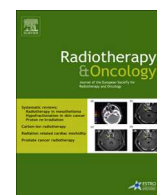




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Original article

Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines

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ABSTRACT

Purpose: Few studies have reported large inter-observer variations in target volume selection and delineation in patients treated with radiotherapy for head and neck squamous cell carcinoma. Consensus guidelines have been published for the neck nodes (see Grégoire et al., 2003, 2014), but such recommendations are lacking for primary tumour delineation. For the latter, two main schools of thoughts are prevailing, one based on geometric expansion of the Gross Tumour Volume (GTV) as promoted by DAHANCA, and the other one based on anatomical expansion of the GTV using compartmentalization of head and neck anatomy. **Method:** For each anatomic location within the larynx, hypopharynx, oropharynx and oral cavity, and for each T-stage, the DAHANCA proposal has been comprehensively reviewed and edited to include anatomic

Abbreviations: AIRO, Italian Association of Radiation Oncologists; CACA, committee of head & neck cancer, the committee of nasopharyngeal cancer, China Anti-Cancer Association; DAHANCA, Danish Head and Neck Cancer Group; EORTC, European Organisation for Research and Treatment of Cancer; GEORCC, Grupo Español de Oncología Radioterapia para Cancer Cabeza y Cuello; GORTEC, Groupe d'Oncologie Radiothérapie Tête Et Cou; HKNPCSG, Hong Kong Naso Pharynx Cancer Study Group; HNCIG, Head & Neck Cancer Inter Group; IAG-KHT, Interdisziplinäre Arbeitsgruppe für Kopf-Hals-Tumore; LPRHHT, Dutch National Platform Radiotherapy Head and Neck Cancer; NCIC-CTG, National Cancer Institute of Canada Clinical Trials Group; NCRI, National Cancer Research Institute; NRG-Oncology, NSABP (National Surgical Adjuvant Breast and Bowel Project) – RTOG (Radiation Therapy Oncology Group) – GOG (Gynecologic Oncology Group) Oncology; PHNS, Polish Head & Neck Society; SBRT, Sociedade Brasileira de Radioterapia; SOMERA, Sociedad Mexicana de Radioterapeutas; SRO, Swiss Society for Radiation Oncology; SSHNO, Scandinavian Society for H&N Oncology; TROG, Trans-Tasman Radiation Oncology Group.

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Gross Tumour Volume (GTV)
Radiotherapy
Head and neck
Guideline

knowledge into the geometric Clinical Target Volume (CTV) delineation concept. A first proposal was put forward by the leading authors of this publication (VG and CG) and discussed with opinion leaders in head and neck radiation oncology from Europe, Asia, Australia/New Zealand, North America and South America to reach a worldwide consensus.

Results: This consensus proposes two CTVs for the primary tumour, the so called CTV-P1 and CTV-P2, corresponding to a high and lower tumour burden, and which should be associated with a high and a lower dose prescription, respectively.

Conclusion: Implementation of these guidelines in the daily practice of radiation oncology should contribute to reduce treatment variations from clinicians to clinicians, facilitate the conduct of multi-institutional clinical trials, and contribute to improved care of patients with head and neck carcinoma.

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A number of retrospective studies have highlighted large inter-observer variability in radiotherapy target volume delineation for patients with head and neck squamous cell carcinoma (SCC) [1,2]. It is likely that such heterogeneity contributes to some extent to patient outcome variability, as suggested in clinical trials reporting on the impact of radiotherapy quality assurance programmes [3,4].

In order to limit such variability, international consensus guidelines have been published for the delineation of the nodal Clinical Target Volume (CTV-node) in the node-negative and in the node positive neck [5,6]. For the primary tumour target volume delineation, such comprehensive guidelines do not exist, and only few general recommendations have been tentatively proposed [7–11]. These recommendations were mainly based on anatomical concepts, i.e. to propose anatomical compartments to be included, and/or boundaries to limit the CTV delineation. Typically, these recommendations did not consider all the subtleties associated with the exact location and staging of the primary tumour, and the use of such guidelines was associated with quite a large inter-observer variability as illustrated by the experience gathered throughout the DAHANCA network [12].

In this context, in 2013, the Danish national guidelines for CTV delineation of head and neck squamous cell carcinoma were revised to propose the concept of isocentric geometric expansion of the primary tumour Gross Tumour Volume (GTV-P), i.e. the so-called “5 + 5 mm expansion” with corrections for natural anatomic boundaries such as bone or air cavities. According to the Danish guidelines, a so-called therapeutic dose is delivered to the PTV associated with the primary tumour GTV + 5 mm (i.e. CTV1), and a lower (prophylactic or intermediate) dose is delivered to the PTV associated to an additional 5 mm rim of tissue (i.e. CTV1 + 5 mm or CTV2). The use of these new guidelines has resulted in much more homogeneous target volume delineation and irradiation among centres [12]. However, as the editing was mainly proposed for natural boundaries, it is expected that the Danish national guidelines include more non-target tissues in the CTV-P than should ideally be included.

For each anatomic location within the larynx, hypopharynx, oropharynx and oral cavity, and for each T-stage, the Danish national guidelines have been comprehensively reviewed and edited to include anatomic knowledge into the geometric CTV delineation concept. A first proposal was written by the leading authors (VG and CG) and then submitted to various stakeholders representing various international head and neck groups and/or institutions; they are all listed as co-authors of this manuscript. Through successive rounds of electronic and face to face discussions, a consensus was progressively reached. All authors have thus participated in the discussions of the proposal and agreed with this final version. For nasopharyngeal carcinoma, a similar approach has been initiated under the leadership of Dr. Anne Lee from Hong Kong and Dr. Joseph Wee from Singapore, who are recognized as worldwide experts for such tumour.

In the following sections, we will present the general concept and procedure for CTV-P delineation first and then we will describe the proposed guidelines for laryngeal, hypopharyngeal, oropharyngeal and oral cavity SCC and for the various T-stages; we will then conclude with a critical discussion of the limitations of such guidelines.

General description of the procedure for the primary tumour (CTV-P) delineation

Acquisition of the planning CT

- The patient should lie in the supine position on the flat tabletop of the simulation CT scanner with his head and neck immobilized in a neutral neck position by a reproducible immobilization device, e.g. 4–5 fixation point thermoplastic mask.
- Thin CT sections should be acquired typically from above the base of skull, cranially, to below the sterno-clavicular joint, caudally; for accurate dose calculation, the upper and lower bound should ideally include at least 5 cm of tissue slab beyond the target. Acquisition of 2-mm thin CT sections is preferable; the use of CT section thickness above 3-mm and overlapping CT sections is not advised.
- CT acquisition should be done with iv iodine contrast enhancement. For T1 glottic carcinoma, the use of contrast enhancement may be omitted. In cases of known allergic reaction to iodine contrast medium, all measures should be taken to ensure the availability of optimal planning-CT images, e.g. premedication with corticosteroids before iv contrast administration, fusion with MR or FDG-PET images.
- Coregistration of a high quality contrast-enhanced diagnostic CT and a non-enhanced planning CT is an option, which is however not favoured as it will likely increase the delineation uncertainties resulting from the registration inaccuracy between the various sets of CT.
- For patients with dental amalgam deteriorating the quality of the planning CT image, depending on the location of the primary tumour (e.g. tonsil fossa), the use of CT-artefact reducing algorithms, and the availability of supplementary images (e.g. MRI), careful consideration could be given to selective extraction of amalgamated teeth before performing the planning CT.

Delineation of the primary tumour GTV

Accurate delineation of the primary tumour GTV (in abbreviation GTV-P) is a key step for proper delineation of the primary tumour CTV (in abbreviation CTV-P). It requires the combination of clinical and imaging data collected during the work-up procedure that will have to be merged and transposed to the planning CT. This information should include at least the following:

- A clinical examination of the oral cavity and pharynx, and a pharyngo-laryngeal fiberoptic examination with a detailed description of the tumour extension and infiltration [13]. Should the Radiation Oncologist not perform this examination himself/herself, photographic images, drawings and/or video performed by an ENT specialist during the work-up procedure should be available. For early laryngeal lesions, narrow band imaging endoscopy may also be used to better assess the mucosal infiltration if available [14].
- A direct endoscopy under general anaesthesia performed by an ENT specialist during the work-up procedure, with photographic images, movies and/or drawing of the tumour extension. For oral cavity tumours, such examination may not be requested for the evaluation of the primary; it is however recommended for a more comprehensive work-up assessment of the pharyngo-larynx.
- A diagnostic contrast-enhanced CT and/or MRI performed not later than 3–4 weeks of the planning CT. Typically, lesions of the oral cavity and oropharynx are better visualized with an MRI, whereas CT may be used to image the larynx and the hypopharynx, especially for patients with breathing and swallowing difficulties [15]. This distinction may however vary according to institutional policy. If felt useful, the diagnostic MRI may be fused with the planning CT, provided it does not increase the uncertainties in tumour delineation due to sub-optimal image co-registration [16].
- The use of FDG-PET/CT images for the delineation of the primary is validated [17]; however, it is only recommended for locally advanced tumours. Indeed, for small tumours (e.g. T1 and T2) and especially for superficial lesions, the lack of spatial resolution of PET camera with partial volume effect does not allow a sufficiently accurate enough delineation of the GTV. PET volumes should preferably be delineated using user-independent segmentation algorithms [18].

Delineation of the primary tumour CTV: rationale behind the concept of a “5 + 5 mm expansion” margin from the GTV-P

According to ICRU definition, the CTV includes the GTV plus a volume of normal tissue at risk for microscopic tumour infiltration with a probability of occurrence considered relevant for therapy [19]. In this framework, 3 studies specifically looked at the pattern of microscopic tumour cell infiltration outside of the GTV-P for head and neck SCC.

- The study of Campbell et al. analysed 10 surgical specimens of mobile tongue SCC (T1–T3, UICC 7th ed, 2007) after surgical resection with curative intent [20]. The fresh surgical specimens were processed by whole-mount histopathology to allow full three-dimensional assessment of microscopic infiltration outside the macroscopic GTV-P in the normal tongue muscle. Corrections were applied to account for tissue shrinkage caused by dehydration and fixation, which on average was less than 1 mm. In this series, the maximum distance of microscopic infiltration was 7.8 mm, and in 95% of the cases, infiltration was observed within 3.95 mm from the edge of the GTV-P. Interestingly, in this series, only continuous growth pattern was observed, and no isolated islands of tumour cells were reported at a distance of more than 4 mm from the edge of the GTV-P. With the low patient number, the influence of the tumour stage on the extent of microscopic infiltration could not be investigated.
- The study of Yuen et al. analysed 50 glossectomy specimens from patients with T1–T3 (UICC 7th ed, 2007) (50% T2) SCC of the mobile tongue [21]. The processing of the specimens was not reported in great detail, but the assessment of local spread

was performed after fixation of the specimen in formalin. The mean extension from the edge of the GTV-P was 3 mm, and 96% of the infiltration was within 12 mm. In one case, intramuscular microsatellite spread was however reported up to 18 mm from the tumour edge. There was no significant correlation between the distance of local spread and the pathological T-stage.

- The study of Fleury et al. analysed 21 surgical specimens of SCC mainly (76%) from the oropharynx or larynx [22]. Samples were processed by whole-mount histopathology and distances from the edge of the GTV-P were assessed after tissue fixation. Among the patients included in this series, 6 had previous treatments with induction chemotherapy and/or radiotherapy. Tumours were T1 or T2 (UICC 7th ed, 2007) in 40% of the cases. In this series, the maximum tumour infiltration outside of the GTV-P margin was 15 mm, but this was observed in a patient already pre-treated with concomitant chemo-radiotherapy. After exclusion of the 6 pre-treated patients, all the microscopic tumour infiltrations were within 5 mm of the GTV-P edge. A possible influence of the primary tumour location was not reported in this series. Likewise, while lymphatic and perineural infiltrations were frequently reported, no information was available on the pattern of growth (i.e. isolated island of cells or continuous growth) outside of the edge of the GTV-P.

Although these 3 studies only included small numbers of patients and were heterogeneous regarding the methodology used, they concurred to indicate that the microscopic tumour infiltration mainly occurs within a distance of 0–10 mm from the edge of the GTV defined as the macroscopic tumour specimen. While it is recognized that a “5 + 5 mm margin” may not encompass 100% of tumour extensions, the benefit of further widening the margin around the GTV-P must be balanced against the increased risk of radiation induced morbidity.

In this framework, an important issue is how accurately imaging modalities assess the GTV-P, and how the CTV margin concept should then be practically implemented. It is known that CT, MRI and FDG-PET overestimate the macroscopic tumour extent, but at the same time underestimate microscopic tumour infiltration [17]. In a recent study by Ligtenberg and colleagues, the microscopic tumour volumes assessed from H&E stained sections of surgical specimens (i.e. the “true CTV”) of 25 patients with T3–T4 laryngeal or hypopharyngeal SCC scheduled for total laryngectomy were compared to pre-operative iodine contrast enhanced CT, T1-weighted gadolinium-enhanced transverse MRI, and FDG-PET [23]. A very comprehensive methodology was used to minimize all uncertainties resulting from image reconstruction and co-registration, and from assessment of the various GTVs. Adequate CTV-P coverage (defined as the distance required to cover at least 95% of the microscopic tumour on each section) could be achieved with a modality-specific margin around the GTV-P of 4.3 mm for CT, 6.1 mm for MRI and of 5.2 mm for FDG-PET. Hence, the CTV-P defined were always smaller than those obtained by applying a fixed 10 mm margin around the imaged GTV-P.

Independently of the above mentioned radiotherapy studies, head and neck surgeons have constantly revisited their surgical procedures and particularly the definition of resection margins aiming at maximizing local tumour control after surgery alone, while maintaining maximal organ function. In oral cavity SCC, a 5 mm margin assessed on a three-dimensional basis has remained the most common consensus distance for a clear margin, whereas for glottic squamous cell carcinoma narrower margins around 1–2 mm have been proposed [24–25].

In a recent retrospective review of 381 patients who underwent surgical resection with curative intent for SCC of the oral tongue (85% were T1–T2 tumours) at Memorial Sloan Kettering Cancer

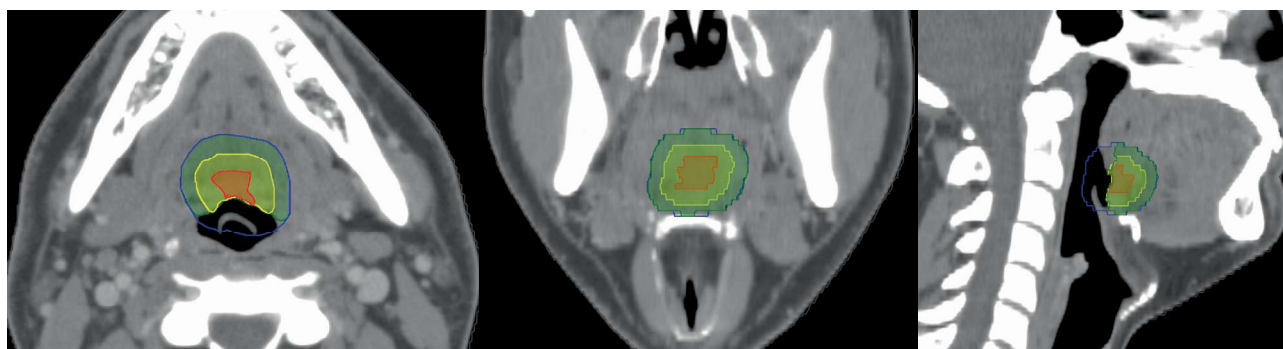


Fig. 1. Schematic illustration on axial (left), coronal (middle) and sagittal (right) CT sections of the “5 + 5 mm” expansion concept from the GTV-P for head and neck SCC. A GTV-P is delineated in red at the level of the base of tongue; a 10 mm expansion is delineated in blue, and edited to remove the air cavity and the epiglottis to get the CTV-P2 (green); CTV-P1 (in yellow) is a 5 mm expansion of the GTV-P contained within the CTV-P2. As explained in the article, depending on the location of the primary tumour, CTV-P2 may have to be edited for more than air cavity, e.g. for bone, muscular structures, thyroid gland, other sub-sites of the Head & Neck area.

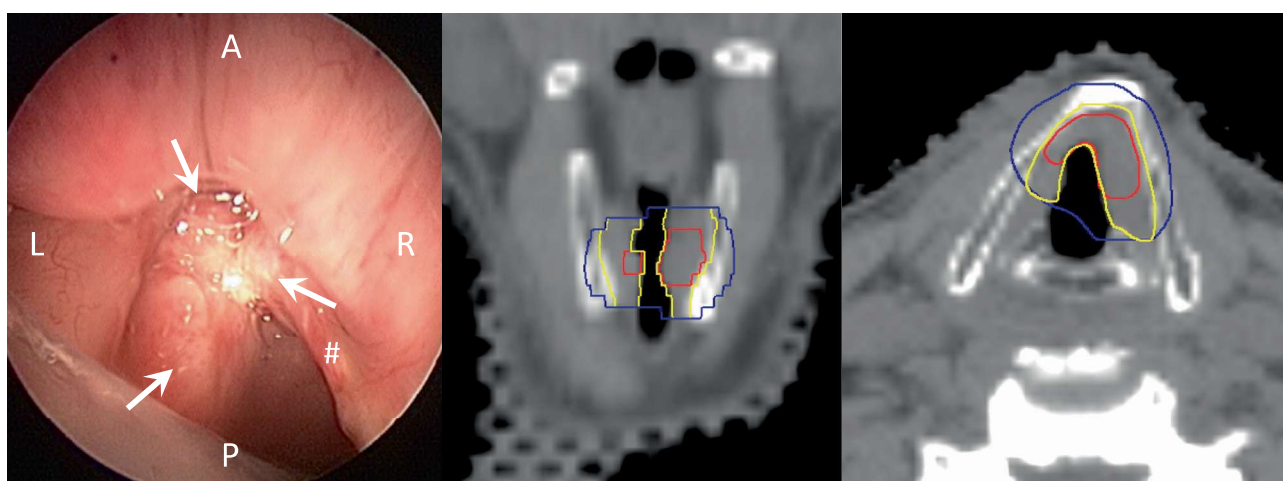


Fig. 2. Endoscopic view (left), and planning CT on coronal (middle) and axial (right) reconstructions of a T1b (UICC 8th edition) SCC of the anterior third of the left vocal cord, the anterior commissure and the anterior third of the right vocal cord. On the endoscopic view, the signs “#” identify the right vocal cord, and the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. Arrows depict the tumour extension. The GTV-P is delineated in red. A 5-mm isotropic expansion is delineated in blue. The CTV-P1 is delineated in yellow after edition for the air cavity, and the thyroid cartilage.

Centre, Zanoni et al. reported that a surgical margin of 2.2 mm was optimal to predict for loco-regional recurrence free survival [26]. Patients with a margin between 2.3 and 5 mm or above 5 mm had similar outcomes.

In patients with tonsillar SCC treated with transoral laser microsurgery or transoral robotic surgery, the local control rate has also been studied as a function of the resection margin. For T1–T2 tumours, a procedure with a margin of at least 2–3 mm and removing the constrictor muscle (particularly for T2 tumours) appears safe with local control rates of above 90% without the use of post-operative radiotherapy [27–30]. It should be noted that the majority of patients included in these series were HPV-positive, and the influence of HPV-positivity on the extent of margin needed is yet unknown.

For laryngeal SCC, ample literature has been published on the use of laser microsurgery for the treatment of T1 or T2 glottic or supraglottic carcinoma using procedures standardized by the European Laryngological Society [31,32]. Typically, using a mucosal margin of 2–3 mm and a deep margin respecting the laryngeal framework, local tumour control rates in the order of 85–95% have been reported without the use of post-operative radiotherapy [33–35]. It should be noted that such excellent outcomes are reported from large institutions having adequate clinical experience for

proper patient selection. Contra-indications for laser microsurgery typically included cases with deep pre-epiglottic space extension, infiltration of the crico-arytenoid joint leading to vocal cord fixation, paraglottic space encroachment, anterior commissure infiltration and inadequate exposure of the larynx.

In all the above mentioned clinical series, the reason why few percent (around 10–15%) of patients presented local relapse is unknown, and could possibly have nothing to do with an inadequate resection margin, but rather with unfavourable tumour biology.

For hypopharyngeal squamous cell carcinoma, the situation may slightly be different. Indeed, surgical series have reported that submucosal tumour extension may extend up to 20–30 mm in the cranio-caudal direction, thus calling for a GTV-P to CTV-P margin larger than the “5 + 5 mm expansion” proposed for other tumour locations [36].

Anatomic editing of the CTV-P

The literature outlined above provides direct (i.e. analysis of tumour infiltration on resection specimens) and indirect (i.e. local control rates after selective surgical procedures) data to promote the use of an expansion margin from the edge of the GTV-P to

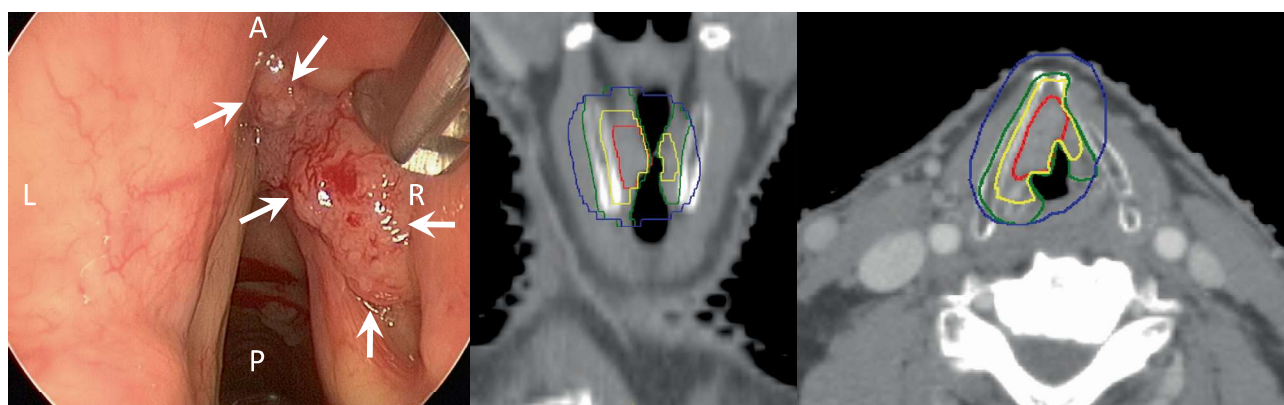


Fig. 3. Endoscopic view (left), and planning CT on coronal (middle) and axial (right) reconstructions of a T2 (UICC 8th edition) SCC of the right vocal cord. The carcinoma infiltrates the anterior commissure and the anterior two-third of the right cord. Cranially, it invades the ventricle. The mobility of the right hemi-larynx is normal. On the endoscopic view, the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. Arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion is delineated in blue. The CTV-P2 is delineated in green after edition for the air cavity, the cricoid cartilage, the left ala of the thyroid cartilage, and the left arytenoid cartilage. The CTV-P1 is delineated in yellow.

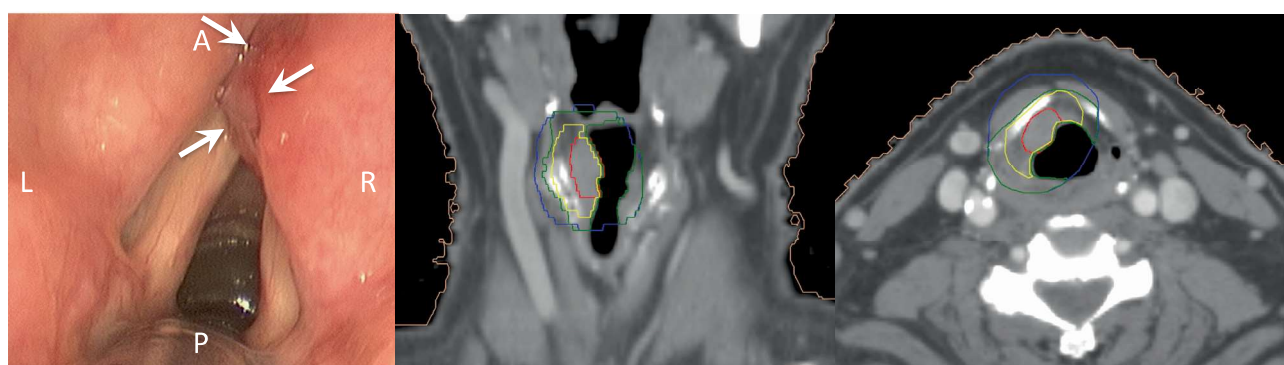


Fig. 4. Endoscopic view (left), and planning CT on coronal (middle) and axial (right) reconstructions of a T3 (UICC 8th edition) SCC of the right vocal cord. The tumour is originating at the anterior commissure and invades the anterior third of the vocal cord and the right ventricle. There is no fixation of the vocal cord. On diagnostic CT-scan, the paraglottic and the pre-epiglottic spaces are invaded. The tumour is staged T3-N0-M0 of the glottic larynx. On the endoscopic view, the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. Arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion is delineated in blue. The CTV-P2 is delineated in green after edition. The CTV-P1 is delineated in yellow.

delineate the CTV-P. Although most of these data were collected for T1 and T2 carcinoma, the pathological analysis of tumour specimens also included larger T3 tumours, and within the limitation of the sample size, the conclusions didn't differ significantly for larger tumour volumes.

CTV-P delineation cannot however be a straightforward geometric expansion of the GTV-P without performing some modification that takes into account patient anatomy, which can be categorized into 4 main themes, (1) adaptation for air cavities, (2) adaptation for the complex head and neck anatomy, (3) adaptation for strong anatomic barriers preventing tumour cells from free diffusion, and (4) adaptation to take into account the experience gained from surgical series. Modification of the “5 + 5 mm expansion” thus implies that anatomic structures may not be fully included into the CTV-P.

- Air cavities: for obvious reasons, the geometric expansion will always have to be edited for air cavities of the pharynx, larynx, oral cavity, and nasal and para-nasal sinuses if applicable.
- Complex head and neck anatomy: the geometric expansion will always have to take into account the intricate anatomic relationship between the various head and neck subsites, i.e. regions of abutting but not directly contiguous mucosal surfaces. For example, a soft-palate GTV-P expansion will likely

be edited at the level of the mobile tongue, as will an inter-arytenoid laryngeal GTV-P at the level of the post-cricoid area.

- Head and neck anatomic barriers: some head and neck structures such as the mandible, the maxillary bone, the cervical spine, the hyoid bone and muscular fascia can be considered as strong barriers to tumour cell diffusion. The GTV-P expansion should be edited for these structures, unless likely infiltrated.
- Surgical consideration: for small tumours (e.g. T1 glottic or T1 tonsillar fossa carcinoma) surgical series with endoscopic surgery (laser or TORS) have reported very high tumour control rate (without the use of post-operative radiotherapy) with lower margins around the GTV-T, which suggests that different margin extension for these small tumours could be adopted. It is however recognized that these series included highly selected patients, and that surgeons have the advantage of the on-line visualization during their resection, especially regarding mucosal infiltration.

It is likely that the primary tumour CTV delineated as proposed will sometimes overlap with the delineation of the nodal levels, especially for locally advanced primary tumours [6]. Modern treatment planning systems have the capacity of handling overlapping volumes, and allow planners to set priorities in case of different dose prescription in the overlapping volumes.

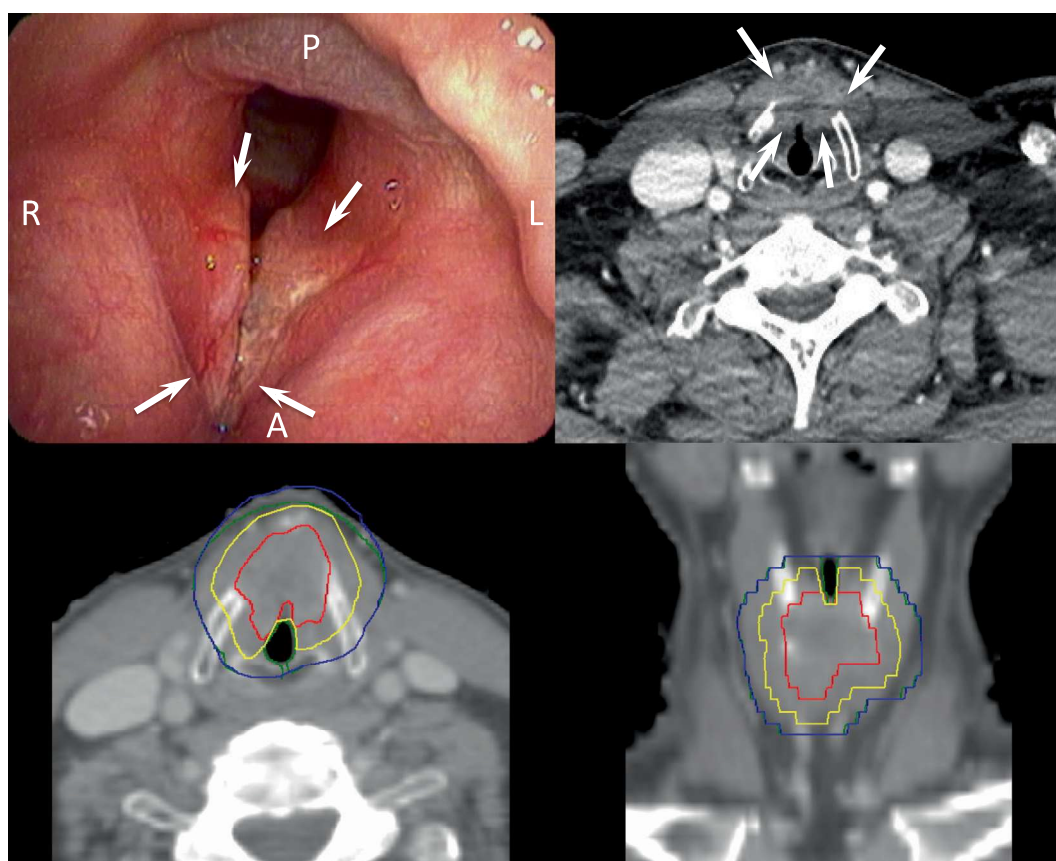


Fig. 5. Endoscopic view (upper left), diagnostic axial contrast enhanced CT (upper right) (arrows to delineate the tumour), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T4a (UICC 8th edition) SCC of the glottic larynx. The tumour invades the anterior commissure, the anterior two-third of both vocal cords and extends into the sub-glottic area. The mobility of both vocal cords was reduced. On diagnostic CT-scan, both paraglottic spaces, the anterior half of the thyroid cartilage and the laryngeal strap muscles (sterno-thyroid muscles) are invaded. On the endoscopic view, the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. Arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities and for the skin. The CTV-P1 is delineated in yellow (courtesy of J. Kaanders).

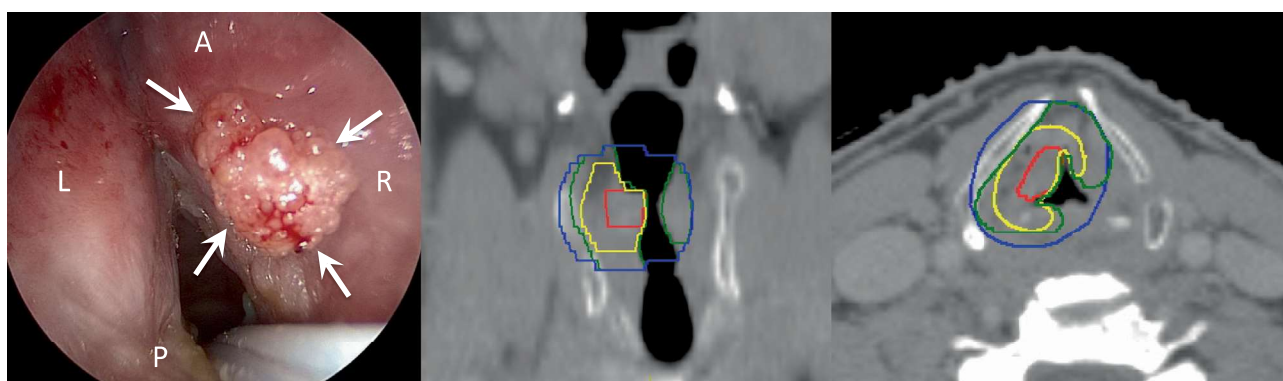


Fig. 6. Endoscopic view (left), and planning CT on coronal (middle) and axial (right) reconstructions of a T1 (UICC 8th edition) SCC of the right supra-glottic larynx (ventricular band not invading the vocal cord). On the endoscopic view, the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientation, respectively. Arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion is delineated in blue. The CTV-P2 is delineated in green after edition. The CTV-P1 is delineated in yellow.

Proposed nomenclature

Throughout the manuscript, the following nomenclature (Fig. 1) will be consistently used.

- GTV-P: delineated from clinical and imaging assessment.
- CTV-P1: CTV-P associated with the high dose prescription; the CTV-P1 correspond to the GTV-P plus a 5 mm margin edited as explained above.

- CTV-P2: CTV-P associated with a lower dose prescription, i.e. so-called prophylactic or intermediate dose prescription; the CTV-P2 correspond to the GTV-P plus a 10 mm margin edited as explained above.

This proposed nomenclature is valid independently of the dose prescription level. Some centres use 2 dose levels, i.e. a high therapeutic dose and a prophylactic dose, whereas other centres may

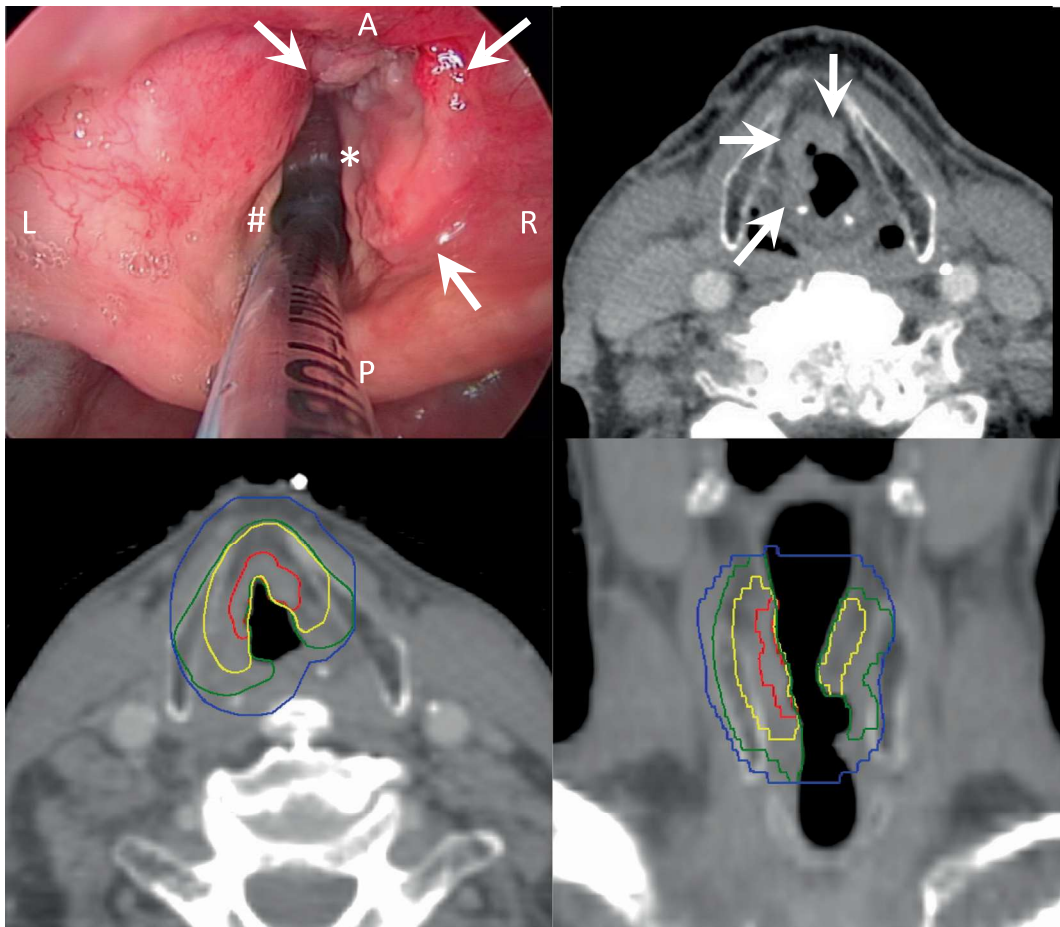


Fig. 7. Endoscopic view (upper left), diagnostic axial contrast enhanced CT (upper right; arrows to delineate the tumour), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T2 (UICC 8th edition; normal laryngeal mobility and no infiltration of the para-glottic space) SCC of the right supraglottic larynx. On the endoscopic view, the signs “#” and “*” identify the left and right vocal cord, respectively; the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. Arrows in the upper panels depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, and the strap muscles. The CTV-P1 is delineated in yellow.

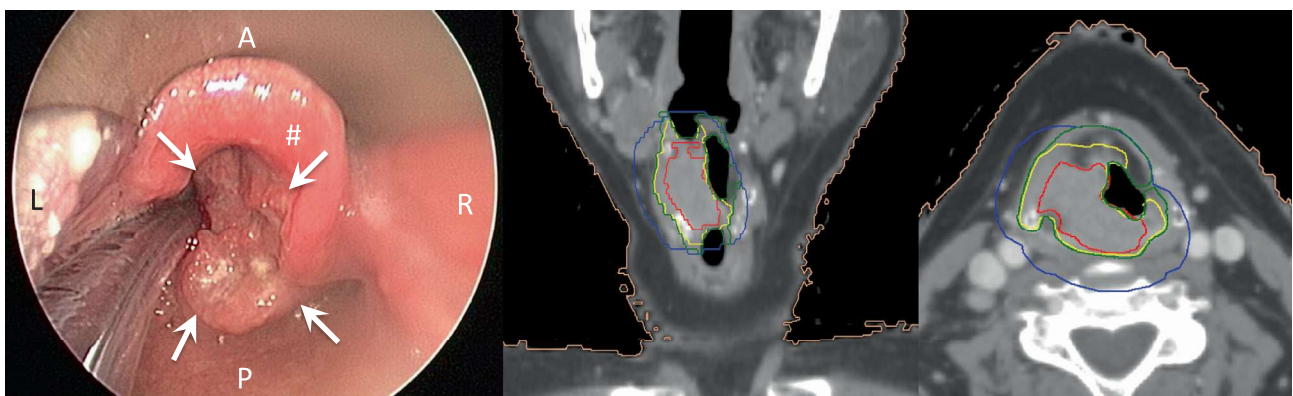


Fig. 8. Endoscopic view (left), and planning CT on coronal (middle) and axial (right) reconstructions of a T3 (UICC 8th edition) SCC of the right supra-glottis with fixation of the right hemi-larynx. The tumour originates from the right hemi-larynx, invading the ventricle, the right ari-epiglottic fold, the laryngeal aspect of the epiglottis and the right arytenoid. On the endoscopic view, the sign “#” identifies the epiglottis; the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively; arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the vertebral bodies, the cricoid cartilage, the hyoid bone, the left part of the thyroid cartilage, the strap muscles (sterno-thyroid and the thyro-hyoid muscles), the pharyngeal constrictor muscles and the right sub-mandibular gland. The CTV-P1 is delineated in yellow.

choose 3 dose levels, i.e. a high therapeutic dose, an intermediate dose and a prophylactic dose. In both scenarios, CTV-P1 corresponds to the target volume associated with the highest dose prescription (typically a dose equivalent to 70 Gy in 2 Gy per fraction

over 7 weeks). For centres using 2 levels of dose prescription, the CTV-P2 is associated with a prophylactic dose prescription (typically a dose equivalent to 50 Gy in 2 Gy per fraction over 5 weeks). For centres using 3 levels of dose prescription, the CTV-P2 is

associated to an intermediate dose level (typically a dose equivalent to 60 Gy in 2 Gy per fraction over 6 weeks), and then a CTV-P3 is delineated and associated to a prophylactic dose level (typically a dose equivalent to 50 Gy in 2 Gy per fraction over 5 weeks).

Practically, unless there is only one CTV-P, it may be easier to first delineate the CTV-P2, and then delineate the CTV-P1, which in any case will not extend outside of CTV-P2.

Guidelines for the delineation of the primary tumour CTV for laryngeal SCC

Glottic carcinoma

- T1 glottic tumour (Fig. 2): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. In the axial plane, CTV-P1 does include the paraglottic space, the anterior commissure for anterior vocal cord tumour, the anterior part of the contralateral vocal cord for tumour extending to the anterior commissure, and the vocal process of the arytenoid cartilage for tumour extending to the posterior vocal cord, but excludes the thyroid cartilage and the air cavity; in the cranio-caudal plane, then, the CTV-P1 includes the sub-glottic and the supra-glottic aspects of the vocal cord.

For T1 glottic SCC, the delineation of a CTV-P2 is not recommended.

- T2 glottic tumour (Fig. 3): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. In the axial plane, CTV-P2 includes the paraglottic space, the anterior commissure, the anterior part of the contralateral vocal cord for tumour extending to the anterior commissure, and the vocal process of the arytenoid cartilage for tumour extending to the posterior vocal cord; CTV-P2 may include the thyroid cartilage in relation to the GTV-P, but excludes the cricoid cartilage and the air cavity; in the cranio-caudal plane, the CTV-P2 includes the cranial part of the subglottis, the ipsilateral ventricle and the caudal part of the supra-glottic mucosa.

For small and/or superficial T2 glottic SCC not originating from the anterior commissure, the treating radiation oncologist may decide not to delineate a CTV-P2. The CTV-P1 will then be delineated as described above for CTV-P2, but with only a 5 mm extension margin.

- T3 glottic tumour (Fig. 4): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV with a concentrically isotropic margin of 10 mm in all directions. CTV-P2 includes part of the thyroid cartilage in

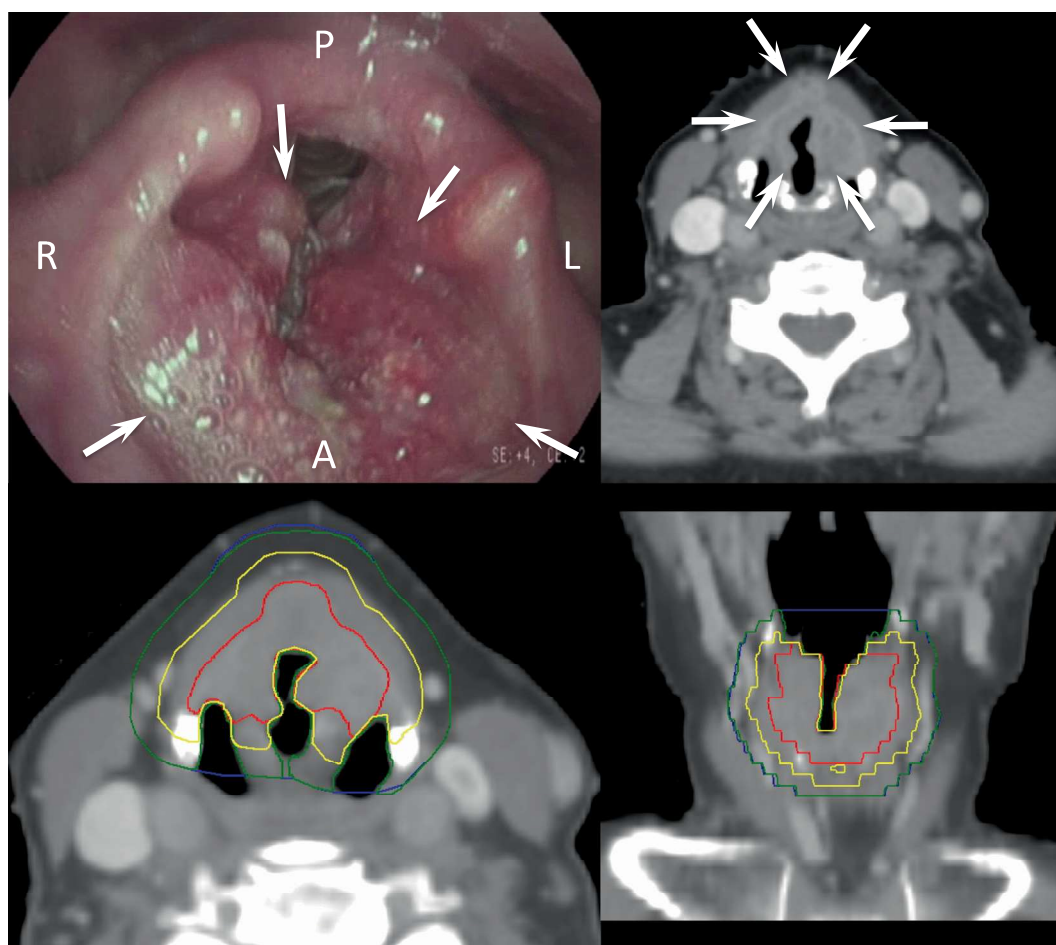


Fig. 9. Endoscopic view (upper left), diagnostic axial contrast enhanced CT (upper right; arrows to delineate the tumour), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T4a (UICC 8th edition) SCC of the supraglottic larynx. The tumour originates from the infra-hyoid epiglottis and extends to both false cords caudally, and the anterior third of both ary-epiglottis folds cranially. The left true vocal cord is not infiltrated, while it is likely that the right true vocal cord is. On diagnostic CT-scan, the tumour invades the pre-epiglottic space and extends outside of the laryngeal structures. On the endoscopic view, the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. Arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the cricoid cartilage and the anterior skin. The CTV-P1 is delineated in yellow (courtesy of J. Kaanders).

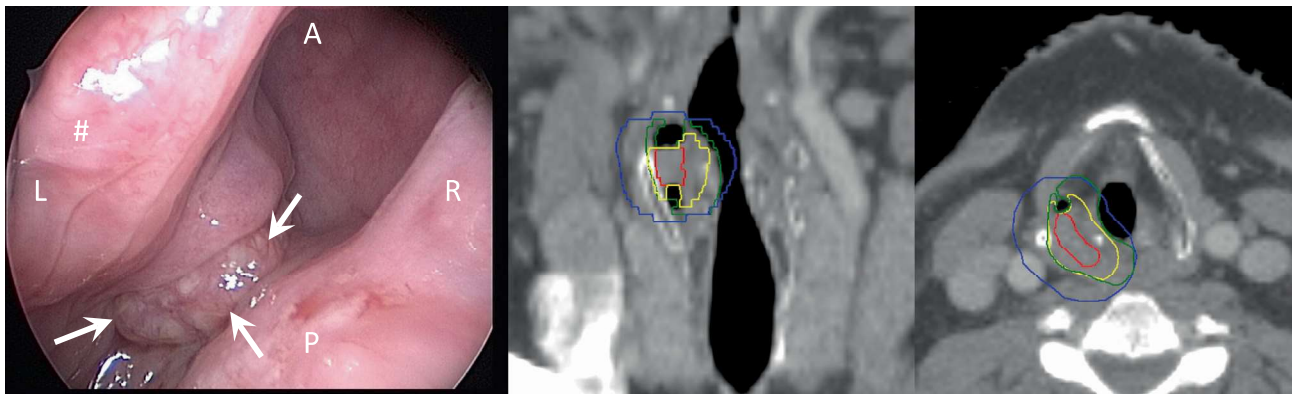


Fig. 10. Endoscopic view (left), and planning CT on coronal (middle) and axial (right) reconstructions of a T1 (UICC 8th edition; max diameter of 15 mm) SCC of the medial wall of the right piriform sinus. On the endoscopic view, the sign “#” identifies the right ary-epiglottic fold; the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively; the arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the thyroid cartilage, the retropharyngeal space and the hyoid bone. The CTV-P1 is delineated in yellow.

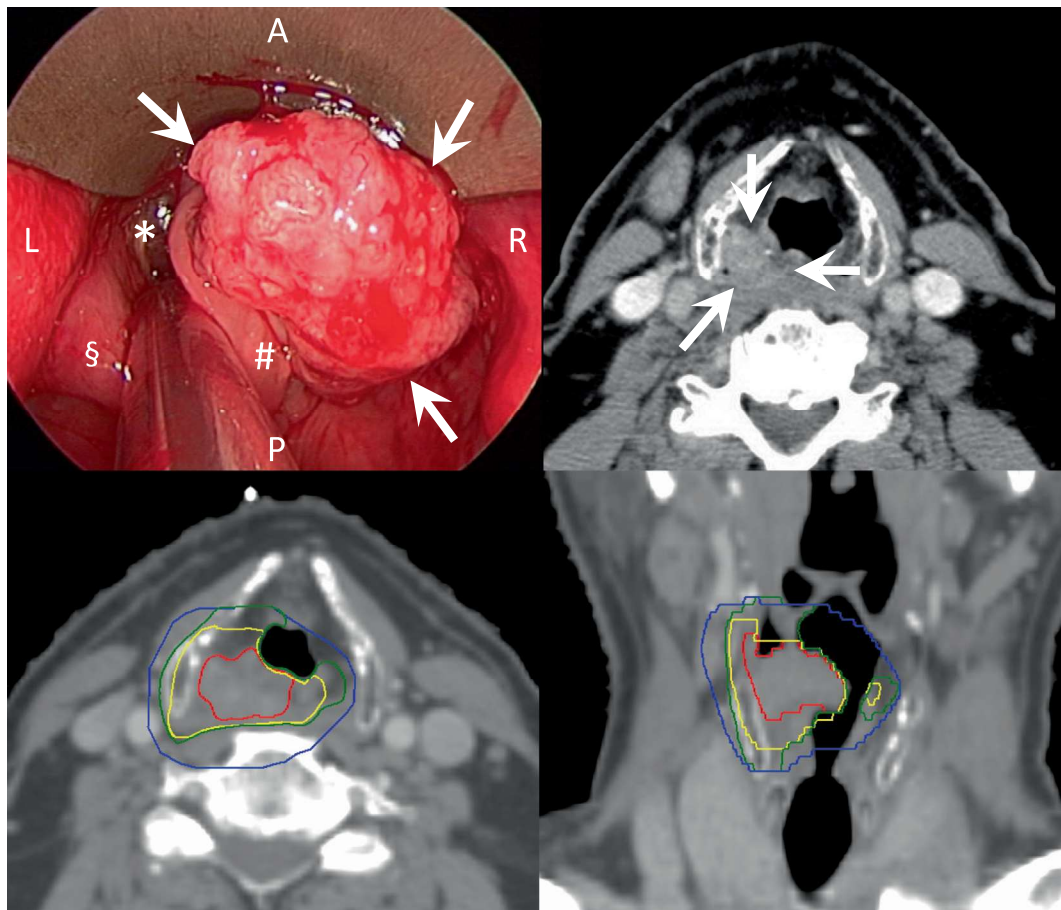


Fig. 11. Endoscopic view (upper left), diagnostic axial contrast enhanced CT (upper right), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T2 (UICC 8th edition; max diameter of 25 mm) SCC of the internal wall of the right piriform sinus. On the endoscopic view, the signs “\$”, “#” and “*” identify the left arytenoid, the right ary-epiglottic fold, and the left vocal cord, respectively; the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the thyroid gland, vertebral bodies, the longus colli and longus capitis muscles, and the hyoid bone. The CTV-P1 is delineated in yellow.

relation to the GTV-P, and most likely part of the cricoid cartilage caudally, the pre-epiglottic space anteriorly and the medial wall of the piriform sinus postero-laterally; it does not extend outside of the thyroid cartilage, except if it is infiltrated; typically it does not extend outside of the larynx into the orophar-

ynx, unless invaded; it should not include the posterior pharyngeal wall.

- T4 glottic tumour (Fig. 5): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-T2.

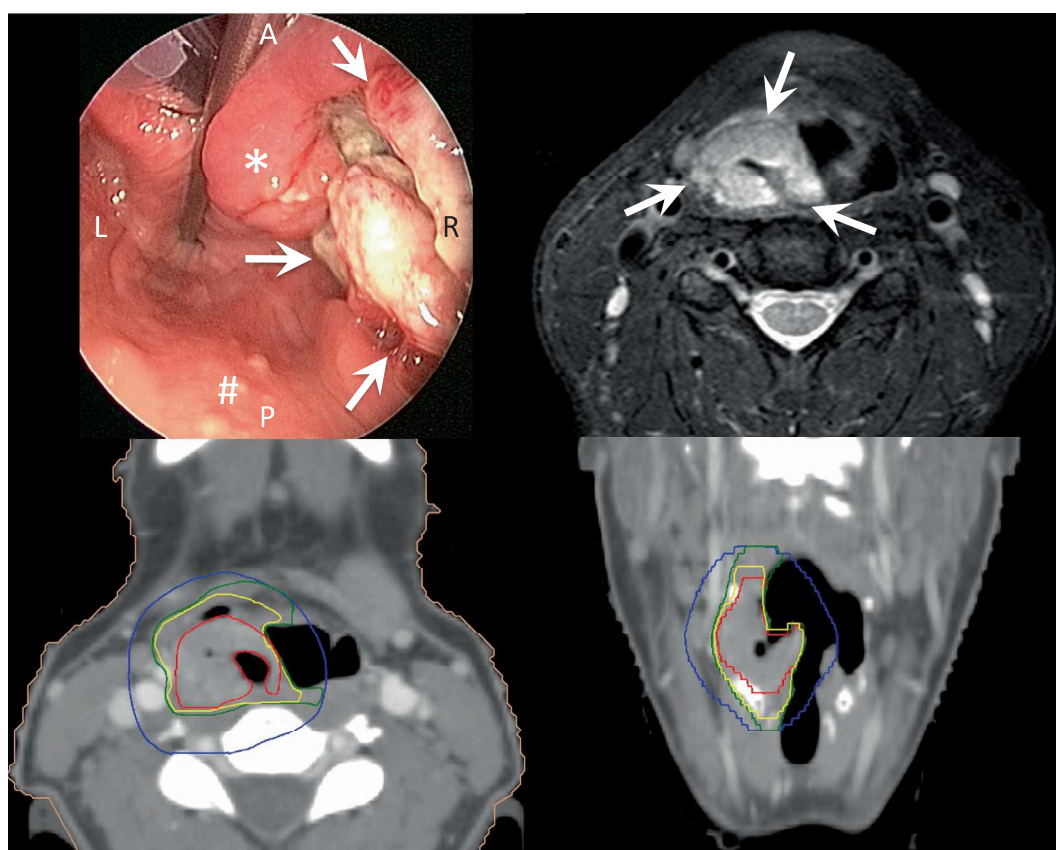


Fig. 12. Endoscopic view (upper left), diagnostic axial T2 MRI (upper right), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T3 (UICC 8th edition; max diameter of 46 mm) SCC of the right piriform sinus. On the endoscopic view, the signs "*" and "#" identify the right arytenoid and the posterior hypopharyngeal wall, respectively; the letters "A", "R", "L" and "P" indicate the anterior, right, left and posterior orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the thyroid gland, vertebral bodies, the longus colli and longus capitis muscles, the hyoid bone and the sub-mandibular gland. The CTV-P1 is delineated in yellow.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. In all cases, CTV-P2 includes part of the thyroid cartilage in relation to the GTV-T, part of the cricoid cartilage caudally, and the pre-epiglottic space, anteriorly; it extends most likely outside of the thyroid cartilage, but it does not go beyond the strap muscles (sterno-thyroid or thyro-hyoid muscles) unless these muscles are macroscopically invaded; in such case, the CTV-P2 likely overlaps with nodal levels III or VIa; it also most likely includes part of the thyroid gland. Bony structures such as the vertebral bodies and the hyoid bone should not be part of CTV-P2, unless invaded. For tumour infiltrating the prevertebral space (i.e. T4b), CTV-P2 may extend into the vertebral body.

Supra-glottic carcinoma

- T1 supra-glottic tumour (Fig. 6): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.
CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. CTV-P2 thus includes the pre-epiglottic space and the para-laryngeal space, but excludes the thyroid cartilage and the air cavity of the larynx, hypopharynx or oropharynx. For tumour of the laryngeal ventricle, the CTV-P2 will thus extend into the glottic area. For tumour of the ary-epiglottic fold and supra-hyoid epiglottis, the CTV-P2 may thus extend into the vallecula. For tumour of the inter-arytenoid mucosa, it is recommended that the posterior pharyngeal wall is excluded from the CTV-P2.

For small and/or superficial T1 supra-glottic SCC, the treating radiation oncologist may decide not to delineate a CTV-P2. The CTV-P1 will then be delineated as described above for CTV-P2, but with only a 5 mm extension margin.

- T2 tumour (Fig. 7): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.
CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. CTV-P2 thus includes the pre-epiglottic space, the para-laryngeal space, the thyroid cartilage, but excludes the strap muscles and the air cavities of the larynx, hypopharynx and oropharynx. For tumours of the laryngeal ventricle, the CTV-P2 thus extends into the glottic area. For tumour of the ary-epiglottic fold and supra-hyoid epiglottis, the CTV-P2 may thus extend into the vallecula. For tumour of the inter-arytenoid mucosa, it is recommended that the posterior pharyngeal wall is excluded from the CTV-P2.
- T3 tumour (Fig. 8): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.
CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. In all cases, CTV-P2 includes part of the thyroid cartilage in relation to the GTV-P and the pre-epiglottic space; it does not extend outside of the thyroid cartilage except if it is infiltrated; it may extend into the oropharynx, e.g. lingual surface of the epiglottis and vallecula. It may include the postcricoid area, but should not include the posterior pharyngeal wall.

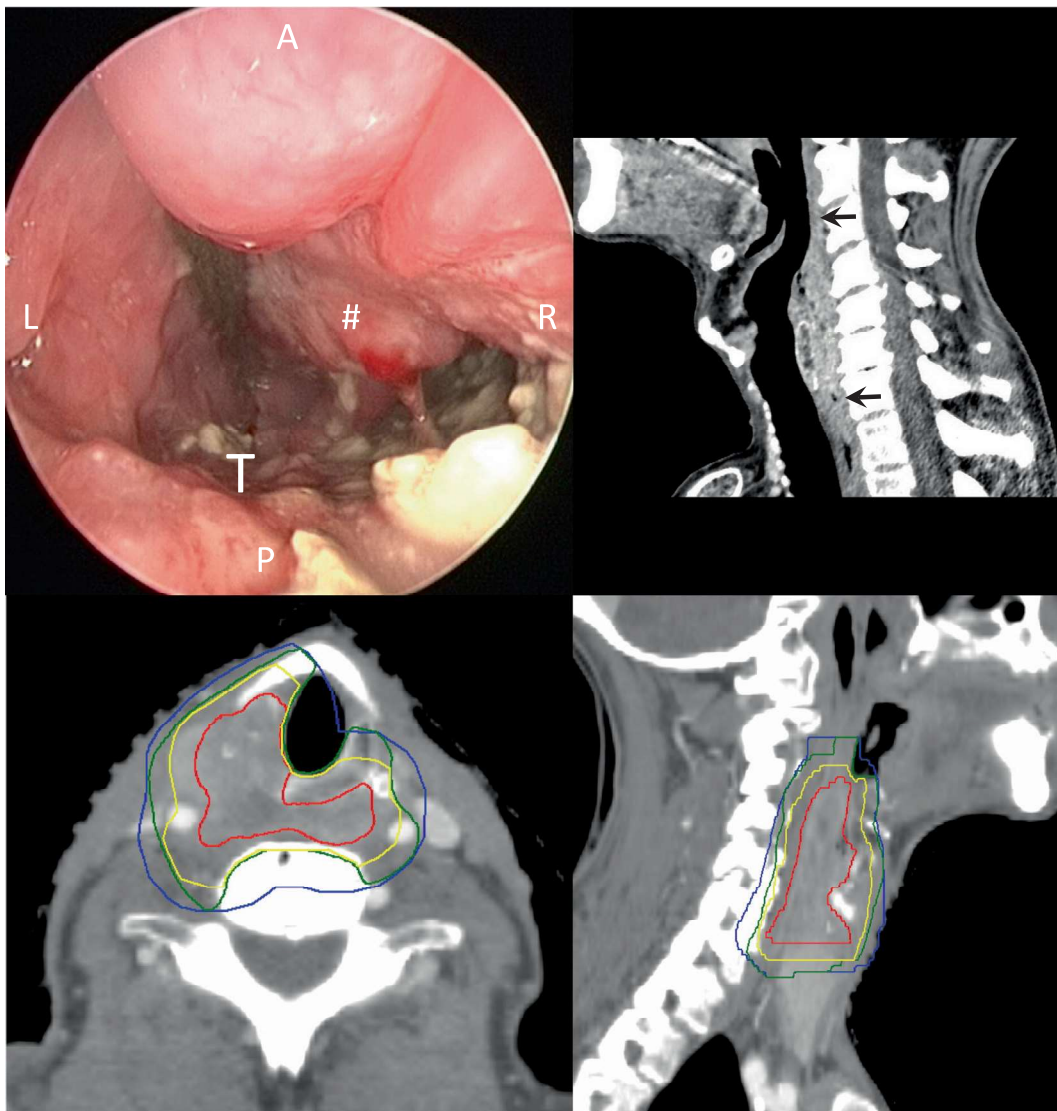


Fig. 13. Endoscopic view (upper left), diagnostic sagittal CT (upper right), and planning CT on axial (lower left) and sagittal (lower right) reconstructions of a T4b (UICC 8th edition); infiltration of the pre-vertebral fascia; max diameter of 56 mm) SCC of the posterior wall of the hypopharynx extending from the level of the tip of the epiglottis to the pharyngo-oesophageal junction. On the sagittal diagnostic CT, the arrows depict the upper and caudal boundaries of the tumour. On the endoscopic view, the signs “#” and “T” identify the inter-arytenoid area and the tumour, respectively; the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. In the cranio-caudal direction, a 15 mm cranio-caudal mucosal expansion has been used. The CTV-P2 is delineated in green after edition for air cavities, the left thyro-hyoid and sterno-thyroid muscles, the right sub-cutaneous tissues and part of the vertebral bodies. The CTV-P1 is delineated in yellow.

- T4 tumour (Fig. 9): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2.
CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. In all cases, CTV-P2 includes the thyroid cartilage in relation to the GTV-P, and the pre-epiglottic space; it extends most likely outside of the thyroid cartilage, but it does not extend beyond the strap muscles (sterno-thyroid or thyro-hyoid muscles) unless macroscopically invaded; in such case, the CTV-P2 will likely overlap with nodal levels III or VIa; it will also most likely include part of the thyroid gland. For tumours infiltrating the prevertebral space (i.e. T4b), CTV-P2 may extend into the vertebral body.
- T1 tumour: CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.
CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. The thyroid cartilage and the air cavity of the larynx are excluded. As the sub-glottic mucosa lies over the cricoid cartilage, a margin extending e.g. 2 mm into the cricoid cartilage is adequate.
For T1 sub-glottic SCC, the treating radiation oncologist may however decide not to delineate a CTV-P2 and thus only delineate a CTV-P1 defined as the GTV-P with a concentrically isotropic margin of 5 mm edited for air cavity and the thyroid cartilage.
- T2 tumour: CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.
CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. CTV-P2 thus includes the cricoid cartilage

Sub-glottic carcinoma

It should be understood that sub-glottic SCC represents less than 5% of the laryngeal SCC; very few data are thus available to develop guidelines for target volume delineation.

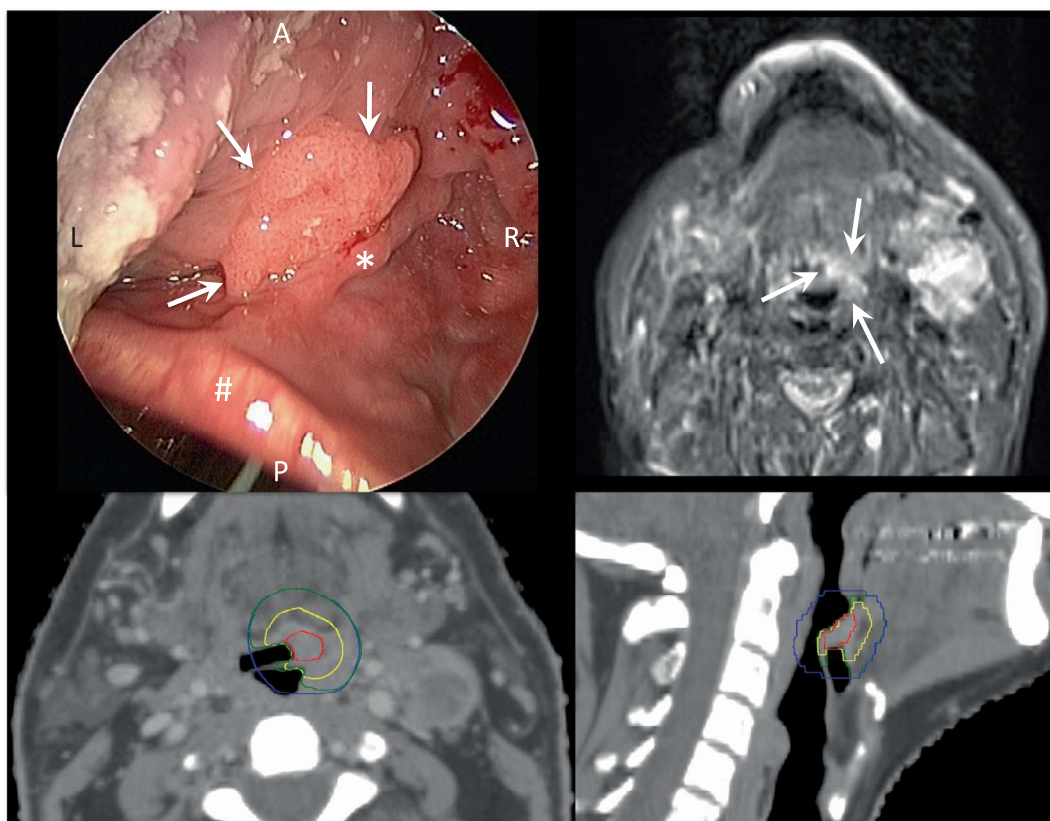


Fig. 14. Endoscopic view (upper left), diagnostic axial MRI T2 (upper right; see arrows for tumour delineation), and planning CT on axial (lower left) and sagittal (lower right) reconstructions of a T1 (UICC 8th edition; max diameter of 16 mm) SCC of the left base of tongue. On the endoscopic view, the signs “#” and “*” identify the epiglottis and the median glosso-epiglottic fold, respectively; the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities. The CTV-P1 is delineated in yellow.

and the inferior aspect of the thyroid cartilage, but it will not extend outside of these cartilages. It also includes the glottic larynx and the mucosa of the upper part of the trachea.

- T3 tumour: CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. In all cases, CTV-P2 includes part of the thyroid cartilage, part of the cricoid cartilage and part of the crico-thyroid muscle in relation to the GTV-P, but it does not extend outside of these cartilages. CTV-P2 is edited to exclude the posterior pharyngeal wall and the cervical oesophagus.

- T4 tumour: CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. In all cases, CTV-P2 includes part of the thyroid cartilage and the cricoid cartilage in relation to the GTV-P; it most likely extends outside of the thyroid cartilage and the cricoid cartilage, but it does not extend beyond the strap muscles (sterno-thyroid or thyro-hyoid muscles) unless macroscopically invaded; when extending outside of the strap muscles, the CTV-P2 likely includes part of the thyroid gland and overlaps with nodal levels III, IVa, VIa or VIb. CTV-P2 is edited to exclude bony structure, such as the vertebral body, except for tumour infiltrating the prevertebral space (i.e. T4b), where the CTV-P2 may extend into the vertebral body.

Guidelines for the delineation of the primary tumour CTV for hypopharyngeal SCC

- T1 tumour (Fig. 10): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. Depending on the location of the GTV-P, CTV-P2 includes the posterior aspect of the para-laryngeal space (i.e. tumour of the anterior angle and the medial wall of the piriform sinus), the inter-arytenoid area and the arytenoid cartilage (i.e. post-cricoid tumour), the posterior pharyngeal wall (i.e. tumour of the posterior pharyngeal wall), and the lateral hypopharyngeal wall (i.e. tumour of the lateral wall of piriform sinus). CTV-P2 will not extend into the oesophagus, unless GTV-P is located close to the oesophageal junction. The CTV-P1 does not include the thyroid cartilage, the cricoid cartilage or the hyoid bone, and it should not include structures outside of the pharynx, e.g. retro-pharyngeal space.

For small and/or superficial T1 hypopharyngeal SCC, the treating radiation oncologist may however decide not to delineate a CTV-P2 and thus only delineate a CTV-P1 defined as the GTV-P with a concentrically isotropic margin of 5 mm edited as described above.

- T2 tumour (Fig. 11): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2.

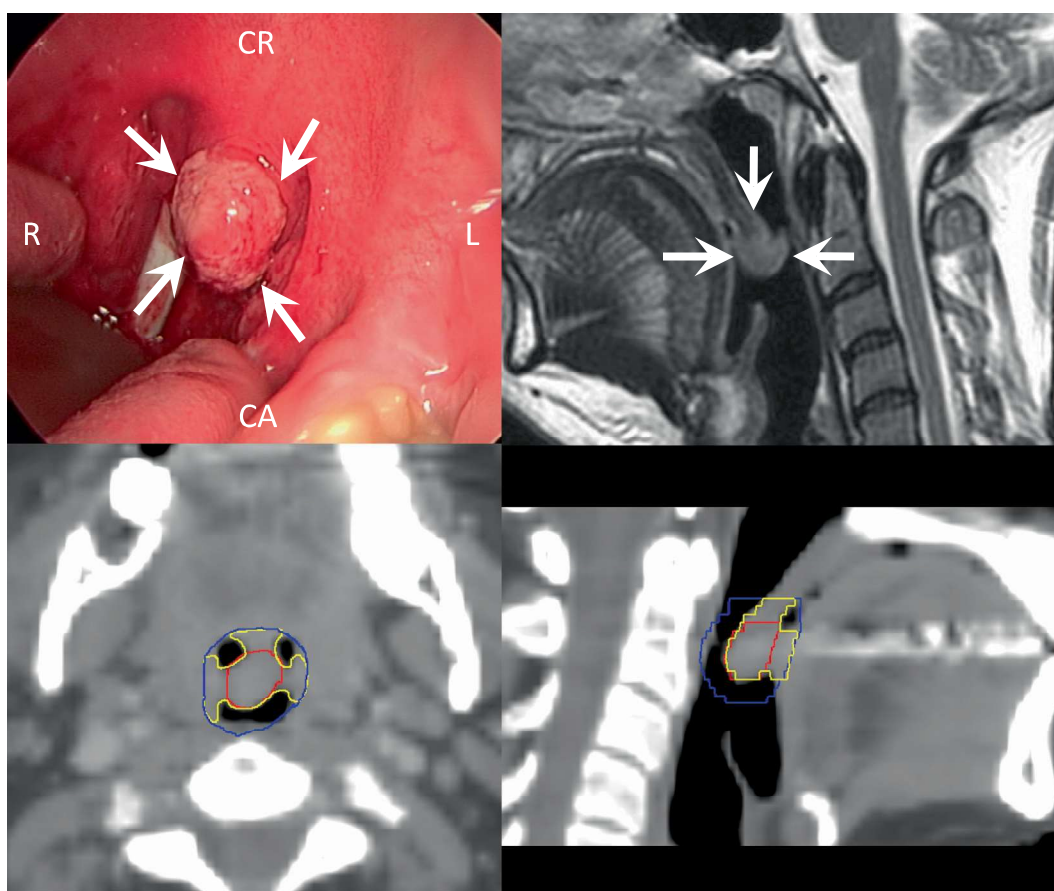


Fig. 15. Open mouth view (upper left), diagnostic sagittal MRI T2 (upper right), and planning CT on axial (lower left) and sagittal (lower right) reconstructions of a T1 (UICC 8th edition; max diameter of 13 mm) SCC of the uvula. On the open mouth view, the letters “CR”, “CA”, “L” and “R” indicate the cranial, caudal, left and right orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 5-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P1 is delineated in yellow after editing for the air cavity and the posterior pharyngeal wall. No CTV-P2 has been delineated for this well circumscribed T1 SCC of the uvula.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. Laterally, CTV-P2 includes the posterior aspect of the para-glottic space, and part of the thyroid cartilage in relation to the GTV-P but does not extend beyond the cartilage; medially, the CTV-P2 includes the ipsilateral arytenoid cartilage and part of the cricoid cartilage but does not extend into the larynx; posteriorly, the CTV-P2 includes part of the pharyngeal constrictor muscle, but does not extend through the pre-vertebral fascia into the longus colli or longus capitis muscles; anteriorly, the CTV-P2 likely includes part of the pre-epiglottic space; caudally, depending on the GTV-P location, the CTV-P2 may extend into the upper cervical oesophagus; cranially, the CTV-P2 may extend into the oropharynx, e.g. the posterior pharyngeal wall, posteriorly, the lateral oropharyngeal wall, laterally, and the vallecula, anteriorly.

In hypopharyngeal SCC, extensive sub-mucosal extension has been reported, and the treating radiation oncologist may consider using a 15 mm margin from the GTV-P to the CTV-P2 in the cranio-caudal direction, instead of a 10 mm margin as described above [36].

- T3 tumour (Fig. 12): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all direction. Laterally, the CTV-P2 includes the posterior aspect of the para-glottic space, part of the thyroid cartilage in relation to the GTV-P (but it does not extend outside of the cartilage, except if it is invaded, but then it does not extend outside

of the strap muscles), and part of the thyro-hyoid muscle (more cranially) in relation to the GTV-P; medially, the CTV-P2 includes at least the ipsilateral arytenoid cartilage, the ipsilateral hemi-larynx and part of the cricoid cartilage; posteriorly, the CTV-P2 includes part of the pharyngeal constrictor muscle, but it does not extend through the pre-vertebral fascia into the longus colli or longus capitis muscles; anteriorly, the CTV-P2 likely includes part of the pre-epiglottic space; caudally, depending on the GTV-P location, the CTV-P2 may extend into the upper cervical oesophagus; cranially, the CTV-P2 may extend into the oropharynx, e.g. posterior pharyngeal wall, posteriorly, lateral oropharyngeal wall, laterally, and the vallecula, anteriorly.

In hypopharyngeal SCC, extensive sub-mucosal extension has been reported, and the treating radiation oncologist may consider using a 15 mm margin from the GTV-P to the CTV-P2 in the cranio-caudal direction, instead of a 10 mm margin as described above [36].

- T4 tumour (Fig. 13): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all direction. In comparison with T3 tumour, the CTV-P2 may extend laterally into the strap muscles (sterno-thyroid or thyro-hyoid muscles) of the larynx, and may even extend into the sub-cutaneous tissue outside of the strap muscles and into the ipsilateral thyroid gland; then it likely overlaps with nodal levels (II), III or VIb; for tumour infiltrating the

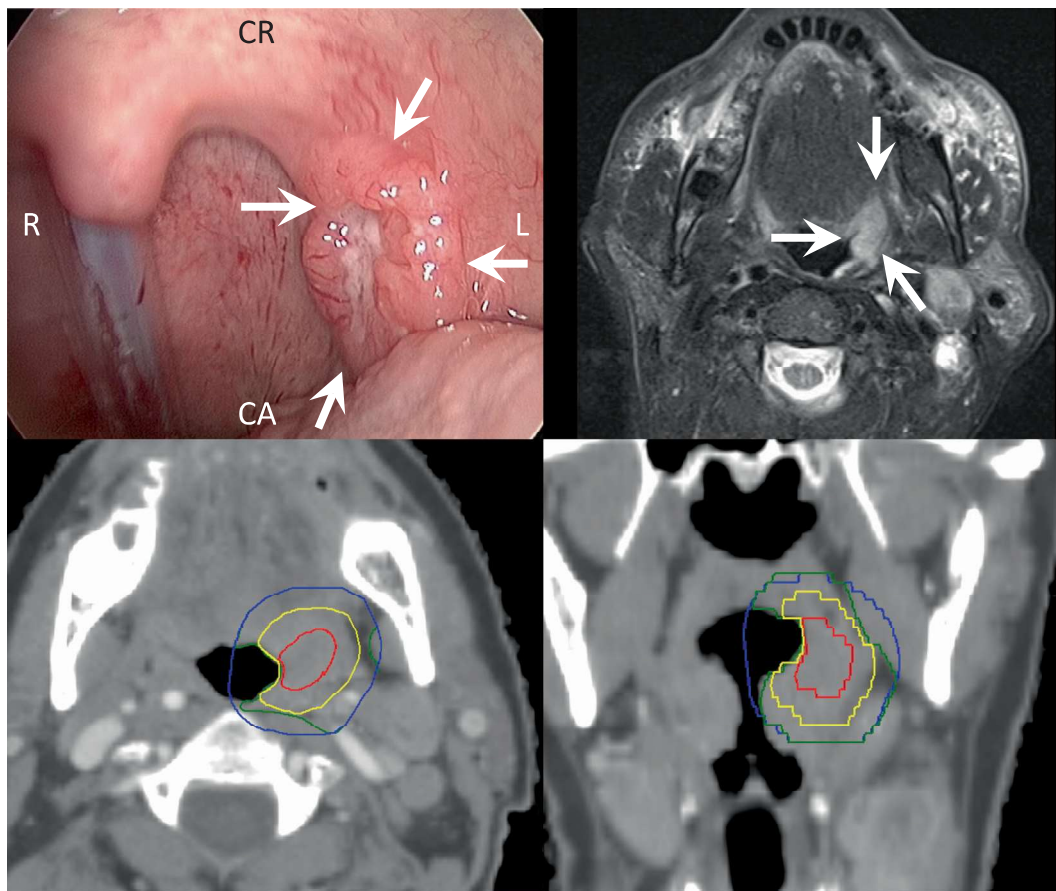


Fig. 16. Open mouth view (upper left), diagnostic axial T2 MRI (upper right), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T2 (UICC 8th edition; max diameter of 21 mm) SCC of the left tonsil fossa. On the open mouth view, the letters “CR”, “CA”, “L” and “R” indicate the cranial, caudal, left and right orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the mobile tongue, the left pterygoid muscle, and the left longus colli and longus capitis muscles. The CTV-P1 is delineated in yellow.

prevertebral space (i.e. T4b), CTV-P2 may extend through the pre-vertebral fascia into the longus colli or longus capitis muscles, and eventually into the vertebral body; caudally, it is likely that the CTV-P2 includes part of the upper cervical oesophagus. In hypopharyngeal SCC, extensive sub-mucosal extension has been reported, and the treating radiation oncologist may consider using a 15 mm margin from the GTV-P to the CTV-P2 in the cranio-caudal direction, instead of a 10 mm margin as described above [36].

Guidelines for the delineation of the primary tumour CTV for oropharyngeal SCC

- T1 tumour (Figs. 14 and 15): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2. CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. The CTV-P2 does however not include any air cavity, bony structures (e.g. hyoid bone, mandible, hard palate), or the mobile tongue. For tonsillar primaries, the CTV-P2 includes the superior pharyngeal constrictor muscle within the 5 mm expansion, but does not extend into the para-pharyngeal space. For tumour of the soft palate, the CTV-P2 comprises the full thickness of the soft palate and may extend into the tonsillar fossae. For posterior pharyngeal wall tumour, the CTV-P2 includes the

pharyngeal constrictor muscle. Although not intended to, it is likely that the retro-pharyngeal space is also part of the CTV-P2. For tumours of the vallecula, the CTV-P2 should not extend into the pre-epiglottic space. For tumours of the base of tongue, the CTV-P2 does not extend laterally into the hyo-glossus muscle. For small and/or superficial T1 oropharyngeal SCC, the treating radiation oncologist may however decide not to delineate a CTV-P2 and thus only delineate a CTV-P1 defined as the GTV-P with a concentrically isotropic margin of 5 mm edited as described above.

- T2 tumour (Figs. 16 and 17): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2. CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. The CTV-P2 does however not include any air cavity, bony structures (e.g. hyoid bone, mandible, hard palate) or the mobile tongue, except for the very large base of tongue tumour. For tonsillar primaries, the CTV-P2 includes the lateral and postero-lateral aspects of the superior pharyngeal constrictor muscle and extends into the fat of the para-pharyngeal space - it may then partly overlap with the level II and the retropharyngeal nodes - but it does not extend into the medial pterygoid muscle. Depending on the location of the tumour, it may include the glosso-tonsillar sulcus, the adjacent base of tongue and/or the adjacent mobile tongue. For soft palate tumours, the

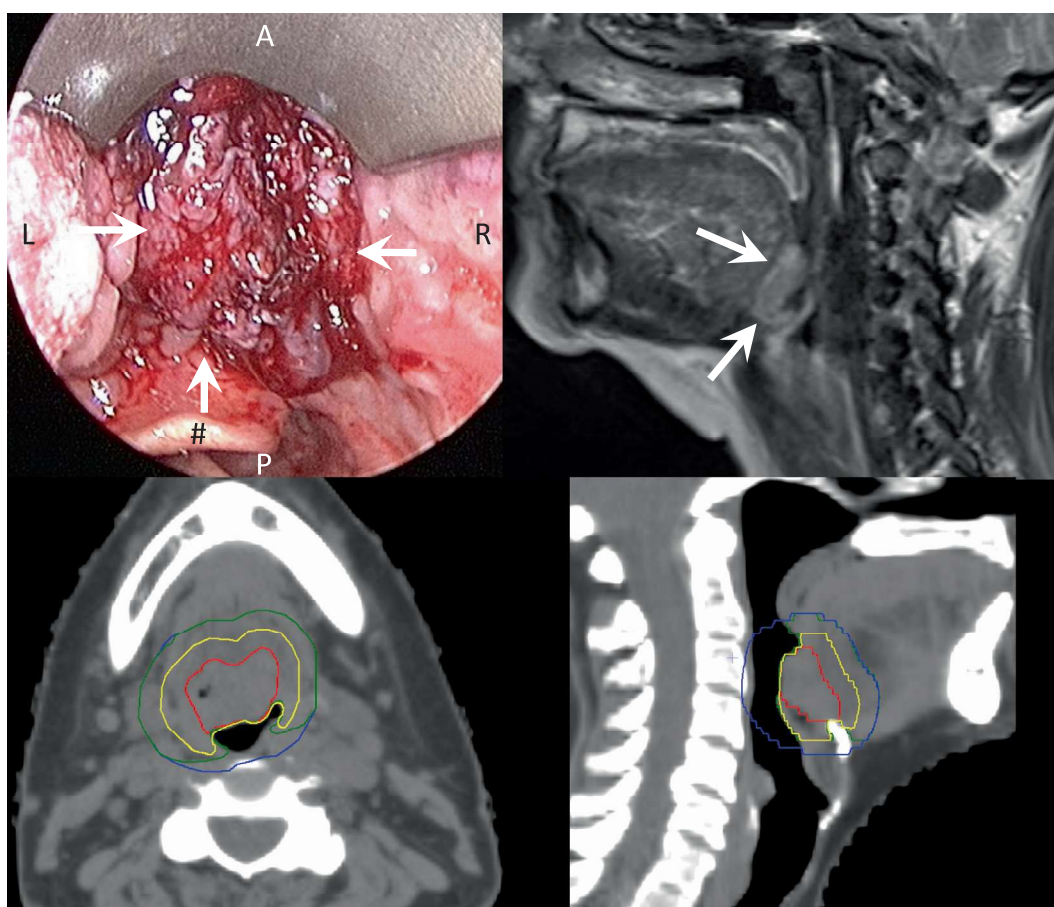


Fig. 17. Endoscopic view (upper left), diagnostic sagittal T2 MRI (upper right), and planning CT on axial (lower left) and sagittal (lower right) reconstructions of a T2 (UICC 8th edition; max diameter of 23 mm) SCC of the base of tongue. On the endoscopic view, the sign “#” identifies the epiglottis; the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the vertebral body, the pre-epiglottic space, the hyoid bone, the medial part of the constrictor muscle, and the soft palate. The CTV-P1 is delineated in yellow.

CTV-P2 likely extends into the hard palate, the lateral pharyngeal wall(s), and the para-pharyngeal space, but it should not extend into the medial pterygoid muscle, nor into the mobile tongue. For posterior pharyngeal wall tumours, the CTV-P2 includes the pharyngeal constrictor muscle(s), the retropharyngeal space – it then partly overlaps with the retropharyngeal nodes – but it does not extend through the pre-vertebral fascia into the longus colli or longus capitis muscles, nor into the adjacent vertebral body(ies). For tumours of the vallecula, the CTV-P2 extends into the pre-epiglottic space. For tumours of the base of tongue, the CTV-P2 extends laterally through the hyo-glossus muscle into the para-pharyngeal space – it then partly overlaps with level Ib and II nodes. It may also include the lateral aspect of the superior pharyngeal constrictor muscle, but the medial part of the muscle should be edited out. Anteriorly, for large T2 tumour of the base of tongue, the CTV-P2 may extend into the mobile tongue.

- T3 tumour (Figs. 18–20): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2.
CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. The CTV-P2 does however not include any air cavity, bony structures (e.g. hyoid bone, mandible, hard palate) or the mobile tongue, except for the very large base of tongue tumour, or tonsil tumours.

For tonsillar primaries, the CTV-P2 includes the superior pharyngeal constrictor muscle and extends into the fat of the para-pharyngeal space – it then partly overlaps with the level II nodes and the retropharyngeal nodes. It may partly extend into the medial pterygoid muscle. Depending on the location of the tumour, it may include the glosso-tonsillar sulcus, the adjacent base of tongue and/or the adjacent mobile tongue. For soft palate tumours, the CTV-P2 likely extends into the hard palate, the lateral pharyngeal wall(s), and the para-pharyngeal spaces. It should not extend into the mobile tongue. For posterior pharyngeal wall tumours, the CTV-P2 includes the pharyngeal constrictor muscles, the retro-pharyngeal space – it then partly overlaps with the retropharyngeal nodes – but does not extend through the pre-vertebral fascia into the longus colli or longus capitis muscles, nor into the adjacent vertebral body (ies). For tumours of the vallecula, the CTV-P2 extends into the pre-epiglottic space. For tumours of the base of tongue, the CTV-P2 extends laterally through the hyo-glossus muscle into the para-pharyngeal space – it then partly overlaps with level Ib and II nodes. It may also include the lateral aspect of the superior pharyngeal constrictor muscle, but the medial part of the muscle should be edited out if possible. Anteriorly, for T3 tumour of the base of tongue, the CTV-P2 may extend into the mobile tongue.

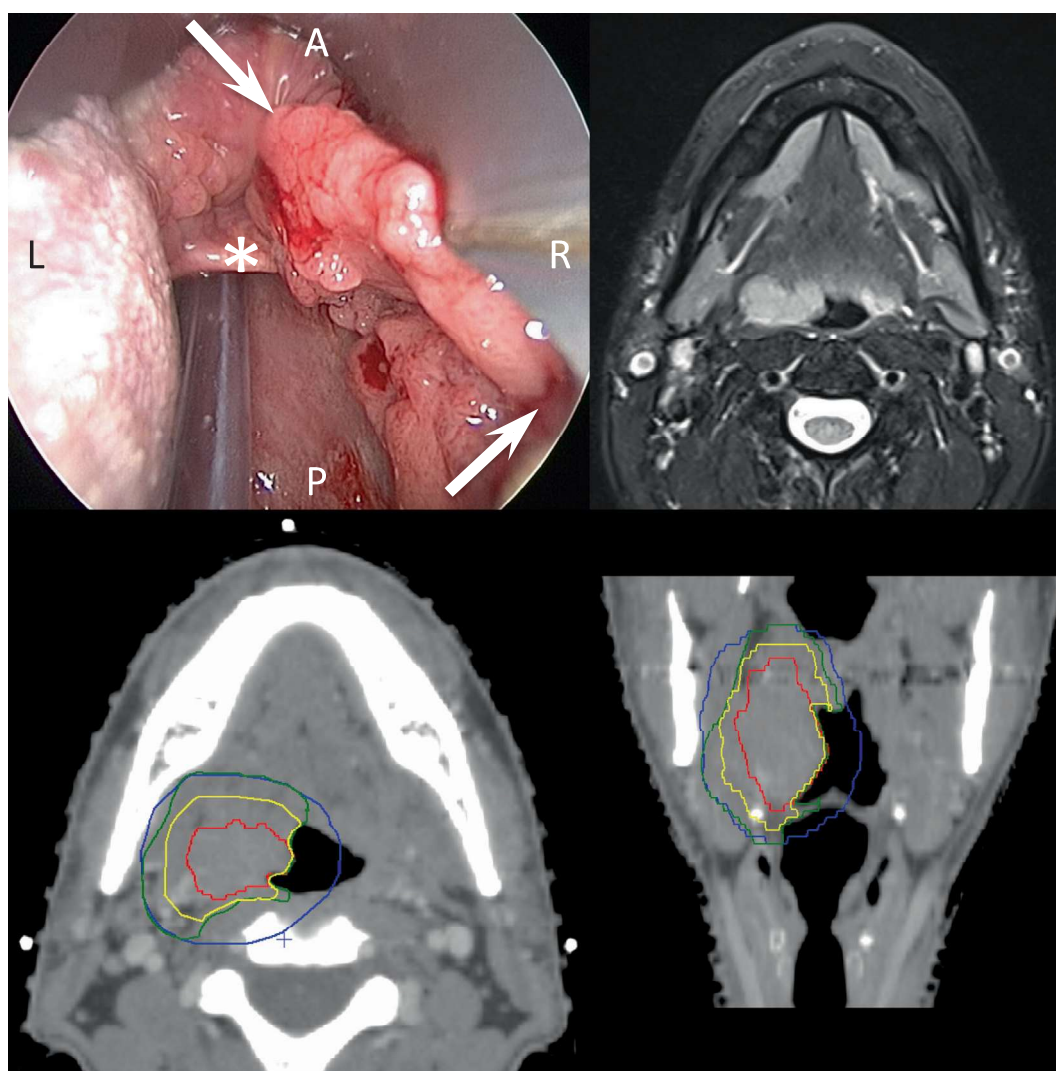


Fig. 18. Endoscopic view (upper left), diagnostic axial MRI T2 (upper right), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T3 (UICC 8th edition; max diameter of 44 mm) SCC of the lateral wall of the right oropharynx. On the endoscopic view, the sign “*” identifies the epiglottis; the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, mandible, and the longus colli, longus capitis, medial part of the constrictor muscle and medial pterygoid muscles. The CTV-P1 is delineated in yellow.

- T4 tumour (Fig. 21): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions cropped for air cavities.

For tonsillar primaries, the CTV-P2 includes the parapharyngeal space and likely extends into the surrounding structures, e.g. (medial and/or lateral) pterygoid muscles, mandible, retromolar trigone, base of tongue, mobile tongue and hard palate. For soft palate tumours, the CTV-P2 likely extends into the hard palate, the lateral pharyngeal wall, the nasopharynx and the nasal cavities. For posterior pharyngeal wall tumours, the CTV-P2 likely extends through the pre-vertebral fascia into the longus colli and longus capitis muscles, and may even extend into the adjacent vertebral body by a few mm. For tumours of the vallecula, the CTV-P2 likely extends into the pre-epiglottic space, the supraglottic larynx and the hypopharynx, caudally, into the hyoid bone and base of tongue, anteriorly, and into the para-pharyngeal space, laterally. For base of tongue tumours, the CTV-P2 likely extends laterally into the para-pharyngeal space, the hyoid bone and the mobile tongue,

anteriorly, and the supra-glottic laryngeal structures, caudally. It is likely that CTV-P2 overlaps with level Ib and II nodes, and with the retropharyngeal nodes.

Guidelines for the delineation of the primary tumour CTV for oral cavity SCC

It is recognized that squamous cell carcinoma of the oral cavity are mainly treated by surgery followed by radiotherapy or concomitant chemo-radiotherapy. However, for the sake of completion, the following guidelines are proposed for patients who will receive primary radiotherapy because of contraindications to surgery (e.g. poor general conditions of the patient, and/or anticipated very poor functional outcome) and/or refusal of surgery.

- T1 tumour: CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. The CTV-P2 does however not include any air cavity, or bony structures (e.g. mandible) unless

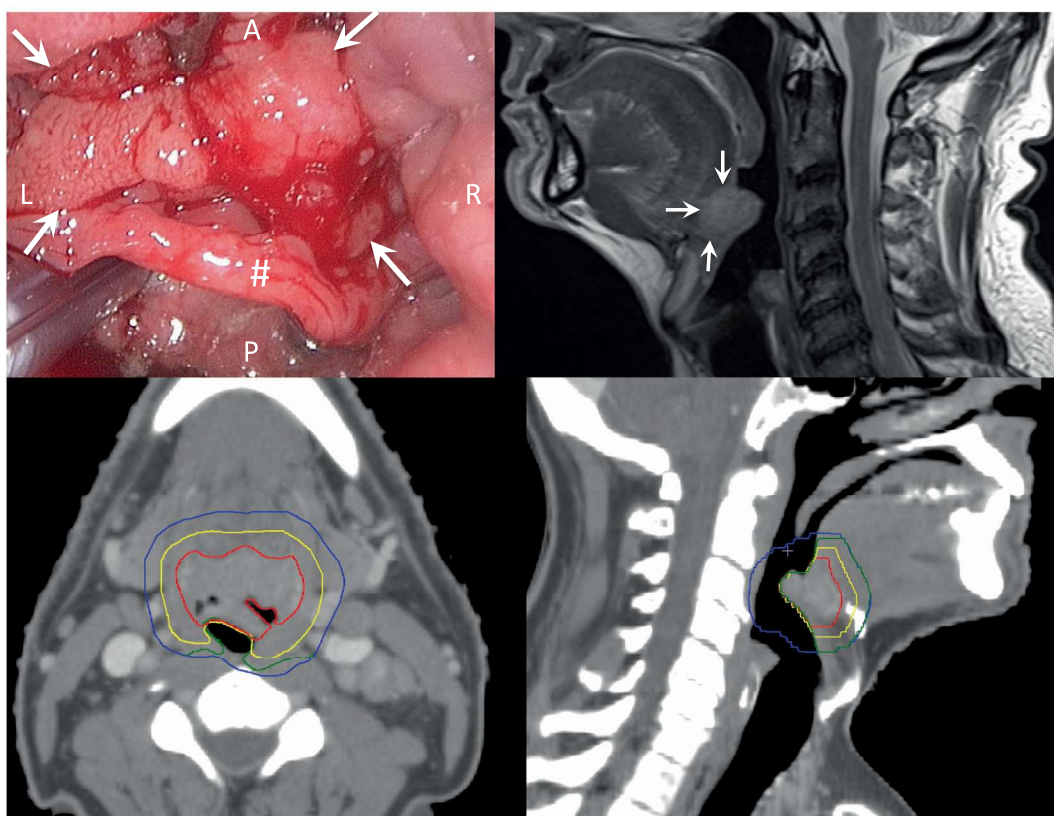


Fig. 19. Endoscopic view (upper left), diagnostic sagittal MRI T2 (upper right), and planning CT on axial (lower left) and sagittal (lower right) reconstructions of a T3 (UICC 8th edition); max diameter of 35 mm; infiltration of the lingual surface of epiglottis) SCC of the vallecula. On the endoscopic view, the sign “#” identifies the epiglottis; the letters “A”, “R”, “L” and “P” indicate the anterior, right, left and posterior orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the longus colli and longus capitis muscles, the thyroid cartilage, the thyro-hyoid muscle and the uvula. The CTV-P1 is delineated in yellow.

otherwise specified.

For superficial T1 tumours of the buccal mucosa, the deep margin of the CTV-P2 does not extend through the buccinator muscle, unless signs of invasion are observed on MRI imaging. For T1 tumours of the floor of mouth fixed to the mandible, and for T1 tumours overlying bony structures (gingiva, hard palate, retromolar trigone), the CTV-P2 may extend by 1–2 mm into the adjacent bone; for thin bony structures (e.g. hard palate), the CTV-P2 does not however extend beyond the bone into the nasal cavity or the cavity of the maxillary sinus.

For small and/or superficial T1 SCC of the oral cavity, the treating radiation oncologist may however decide not to delineate a CTV-P2 and thus only delineate a CTV-P1 defined as the GTV-P with a concentrically isotropic margin of 5 mm edited as described above.

- T2 tumour: CTV-P1 = GTV-T with a concentrically isotropic margin of 5 mm in all directions. The CTV-P1 does however not include any air cavity, or bony structures (e.g. mandible, hard palate). CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. The CTV-P2 does however not include any air cavity, or bony structures (e.g. mandible, hard palate). For T2 tumours of the cheek, the deep margin will include the buccinator muscle, but it does not go beyond, unless signs of muscular infiltration are observed on MRI. For T2 tumours of the floor of mouth fixed to the mandible, and for T2 tumours overlaid on bony structures (gingiva, hard palate, retromolar trigone), the CTV-P2 may extend by 5 mm into the adjacent bone; for thin bone structures (e.g. hard palate), the CTV-P2

does however not extend beyond the bone into the nasal cavity or the cavity of the maxillary sinus. For T2 tumours of the floor of mouth, the CTV-P2 is contained within the mylohyoid muscle. Thus, the submandibular gland should be edited out.

- T3 tumour: CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. The CTV-P1 does however not include any air cavity, or bony structures (e.g. mandible, hard palate) if possible. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. The CTV-P2 does however not include any air cavity, or bony structures (e.g. mandible, hard palate) if possible. For T3 tumour of the cheek, the deep margin includes the buccinator muscle and the subcutaneous fat. For T3 tumours of the floor of mouth fixed to the mandible, and for T3 tumours overlaid on bony structures (gingiva, hard palate, retromolar trigone), the CTV-P2 may extend by 5 mm into the adjacent bone; for thin bone structures (e.g. hard palate), the CTV-P2 will not extend beyond the bone into the nasal cavity or the cavity of the maxillary sinus. For T3 tumours of the floor of mouth, the caudal margin may include the mylohyoid muscle, but does not go beyond.

- T4 tumour (Fig. 22): CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm in all directions. The CTV-P1 does however not include any air cavity, or bony structures (e.g. mandible, hard palate), unless invaded. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. The CTV-P2 does however not include any air cavity, or, unless invaded, bony structures

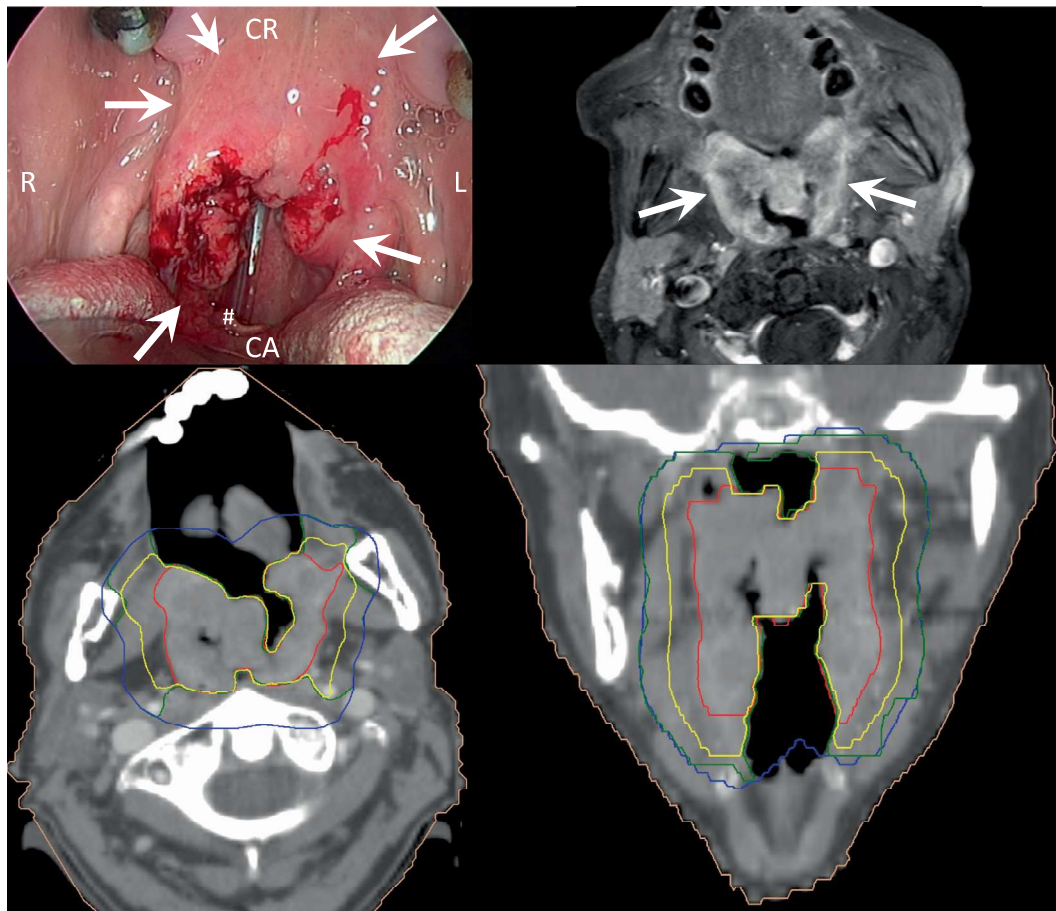


Fig. 20. Endoscopic view (upper left), diagnostic axial MRI T2 (upper right), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T3 (UICC 8th edition; max diameter of 55 mm) SCC of the soft palate invading both tonsillar fossae, but not extending to the posterior pharyngeal wall. On the endoscopic view, the sign “#” identifies the epiglottis; the letters “CR”, “CA”, “L” and “R” indicate the cranial, caudal, left and right orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after exclusion of the air cavities, the mobile tongue, the mandible, the pterygoid process, the vertebral body, the longus colli and longus capitis muscles, the posterior pharyngeal wall, the epiglottis, and the hyoid bone. The CTV-P1 is delineated in yellow.

(e.g. mandible, hard palate). Depending on the location of the primary tumour, CTV-P2 likely includes the deep extrinsic muscles of the tongue, the mandible, the chin, the skin of face, the maxillary sinus, the pterygoid plate, the masseter muscle; it may extend into the oropharynx, e.g. into the base of tongue, the tonsillar fossa, the soft palate, the para-pharyngeal space, the medial pterygoid muscle.

Discussion

When considering implementing these guidelines, several issues potentially impacting on their clinical use need to be addressed. These are briefly discussed below.

Delineation of the planning target volume

The recommendations proposed in the present guidelines are for the delineation of the primary tumour Clinical Target Volume (CTV-P), and thus do not account for organ motion and/or set-up uncertainty. The magnitude of the security margin required to generate the Internal Target Volume (ITV) and the Planning Target Volume (PTV) will be based on infrastructure and experience of each centre, immobilisation method, use of on-line imaging (e.g. CBCT, MVCT), and on the location of the CTV-P, e.g. a CTV associated with a laryngeal T1 carcinoma versus an oral cavity T4 carcinoma. It should be clearly stated that a PTV should be delineated for both

the CTV-P1 and the CTV-P2. It is beyond the scope of these guidelines to discuss the extent of the CTV to PTV margin, but typically margins around 3–5 mm have been proposed [37]. In the future, it is likely that the use of robust planning will directly integrate the organ motion and/or set-up uncertainty in the dose distribution planning [38]. The use of daily imaging may reduce such margin, but a CTV-to-PTV margin below 2 mm is not recommended [39].

Limit of validity

The recommendations proposed in the present guidelines are meant for the delineation of the primary tumour CTV (CTV-P) only in a primary treatment setting. They do not address the post-operative situation, nor recurrent disease, two clinical situations where the anatomy has been perturbed by previous treatments, and for which the “5 + 5 mm” margin concept may not be valid.

The use of consecutive rims of normal tissue around the primary tumour GTV to define the CTV is based on the assumption that the tumour cell density decreases with the distance from the GTV boundaries as illustrated in pathological studies [20–22]. However, it is known that some tumours present with a more infiltrative than pushy border, and for the former the accurate delineation of the GTV even on optimal diagnostic and planning images may be difficult and associated with larger inter-observer variability [40]. Furthermore, the presence of small clusters of

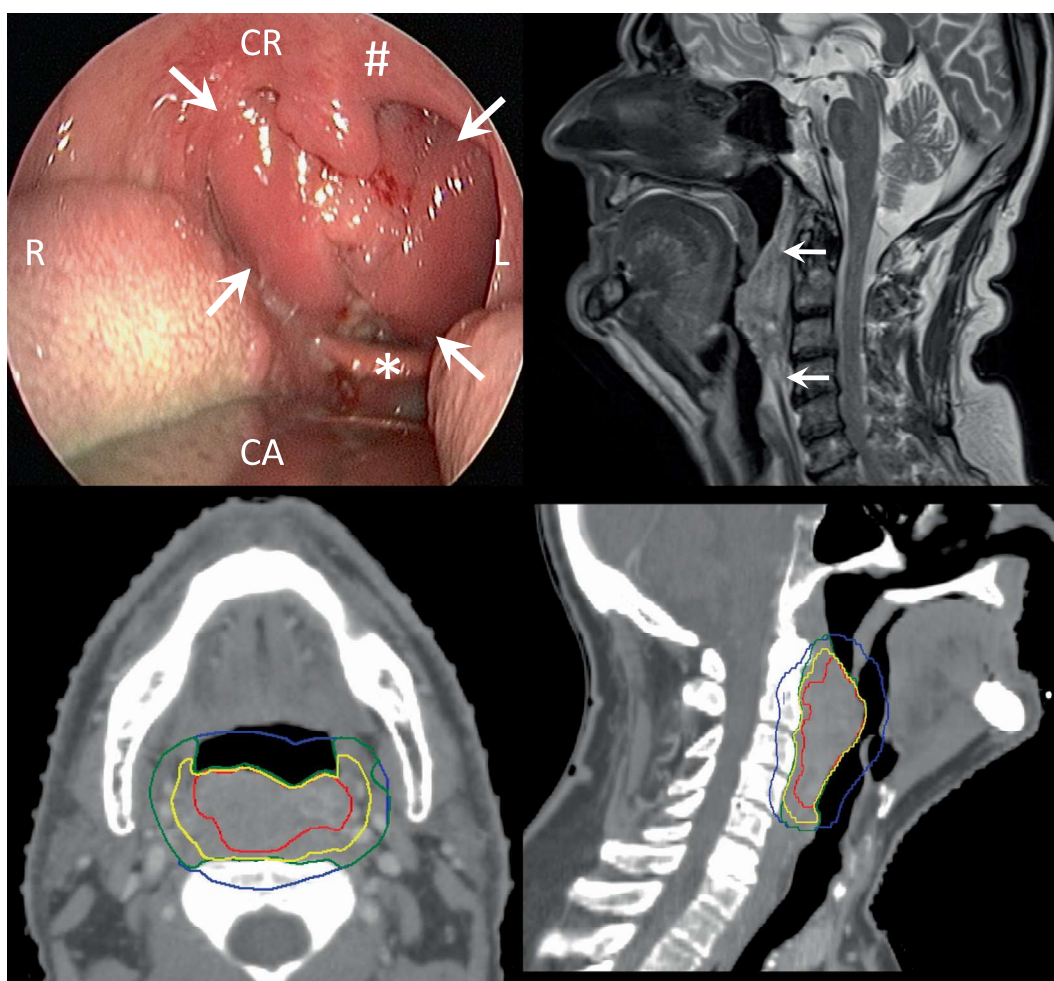


Fig. 21. Endoscopic view (upper left), diagnostic sagittal MRI T2 (upper right), and planning CT on axial (lower left) and sagittal (lower right) reconstructions of a T4b (UICC 8th edition; infiltration of the right longus capitis muscle; max diameter of 42 mm) SCC of the posterior oropharyngeal wall. On the endoscopic view, the signs “#” and “*” identify the soft palate and the epiglottis, respectively; the letters “CR”, “CA”, “L” and “R” indicate the cranial, caudal, left and right orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, vertebral bodies, epiglottis, soft palate, medial pterygoid muscles and thyroid cartilage. The CTV-P1 is delineated in yellow.

isolated cells (the so-called “tumour budding”) further away from the invasive tumour front has been described mainly in oral cavity SCC [41]. This explains why the proposed guidelines are advocating the use of a “5 + 5 mm” margin concept, although smaller margins have been reported as safe in few surgical and imaging-pathology correlation studies. Conversely, as highlighted in the section devoted to hypopharyngeal SCC, some tumours have been reported to have large mucosal and sub-mucosal infiltration, which may justify the use of a larger CTV-to-PTV margin [36].

Is tumour infiltration from the GTV influenced by the primary tumour T-stage and tumour location? It is true that the majority of the surgical series recommending the use of small margins around the macroscopic tumour mainly dealt with selected laryngeal and oropharyngeal T1 and T2 tumours. However, in the 3 pathological series reported, tumour stages from T1 to T3 were included, and no difference in distance of infiltration could be observed as a function of tumour volume. Also, no data have been published on difference in infiltration pattern as a function of tumour location. Additional data may be available in the future to challenge the present proposal, but today in the absence of such data, it is believed that such guidelines hold true irrespective of tumour location and tumour stage.

The proposed guidelines are valid for any radiation regimens (e.g. radiotherapy alone, concomitant chemo-radiotherapy, concomitant

EGFR-inhibitor-radiotherapy), but not for the delineation of the CTV-P after induction chemotherapy. For this latter situation, the use of the pre-chemotherapy images has been advocated [42].

The proposed guidelines do not address the issue of target volume delineation during treatment in the framework of adaptive radiotherapy. It is common for tumours and to some extent for OARs to change over the course of curative radiotherapy [43]. However, tumour shrinkage may not be concentric especially at the microscopic scale, and the application of a new fixed margin around a shrinking GTV might thus likely leave undertreated cells behind, in particular the more radioresistant stem cells [44]. The only reasonable recommendation is that if dose distribution is adapted during treatment based on modifications of normal anatomy, the volume of normal tissue that was included into the pre-treatment CTV remains the same throughout the course of radiotherapy, even if the GTV shrinks.

The proposed guidelines are only valid for invasive squamous cell carcinoma, and are not appropriate for *in situ* carcinoma or for other histopathologies, such as adenocarcinoma or adenoid cystic carcinoma of minor salivary gland tumour, sarcoma or haematologic malignancies. Such tumours may have a different growth and infiltrative pattern that may prevent the use of fixed margin. For example, adenoid carcinoma is known for its propensity for perineural infiltration [45].

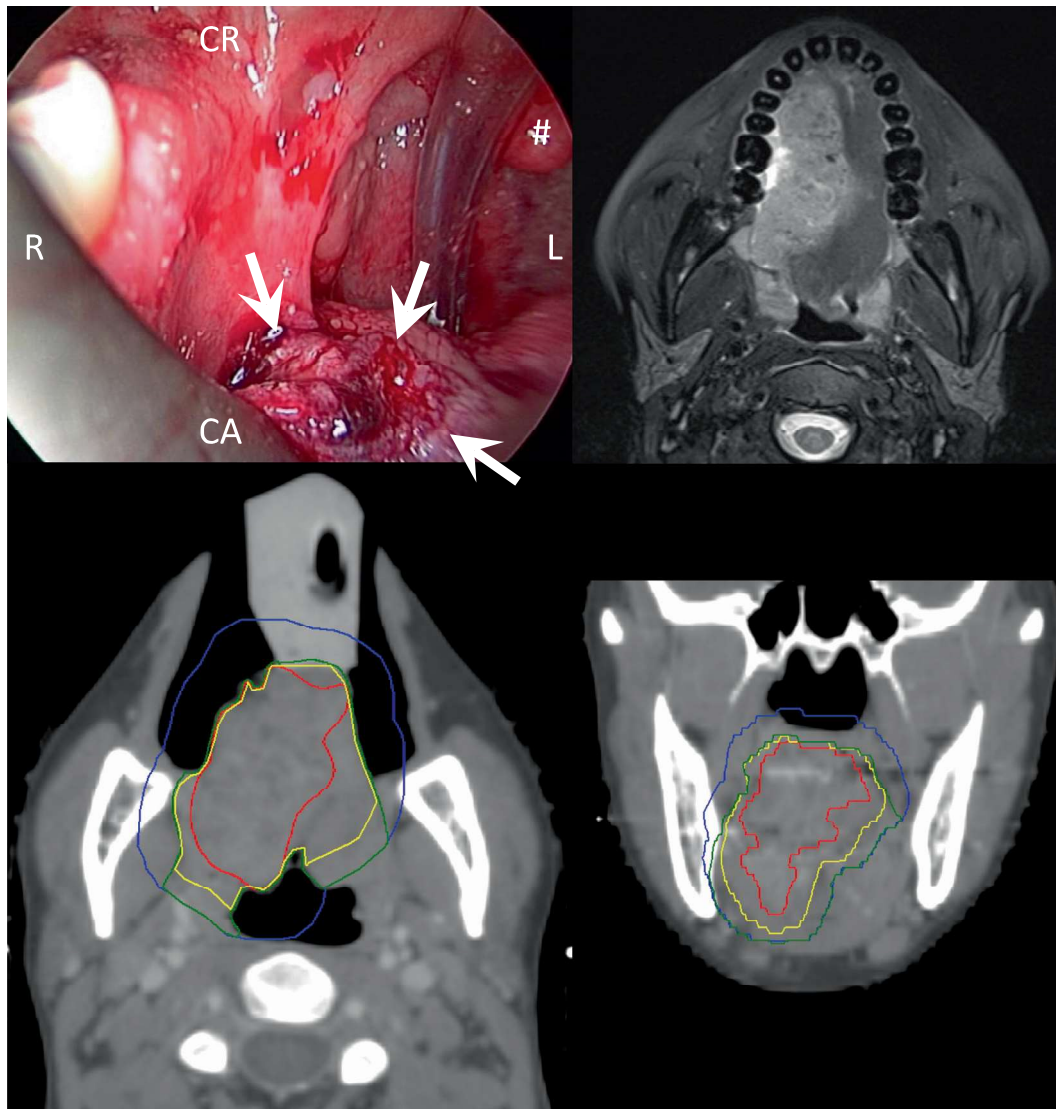


Fig. 22. Open mouth view (upper left) of the oral cavity, diagnostic axial MRI T2 (upper right), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T4 (UICC 8th edition); bilateral tongue involvement; maximal diameter of 54 mm and depth of infiltration of more than 2 cm) SCC of the right mobile tongue extending towards the base of tongue. On the open mouth view, the sign “#” identifies the uvula; the letters “CR”, “CA”, “L” and “R” indicate the cranial, caudal, left and right orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, mandible, soft and hard palate, upper gum, and medial pterygoid muscles. The CTV-P1 is delineated in yellow.

The proposed guidelines are valid for both oropharyngeal p16-negative and p16-positive SCC. Indeed, although the clinical behaviour of these two distinct entities is different, there is no data yet to suggest that different CTV-P delineation could be proposed for the latter. Clinical trials in this patient population are ongoing. For example, the ECOG 3311 trial, which includes a follow-up only arm for patients with p16-positive pT1/T2-pN0/N1 oropharyngeal SCC with a resection margin of more than 3 mm will provide information on whether a smaller margin around the GTV is adequate. Similar information will also be obtained from the EORTC-1420 trial, which randomises patients with early stage tonsil or base of tongue tumour between primary endoscopic surgery and radiotherapy; in this trial, no post-operative radiotherapy will be delivered for tumour margin above 3 mm.

Lastly, as these guidelines may be different than what radiation oncologists may have been trained and used to do in their routine practice, it is suggested to set-up some form of quality assurance programme at the level of centres and/or country to assess inter- and intra-observer variation in target volume delineation, and

appreciate how their implementation impact on clinical outcome. Peer-reviewing has indeed been shown to qualitatively and quantitatively decrease inter-observer variations and significantly improve the treatment plan [13].

A word of caution

These guidelines heavily rely on the correct delineation of the GTV-P, which integrates both clinical and imaging information. All the requested information (e.g. fiberoptic examination, endoscopy under GA, imaging work-up) needs to be available to the radiation oncologist, and needs to have been properly acquired and interpreted. In the near future, virtual endoscopy or augmented reality may help radiation oncologists to further improve the GTV-P delineation, especially to assess mucosal and sub-mucosal infiltration [46]. Considering the extent and complexity of the information needed to properly delineate the GTV-P and consequently the CTV-P, it is important to emphasize that the management of patients with Head and Neck SCC should be

performed in reference centres combining in one location all the expertise needed; such policy has been shown to directly impact on patient outcome [47,48].

In case of missing information, radiation oncologists need to perform a comprehensive clinical examination including a fiberoptic examination and/or seek expertise from ENT colleagues who may perform an endoscopy under GA. In cases of missing information not recoverable, or in case of sub-optimal imaging including the planning CT, e.g. where the planning CT is heavily degraded by dental amalgam or implants, the treating radiation oncologist may decide to deviate from these guidelines and choose to delineate a larger GTV-P and thus most likely a larger CTV-P. The ultimate consequences of such decision, i.e. minimizing the risk of geographical miss, will have to be balanced to the irradiation of a larger volume of normal tissue with possible higher rate of complications.

Disclaimer

The present guidelines are not meant to recommend the use of radiotherapy for every oral cavity, laryngeal, oropharyngeal and hypopharyngeal SCC. These guidelines have been developed as a guide to help radiation oncologists to delineate their target volumes as accurately as possible, should (chemo)-radiotherapy be chosen as the primary treatment modality. It is likely that the use of such guidelines will also help in reducing inter-clinician variability, and be of interest when writing clinical protocols and elaborating Quality Assurance guidelines for Head and Neck SCC.

Lastly, it should be clearly stated that the authors of the present guidelines are not responsible for any misuse of this material by any third parties.

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Ethical considerations

None to declare.

Conflict of interest

All authors declare no conflict of interest.

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