<58Gy D_{max}≤ 68Gy Avoid hotspots.		At D_{max}=72 Gy the risk of **necrosis is** 5% at 5 years. **Cognitive disturbances** may be seen at lower doses.	Su (46) Lawrence(47)
	Cochlea_L Cochlea_R	D_{mean} ≤ 45Gy and $D_{5\%}$ ≤ 55Gy	D_{mean} ≤ 50Gy and $D_{5\%}$ ≤ 60Gy	Risk of clinically relevant **hearing loss** may be as high as 15% at mean doses of 47 Gy when using concomitant cisplatin.	Bhandare(48) Chan(49) Hitchcock(50)

	Esophagus (cervical esophagus+ esophagus inlet muscle+ cricopharyngeal muscle)	D_{mean} ≤ 30Gy	Limited data for radiation induced **swallowing problems** for the esophagus.	
	LarynxG (glottic larynx)	D_{mean} < 40 Gy,	Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth(51)
	LarynxSG (supraglottic larynx)	D_{mean} < 40 Gy	Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth (51)
	Mandible	D_{max}≤ 72Gy Dmean<30Gy V35Gy<30%	**Osteoradionecrosis.** Limited data.	Eisbruch (52) Aarup-Kristensen(53) Van Dijk (54)
	OralCavity	D_{mean} ≤ 30Gy	***Xerostomia, dysphagia, and mucositis***	Hawkins (55) Dean(56) Hansen(57)
	Parotid_L Parotid_R	1) Contralateral parotid: D_{mean}≤ 20Gy 2) Both parotids: D_{mean}≤26Gy	*Xerostomia*	Deasy (58)
	PCM_Low (lower pharyngeal constriktor)	D_{mean} < 55 Gy	Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth (51)
	PCM_Mid	D_{mean} < 55 Gy	Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth(51)

	(middle pharyngeal constrictor)			
	PCM_Up (upper pharyngeal constrictor)	D_{mean} < 55 Gy	Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth (51)
	Pituitary	D_{mean}≤20Gy	No certain threshold. The risk of **hormonal disturbances** increases at >20 Gy	Darzy(59). Paulissen(60)
	Submandibular_L Submandibular_R	D_{mean} ≤ 35Gy	**Xerostomia**	Deasy(58)
	Thyroid	D_{mean}≤40 Gy	No specific threshold for **biochemical hypothyroidism**	Rønjom (61) Boomsma (62)
CAN	Carotid_L Carotid_R	D_{max}≤40 Gy	Should be spared to avoid **stenosis and cerebral ischemia** in case no elective volume is irradiated e.g. $T1_{a/b}$ glottic cancer or ipsilateral radiotherapy	Choi (63)
	BuccalMuc_L/R Buccal mucosa	D_{mean} ≤ 30Gy	**Xerostomia** (and perhaps mucositis) Data only available as a part of oral cavity	Dean (56) Hawkins(55)
	Lips	D_{mean} ≤ 20Gy	Mucositis, Cheilitis	RTOG 1016
	Hippocampus	D40% < 7.2Gy [EQD2] (i.e. < 11Gy on 33fx with α/β=3)	Risk of **poor memory** at 11% and 66% at doses below and above constraint. The consequences for other OARs resulting from hippocampal sparing should be monitored carefully at dose optimization due to the very low constraint.	*Gondi (64)

ABSOLUTE: Organs of critical importance that must be prioritized over target coverage, as a rule
MUST: Serial organs that must be delineated, but not necessarily prioritized over target coverage.
SHOULD: Organs at risk with some evidence for sparing, and OAR with serious but manageable toxicity.
CAN: Poor evidence, uncertain endpoints or manageable toxicity. Organs may be delineated according to local guidelines/research projects.

Dose constraints for palliative treatment

In case of disseminated disease, poor performance status etc. where long term survival or disease control may be unlikely, a hypofractionated treatment may be administered using e.g. 52 Gy in 13 fractions, 4 Gy per fractions . In that case, dose constraints should be modified using an α/β=3:

Table 2: Dose constraints for treatment to 52 Gy in 13 fractions..

	Structure (alphabetically within groups). Nomenclature and explanation	Dose constraint OAR [Gy]	Dose constraint PRV/ wc [Gy]
ABSOLUTE	BrainStem	D_{max} ≤ 43Gy	D_{max} ≤ 46Gy
	SpinalCord	D_{max} ≤ 38Gy	D_{max} ≤ 41Gy
MUST	Chiasm OpticNerve_L OpticNerve_R	D_{max} ≤ 43Gy	D_{max}≤ 46Gy
	EyeBack_L EyeBack_R	D_{max}≤ 38Gy	D_{max}≤ 41Gy

Reirradiation: Optimization and suggestions for dose constraints

Due to previous dose deposition, adherence to the above mentioned constraint may be difficult in case of reirradiation. The cumulative doses of the combined initial radiotherapy and re-irradiation must be considered for all late effects. Therefore, a cumulated dose plan of previous and present treatment must be made (see below) in order to evaluate risks and benefits.

The spinal cord and brain stem are spared according to DAHANCA constraints if possible. The effects of fractionation, according to the LQ model assuming an α/β=3 and a recovery of 25% of primary dose after 6 months (65) may be used in order to obtain target coverage.

Calculation example

Primary radiotherapy: 2 years ago. 66 Gy in 33 fraction with integrated boost. Spinal cord dose Dmax 36 Gy

Current radiotherapy: 60 Gy in 50 fractions. Spinal cord dose Dmax 30 Gy

Prior: Sp.c. EQD2: 36*((36/33)+3)/(2+3)*(1-0,25)= 22 Gy

Current Sp.c. EQD2: 30*((30/50)+3)/(2+3)=22 Gy

Cumulative Spinal cord EQD2 =22+22=44 Gy i.e. safe treatment irrespective of Dmax position.

The carotid arteries: ALARA. EQD2<119 Gy has been suggested (66).

Cumulated treatment plan for evaluation and planning of re-irradiation

No evidence-based consensus exists on how to accumulate doses. Accumulating doses on treatment plans often made years apart, requires that many factors are taken into account. The tumour on the initial dose plan has disappeared, many patients have been through surgery, some including reconstructive procedures, and some lost or gained weight and stature. Nevertheless, an attempt to accumulate doses may greatly improve the evaluation of dose plans, aiding decisions as to – whether dose outside the target should be redistributed or whether the treatment is feasible altogether. Rigid or well-defined structures, such as the spinal cord, may be easier to evaluate than soft tissues such as the oral cavity. The most informative dose accumulation is probably done using deformable image registration with deformation of the initial dose matrix onto the new scan. Further information can be added by correcting doses for repair and fractionation effect (67). As OARs receive less than target dose this should be done irrespective of fractionation. Great care should be given to areas with anatomical changes and steep dose gradients as any attempt to do dose summation will be especially hampered by uncertainties

29. A cumulated treatment plan, even corrected for recovery and fractionation, may be beneficial for the planning of re-treatment, but physical and biological uncertainties should be considered (D)

Patient values and preferences

Not relevant

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated, and the international literature is closely monitored

Comments and considerations

No *special comments or considerations*

Literature and evidence review

The evidence is sparse, and the recommendations are based on consensus or other guidelines

Patient values and preferences

Not relevant.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated, and the international literature is closely monitored.

Comments and considerations

No special comments or considerations

Radiotherapy dose planning

30. Dose planning should attempt to comply with the tolerance levels for target-coverage and normal tissue sparing described in Table 2 (D)

Literature and evidence review

The treatment planning process for radiotherapy consists of a series of patient-related procedures and machine work tasks that eventually result in a treatment plan that enables a radiation dose prescription to be applied effectively for tumour control, and safely for the patient. This entails a long string of hardware and software equipment that is involved in application of photon beams, electron beams, and particles, such as protons.

Economic issues are strongly involved in radiation treatment, and thus treatment planning and delivery is not only based on clinical experience and scientific evidence, but also on the performance and availability of technical equipment from commercial manufacturers. Therefore, Oxford-levels of recommendation are considered D, however, due to patient safety and legal issues, radiotherapy is carried out at the highest level of approval by authorities.

Non-coplanar fields

The use of non-coplanar fields or -partial arcs should be used with the awareness of added complexity in quality assurance of patient positioning as CBCT's can't be used to verify couch position after shift, but 2D-kV images/ surface guidance should be used, and couch position quality assured.

Air within the target

In case there is air within the target, any influence of increase or decrease of the volume should be evaluated and ideally incorporated in the treatment plan optimization and evaluation, e.g. examining the influence of adding/ substracting water or air.

Bolus/ target close to skin

When the target volume is close to the skin surface, the use of a bolus is often recommended to ensure adequate superficial dose delivery, thereby enhancing treatment efficacy for superficial tumors.

It is a clinical decision whether or not to apply bolus; however, this decision should be based on a dosimetric understanding: When using static field RT, the beam direction plays an important role since the build-up effect and the lack of lateral scatter in the skin surface is directly linked to the beam angle. When using VMAT, beam intensity becomes important, as the need for bolus relies on the amount of fluence planned in the specific directions.

The bolus should be as close to the skin as possible, and air gaps between the skin and bolus should be minimized to improve the dose robustness and effect of the bolus (68).

If there is tumor involvement of the skin, bolus should be used to ensure dose to the GTV.

If the CTV1 is in the skin area, typically the outermost 3 mm, it is often necessary to use a bolus to achieve the required dose. If involvement near the skin is not suspected, the CTV1 and CTV2 volume should be cropped away from the skin, and a bolus can be avoided.

If the CTV3 approaches the skin area, it is often recommended to crop the target and avoid a bolus.

Bolus should be matched to the patient and, when placed on the patient, verified using CBCT or surface scanning. The thickness depends on the clinical case and treatment technique. However, a thicker bolus is often better in dose capabilities but less flexible. A 3D printed bolus offers both a high degree of flexibility and good dose capabilities.

Dose prescription

The prescribed dose for a target (CTV) is the mean dose.

Dose calculation

For *photon and proton* treatment, the mean dose must be the prescribed dose. Dose in $CTV2_{only}$ (CTV2 minus CTV1) and $CTV3_{only}$ (CTV3 minus CTV2) must be as close to prescription dose, for the specified volume, as achievable.

CTV1 must be covered with 95%-107% of the prescribed dose. CTV2 and CTV3 must be covered with 95% of the prescribed doses. The 95% isodose curve for PTV1, PTV2, and PTV3 must be as close to the delineation of PTV1, PTV2, and PTV3 respectively, as achievable. Adherence to this is defined by QA measures, see Table 2.

A maximum volume of 1.8 cm^3 in the patient may receive >107% of the prescribed dose to CTV1.

Dose calculation must take differences in patient density into account. This applies to both primary and scattered radiation.

For *electrons* the minimal dose for PTV must be 92.5% of the prescribed dose, and the maximum dose should be <107% of the prescribed dose. Dose calculation for electrons should preferably be based on density information of a CT scanning, but for tumours close to the skin, a manual calculation may be performed.

Simultaneous integrated boost (SIB) is used as the standard technique, with different dose levels for CTV1, CTV2 and CTV3, but with all volumes treated at each fraction. The total dose to the low-riskelective regions has therefore been increased from 46 Gy (2 Gy/fx) to 50 Gy (1.5 Gy/fx) and 56 Gy (1.0 Gy/fx), see Appendix 2.

Prioritization of treatment goals
Optimization algorithms and dose planning systems requires a prioritization of the treatment goals. The prioritization listed below is recommended for maximal clinical benefit, but individual prioritization may differ according to patient wishes and the clinical situation. The OARs are not listed by priority within groups.

1. Critical normal tissues, potentially lethal complication

SpinalCord
BrainStem

2. Target coverage

GTV
CTV1

3. Critical serial normal tissues
EyeFront
Chiasm
EyeBack

4. Target coverage
CTV2
CTV3
PTV1

PTV2
PTV3

5. Sensitive normal tissue
Not prioritized
Brain
Cochlea
Esophagus
LarynxSG
LarynxG
Mandible
OralCavity
Parotid
PCM
Pituitary
Submandibular
Thyroid
Carotid
BuccalMuc
Lips
Hippocampus

6. Avoid overdosage of CTV2 and CTV3

7. Plan complexity
The use of added fields, especially non-coplanar fields and added modulation should be evaluated, and if the benefits does not significantly outweigh the disadvantages in dose uncertainty, a less complex treatment plan should be used.

Patient values and preferences
Not relevant.

Rationale
Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated, and the international literature is closely monitored.

Comments and considerations
No special comments or considerations

Complex dose planning

Literature and evidence review

In some cases, a target ca- not be covered by dose without violating constraints for critical normal structures. In these cases, a compromise between target coverage and normal tissue doses should be discussed with the patient. The present guidelines do not contain any advice or criteria for HOW to prioritise, but only for reporting and quality assurance. DAHANCA has successfully carried out QA of treatment plans and analysed recurrences. This is difficult or even impossible if compromises have been made (69), as many (unknown) strategies has been applied. It is therefore necessary for these analysis that the treatment priorities are evident. This can be ensured by:

- Creating a "according to guidelines" CTV. A CTV created by adhering to the present guidelines without prioritizing OAR's
- A "by necessity" CTV: A CTV that contains the part of the target that is **prioritized** above some critical OAR's

In case a comparative treatment plan is made for deciding if a patient could benefit from proton radiotherapy, it is important to define the priorities, i.e. which OARs should be prioritized over target coverage, and which constraints should be used, before treatment planning.

Terminology

CTV "according to guidelines": CTV1, CTV2, CTV3 (as normal)

CTV "by necessity": CTV1_prio, CTV2_prio

OAR_prio could be defined in the same way.

PTV should be defined geometrically. A non-isometric margin could be used, if it is reflected in the setup/ IGRT strategy (e.g. a lower tolerance at setup in a certain direction).

Volumes should be prioritized as follows

1: Critical normal tissues (OAR_prio)

2: GTV, CTV_prio

3 Other normal tissues

4: Other CTV's

5: PRV, PTV, wcOAR and wcCTV (wc= worst case)

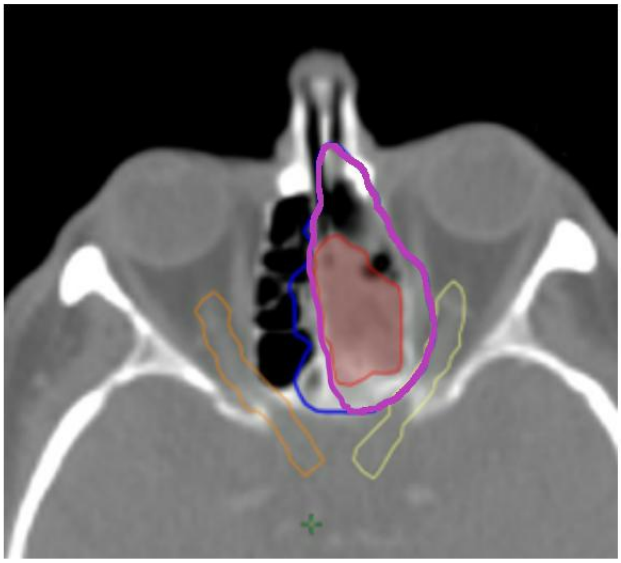


Figure 3 Example of target definition and nomenclature. GTV: Red translucent. CTV1_prio: Magenta. CTV1: Blue. Optic nerve: Yellow and orange. GTV is suspected to involve the medial wall of the orbita and the left sphenoid sinus but not the septum. Therefore, the CTV1_prio includes the orbital content and posterior bone but not the right part of the sphenoid bone or nasal cavity, and it is prioritised above the left optic nerve (OpticNerve_L). CTV1 includes GTV with a geometric margin of 5 mm, modified not to include the right uninvolved nasal cavity, and is prioritised below the right optic nerve (OpticNerve_R_prio). The dose distribution (not shown) is expected to include the left optic nerve above constraint but to spare the right optic nerve. The clinical goals are visible from the modification of the volumes, and the treatment plan can be quality assured for CTV1_prio, and any recurrence can be analysed with respect to both volumes and doses

Non-standard normal tissue constraints could be used in order to treat the patient with curative intend with low risk of serious side effects:

Table 3 Non-standard normal tissue constraint

	Structure Nomenclature and explanation	**Dose constraint OAR [Gy]**	**Dose constraint PRV/wc OAR [Gy]**	**Factors of importance when considering treatment planning compromises. Endpoint in bold**	**References**
	BrainStemCore	D_{max} ≤ 54Gy	D_{max} ≤ 60Gy	Treating ≤10 cm^3 of the OAR to a maximum of 59 Gy results in a low risk of **neurological damage.** If over-dosage is unavoidable due to target coverage, it may be done. In the peripheral 3 mm rim of the brain stem, 64 Gy causes a low risk of neurological sequelae *.	(40) (41) (42)

				Brainstem constraints may be used for C1 SpinalCord, as this is anatomically brainstem.	
	BrainstemSurface	D0,5ccm <64Gy			EP TN (70)
	SpinalCord*	D_{max} ≤ 45Gy	D_{max} ≤ 50Gy	Risk of **neurological damage** is estimated to 6 % for doses at 60 Gy. Limited over-dosage may therefore be allowed to achieve target coverage. *SpinalCordC1 is sometimes considered having the same constraint as brainstem (71)	(43)
	SpinalCord_Core	D2%<54 Gy		4% risk of Gr>=2 late neurological toxicity (40% if exceeded)	(72)
	SpinalCord_Surface	D2%<64 Gy			
	Chiasm	D_{max} ≤ 58Gy			(73)
	OpticNerve_L OpticNerve_R	D_{max} ≤ 58Gy			(73)

Normalisation/prescription – complex planning

If there is a significant difference between CTV and CTV_prio, dose should be normalized to CTV_prio. Dose to CTV should also be reported.

Patient values and preferences

Not relevant.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated, and the international literature is closely monitored

Comments and considerations

No special comments or considerations

Treatment

Literature and evidence review

Like the treatment planning process for radiotherapy described above, radiation treatment delivery is defined by a series of patient-related procedures and technical aspects related to accelerators and additional equipment. Therefore, the Oxford-level of recommendation is considered D. However, due to patient safety and legal issues, radiotherapy is carried out at the highest level of approval by authorities.
According to ICRU, the dose rate must be at least 0.1 Gy/min inside the CTV in photon radiotherapy.

Image guidance

Patient positioning should be verified with CBCT-scans according to local guidelines. Tolerances and imaging frequency should be defined locally with respect to local PTV and PRV margins originating from measurements of random and systematic uncertainties in the whole process of treatment preparation and delivery (74).

The anatomical structures used for matching must be defined with respect to target localisation. For example, emphasis must be put on more cranial structures for nasopharyngeal tumours than for hypopharyngeal tumours. The 'region of interest' (ROI) for the matching process must also take the extent of the elective areas into account. Match structures with limited internal movements should be chosen, e.g. not the hyoid bone, but preferably the cervical spine. Soft tissue matching is often possible when CBCT scans are available. The ROI must be chosen to include both target and critical normal tissue. Both automatic and manual match must be visually verified according to bony anatomy and visible soft tissue.

In case of non-adherence to pre-specified tolerances, target coverage and normal tissue sparing should be prioritized as described above, and the reasons for non-adherence should be documented.

Re-planning

It should be continuously evaluated whether patient anatomy and the effectiveness of the immobilisation device change to a degree that may have significant implication on the dose distribution. In case of larger changes, an evaluation of the dosimetric consequences should be performed and the need for a new immobilisation and/ or treatment plan must be evaluated. Re-planning must always take place in case of risk of critical normal tissue overdose or insufficient high dose target coverage. If dose evaluation and especially dose planning for adaptative plan is performed on CBCT or virtual CT, these calculations must be quality assured

Patient values and preferences

Not relevant.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated, and the international literature is closely monitored

Comments and considerations

No special comments or considerations

Special considerations for proton therapy

Potential candidates for proton therapy are identified at the local departments of oncology, often after a comparative treatment plan, i.e. comparison of two treatment plans using protons and photons, respectively. The dosimetric differences are quantified and applied to normal tissue complication models (NTCP) to estimate a potential benefit of proton therapy, if available. If it is decided that the patient should be offered referral to the Danish Centre for Particle Therapy (DCPT), and the patient accepts, further planning will take place at DCPT. The patients are referred to the local department of oncology for follow-up after end of treatment.
The principles regarding dose prescription, definitions of clinical target volumes (CTV1, CTV2, or CTV3), target selection, normal tissue definition, nomenclature, and normal tissue constraints are applicable for both photons and protons. Several factors are qualitatively different between proton and photon planning as described below. The advantages, as well as disadvantages of proton therapy are well illustrated by the depth-dose curve and the Bragg peak.

Preparation and scanning

There are special considerations regarding homogeneity and blunt edges of the immobilisation devices. The CT-scanners must be calibrated and optimized for the translation of HU to proton stopping power, using e.g. dual energy CTs. Nevertheless, mono energetic, non-calibrated CTs or even synthetic CT based on diagnostic MRI scans can be used for comparative treatment plans. The dosimetric differences of the comparative dose plan should be quantified using differences in dose and expected NTCPs of specific OARs if models are available.

Dose planning

Proton therapy planning includes other solutions than photon therapy regarding choice of field angles, number of fields, techniques for skin coverage, and lateral penumbra. The final treatment plan at DCPT, as well as comparative dose planning, requires special skills and training defined by the DCPT.
The PTV concept is not an optimal solution for uncertainties from immobilization, scanning, setup errors, and dose calculation in proton therapy. In dose optimization, CTV coverage and critical normal tissue sparing are ensured in multiple ‘worst-case scenarios’ of setup errors and range uncertainties, referred to as robust optimization. Dose to CTV and dose limits to OARs are prescribed and reported for the nominal plan, i.e. the robustly optimized dose plan with no introduced errors.

DCPT will ensure that proton treatment plan guidelines are updated.

The CTV in head and neck cancer is often located close to the skin. The lowest possible energy delivered by the cyclotron at DCPT is 70 MeV, which is equivalent to a Bragg peak depth of 4 cm. Therefore, a range shifter (a water equivalent plastic plate) is introduced between the snout and the patient. This reduces the energy and deposits the dose closer to the surface. Unfortunately, the range shifter also limits the space around the patient and restricts the possible field directions as well as increases the spot sizes, whereby the lateral penumbra is degraded.

Treatment
Patient positioning is very similar to photon treatment. CBCTs are used for correction of translational and rotational errors. Nevertheless, proton therapy requires greater attention to changes in depth and density, e.g. shoulder position, immobilization devices and anatomical changes, since the energy deposition of protons relies heavily on these parameters. The duration of proton therapy is increased. Often the patients are immobilised for >30 minuttes.

Literature and evidence review
The evidence is sparse, and the recommendations are based on consensus or other guidelines

Patient values and preferences
Not relevant.

Rationale
Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated, and the international literature is closely monitored

Comments and considerations
No special comments or considerations

Treatment prolongations

All fields must be treated at all fractions. Patients treated with 6 fractions per week must receive a single fraction Monday to Friday and the sixth fraction should be administered during the weekend or as an extra fraction on a weekday. An interval of at least 6 hours between fractions must always be ensured. For patients receiving 10 fractions per week, two daily fractions with an interval of at least 6 hours are used.
Before the first treatment interruption (e.g. a weekend), at least 4 Gy should be administered, and similarly, not less than 4 Gy should be administered after a weekend.

In case of treatment prolongation, either acutely e.g. due to comorbidity, or expected, e.g. public holidays, the overall treatment time, from first to last fraction, should be maintained if possible. The missing fraction(s) must be administered as soon as possible and ideally within a week, if clinically applicable. This can be done by delivering an extra fraction during weekends or on the day of a planned fraction (but at least 6 hours apart).

Considering acute toxicity, treatment breaks should not be compensated with more than one extra fraction per week, and no more than 13 consecutive treatment days. Furthermore, no more than 3 days of double fractionation must take place within 2 weeks for conventional fraction sizes.
To compensate for longer treatment breaks, hyper-fractionation and dose escalation may be worth considering (75).

Literature and evidence review

The evidence is sparse, and the recommendations are based on consensus or other guidelines

Patient values and preferences

Patients may be involved in decision-making if more options of compensating procedures are available.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated, and the international literature is closely monitored.

Comments and considerations

No special comments or considerations

Radiotherapy quality assurance

31. Dose planning should strive to achieve the tolerances for target-coverage and normal tissue sparing mentioned in table 2 (D)

Literature and evidence review

Treatment methods must be quality assured and reported in clinical trials. QA can be divided into three steps:

Step 1: Preparation including writing guidelines, dose audits, and delineation workshops.

Step 2: Daily QA: Technical QA of the performance of the accelerators, verification of delineation, dose plans, and setup procedures.

Step 3: Follow-up on the given treatments; reporting, sampling, and evaluation according to predefined criteria of minor and major deviations.

Preparation
The principles of technical QA in DAHANCA refer to ”Practical Guidelines for the Implementation of a Quality System in Radiotherapy” from the European Society for Therapeutic Radiology and Oncology (ESTRO), ”Comprehensive QA for Radiation Oncology”, Reports of AAPM Radiation Therapy Committee Task Group 40, and ”Absorbed Dose Determination in Photon and Electron Beams”, Technical Report Series 398, from the International Atomic Energy Agency (IAEA).
It will be described below how the correct treatment of head and neck cancer is ensured under the auspices of DAHANCA. Also, local guidelines must exist in all centres to ensure adherence to the national guidelines by DAHANCA.

Dose audit
The path from CT scanning, dose planning, and treatment delivery is complex, and all steps must be verified. Nevertheless, transitions from one step to another may also introduce errors that may escape a stepwise QA. One way to assure that all steps and transitions are retained is by performing a dose audit: A dose audit includes treating a standardized phantom according to specified guidelines to certain doses. Dose to the phantom is measured and compared to the dose plan produced at the centre. It is recommended that an external dose audit is performed at least every 5 years under the auspices of the DAHANCA Radiotherapy Quality Assurance Group.

Delineation workshops
The basis of dose planning is the delineation of the tumour and clinical target volume. Delineation guidelines for the OARs and CTVs contained in the present guidelines are aimed at increasing consistency and comparability between patients and centres. Nevertheless, no gold standard exists, and delineation practices must be continuously evaluated through participation in national workshops. National delineation workshops will be arranged every 3 years through the DAHANCA Radiotherapy Quality Assurance Group.

Daily quality assurance
A guideline for daily QA must be present at all centres.

Delineation verification and approval
Delineation of targets and normal tissues must be approved by a trained specialist. Delineation must, as a rule, follow the present guidelines, and deviations from the guidelines should be described in the medical records.

Dose planning control and approval
All dose plans must be controlled by an independent dose planner or a physicist. Prescribed dose and target coverage on all CT slices, as well as dose to the normal tissues, must be verified.

Imaging calibration
A procedure for the calibration and QA of the localisation of imaging and treatment isocentre must be available in all centres.

Follow-up
A continuous adaptation of QA and guidelines to technical and clinical developments is essential. Reports of the delivered treatment are therefore important.

Reports of radiotherapy
Prescribed dose to CTV1, CTV2 and CTV3, as well as date of first and last fraction should be reported in the "Primary Treatment" charts of the DAHANCA data-base.

Central quality assurance
For all patients participating in clinical protocols with planned central QA, dose plans in the DICOM format must be electronically transferred to a central data base according to specific guidelines.

QA Audits
According to pre-defined agreements, QA audits are performed in all DAHANCA protocols, either by sample or for the entire cohort. Appointed experts will audit the clinical data as well as the treatment plans. The evaluations will be graded according to any degree of protocol deviation as minor or major. Major deviations are defined as deviations with potential influence on survival.

Table 4 QA Parameters

	Per protocol	Minor deviations	Major deviations
Dose prescription for the CTV1	66, 68, 70, 76 Gy		
Mean dose to CTV1	$\pm$1 %	$\pm$2 %	
Minimum dose to CTV1	95% of dose to 99% of CTV1, and 90% of dose to the last 1 % of CTV1	95% of dose to 98% of CTV1, and 90% of dose to the last 2 % of CTV1	< 95% of dose to ≥2% CTV1
Minimum dose to PTV1 (skin excluded)	95% of dose to 98% of PTV1, and 90% of dose to the last 2 % of PTV1	95% of dose to 95% of PTV1, and 90% of dose to the last 5 % of PTV1	< 95% of dose to ≥5% of PTV1
Maximal dose to > 1,8 cm^3 ($D_{1.8cm^3}$)	≤107% of CTV1 dose	≤ 110% of CTV1 dose	> 110% of CTV1 dose
Maximal dose to spinal cord ($D_{0.027\ cm^3}$)	≤ 45 Gy	45-50 Gy	> 50 Gy
Maximal dose to PRV spinal cord / wc spinal cord ($D_{0.027\ cm^3}$)	≤ 50 Gy	50-55 Gy	> 55 Gy
Maximal dose to brain stem ($D_{0.027\ cm^3}$)	≤ 54 Gy	54-59 Gy	> 59 Gy
Maximal dose to PRV brain stem/ wc brain stem ($D_{0.027\ cm^3}$)	≤ 60 Gy	60-65	> 65 Gy

Length of the treatment course	Accelerated radiotherapy (6 and 10 fx/week): ≤41 days. 5 fx/weeks: ≤48 days	Accelerated radiotherapy (6 and 10 fx/week): 42-46 days 5 fx/week: 49-53 days	Accelerated radiotherapy (6 and 10 fx/week): >47 day 5 fx/week: > 54 days

Patient values and preferences

Not relevant.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated and the international literature is closely monitored.

Comments and considerations

No special comments or considerations

Guidelines for elective lymph node irradiation

The recommended elective nodal volumes irradiated within the DAHANCA guidelines, are highly dependent on the T-site and –extension. This is in contrast with e.g. [Biau], where the nodal stage also defines the elective volumes. DAHANCA have failed to find any clinical data to support an expansion of the elective volumes beyond what is mentioned below for specific tumour sites, but some volumes need a clarification:

Level V

The only indication for level V irradiation is involvement of the nasopharynx, or involvement of level V itself. I.e. posterior level II-IV or level X involvement is not an indication for adding level V to the elective volume.

Retropharyngeal nodes

Retropharyngeal nodes are included in case of nasopharyngeal or posterior oropharyngeal wall involvement. In these circumstances they are always included bilaterally. In case of limited retropharyngeal node involvement, in case of lateralized oropharynx cancer (see below), ipsilateral irradiation only may be sufficient.

Literature and evidence review

See the DAHANCA guidelines concerning the specific tumour sites

Patient values and preferences

Not relevant

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated and the international literature is closely monitored

Comments and considerations

No special comments or considerations

Guidelines for specific tumour sites

Oral Cavity

Anatomy: The oral cavity includes buccal mucosa, gingiva, hard palate, anterior 2/3 of the tongue, and floor of mouth. Lateral tumours are defined as tumours of the buccal mucosa, gingiva and retromolar trigone, with no involvement of contralateral nodes. Midline tumours are defined as tumours of the tongue, floor of mouth, and hard palate, *and any tumours with involvement of these structures*. Midline tumours have the propensity of bilateral nodal involvement. Drainage to the lymphatic system from the anterior tongue rarely spreads to level III and IV without involvement of proximal nodes.

Primary treatment is described in the national guidelines (dahanca.dk). Shortly, the mainstay of treatment is surgery for resectable tumours whenever a good functional and cosmetic result can be expected. Postoperative radiotherapy is added in case of non-radical surgery (R1 or R2) in N or T-site, pN2-3, and or pT3-4, or any N stage with ENE. Target delineation is often greatly improved when the operating surgeon takes part in the procedure.

Radical radiotherapy:
CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural anatomical barriers such as bone, unless bone involvement is evident.

CTV2: GTV-T and -N with an isotropic margin of 10 mm. Margins should be cropped for air and natural borders such as bone, unless bone is adjacent to the GTV Here, 2 mm cortical bone is included for T1 and T2 tumours. The CTV2 should not be cropped in case of T3 and T4 tumours adjacent to bone. CTV2 can be individually expanded to include high-risk anatomical areas, e.g. the ipsilateral or whole tongue in case of tongue involvement or ipsilateral floor of mouth.

CTV3: Midline tumours are treated with bilateral elective regions, and lateral tumours with ipsilateral elective regions. Ia is included if anterior part of floor of mouth, gingiva, tongue, or lower lip is involved. Elective nodal regions are:

- N0: level Ib, II, III

- N1-3: level Ib, II, III. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle is suspected, the entire muscle is included at least 2 cm above and below GTV-N.

Postoperative radiotherapy:
CTV1: Macroscopic tumour (R2), microscopically non-radically resected (R1), or areas of ENE, with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours, and margins should be cropped for air and natural anatomical barriers such as bone, unless bone involvement is evident

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone.

In case of an absent CTV1, i.e. in radically resected patients (R0), CTV2 is defined as the pre-operative GTV with at least 10 mm margin. In case of uncertainties as to the localization of involved nodes, or if the involved nodes are not identified on a pre-operative scan, the entire involved level is included. Due to the difficulties of irradiating a T-site recurrence, the T-site should be included in CTV2, even if the indication for postoperative radiotherapy is in the N-site e.g. non-radically removed nodes, ENE, or N2-N3.

CTV3: Remaining surgical bed and elective nodal levels without a margin. As a rule, bilateral irradiation of elective levels is used, but ipsilateral irradiation only is used in case of primaries in the cheek, lateral gingiva, and retromolar trigone without invasion of the floor of mouth, base of tongue, or hard palate, as well as absence of contralateral pathological nodes. Ia is included if anterior part of floor of mouth, gingiva, tongue, or lower lip is involved.

Note: If the indication for radiotherapy is due to R1-R2 resection in the T-site alone, no elective nodal irradiation should be performed for pT1-2.

Elective nodal regions are

- pN0: level Ib, II, III.
- pN1-3: level Ib, II, III. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle is suspected, the entire muscle is included at least 2 cm above and below GTV-N.
- In case of involvement of macroscopic cranial nerve, the nerve is included to the base of scull.

Nasopharynx

Anatomy: The nasopharynx is limited by the choanae (anteriorly), pre-vertebral muscles (posteriorly), medial border of the parapharyngeal space (laterally), scull base (superiorly), and caudal border of C1 (inferiorly).

The target is defined by both a CT and MRI scan.

CTV1: Includes the primary tumour (GTV-T) and involved nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins are used in case of a poorly defined primary, and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: GTV-T and -N with an isotropic margin of 10 mm, cropped for air and natural barriers such as bone, unless bone is involved. Furthermore, CTV2 includes

A) The remaining nasopharynx
B) Skull base with bilateral foramina ovale, foramina rotunda and foramina lacera
C) Inferior 5-10 mm of the sphenoid sinus, (the entire sinus in case of involvement)
D) Posterior 5 mm of nasal cavity and maxillary sinus (the entire sinus in case of involvement)
E) Anterior one third of clivus, (the entire clivus in case of involvement)
F) The ipsilateral cavernous sinus if invasion is suspected

An example of CTV2 in nasopharynx cancer is illustrated in Appendix 5.

CTV3: Elective nodes
N0: Bilateral level II-III, Va, VIIb (retro-styloid) , VIIa (retropharyngeal) and the parapharyngeal space.
The parapharyngeal space (PPS) is an inverted pyramidal fat-filled space in the lateral suprahyoid neck, with its base attaching to the skull base and the apex extending to the superior cornus of the hyoid bone. Anatomically, PPS is bordered anteriorly by the pterygo-mandibular raphe, anterolaterally by the medial pterygoid muscle, and posterolaterally by the deep lobe of the parotid gland) (76).

N+: Includes N0 volume plus ipsilateral level IV and Vb. Level Ib is included in case of invasion of the submandibular region, oral cavity. or anterior nasal cavity. Ib may be included ipsilaterally only, in selected cases. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N.

Oropharynx

Anatomy: Oropharynx is limited by the anterior faucial pillars, macroscopic taste buds (papillae vallatae), soft palate including uvula, and vallecula. The laryngeal surface of the epiglottis belongs to the supraglottic region. Oropharynx thereby includes the posterior third of the tongue, vallecula, tonsils, tonsillar pillars, posterior pharynx and soft palate.

Radical radiotherapy
CTV1: Includes the primary tumour (GTV-T) and involved nodes (GTV-N) with an isotropic margin of 5 mm in all directions. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

After diagnostic tonsillectomy, the tonsillar fossa and pillars are considered as the CTV1 to a depth of 5 mm. The clinical examination is very important in the evaluation of the extent to soft palate and especially the base of tongue. Base of tongue tumours are often difficult to depict on CT or MRI and it is often necessary to include a large part of the base of tongue in CTV1 or CTV2.

CTV2: GTV-T and -N with an isotropic margin of 10 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. CTV2 can be individually expanded to include high risk areas such as the entire or ipsilateral base of tongue in case of base of tongue primary, or invasion from an adjacent tonsillar primary.

CTV3: Tumours confined to the tonsillar fossa and tonsillar pillars are considered lateral tumours and are treated with ipsilateral radiotherapy. Ipsilateral radiotherapy can be used in case of ipsilateral retropharyngeal nodal involvement if the primary does not involve midline structures. Tumours arising in, or extending to, the base of tongue, soft palate, or posterior pharyngeal wall are considered midline tumours and should be treated with bilateral elective irradiation.

Elective nodal regions are:

- N0: Level II, III. The retropharyngeal nodes are included in case of posterior pharyngeal wall involvement and level Ib is included in case of oral cavity involvement. Ib may be included ipsilaterally only, in selected cases
- N1-3: Level II, III. Level IV on the side of nodal involvement. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected, the entire muscle is included at least 2 cm above and below GTV-N. The retropharyngeal nodes are included in case of posterior pharyngeal wall involvement and level Ib is included in case of oral cavity involvement. Ib may be included ipsilaterally only, in selected cases.

Postoperative radiotherapy

Indication for postoperative radiotherapy after primary surgery is done in accordance with the DAHANCA 34 protocol:

- T-site: < 2 mm free margin or pT3/ pT4 tumours
- N- site: more than 2 positive nodes, or 2 node metastases both >1 cm. Extranodal extension (ENE). Less than 10 removed nodes in each side of the neck dissection.

CTV1: Any macroscopic tumour (R2), areas of non-radical surgery (R1) or ENE, plus an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone.

CTV2: Includes CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone cropped for air and at natural barriers such as bone.

In case of an absent CTV1, i.e. radiotherapy after radical surgery (R0), CTV2 includes pre-operative GTV with a minimum 10 mm margin. If the indication for postoperative radiotherapy is due to N-site alone, the primary tumour volume (R0) is included in the target, as in oral cavity tumours. In case of uncertainties as to the localization of involved nodes, or if the nodes are not identified on a pre-operative scanning, the entire involved level is included.

CTV3: The remaining surgical bed and elective nodal areas.

Note: If the indication for radiotherapy is in the T-site alone, no elective nodal irradiation should be per-formed in pT1 or pT2 tumours.

Tumours confined to the tonsillar fossa and tonsillar pillars are considered lateral tumours and should be treated with ipsilateral radiotherapy. Tumours arising in, or extending to, the base of tongue, soft palate or posterior pharyngeal wall are considered midline tumours and should be treated with bilateral elective irradiation. In pT1-2 with ipsilateral nodal metastasis and contralateral neck dissection with >=10 nodes removed without any metastasis, contralateral elective nodal irradiation should be omitted.

Elective nodal areas

- pN0: Bilateral level II, III. Retropharyngeal nodes are included in case of posterior wall invasion, and level Ib is included in case of oral cavity involvement. Ib may be included ipsilaterally only, in selected cases
- N1-3: Level II, III. Level IV on the side of nodal involvement. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N. The retropharyngeal nodes are included in case of posterior pharyngeal wall involvement and level Ib is included in case of oral cavity involvement. Ib may be included ipsilaterally only, in selected cases.

Hypopharynx

Anatomy: Hypopharynx is limited by oropharynx, larynx, and oesophagus. The anterior wall includes arytenoid cartilage and aryepiglottic fold to the lower cricoid cartilage. Pyriform sinus includes pharyngo-epiglottic fold and the upper extension of oesophagus, laterally to the thyroid cartilage and medially from the hypopharyngeal surface of the aryepiglottic fold, arytenoid cartilage, and cricoid cartilage. The hypo-pharyngeal posterior wall extends from a level through the hyoid bone (bottom of vallecula) to the lower border of the cricoid cartilage and from apex of one pyriform sinus to the other.

CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: GTV-T and -N with an isotropic margin of 10 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. In case of T1/T2 primaries, the prevertebral fascia and the thyroid cartilage can be considered as a natural barrier.

CTV3: Elective nodal regions are:

- N0: bilateral level II, III and IV. The cranial part of level II can be excluded after individual consideration on the uninvolved side(s).
- N1-3: bilateral level II, III and IV. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N. In case of subglottic or oesophageal involvement level VIa+b is included.

Supraglottic larynx

Anatomy: Supraglottic larynx includes larynx above the vocal folds i.e. the suprahyoid part of epiglottis (lingual and laryngeal surface above hyoid bone), aryepiglottic folds, infrahyoid epiglottis, ventricular folds, and sinus of Morgagni.

CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: GTV-T and -N with an isotropic margin of 10 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. For T1 tumours the thyroid cartilage and prelaryngeal muscle is considered a natural barrier. For T2 tumours the pre-laryngeal muscles are considered as a natural barrier.

CTV3: Elective nodal regions:

- N0: bilaterally level II and III.
- N1-3: bilaterally level II and III. Level IV on the side of nodal involvement or bilateral in case of hypopharyngeal involvement. Elective regions are ex-tended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N
- In case of subglottic or oesophageal involvement, level VIa+b is added
- The stoma is included in case of tracheostomy. The stoma is defined as the incision + 5mm

Glottic larynx

Anatomy: The region includes vocal cords, anterior and posterior commissure

For T1N0

CTV1: Includes primary tumour (GTV-T) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers. The thyroid cartilage is considered a natural barrier. There is no CTV2.

For T2N0:
CTV1: Includes primary tumour (GTV-T) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers. The thyroid cartilage is considered a natural barrier.

CTV2: GTV-T and -N with an isotropic margin of 10 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers. CTV2 can be individually expanded to include high risk areas. CTV2 could be left out in case of superficial tumours without involvement of the anterior commissure.

CTV3:

- As a rule, no elective irradiation is used.
- Nodal irradiation could be considered in non-superficial T2N0. Elective areas are dependent on areas of involvement. Often level III and caudal level II
- In case of supraglottic extension, elective nodes should be irradiated according to recommendations for that site
- In case of subglottic or oesophageal involvement, level VIa+b is added
- The stoma is included in case of tracheostomy. The stoma is defined as the incision + 5mm

T3-4N0 and all N+:
CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident. Mucosa inside the thyroid cartilage should be included.

CTV2: GTV-T and -N with an isotropic margin of 10 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. CTV2 can be individually expanded to include high risk areas, e.g. supra- or subglottic larynx.

CTV3: Elective nodal regions

- N0: bilaterally level II and III.
- N1-3: bilaterally level II and III. Level IV on the side of nodal involvement, or bilateral in case of hypopharyngeal involvement. Elective regions are ex-tended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N
- In case of subglottic or oesophageal involvement, level VIa+b is added
- The stoma is included in case of tracheostomy. The stoma is defined as the incision + 5mm

Subglottic larynx

Anatomy: The region includes larynx below vocal cords.

CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: GTV-T and -N with an isotropic margin of 10 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. CTV2 can be individually expanded to include high risk areas, e.g. glottic or supraglottic larynx.

CTV3: Elective nodal regions

- N0: bilateral level III, IV, VI, and level II in case of supraglottic extension
- N1-3: bilateral level III, IV, VIa+b, and level II in case of supraglottic extension. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected, the entire muscle is included at least 2 cm above and below GTV-N.
- The stoma is included in case of tracheostomy. The stoma is defined as the incision + 5mm

Postoperative radiotherapy after primary laryngectomy
Elective nodal treatment can be performed using (chemo)irradiation or surgery in case of primary total laryngectomy. The target is individually defined by the multidisciplinary team.

CTV1: Macroscopic tumour (R2), microscopically non-radical operated areas (R1) or areas of ENE, with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. CTV2 can be individually expanded to include high risk areas.

In case of an absent CTV1, i.e. after radical (R0) surgery, CTV2 includes the pre-operative GTV with at least 10 mm margin. In case of uncertainties as to the localization of involved nodes, or if the nodes are not identified on a pre-operative scanning, the entire involved level is included.

CTV3: Includes the remaining surgical bed and potentially elective areas. As a rule, elective nodal areas without additional margin and the tracheostoma with a 5 mm margin is included. Nodal areas as mentioned above for the individual sub-sites.

Sinonasal tumours

Anatomy: The region includes nasal cavity posteriorly to the vestibule, the maxillary sinus, ethmoid sinuses, sphenoid sinus, and frontal sinus. All areas are bordered by bone except the anterior and posterior extent of the nasal cavity.

Treatment is decided according to national guidelines (dahanca.dk). The mainstay of treatment is surgery in all operable patients with a R0 resections as the goal. Postoperative radiotherapy is indicated in pT3-pT4 tumours even after radical surgery (R0), in case of R1 or R2 resection and in all cases of uncertainty as to the sufficiency of the margins. Furthermore, postoperative radiotherapy can be considered in pT2.
Often, target coverage and normal tissue sparing must be prioritized, based on a case-specific evaluation.

Primary radiotherapy
CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: GTV-T and -N with an isotropic margin of 10 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. Furthermore, the entire involved sinus(es) or ipsilateral nasal cavity is included, as well as other high-risk areas after individual consideration.

CTV3: The elective nodal areas are:

- N0: Elective nodal irradiation is considered only in case of involvement of skin, oral cavity, or pharynx. In that case, level Ib and II are included. Level III can be included. Level IV, V, VIIa (retropharyngeal), and VIIb (retrostyloid) are included in case of nasopharyngeal invasion. Ipsilateral radiotherapy can be used in case of limited involvement of e.g. gingiva, without involvement of midline structures. Elective treatment of the neck (surgery or radiotherapy) can be considered in case of T3-T4 tumours, especially in case of squamous cell tumours of the maxillary sinus.
- N1-3: Involved elective regions including the volumes mentioned above. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected, the entire muscle is included at least 2 cm above and below GTV-N. Ipsilateral radiotherapy can be used in case of limited involvement, e.g. gingiva, without involvement of midline structures.

Postoperative radiotherapy
CTV1: Includes non-radically operated areas (R2 and R1) with a 5 mm isotropic margin. Margins could individually be enlarged to include high-risk regions and cropped for air and at natural barriers such as bone.

CTV2: Includes CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. Should also include the entire involved region, i.e. the involved sinus(es) and/or ipsilateral nasal cavity.

In case of an absent CTV1, i.e. after radical surgery (R0), CTV2 includes the pre-operative GTV plus at least 10 mm and the entire region i.e., the entire involved sinus(es) and/ or nasal cavity.
In case of uncertainties as to the localization of involved nodes, or if the nodes are not identified on a pre-operative scanning, the entire involved level is included.

CTV3: Surgical bed plus elective nodal areas.

- N0: Elective treatment is given only in case of involvement of skin, oral cavity, or pharynx. In that case, level Ib and II are included. Level III can be included. Level IV, V, VIIa (retropharyngeal) and VIIb (retrostyloid) are included in case of nasopharyngeal invasion. Ipsilateral radiotherapy can be used in case of limited involvement of e.g. gingiva, without involvement of midline structures. Elective treatment of the neck (surgery or radiotherapy) can be considered in case of T3-T4 tumours, especially in case of squamous cellular tumours of the maxillary sinus.
- N1-3: In case of pN1 without ENE, no elective irradiation is recommended after neck dissection. In case of pN2-pN3, postoperative radiotherapy is recommended irrespective of the result of the neck dissection. T-site irradiation is considered relative to the possibility of irradiating any local-recurrence. CTV3 includes elective regions mentioned above. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N -N. Ipsilateral radiotherapy can be used in case of limited involvement of e.g. gingiva, without involvement of midline structures.

Salivary gland

Anatomy: Salivary gland tumours arise in the macroscopic glands (parotid, submandibular, and sublingual glands) as well as the entire mucous membranes of the head and neck, predominantly in the oral cavity.

DAHANCA has divided salivary gland tumours into prognostic groups based on histology. The treatment principles are determined by national guidelines (www.dahanca.dk). As a rule, surgery is performed as the primary treatment of all operable tumours. Postoperative radiotherapy is recommended after non-radical surgery of the T site (R1 or R2), T≥T3, N+, perineural invasion, recurrences, and high-grade tumours, irrespective of other risk factors.

DAHANCA has divided salivary gland tumours into prognostic groups based on histology:
Low grade: Acinic cell carcinoma, polymorphous low-grade adenocarcinoma, basal cell adenocarcinoma, epithelial-myoepithelial carcinoma, high and intermediate grade mucoepidermoid carcinoma, well-differentiated adenocarcinoma NOS (Not Otherwise Specified), well-differentiated non-invasive or minimally invasive carcinoma of pleomorphic adenoma, clear cell carcinoma NOS, sialoblastoma.

High grade: Adenoid cystic carcinoma, intermediate and poorly differentiated adenocarcinoma NOS, intermediate and poorly differentiated carcinoma in pleomorphic adenoma with invasive depth of >1,5 mm, poorly differentiated mucoepidermoid carcinoma, salivary duct carcinoma, primary squamous cell carcinomas,

undifferentiated carcinoma (lymphoepithelial carcinoma), large cell carcinoma, mucinous adenocarcinoma, oncocytic carcinoma, carcino-sarcomas, small cell carcinoma, myoepithelial carcinoma.

Perineural invasion (PNI) is a histopathological description and a potential risk factor of loco-regional recurrence and distant metastasis. Perineural spread (PNS) is a clinical /macroscopic concept that describes growth along macroscopic nerves. It is often asymptomatic and observed per-operatively or on MRI scans. PNI does not imply PNS. PNI is an indication for postoperative radiotherapy. PNS is an indication to expand the CTV along macroscopic nerves. See e.g. (77) for delineation guidelines.

Radical radiotherapy:
CTV1: Includes the primary tumour (GTV-T) with a 5 mm isotropic margin plus the entire involved salivary gland. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: GTV-T and -N with an isotropic margin of 10 mm. cropped for air and at natural barriers such as bone.

CTV3: As a rule, elective ipsilateral regions are irradiated only. In case of involvement of midline structures both sides of the neck are irradiated

- Parotid: level II + III + VIII (parotid group)
- Submandibular: level Ia + Ib + II + III
- For all other glands, the principles for the specific region (often oral cavity) are applied. Elective regions are extended at least 2 cm cranially and caudally of any GTV-N. If extension to nearby muscle involvement is suspected, the entire muscle is included at least 2 cm above and below GTV-N.
- In case of PNS along the major branches of the cranial nerves, these are irradiated to the base of scull.

Postoperative radiotherapy
CTV1: Macroscopic tumour (R2), microscopically non-radical operated areas (R1) or areas of ECE, with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone.
If no CTV1 is present in case of radical surgery (R0), CTV2 is the pre-operative GTV with an isotropic margin of 10 mm.
Furthermore, the entire salivary gland should always be included in the CTV2.
In case of uncertainties as to the localization of involved nodes, or if the nodes are not identified on a pre-operative scanning, the entire involved level is included.

CTV3: Includes the surgical bed and elective areas.

- In case of PNS along the main branches of the cranial nerves, these are irradiated to the base of scull.

- pN0: No elective nodal irradiation is performed.
- N+: As a rule, selective ipsilateral regions are irradiated only. In case of involvement of midline structures both sides of the neck are irradiated
- Parotid: level II + III
- Submandibular: level Ia+ Ib + II + III
- For all other glands the principles for the relevant region (often oral cavity) is applied. Elective regions are extended at least 2 cm cranially and caudally of any GTV-N If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N.

Lymph node metastasis from unknown primary tumour (CUP)

Anatomy: Neck metastasis from an unknown primary tumour is defined as an undiagnosed primary tumour after thorough diagnostic procedures, at the beginning of treatment.

Diagnostic procedures and treatment follow national guidelines (dahanca.dk).

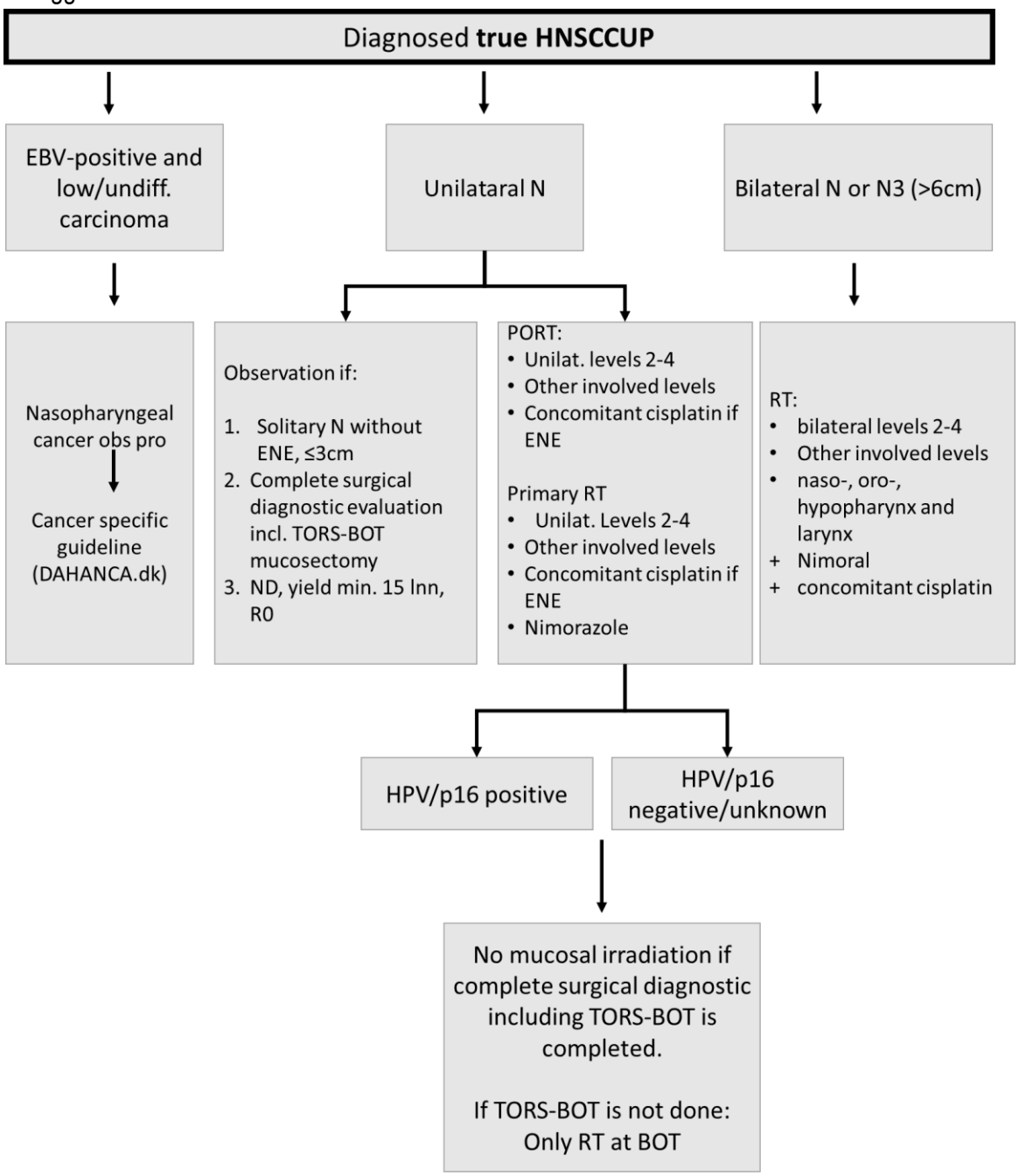
A distinction is made between squamous cell carcinomas and other histologies.

Neck nodes containing squamous cell carcinoma will often originate from the mucous membranes especially of the base of tongue area. For other histologies, multiple origins may exist. Some can be treated with curative intent, e.g. germ cell tumours, small cell lung cancer, and some are relatively treatment resistant such as melanomas.

Radiotherapy for squamous cellular carcinomas
In case of nodal metastasis from a squamous cellular carcinoma there is, indication for treatment of regional lymph nodes as well as nodal levels at highest risk This is *not* the case for other histologies.

Irradiation of the ipsilateral neck is in general recommended for ipsilateral disease. Bilateral irradiation is only recommended in case of bilateral lymph node involvement or N3 disease. In these cases, mucosal irradiation

is suggested as irradiation of a mucosal recurrence is difficult.



CTV1: Includes known macroscopic tumour (non-operated or R2), insufficiently operated areas (R1) or areas of ENE. CTV1 includes involved nodes with an isotropic margin of 5 mm in all direction, cropped for air and at natural barriers such as bone.

CTV2: GTV-N with an isotropic margin of 10 mm. Margins can individually be enlarged to include high risk regions, such as mucosal areas with an increased risk of harbouring a primary and cropped for air and at natural barriers such as bone.

CTV3: For unilateral disease, elective lymph node areas include levels II, III, and IV unilaterally, while levels I and V are only irradiated if there are metastases in those levels.

For bilateral disease og N3 disease, elective lymph node areas include levels II, III, and IV bilaterally, while levels I and V are only irradiated if there are metastases in those levels. Elective regions are extended at least 2 cm cranially and caudally of any GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N.

Elective mucosal areas of the larynx and pharynx is only included in case of bilateral or N3 disease due to the technical difficulties in reirradiation in these situations if the primary tumor occurs at a later stage: The entire mucous membrane of 5 mm depth, in the pharynx and larynx, from the base of scull to below the cricoid cartilage, including tonsillar fossa on both sides.

The base of tongue is only included in case base of tongue mucosectomy by TORS has not been performed as a part of the diagnostic work-up. In this case, base of tongue should be included with a 10 mm margin due to its irregular surface.

Suspected nasopharyngeal origin

In case of EBV-positive and low/undifferentiated carcinoma, the patient is treated according to to DAHANCA guidelines for nasopharyngeal carcinoma.

Radiotherapy for non-squamous cell histologies
In case of adenocarcinoma, treatment depends on the likely localisation of a primary. Localisations include salivary and thyroid glands, nasal cavity and paranasal sinuses, lung, breast, gastro-intestinal canal, uterus, ovary, and prostate. Localisation, immuno-histochemistry, serology and iodine scintigraphy may aid in the search of a primary and guide the treatment. In case of unknown primary after relevant diagnostics, involved field irradiation to curative doses may be indicated, but elective nodal or mucosal irradiation is not recommended.
Radiotherapy for isolated SCC nodes in level I, level VIII (intra-parotid), and distal level IV distal level V are individually treated after MDT discussion.
recommended.

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5. Method

Literature search

No formalized literature search has been performed.

Literature review

The evidence level is in general low, but most often international agreement has been reached on the overlying principles of therapy. Some recommendations rely on international guidelines e.g. by the ICRU (International Commission on Radiation Units and Measurements)

Formulation of the recommendations

All recommendations have been reviewed and discussed among the DAHANCA radiotherapy quality assurance group with physician and physicist representatives from all centres.

Stakeholder involvement

Patient values and preferences are not relevant in this technical aspect and therefore no attempt has been made for establishing a patient panel.

Hearing

No formal peer review process has been performed although the Danish Head and Neck Cancer group have formally also approved the guidelines. This multidisciplinary group represents all medical specialties and medical physicists involved in the diagnosis, treatment, and follow up of head and neck cancer patients.

Approval

Content approval:
DAHANCA

Administrative approval:
12.12.2025

Recommendations that entail significant additional costs

No new specific resource-demanding recommendations have been proposed in the present guidelines, although all guidelines add to the increasing complexity of treatment.

Need for further research

The target margins and normal tissue sparing are the subject for several projects within the DAHANCA group.

Authors and conflicts of interest

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None of the authors of the guidelines have declared conflicts of interest with regard to any medico-technical compagnies relevant for the guidelines.

For detailed cooperative relationships, please refer to the declaration via the Danish Medicines Agency's website

Plan for revision

The guidelines will be frequently updated as site specific guidelines are approved by DAHANCA and technical development within the field will be closely monitored

Version of guideline template

The guideline has been developed in the 3.0 version of the template.

6. Monitoring

Standards and indicators

Development of quality in this area is supported by knowledge from the DAHANCA database) under the auspices of the Danish Healthcare Quality Institute (SundK), as the indicators in the database must illuminate relevant clinical guidelines.
The clinical quality database's steering group has the mandate to decide on the database's indicator set, including which specific processes and results are monitored in the database.
If the author group has proposals for specific recommendations that can be usefully included in the steering group's discussion in connection with the ongoing revision of the indicator set, they can be listed here:

Adherence to the guidelines is monitored for the large number of patients included in clinical protocols. Many overall quality indicators are monitored in the clinical DAHANCA database and included in the yearly report.
Furthermore: See chapter on “Quality assurance”

Plan for audit and feedback

The guidelines are evaluated at each meeting in the DAHANCA quality assurance group, with meetings two-three times annually. Work has been initiated for the next update.

7. Appendices

Appendix 1: Delineation of organs at risk

Organ	Cranial	Caudal	Anterior	Posterior	Lateral	Medial	Reference delineation*
BrainStem	**Bottom of the 3rd ventricle**	Tip of the dens of C2					Brouwer(78). Except craniel extended to the bottom of 3rd ventricle.
SpinalCord	Tip of the dens of C2						Brouwer[](78)
Chiasm			Optic nerve. Ie. chiasma is a Line" not a "H"	Optic tract	A. carotis interna/ cerebri media		
OpticNerve_L OpticNerve_R							
EyeBack_L EyeBack_R (Eye except EyeFront)			EyeFront				
EyeFront_L EyeFront_R (cornea, iris, lens)*			Structures anterior of the vitreous humour				
Lacrimal_L Lacrimal_R (gl. lacrimalis)	Supralateral to the eye						
Brain	Entire Brain except brainstem						
Cochlea_L Cochlea_R	Hypodense volume in temporal bone anterior to canalis auditoria interna						
Esophagus (cervical esophagus+ esophagus inlet muscle+ cricopharyngeal muscle)	First slice caudal to the arytenoid cartilages	Sternal notch	Posterior edge of cricoid cartilage. tracheal lumen	Prevertebral muscle	Thyroid cartilage, fatty tissue, thyroid gland. Thyroid cartilage		Cervical esophagus+ esophagus inlet muscle+ cricopharyngeal muscle as in Christianen(79)

LarynxG (glottic larynx)	Upper edge of the arythenoid cartilages	Lower edge of cricoid cartilage (if soft tissue is present)	Thyroid cartilage	Inferior PCM, pharyngeal lumen/ cricoid cartilage	Thyroid cartilage	Pharyngeal lumen (lumen excluded)	Christianen(79)
LarynxSG (supraglottic larynx)	Tip of epiglottis	First slice cranial to the upper edge of the arytenoid cartilages	Hyoid bone, pre-epiglottic space, thyroid cartilage	Pharyngeal lumen, inferior PCM	Thyroid cartilage	Pharyngeal lumen (lumen excluded)	
Mandible	Mandible teeth excluded						Brouwer(78)
OralCavity (=Brouwer extended oral cavity)	Hard palate mucosa and mucosal reflections near the maxilla	The base of tongue mucosa and hyoid posteriorly and the mylohyoid m. and ant. belly of the digastric m. anteriorly	Inner surface of the mandible and maxilla	Post. borders of soft palate, uvula, and more inferiorly the base of tongue	Inner surface of the mandible and maxilla		
Parotid_L Parotid_R							
PCM_Low (lower pharyngeal constrictor)	First slice caudal to the lower edge of hyoid bone	Lower edge of the arythenoid cartilages	Soft tissue of supraglottic/ glottic larynx	Prevertebral muscle	Superior horn of thyroid cartilage		Christianen(79)
PCM_Mid (middle pharyngeal constrictor)	Upper edge of C3	Lower edge of hyoid bone	Base of tongue, hyoid	Prevertebral muscle	Greater horn of hyoid bone	Pharyngeal lumen	
PCM_Up (upper pharyngeal constrictor)	Caudal tip of the pterygoid plates (hamulus)	Lower edge of C2	Hamulus of pterygoid plate; mandibula; base of tongue; pharyngeal lumen	Prevertebral muscle	Medial pterygoid muscle	Pharyngeal lumen	
Pituitary	Gland as seen on MRI or inner part of sella turcica						Brouwer(78)
Submandibular_L Submandibular_R	Med. pterygoid m., mylohyoid m.	Fatty tissue	Lat. Surface mylohyoid m., hyoglossus m.	Parapharyngealspace, sternocleidomastoid m.	Med. surface med. pterygoid m., med. surface mandibular	Lat. surface mylohyoid m.,hyoglossus m., superior and middle pharyngeal	

					bone, platysma	constrictor m., anterior belly of the digastric m.	
Thyroid							
A_Carotid_LA_Carotid_R							
Buccal mucosa	Bottom of maxillary sinus	Upper edge teeth sockets	Lips, teeth	Med. pterygoid m.	Buccal fat	Outer surface of the mandible and maxilla, oral cavity/base of tongue/soft pallate	
Lips	Hard palate (lateral), anterior nasal spine (at the midline)	Lower edge teeth sockets, cranial edge mandibular body	Outer surface of the skin	Mandibular body, teeth, tongue, air (if present)	Depressor anguli oris m.buccinator m. levator anguli oris, m./risorius m. (the mentioned mucles are all lateral to the m. orbicularis oris)	Hard palate (lateral), anterior nasal spine (at the midline)	
Hippocampus	Bilateral structures. Defined by MRI T1-hypointense signal medial to the temporal horn.						Gondi(80) https://www.nrgoncology.org/about-us/center-for-innovation-in-radiation-oncology/brain-tumors/

Appendix 2: Applicable dose and fractionation schedules

Using IMRT with simultaneous integrated boost, the following dose and fractionation schedules may be prescribed.

Fractionation schedules DAHANCA 2019	CTV1				CTV2		CTV3	
	Total dose	Dose/fx	fx	Fx/W	Total dose	Dose/fx	Total dose	Dose/fx
Conventional fx	66	2	33	5*	60	1.82	50	1.52
Conventional fx	68	2	34	5*	60	1.76	50	1.47
Accelerated fx	66	2	33	6	60	1.82	50	1.52
Accelerated fx	68	2	34	6	60	1.76	50	1.47
Accelerated hyperfx	76	1.36	56	10	66	1.18	56	1

*5 fractions per week is used for non-squamous cell carcinoma, postoperative and unknown primaries only

Appendix 3: DAHANCA – guidelines 2000-2025

The guideline is to a large extent a product of discussion within the DAHANCA Radiotherapy Quality Assurance Group, through an extended period from the very first guidelines in 2000.

DAHANCA, the Danish Head and Neck Cancer Group, was founded in 1976. The group has a long-standing tradition for conducting clinical trials as well as establishing national guidelines for radiotherapy for head and neck cancer. DAHANCA was the first Danish cooperative group to introduce national guidelines for CT-based conformal RT and IMRT.

The first edition of the guidelines was implemented in 2000 after it was approved by the DAHANCA group in December 1999. With that, ICRU compatible terminology was implemented at all Danish referral centres for head and neck cancer.

The second edition (2002) was approved at the DAHANCA meeting on the 13th of December 2001. The following minor adjustments were made:

- The possibility of treating T1a carcinomas of the vocal cord with only 62 Gy was removed.
- The elective target for primaries of the oropharynx was changed from level II-IV to level II, III (+ retro-pharyngeal nodes in case of tumour in the posterior pharyngeal wall, and potentially level IV in case of N2-3.

The third edition (2004) was approved at the DAHANCA Radiotherapy Quality Assurance Group meeting 14th of September 2004. The following major changes were made:

- CTV-T(umour) was redefined to ”Areas of known macroscopic tumour (GTV), microscopically incompletely resected tumour, or areas of known extra-nodal extension” to comply with post-operative radiotherapy recommendations.
- CTV-E(lective) was divided into CTV-E(high-risk) and CTV-E(low-risk). CTV-high-risk was only relevant for post-operative radiotherapy or IMRT and treated to 60 Gy.
- Elective nodal regions were defined according to the Brussels-Rotterdam consensus, instead of Nowak(81). Tables and figures from the original publication were included as appendices.
- A modification of the inclusion of the upper part of level 2 was allowed for cancers of the larynx and hypopharynx.
- An appendix with guidelines for the use and implementation in IMRT, including fractionation and normal tissue constraints, was included as an appendix.

The fourth edition (2013) was approved at the DAHANCA meeting 10th of December 2012. All chapters were thoroughly revised in order to comply with the ICRU guidelines and to define important parameters of quality assurance. Furthermore,

- A detailed list of sensitive normal tissues and constraints was added.
- The terms CTV-T, CTV-N, CTV-E(high-risk), CTV-E(low-risk) were renamed into the new terms CTV1, CTV2 and CTV3, and ITV was included into the definition of CTV.
- The margins around GTV were thoroughly discussed. The existing guidelines had been interpreted with large departmental variations. Margins of 0-10 mm from GTV to CTV had been used. The adopted margins were thus a compromise: A 5 + 5 mm margin from GTV to CTV1, and from CTV1 to CTV2, respectively, were suggested.

- A table of minor and major deviations for dose and fractionation for QA, and a table of recommended dose-fractionation schedules were added.

The following minor revisions have been approved May 22nd 2014

- A precision that the added margin, GTV to CTV2, should not exceed 12 mm.
- Grégoire (33) added as reference.
- It is emphasized that the spinal cord should always be delineated and that the brain stem should be delineated in case of elective irradiation.
- The constraint of cochlea is corrected to $D_{5\%} \leq 55Gy$.
- All treatment interruptions and prolongations must be compensated. The word “unintended” has been erased.
- Oropharyngeal and supraglottic tumours: Level IV has been excluded in case of N1-3 neck disease and the sentence: “Level IV on the side of nodal involvement” has been inserted in order to avoid level IV irradiation to the non-involved side of the neck.
- Regarding postoperative radiotherapy after laryngectomy: In case of planned primary total laryngectomy, with postoperative (chemo-)radiotherapy, elective nodal areas can be treated with radiotherapy. The treatment plan is made individually by the multidisciplinary team.
- Regarding postoperative radiotherapy for salivary gland tumours: In case of pN0, the elective nodes are not to be irradiated.
- Regarding Unknown primary: The wording has been brought up to date with the “National Guidelines for the Treatment of Lymph Node Metastasis from Unknown Primary”

Fifth edition (2018) was approved at the DAHANCA meeting September 19th, 2018. All chapters were thoroughly revised, with the following major revisions:

- New chapters and sections on proton therapy and perineural spread.
- Normal tissue delineations according to new international guidelines. Among others, the hippocampus was included as a new organ at risk.
- The guidelines by Lee (4) has inspired a thorough revision of the guidelines regarding nasopharyngeal CTV
- The guidelines by Grégoire (5) inspired a thorough revision of the guidelines for larynx and pharynx cancer.
- The standardized nomenclature for OARs and targets(39) were included and mentioned in an appendix.

In the sixth edition (2020), a separate chapter has been added on postoperative radiotherapy. The chapter regarding GTV delineation was added and published(82). From, and including the sixth edition, the English version is considered the reference document and the Danish version is the translation. The 2020 Guidelines were published(83).

In the present 2025 guidelines the following issues are included: Constraints for hypofractionation, planning of reirradiation, target definition after induction chemotherapy, planning of complex target, and clarification of the guidelines for elective targets. The chapter of unknown primary tumours are updated and rewritten.

Appendix 4 Comments to the elective nodal areas of Gregoire

DAHANCA QA Comments to the guidelines and atlas for elective nodal volumes

[Gregoire Radiotherapy and Oncology 110 (2014) 172–181](33)

General Comments
In patients with “non-average” anatomy or positioning, levels may be modified.
Examples:
Long neck: Level 4 may be shortened more caudal than 2 cm above the manubrium
Short Neck: Level 4 may not be present or very short, and elective areas may be defined more caudally.
"Low" manubrium: As short neck
Hyperextended neck: Transverse process of C1 and hyoid bone may not be ideal landmarks for nodal levels
Severe obesity: Platysma/ skin should not always be used as boundaries, but levels (Ia+b, II) may be shortened in the periphery
Visible lymph nodes, without any signs of malignancy, outside defined levels should not be included
Whenever the SCM is the anterior/ posterior border of a level, the border is defined radially toward the centre of the patient and not a "horizontal" line

Level 1b

The submandibular gland is a part of level 1b. Level 1b therefore continues caudally to caudal tip of submandibular gland.

Clarification: Anterior border of level 1b below hyoid bone (If the caudal edge of the submandibular gland is present below the hyoid bone): To the mid-line.

Level II

Note: The lateral border of level II is m. digastricus venter post. That allows for better parotid sparing!
Note: The caudal edge of the lateral process of C1 is the cranial boundary. Any extension will harm parotid sparing
Note: The area between anterior SCM and posterior mandible/ submandibular gland caudal of parotid gland should be included to the platysma.

Clarification: Cranially: Level II is defined below the SCM posteriorly, only where a space is visible. SMC becomes an aponeurosis cranially and continues far posteriorly. This varies according to patient positioning.

Level III

Correction: Level III cranially extends anteriorly to the submandibular gland. Caudal of the submandibular gland, the anterior border of SCM defines the level. (In Gregoire: the atlas shows an anterio-lateral extension not mentioned in the table)

Clarification: Anterior level III between SCM and pre-laryngeal muscles is sometimes not visible. In that case a target is defined anyway, as a 3 mm wide line.

Level IV (=Level 4a in Gregoire)

Clarification: The caudal border is defined as 2 cm above manubrium. In patients with a very long or short neck, this may be modified. Level 4b is included only in order to achieve 2 cm elective irradiation below GTV-N

Clarification: Anterior level IV between SCM and pre-laryngeal-/ pre-tracheal muscles / thyroid gland is sometimes not visible. In that case a target is defined anyway, as a 3 mm wide line.

Level V

Clarification: The posterior border of level 5 is defined as an arbitrary horizontal line from the anterio-lateral border of the trapezoid muscle.

Clarification: Above the hyoid bone, the space between the posterior border of SCM and trapezoid muscle is called the occipital level (Xb) and should be included in patient with cranial posterior nodes, e.g. in nasopharyngeal cancer patients

Level VIIb

Clarification: The upper border of the jugular foramen forms the cranial boundary

Appendix 5 Nasopharynx CTV2 Atlas

See Dahanca.dk

8. About this clinical guideline

This clinical practice guideline is developed in collaboration between the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Danish Healthcare Quality Institute (SundK). The development is part of an intensified guideline effort launched in relation to the National Cancer Plan IV. The aim is to support high-quality cancer care across the Danish healthcare system. The guideline content is approved by the disease-specific Multidisciplinary Cancer Group, whereas the format is approved by the Center for Clinical Practice Guidelines | Cancer. Further information about clinical practice guidelines concerning cancer treatment in Denmark can be found here: www.dmcg.dk/kliniske-retningslinjer

The guideline targets clinically active healthcare professionals in the Danish healthcare system and contains systematically developed statements that can be used as decision support by professionals and patients when deciding on appropriate and correct healthcare services in specific clinical situations.

Clinical practice guidelines concerning Danish cancer care is characterized as professional advice. The guidelines are not legally binding and professional judgment in the specific clinical context will always determine what the appropriate and correct medical care is. Adherence to the guideline recommendations is no guarantee for a successful outcome. Sometimes care corresponding to a lower level of evidence will be preferred due to the individual patient's situation.

The guideline includes, in addition to the central recommendations (chapter 1 – quick guide), a description of the basis for the recommendations – including the underlying evidence (chapter 3), references (chapter 4), and applied methods (chapter 5).
Recommendations marked A are based on the strongest evidence, while recommendations marked D are based on the weakest evidence. For further information on strength of evidence see the "Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations",
https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
This guideline also includes information on the target population (chapter 2) and the method of development (chapter 5) is also included in the guideline. See the table of contents for page references.

The guideline template has been prepared based on international quality requirements for the development of clinical guidelines as described by AGREE II, GRADE, and RIGHT.
For information on the Danish Health Authority's cancer packages – descriptions of the entire standard patient pathway specifying requirements for timelines and content – refer to the relevant disease area at:
https://www.sst.dk/en/english

The Danish Health Authority (National Cancer Plan IV) and the Danish Healthcare Quality Institute (SundK) funded the development of this clinical practice guideline.