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Review Article

Delineation of the post-operative primary tumour and nodal clinical target volumes in oral cavity squamous cell carcinoma: European Society for Radiotherapy and Oncology (ESTRO) clinical guidelines

Mererid Evans [a,*], Pierluigi Bonomo [b], Po Chung Chan [c], Melvin L.K. Chua [d], Jesper Grau Eriksen [e], Keith Hunter [f], Kenneth Jensen [e], T.M. Jones [f], Sarbani Ghosh Laskar [g], Roberto Maroldi [h], Brian O'Sullivan [i], Claire Paterson [j], Luca Tagliaferri [k], Silke Tribius [l], Sue S. Yom [m], Vincent Gregoire [n]

[a] Division of Cancer and Genetics, Cardiff University and Dept. of Clinical Oncology, Velindre University NHS Trust, Wales, UK
[b] Dept. of Radiation Oncology, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Italy
[c] Dept of Clinical Oncology, Velindre University NHS Trust, Wales, UK
[d] Division of Radiation Oncology, National Cancer Centre Singapore, Singapore
[e] Dept of Experimental Clinical Oncology, Aarhus University Hospital, Denmark
[f] Liverpool Head and Neck Centre, Molecular and Clinical Cancer Medicine, University of Liverpool, UK
[g] Dept. of Radiation Oncology, Tata Memorial Hospital, and Homi Bhabha National Institute, Mumbai, India
[h] Dept. of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Italy
[i] Dept. of Radiation Oncology, Princess Margaret Cancer Center, University of Toronto, Canada
[j] Beatson West of Scotland Cancer Centre, Glasgow, UK
[k] Dept of Diagnostic Imaging and Oncology, Fondazione Policlinico, Gemelli University Hospital, Rome, Italy
[l] Dept of Radiation Oncology, Asklepios Klinik St.Georg, Hamburg, Germany
[m] Dept. of Radiation Oncology, University of California, San Francisco, USA
[n] Dept of Radiation Oncology, Centre Léon Bérard, Lyon, France

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ABSTRACT

Background and purpose: To date, no consensus guidelines have been published that systematically guide delineation of primary and nodal Clinical Target Volumes (CTVs) in patients who require post-operative radiotherapy (PORT) for mucosal Head and Neck squamous cell carcinoma (HNSCC). As a result, significant individual, institutional and national variation exists in the way that CTVs are delineated in the post-operative setting, leading to considerable heterogeneity in radiotherapy treatment.
Methods: A multi-disciplinary group of experts convened by the European Society for Radiotherapy and Oncology (ESTRO) set-out principles for the multi-disciplinary management of oral cavity squamous cell carcinoma (OCSCC). Building on these, and adapting the geometric expansion approach described in previous primary CTV delineation guidelines, new consensus guidelines for the delineation of post-operative CTVs, both for the primary tumour and nodal regions, were proposed by the expert group, before being shared with a second tier of international experts to ensure their worldwide acceptability and applicability.
Results: These guidelines propose that surrogate volumes representing the resected primary and nodal Gross Tumour Volumes (GTV-P and GTV-N respectively) are re-created on the radiotherapy planning scan, either by registration with diagnostic imaging or via reference to anatomical landmarks. A post-operative CTV for the primary tumour (CTV-P) is created as a composite volume that includes: i) geometric expansion around the surrogate GTV-P, and ii) geometric expansion around the surgical defect and/or reconstruction flap. A post-operative CTV for the nodal region (CTV-N) is created as a composite volume that includes: i) geometric

* Corresponding author at: Velindre Cancer Centre, Whitchurch, Cardiff, Wales CF14 2TL, UK.
E-mail addresses: Mererid.Evans@wales.nhs.uk (M. Evans), bonomop@aou-careggi.toscana.it (P. Bonomo), po.chan@wales.nhs.uk (P.C. Chan), melvin.chua.l.k@singhealth.com.sg (M.L.K. Chua), jesper@oncology.au.dk (J.G. Eriksen), keith.hunter@liverpool.ac.uk (K. Hunter), kennjens@rm.dk (K. Jensen), tmjones@liverpool.ac.uk (T.M. Jones), sarbanilaskar@gmail.com (S.G. Laskar), rmaroldi@gmail.com (R. Maroldi), Brian.OSullivan@uhn.ca (B. O'Sullivan), claire.paterson2@ggc.scot.nhs.uk (C. Paterson), luca.tagliaferri@policlinicogemelli.it (L. Tagliaferri), stribius@gmail.com (S. Tribius), sue.yom@ucsf.edu (S.S. Yom), Vincent.GREGOIRE@lyon.unicancer.fr (V. Gregoire).

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expansion around the surrogate GTV-N, and ii) the involved nodal level (CTV-N1). Guidelines for delineating at-risk nodal levels in a prophylactic dose CTV (CTV-N2) are included, and for making decisions regarding the need for unilateral and/or bilateral neck treatment.
Conclusions: Implementation of these guidelines into clinical practice should reduce variation, and by promoting consistency of approach, facilitate multi-institutional audits and clinical trials including Radiation Therapy Quality Assurance (RTQA) in patients with OCSCC. It is anticipated that they will form the basis for future guidelines aiming to standardise post-operative CTV delineation in other head and neck subsites.

Introduction

To date, no consensus guidelines have been published to guide the delineation of the primary and nodal Clinical Target Volumes (CTVs) in patients requiring post-operative radiotherapy (PORT) for mucosal Head and Neck squamous cell carcinoma (HNSCC). In 2018, international consensus guidelines were published to guide the delineation of the primary tumour Clinical Target Volume (CTV-P) in HNSCC patients receiving definitive radiotherapy or chemo-radiotherapy [1]. The aim of the guidelines was to reduce the occurrence, and potential clinical impact, of variability in primary tumour CTV delineation. These guidelines proposed the concept of utilizing a "5 mm + 5 mm" isocentric or geometric expansion of the primary Gross Tumour Volume (GTV-P), edited for bone, air and fascial planes, to create the CTV-P, and included guidance for adapting and applying this concept for each subsite within the larynx, hypopharynx, oropharynx and oral cavity. International guidelines developed in parallel for CTV delineation in nasopharyngeal cancer used the same principle, modified to account for the complex anatomy at the base of skull and infiltration routes for potential cell dissemination [2]. Implementation of geometric GTV to CTV margin expansion has been shown by the Danish Head and Neck Cancer (DAHANCA) group to result in more conformal CTV delineation compared to an anatomical margin, which is more open to misinterpretation and variation [3]; furthermore, a change in protocol from an anatomical to geometric CTV margin has been correlated with lower late dysphagia rates in an unplanned post-hoc analysis of patients recruited to the De-ESCALaTE HPV clinical trial [4]. Early, non-randomised studies from the Netherlands have reported that reducing the high-risk GTV to CTV geometric margin from 10 mm to 6 mm results in reduced radiation doses to the salivary glands and constrictor muscles, and lower acute and late toxicity rates compared to historical controls treated with a 10 mm CTV margin [5,6].

In contrast to the definitive setting, comprehensive guidelines for delineating target volumes in the post-operative setting do not exist, and arguably are even more necessary in view of the significant changes in anatomy that can occur following surgery, and the inherent differences that exist in interpreting the many risk factors for recurrence included in the post-operative histology report. To address this, a multi-disciplinary group of experts convened by the European Society for Radiotherapy and Oncology (ESTRO) have, through discussion and review of current evidence and international practice, developed guidelines for the delineation of post-operative CTVs, both for the primary tumour and nodal regions in patients with oral cavity squamous cell carcinoma (OCSCC). These guidelines build on the background set-out in the manuscript from the same group which summarises important principles regarding the multi-disciplinary management of OCSCC, including indications for PORT [7] and, for the first time, aim to reduce variability in approach to the delineation of primary and nodal CTVs in the post-operative setting for OCSCC. The terms 'required' and 'recommended' are used throughout these guidelines to refer to elements that 'should be done' and those that 'could be done but are left to the interpretation of the treating clinician' respectively. The guidelines developed by the group were reviewed by international HNSCC experts from countries not represented by the authorship, including Japan, Hong Kong, Australia, Brazil, Mexico, Canada, Denmark, France, Spain, Poland, Ireland and the UK (see acknowledgements for list of reviewers); the guidelines have been modified according to their feedback to ensure their widespread acceptability and applicability in countries across the world.

Preparing for treatment- acquisition of the planning scan and fusion with pre-operative imaging

The principles of planning Computed Tomography (CT) acquisition are the same as in the primary treatment setting as outlined in the 2018 guidelines [1]. In brief:

- The patient should be in a supine position, with a neutral neck, and immobilised in a custom-fitted immobilisation shell or mask.
- An intra-oral prosthesis (or "mouth bite") may be used to depress the tongue inferiorly, therefore separating the upper and lower jaws, in cases with anterior OCSCCs where there is sufficient mouth opening. Intra-oral protheses should only be used if they can be inserted in a reproducible position and are tolerated by the patient. They should be used with caution for OCSCCs extending posteriorly into the tongue base (which tends to 'bulge' upwards behind the device).
- 2.0 mm (range 1–3 mm) CT slices should be acquired from the skull base to below the sterno-clavicular joint, and use of intravenous (IV) contrast is mandatory (unless there is a contraindication including history of allergy to contrast)
- Rigid (or non-deformable) co-registration of a high-quality pre-operative contrast-enhanced diagnostic CT and/or Magnetic Resonance Imaging (MRI) of the neck with the planning CT scan is recommended to aid delineation of the post-operative target volumes. Typically, lesions of the oral cavity are better visualised with an MRI scan [8], but a CT can be used as an alternative in cases where no diagnostic MRI of the oral cavity exists. Matching to the vertebral body and spinal canal of the upper cervical vertebrae (C1-C3), and/or other bony structures that lie in close proximity to the epicentre of the primary tumour, including the mandible (in the case of oral tongue, floor of mouth and retromolar trigone cancers) or hard palate/maxilla (in the case of hard palate cancers) is recommended. Soft tissue anatomy is likely to have been significantly changed by surgery and therefore matching to soft tissues is not generally recommended.

Principles of post-operative CTV delineation:

According to the ICRU definition [9], the CTV includes the GTV together with a volume of surrounding normal tissue at risk for microscopic tumour infiltration with a probability of occurrence considered relevant for therapy. In addition to microscopic infiltration around the GTV, the CTV must take into account the natural pathways of spread for a particular tumour, including the propensity for lymph node, perivascular and perineural extension. The CTV is relevant for the primary tumour ($CTV_{primary}$ or CTV-P), involved lymph nodes and/or lymph node regions (CTV_{nodal} or CTV-N, which can be designated CTV-N1, CTV-N2 and so on). In the post-operative setting, where the GTV has

Table 1
Summary of step-by-step guide to post-operative primary CTV delineation.

Step 1: Defining surrogate volumes to represent the pre-operative primary tumour and operative bed	
1a	– Re-create GTV-P pre-op on diagnostic MRI/CT – Edit GTV-P pre-op on planning CT
1b	– Delineate surgical defect/flap
Step 2: Creating the CTV-P	
2a	– GTV-P pre-op + 10 mm isotropic margin
2b	– Surgical defect/flap + 5 mm isotropic margin
2c	– CTV-P = (GTV-P pre-op + 10 mm) + (Surgical defect/flap + 5 mm) – Edit CTV-P for anatomical barriers and for intra-oral prothesis (if used)

CTV, Clinical Target Volume; GTV-P pre op, pre-operative primary Gross Tumour Volume; CTV-P, post-operative primary Clinical Target Volume.

been removed by radical surgery, the volumes at risk for recurrence can still be designated CTV-P and CTV-N [10], however delineating the CTV in the absence of a GTV requires a careful and systematic approach, to ensure that tissues at risk of subclinical disease (and therefore recurrence) are consistently included in the target volume. These guidelines propose a structured method for CTV delineation in the post-operative setting for OCSCC.

Proposed nomenclature:

The following nomenclature, which is consistent with the previously published guidelines for CTV delineation in the primary treatment setting [1], will be used throughout the manuscript:

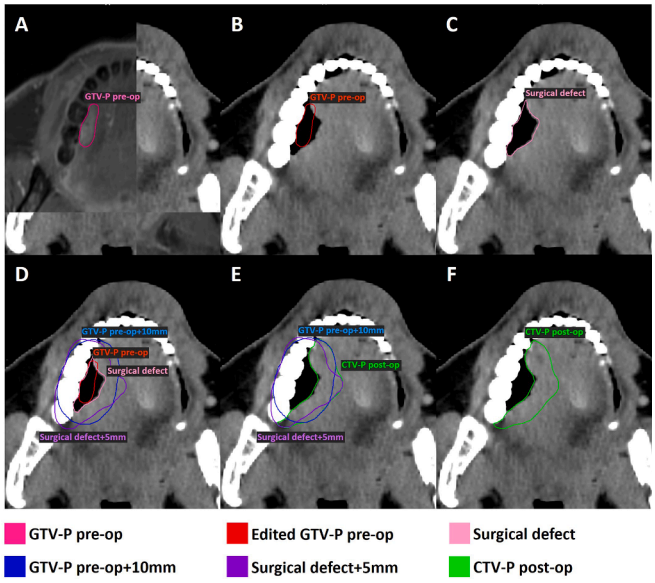

Fig. 1. Example outlining of a case with a squamous cell carcinoma (SCC) of the right lateral border of the oral tongue that underwent right partial glossectomy with no reconstruction. Histology showed a pT2 (UICC/AJCC TNM8th edition) moderately differentiated SCC with a 4 mm mucosal resection margin, a 3 mm deep resection margin and perineural invasion (PNI). Images show: A) Diagnostic MRI fused with planning CT scan at the level of the resected primary tumour with GTV-P pre-op re-created on MRI (dark pink); B) edited for anatomical change on planning CT (red); C) surgical defect delineated on the planning CT (light pink); D) a 10 mm isotropic margin added to GTV-P pre-op (navy), and a 5 mm margin added to surgical defect (purple); E) and F) CTV-P post-op (green) is a composite volume delineated by combining GTV-P pre-op + 10 mm and surgical defect + 5 mm and editing for air, bone and teeth. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

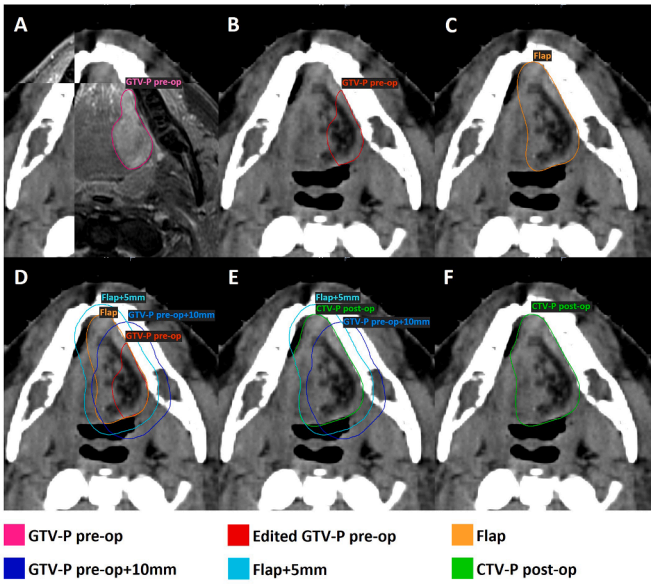

Fig. 2. Example outlining of a case with a SCC of the left oral tongue that underwent left hemi-glossectomy and radial forearm free flap (RFFF) reconstruction. Histology showed a pT4 (UICC/AJCC TNM8th edition) moderately differentiated SCC with clear (>5 mm) resection margins but extensive lymphovascular invasion (LVI) and PNI. Images show: A) Diagnostic MRI fused with planning CT scan at the level of the resected primary tumour with GTV-P pre-op re-created on MRI (dark pink); B) edited for anatomical change on planning CT (red); C) RFFF delineated on the planning CT (orange); D) a 10 mm isotropic margin added to GTV-P pre-op (navy), and a 5 mm margin added to RFFF (cyan); E) and F) CTV-P post-op (green) is a composite volume delineated by combining GTV-P pre-op + 10 mm and flap + 5 mm and editing for air, bone and teeth. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

- GTV-P pre-op: pre-operative primary tumour GTV delineated based on pre-operative imaging.
- GTV-N pre-op: pre-operative nodal GTV delineated based on pre-operative imaging.
- CTV-P post-op: post-operative primary CTV associated with post-operative dose prescription.
- CTV-P high-risk: post-operative primary CTV associated with high dose prescription.
- CTV-N1: post-operative nodal CTV associated with post-operative dose prescription.
- CTV-N2: post-operative nodal CTV associated with prophylactic dose prescription.
- CTV-N high-risk: post-operative nodal CTV associated with high dose prescription.

Delineating the post-operative primary CTV:

In the absence of a GTV-P, the use of a surrogate volume can aid definition of the post-operative CTV-P. Possible surrogate volumes are:

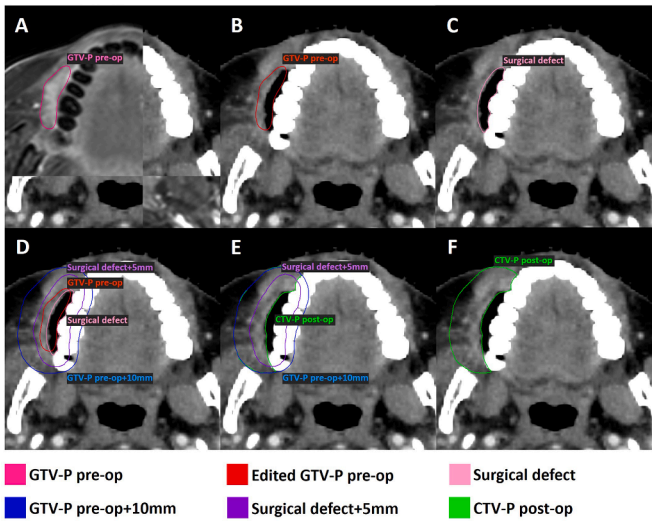

Fig. 3.1. Example outlining of a case with a SCC of the right upper buccal mucosa that underwent wide local excision with no reconstruction. Histology showed a pT2 (UICC/AJCC TNM8th edition) moderately differentiated SCC with a 6 mm mucosal resection margin, and a 2 mm deep resection margin. Images show: A) Diagnostic MRI fused with planning CT scan at the level of the resected primary tumour with GTV-P pre-op re-created on MRI (dark pink); B) edited for anatomical change on planning CT (red); C) surgical defect delineated on the planning CT (light pink); D) a 10 mm isotropic margin added to GTV-P pre-op (navy), and a 5 mm margin added to surgical defect (purple); E) and F) CTV-P post-op (green) is a composite volume delineated by combining GTV-P pre-op + 10 mm and surgical defect + 5 mm and editing for air, bone and teeth. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
In this case, the re-created GTV-P pre-op extends further superiorly than the surgical defect as shown in the coronal screenshots below (Fig. 3.2). Failure to delineate the GTV-P pre-op in this case, and relying solely on the surgical defect to define the pre-operative tumour bed, would have resulted in a geographical miss superiorly in the region of the infratemporal fossa. This illustrates the added value of delineating the GTV-P pre-op, as well as the surgical defect, when delineating the post-operative CTV-P in OCSCC.

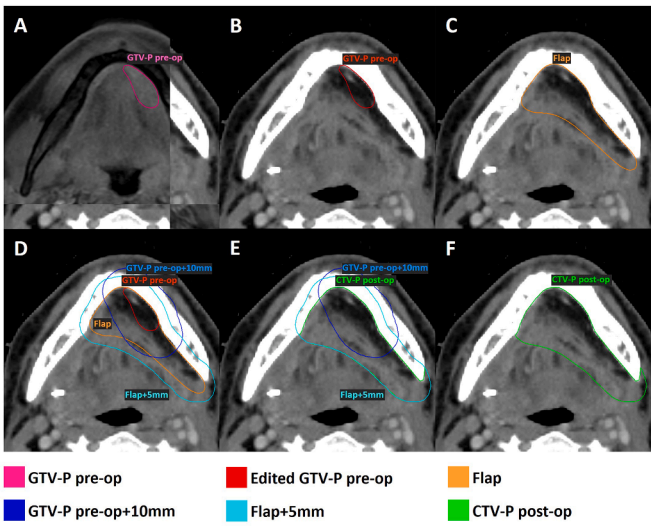

Fig. 4. Example outlining of a case with a SCC of the left floor of mouth that underwent wide local excision with RFFF. Histology showed a pT2 (UICC/AJCC TNM8th edition) moderately differentiated SCC with a 5 mm mucosal resection margin, and a 1.2 mm deep resection margin, with LVI. Images show: A) Diagnostic MRI fused with planning CT scan at the level of the resected primary tumour with GTV-P pre-op re-created on MRI (dark pink); B) edited for anatomical change on planning CT (red); C) RFFF delineated on the CT (orange); D) a 10 mm isotropic margin added to GTV-P pre-op (navy), and a 5 mm margin added to the RFFF (cyan); E) and F) CTV-P post-op (green) is a composite volume delineated by combining GTV-P pre-op + 10 mm and flap + 5 mm and editing for bone and teeth. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
In this case the RFFF extends to include most of the left of the oral cavity, as surgery included resection of an area of severe dysplasia posterior to the invasive tumour in the left floor of mouth.

- The pre-operative GTV-P
- The post-operative surgical defect (in cases where no reconstruction has been carried out)
- The reconstruction flap (in cases where flap reconstruction has been carried out)

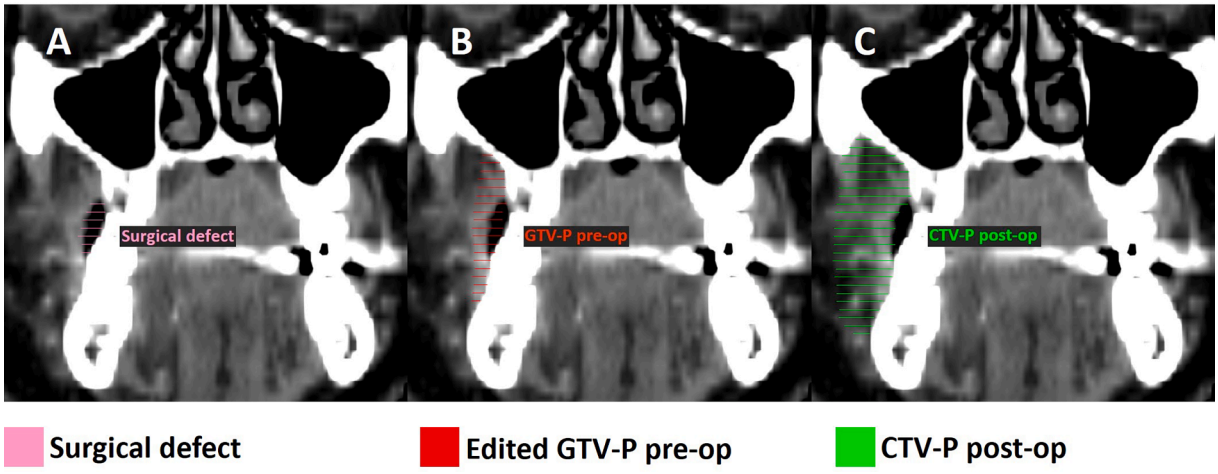

Fig. 3.2. Coronal views of the planning CT scan of the case illustrated in Fig. 3.1. Images show: A) Surgical defect (pink); B) GTV-P pre-op (red); C) CTV-P post-op (green) which is a composite volume delineated by adding a margin to the re-created GTV-P pre-op and surgical defect. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

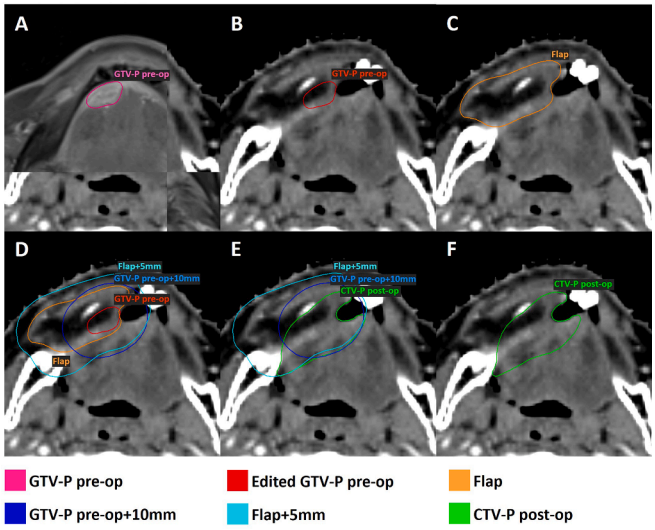

Fig. 5.1. Example outlining of a case with a SCC of the right floor of mouth/ventral surface of the tongue that underwent wide local excision and reconstruction with a nasolabial flap. Histology showed a pT2 (UICC/AJCC TNM8th edition) moderately differentiated SCC with a 2 mm mucosal resection margin, and a 6 mm deep resection margin, with LVI and PNI. Images show: A) Diagnostic MRI fused with planning CT scan at the level of the resected primary tumour with GTV-P pre-op re-created on MRI (dark pink); B) edited for anatomical change on the planning CT (red); C) nasolabial flap delineated on the planning CT (orange); D) a 10 mm isotropic margin added to GTV-P pre-op (navy), and a 5 mm margin added to the nasolabial flap (cyan); E) and F) CTV-P post-op (green) is a composite volume delineated by combining GTV-P pre-op + 10 mm and flap + 5 mm and editing for bone of the mandible. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
In this case the nasolabial flap (in orange) rotates from the facial region through the right angle of mouth into the oral cavity. As a result, part of the composite volume extends outside the oral cavity which is considered not at risk clinically. In this case therefore, the CTV-P post-op is edited along the mandible to spare part of the flap outside the mandible which is not at risk (see Fig. 5.2).

Whenever possible, we recommend using a combination of the pre-operative GTV-P (which defines the size and position of the primary tumour prior to surgery, providing it can be accurately re-created on the post-operative CT planning scan [see below]) and either the post-operative surgical defect or the reconstruction flap (both of which define the margins of resection, or primary tumour operative bed) to define the area around which a volume of surrounding normal tissue is included to create the CTV-P. The recommended dose prescription to the Planning Target Volume (PTV) associated with CTV-P is Equivalent Dose in 2 Gy Fractions (EQD_2) 60 Gy.

Step-by-step guide to post-operative primary CTV delineation

Pre-operative anatomical imaging (MRI and/or CT for co-registration), clinical photographs, pan-endoscopy reports, intra-operative findings and the final pathology result should be available to inform treatment volume delineation. In complex cases, input from the operating surgeon may also be helpful in accurately delineating the target volumes. The aim is to identify the tissues that are at risk of recurrence post-operatively using a step-wise, systematic approach, based on the fundamental principles of CTV delineation for definitive radiotherapy. This step-by-step approach is summarised in Table 1.

Step 1: Defining surrogate volumes to represent the pre-operative primary tumour and operative bed.

- **Step 1a**: Re-creating the pre-operative primary tumour GTV (GTV-P pre-op).

Accurate delineation of the pre-operative primary tumour GTV (GTV-P pre-op) is a useful step to guide the delineation of the CTV-P. Where co-registration of the pre-operative MRI or CT scan with the planning CT scan has been successful, the GTV-P pre-op should be delineated on the pre-operative imaging, and (if required) edited for changes in post-operative anatomy on the planning CT. Information from the pre-operative examination (including photographic images and/or a drawing of the tumour if available) and the operative findings should be used to augment delineation of the GTV-P pre-op. Where there is suboptimal image co-registration of the diagnostic MRI or CT scan with the planning CT scan, such that it increases the uncertainties in

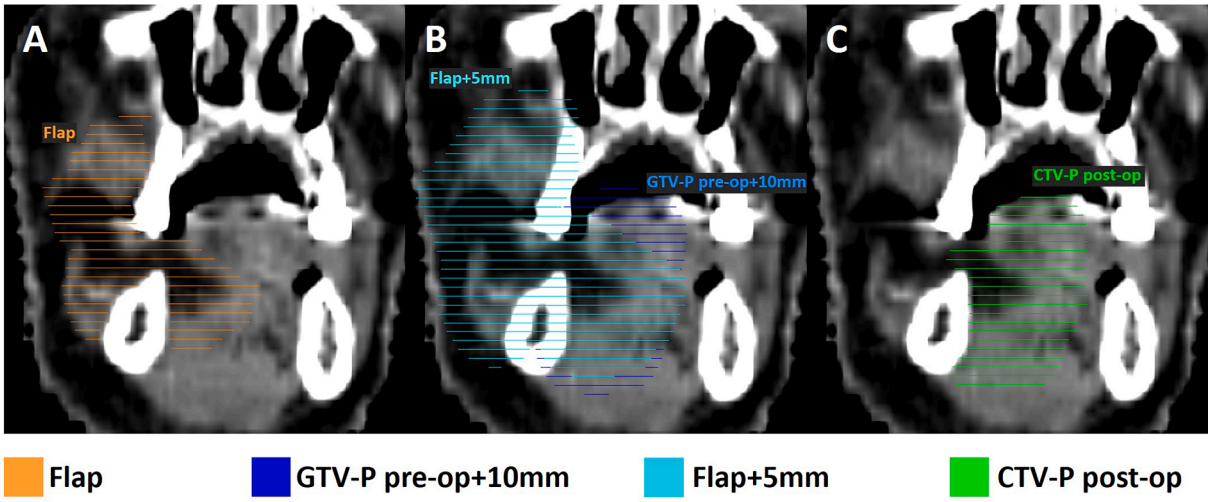

Fig. 5.2. Coronal views of the planning CT scan presented in Fig. 5.1. Images show: A) Nasolabial flap (orange); B) Composite volume; C) CTV-P post-op (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tumour delineation, delineate the GTV-P pre-op based on information from the pre-operative examination/photographs/drawings, radiology reports/images and operative findings only, without co-registration of the pre-operative images.

- **Step 1b**: Delineating the primary tumour operative bed.
  - o In cases where no flap reconstruction has been carried out (as in Fig. 1), the primary tumour operative bed is represented (at least in part) by the surgical defect.
  - o In cases where flap reconstruction has been carried out (as in Fig. 2), the primary tumour operative bed is typically represented by the body of the reconstruction flap. An MRI simulation scan, if available, can help to visualize the flap and aid delineation of the operative bed.

In some cases, the surgical defect may not fully represent the primary tumour operative bed (as in Figs. 3.1 and 3.2); and in others the flap may be ill-defined (as in Fig. 6) or significantly larger than the primary tumour operative bed (e.g. if it is a pedicled flap) (as in Figs. 8.1 and 8.2). In these cases, the re-created pre-operative primary tumour GTV (GTV-P pre-op) can significantly aid delineation.

Step 2: Creating the Clinical Target Volume (CTV).

- **Step 2a**: A 10 mm isotropic margin is added to the GTV-P pre-op, to account for potential microscopic spread around the primary. Addition of a 10 mm isotropic margin is consistent with the 5 + 5 (=10) mm isotropic margin advocated for CTV definition in the definitive radiotherapy setting [1] and reflects findings from surgical

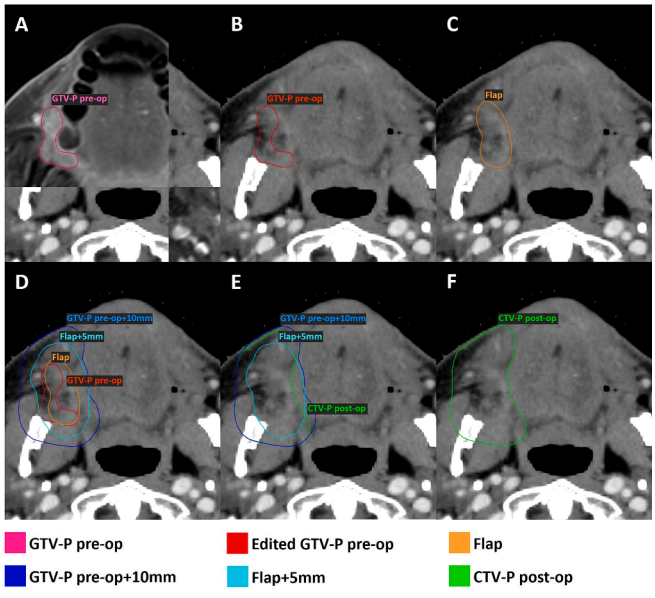

Fig. 6. Example outlining of a case with a SCC of the right retromolar trigone that underwent wide local excision with a buccal fat pad reconstruction. Histology showed a pT2 (UICC/AJCC TNM8th edition) moderately differentiated SCC with a 3 mm mucosal resection margin, and a 2 mm deep resection margin. Images show: A) Diagnostic MRI fused with planning CT scan at the level of the resected primary tumour with GTV-P pre-op re-created on MRI (dark pink); B) edited for anatomical change on planning CT (red); C) buccal fat pad reconstruction (which is ill-defined) is delineated on the planning CT (orange); D) a 10 mm isotropic margin added to GTV-P pre-op (navy) plus a 5 mm margin added to the buccal fat pad (cyan); E) and F) CTV-P post-op (green) is a composite volume delineated by combining GTV-P pre-op + 10 mm and flap + 5 mm and editing for mobile part of oral tongue and teeth. The mandibular ramus is not edited from the CTV-P post-op because of the limited thickness of bone cortex at this region. CTV-P post-op may be edited 2 mm within the skin surface as the skin is not involved. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
In this case, the fat pad reconstruction is ill-defined on the planning CT. It is outlined as far as possible on the CT slices where it can be identified, albeit with significant uncertainty. This case illustrates the added value of delineating the GTV-P pre-op, as well as the ill-defined fat pad reconstruction, to delineate the post-operative CTV-P.

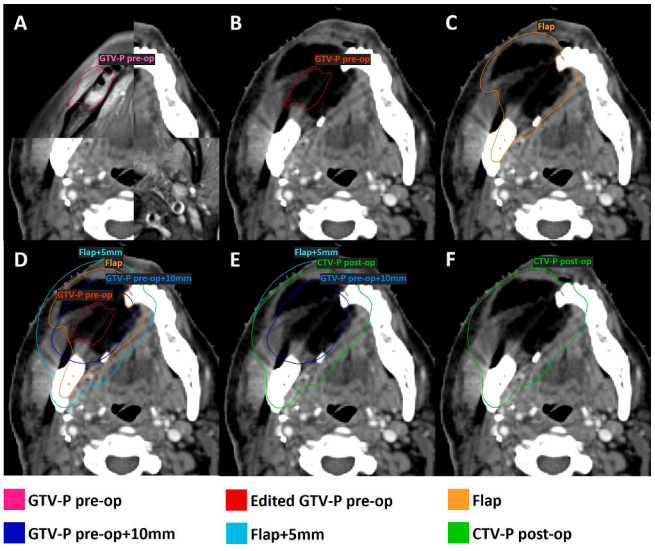

Fig. 7.1. Example outlining of a case with a SCC of the right mandibular alveolus involving the buccal sulcus, that underwent right segmental mandibulectomy with a fibula free flap reconstruction. Histology showed a pT4a (UICC/AJCC TNM8th edition) moderately differentiated SCC with a 5 mm mucosal resection margin, and a 2 mm deep resection margin, with marrow space invasion. Images show: A) Diagnostic MRI fused with planning CT scan at the level of the resected primary tumour with GTV-P pre-op re-created on MRI (dark pink); B) edited for anatomical change on planning CT (red); C) fibula free flap reconstruction is delineated on the planning CT (orange); D) a 10 mm isotropic margin added to GTV-P pre-op (navy) plus a 5 mm margin added to the fibula free flap (cyan); E) and F) CTV-P post-op (green) is a composite volume delineated by combining GTV-P pre-op + 10 mm and flap + 5 mm and editing for skin. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
In this case, bone (mandible and fibula) has not been edited when delineating the CTV-P post-op in view of the bone marrow invasion. Delineating the fibula flap and adding a 5 mm margin ensures adequate coverage of the at-risk area in the residual mandible. This case illustrates that editing of anatomical barriers needs to be based on clinical risk assessment (see Fig. 7.2).

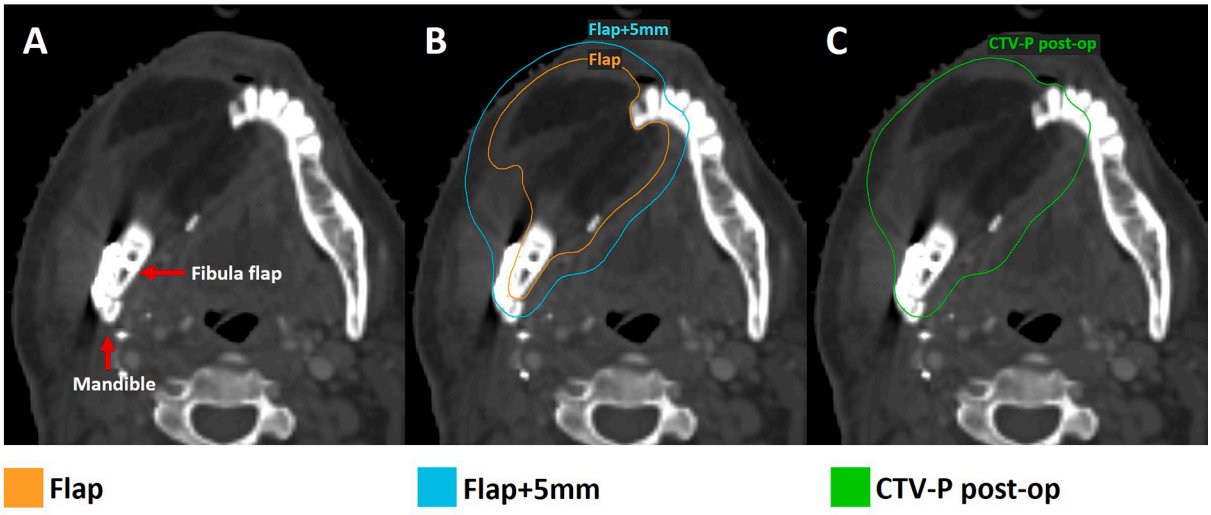

Fig. 7.2. Bone window of the planning CT scan presented in Fig. 7.1. Images show: A) Fibula flap and residual mandible (red arrows); B) fibula free flap (orange) and flap + 5 mm (cyan); C) CTV-P post-op (green) covering the at-risk area of the residual mandible. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

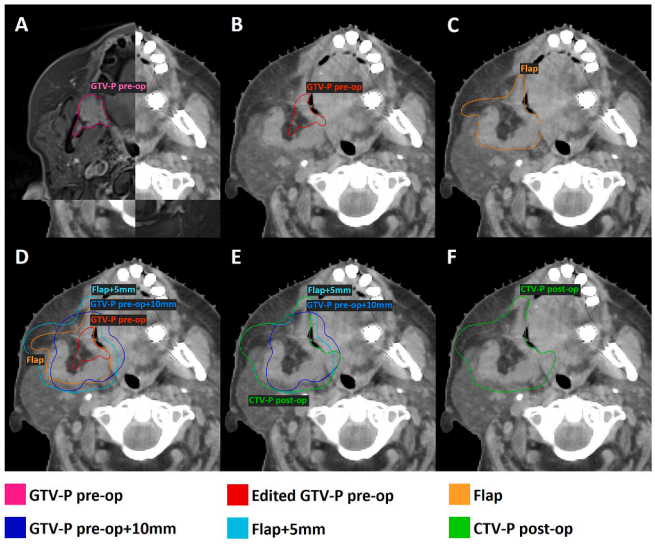

Fig. 8.1. Example outlining of a case with a SCC of the right retromolar trigone that underwent right hemi-mandibulectomy with a pectoralis major pedicled flap reconstruction. Histology showed a pT4a (UICC/AJCC TNM8th edition) moderately differentiated SCC with a 2.5 mm mucosal resection margin, and a 3 mm deep resection margin. Images show: A) Diagnostic MRI fused with the planning CT scan at the level of the resected primary tumour with GTV-P pre-op re-created on MRI (dark pink); B) edited for anatomical change on CT (red); C) pectoralis major flap reconstruction is delineated on the planning CT (orange); D) a 10 mm isotropic margin added to GTV-P pre-op (navy) plus a 5 mm margin added to the pectoralis major flap (cyan); E) and F) CTV-P post-op (green) is a composite volume delineated by combining GTV-P pre-op + 10 mm and flap + 5 mm and editing for mobile part of oral tongue, bone and teeth, as well as regions of the flap that are not at risk (see Fig. 8.2). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In this case, the pectoralis major pedicled flap (orange) rotates from the chest into the neck, together with its vascular pedicle. As a result, part of the composite volume extends outside the oral cavity which is considered not at risk clinically. In this case therefore, the CTV-P post-op is edited to exclude the vascular pedicle and the portion of the flap inferior to the oral cavity which is not at risk (see Fig. 8.2).

series that microscopic tumour infiltration is observed within 5 mm from the edge of the GTV-P in > 95 % of resected OCSCC cases [11].

- **Step 2b**: Independently of the previous step, a 5 mm isotropic margin is added to the surgical defect or flap to account for potential microscopic spread beyond the surgical resection margin. Addition of a 5 mm isotropic margin to the surgical margin is deemed sufficient, except where there is macroscopic residual disease (R2 resection – not covered by these guidelines).
- **Step 2c**: The CTV-P is a composite volume, which includes GTV-P pre-op + 10 mm and the surgical defect/flap + 5 mm. CTV-P should be edited for anatomical barriers such as bone, fascia, air and for an intra-oral prosthesis (if used); in some cases, the CTV-P may also be edited to exclude areas outside the oral cavity (see Figs. 5.1, 5.2 and Figs. 8.1 and 8.2).

Example cases of oral tongue carcinoma, illustrating the steps laid out above, are shown in Fig. 1 and Fig. 2. Example cases from other subsites within the oral cavity, and with different types of reconstruction, are included in Figs. 3.1–8.2 to illustrate how the steps laid out above can be applied in different scenarios.

The principles of CTV-P delineation outlined above are recommended for all OCSCC patients requiring PORT, regardless of the margin status, and other histological risk factors. Flap delineation guidelines for HNSCC patients requiring PORT published by GORTEC in 2020 are a useful adjunct to standardise flap delineation [12]. They delineated the flap body (filling the surgical defect) and its vascular pedicle separately, and rightly highlight the importance of including the recipient/surgical bed and the locations of high-risk margins, defined by discussion with the surgeon and pathologist, in the delineated volumes. Some groups advocate reducing radiotherapy dose to the body of the flap/central flap structures which are not close to the flap-native tissue interface and not therefore at risk of recurrence, but there is a lack of data, and consequently a lack of consensus, on the value of doing so [13]. For clinicians who wish to pursue this approach, delineation of a 'flap avoidance structure' as described below (Fig. 9) may help to standardise practice and ensure that the flap-native tissue interface is consistently included in the CTV-P.

Post-operative primary CTV delineation in cases with a positive (<1mm) margin from the GTV-P

In the case of a positive (<1mm) surgical margin around the primary tumour, the principles of CTV-P delineation described above should still be applied. Concurrent chemotherapy with cisplatin is recommended in

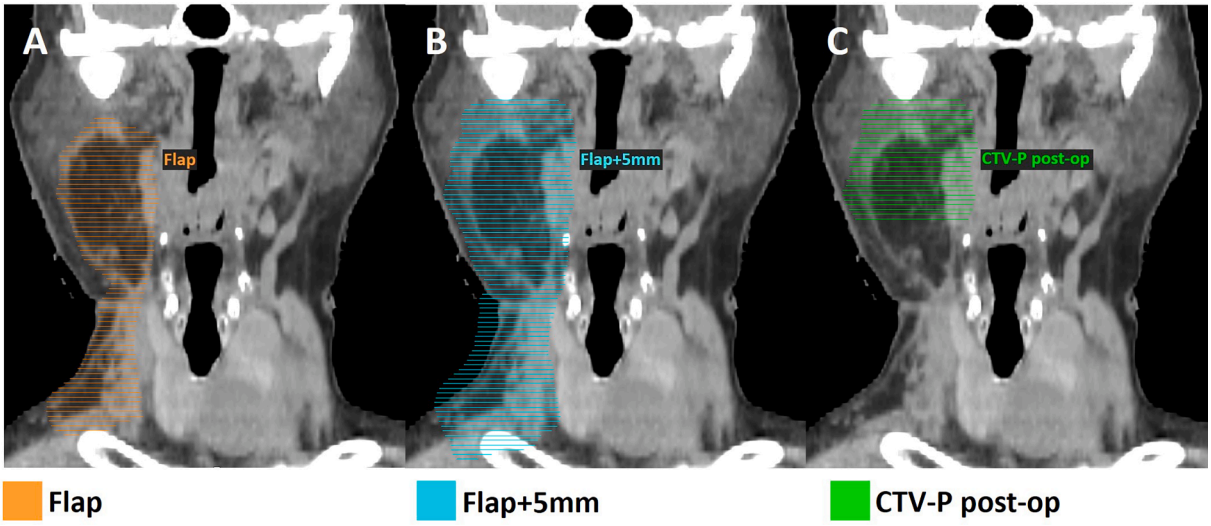

Fig. 8.2. Coronal views of the planning CT scan presented in Fig. 8.1. Images show: A) Pectoralis major pedicled flap (orange); B) composite volume; C) CTV-P post-op (green) after editing. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

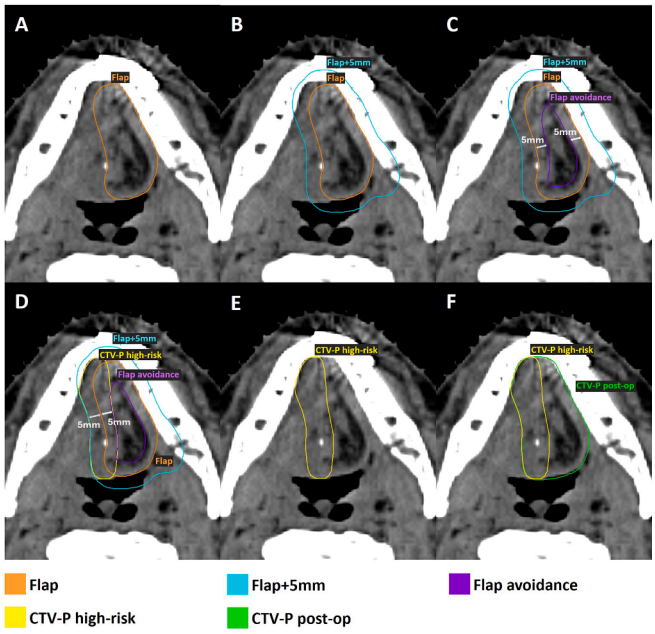

Fig. 9. Example outlining of a case with a SCC of the left oral tongue who underwent left hemi-glossectomy and RFFF reconstruction. This is the same case as in Fig. 2 but with a < 1 mm deep resection margin localised in the histology report to be towards the midline of the native tongue. The surgeon has placed a surgical clip at the deep margin which can be seen on the planning CT scan. In this case with a positive resection margin which can be accurately localised, there are two options: ● the whole CTV-P may be labelled CTV-P high-risk and may be prescribed a dose over 60 Gy, for example EQD_2 64–66 Gy (refer to Fig. 2). ● the at-risk area within the CTV-P is delineated (see below), may be labelled CTV-P high-risk, and may be prescribed a dose over 60 Gy, for example EQD_2 64–66 Gy. The rest of CTV-P is prescribed a dose EQD_2 60 Gy. Images show: A) RFFF delineated on planning CT (orange); B) 5 mm margin added to RFFF (cyan); C) flap avoidance structure (purple) created from flap minus 5 mm isotropic margin; D) and E) CTV-P high risk (yellow) is a 10 mm thick strip of tissue, lying 5 mm each side of the flap-native tissue interface; F) CTV-P post-op (green) is delineated as per Fig. 2 and includes the rest of the primary tumour operative bed.

suitable patients, based on the results of randomised trials [14–16]. A dose over EQD_2 60 Gy *may* be prescribed in cases with a positive margin, although variation in dose prescription exists in practice (see background manuscript for full discussion on dose [7]); if a higher dose is given, this can either be prescribed to the whole PTV associated with the CTV-P or, if the positive margin can be identified, to the high-risk area only as demonstrated in the example case below (Fig. 9).

Delineating the post-operative nodal CTV:

General principles are outlined in the background manuscript [7] as follows:

- Most patients with OCSCC should undergo unilateral or bilateral neck dissection – where neck dissection has not been carried out, PORT to the neck should be given (Table 2).
- For non-lateralised tumours, neck dissection to the contralateral cN0 neck is recommended; where neck dissection has not been carried out, PORT to the neck should be given (Table 2).
- If the neck is pN0 after an adequate (≥18 node) neck dissection [17], then PORT to the neck is generally not required. In pN0 cases where PORT is being given because of adverse features at the primary site, then selective irradiation of adjacent levels (I, II +/- III) *may* be considered.
- If the neck is pN1 after an adequate (≥18 node) neck dissection, then PORT to the neck may not be required. In pN1 cases where a single node is > 10 mm but ≤ 30 mm, or where PORT is being given because of adverse features at the primary site, then selective irradiation of the neck is recommended to the involved nodal level, adjacent nodal levels and levels Ib-III; level Ia should also be included for floor of mouth and anterior third/ tip of tongue tumours (Table 2).
- If there are indications for PORT in the neck but not at the primary site, radiotherapy to both the primary site and neck is generally recommended to cover the path of microscopic disease spread from the primary to the neck (including the T-N tract and lingual lymph nodes [7]).
- In cases of pN2-N3 disease, PORT to the neck is required. The nodal CTV should include:

o Involved nodal level(s), representing the nodal tumour bed and surrounding tissues at risk for direct microscopic infiltration or lymphovascular spread (CTV-N1).

Table 2
Selection of the nodal levels for prophylactic PORT as a function of the laterality of the primary tumour and the nodal status.

Lateralised tumors*		
pN-category (UICC/AJCC 8th ed.)	Levels to be included in the low risk (prophylactic dose) CTV	
	Ipsilateral neck	Contralateral neck
pN0 – pN1[a]	No PORT	No PORT
pN2a (includes a single ipsilateral node ≤ 3 cm with ENE) pN2b, pN3 (ipsilateral neck)	Ia[b]-Ib, II[c], III, + IVa[d,e], +Va-b[e], +IX[f], +VIIb[g], + IVb[h] + Vc[i]	No PORT
Non-lateralised tumors^		
pN-stage (UICC/AJCC 8th ed.)	Levels to be included in the low risk (prophylactic dose) CTV	
	Ipsilateral neck	Contralateral neck
pN0 – pN1[a]	No PORT	No PORT if neck dissection performed Levels I-III if no neck dissection performed.
pN2a (includes a single ipsilateral node ≤ 3 cm with ENE) pN2b, pN3 (ipsilateral neck)	Ia[b]-Ib, II[c], III, +IVa[d,e], +Va-b[e], +IX[f], +VIIb[g], + IVb[h] + Vc[i]	No PORT if neck dissection performed Levels I-III if no neck dissection performed
pN2c, pN3	According to the pN-status on this side of the neck	According to the pN-status on this side of the neck

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CTV, Clinical Target Volume; PORT, post-operative radiotherapy; ENE, extra-nodal extension.

* **Lateralised tumours** are defined as tumours arising in the buccal mucosa, retromolar trigone and upper & lower alveolar ridges, providing there is ≥ 10 mm clearance from midline and T1 and some T2 tumours (UICC 8th ed.) arising on the lateral border of the oral tongue, or laterally within the floor of mouth providing there is ≥ 10 mm clearance from midline, and there is no involvement of the anterior third/tip of the tongue and anterior floor of mouth [7].

^ **Non-lateralised tumours** are defined as all tumours arising in the floor of mouth or oral tongue, apart from some T1 and T2 tumours arising on the lateral border of the tongue and lateral floor of mouth with ≥ 10 mm clearance from midline and all tumours extending to within ≤ 10 mm of the midline [7].

[a] pN1 category with single node > 10 mm but ≤ 30 mm may be regarded as 'intermediate risk' and an indication for radiotherapy, particularly when combined with other risk factors. Adjuvant radiotherapy for a single node ≤ 10 mm is not routinely recommended.

[b] Include level Ia for all anterior third/ tip of tongue and floor of mouth tumours, and when level Ib is involved.

[c] Omit level IIb if no infiltration in level IIa.

[d] Include IVa for anterior third/ tip of tongue and/or anterior floor of mouth and/or oropharyngeal infiltration

[e] Include IVa and Va-b in case of level II, III or IVa infiltration

[f] Include IX (bucco facial nodes) in case of buccal mucosa SCC.

[g] Include VIIb in case of bulky infiltration of level II.

[h] Include IVb in case of infiltration of level IVa.

[i] Include Vc in case of infiltration of level Vb.

- o Uninvolved nodal level(s) at risk of microscopic lymphovascular spread, which include:
  - adjacent nodal levels, whether they have been dissected or not
  - undissected 'at-risk' levels (CTV-N2, Table 2)

The recommended nodal dose prescription is as follows:

- Involved nodal levels: CTV-N1 EQD_2 60 Gy
- Uninvolved nodal levels at risk of microscopic lymphovascular spread:
  - o Undissected 'at risk' levels (Table 2): CTV-N2 EQD_2 50 Gy
  - o Dissected 'at risk' levels: the optimal dose is unknown; a 1993 study from the MD Anderson Cancer Centre suggested a slightly higher dose to tissues that had been perturbed (and potentially had become hypoxic as a result of surgical manipulation) than to those that had not [18,19]. This principle has not been tested in a prospective study, and variation in dose prescription to dissected, uninvolved levels exists in practice, and in ongoing clinical trials. The dose prescription is therefore left to the discretion of the treating clinician (doses between EQD_2 50 Gy to 60 Gy are typically prescribed).
- Cases with pathological extranodal extension (pENE): CTV-N high-risk in cases with pENE is typically prescribed a dose > 60 Gy, for example EQD_2 64–66 Gy [7].

Delineating the CTV-N

In general, co-registration of the pre-operative diagnostic imaging is recommended to guide delineation of the CTV-N. This is however not a useful exercise for nodes that cannot be identified on pre-operative imaging and/or when registration of the diagnostic imaging modality and the planning CT cannot be accurately done.

Delineating the CTV-N for nodes that cannot be identified on pre-operative imaging and/or when registration between the pre-op imaging modality and the planning CT cannot be done accurately:

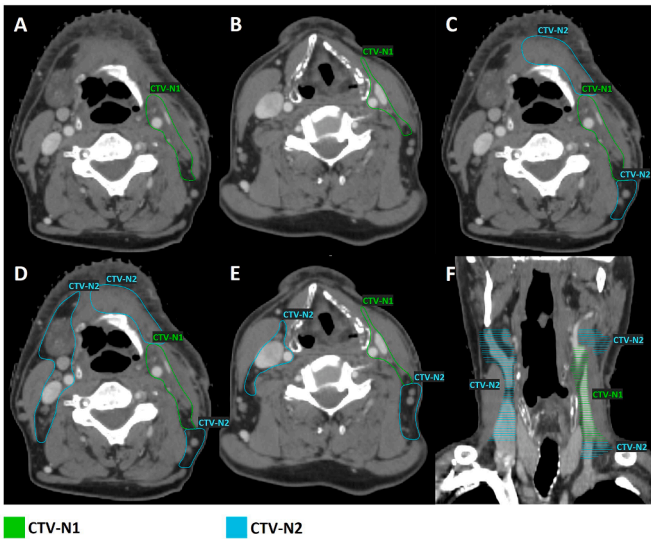

Fig. 10. Example outlining of a case with a SCC of the left anterior lateral border of the tongue reaching the midline. No clinically suspicious nodes were identified on pre-op imaging (cT3-N0-M0 UICC/AJCC TNM8th edition). Primary tumour resection and left (ipsilateral) level I-V neck dissection was carried out. Right neck dissection was not carried out due to patient fitness. Histology showed a pT3pN2b (UICC/AJCC TNM8th edition) moderately differentiated SCC; out of 33 dissected nodes, 2 were positive: one left level II node with a tiny focus of carcinoma, and one left level III node with 2 mm deposit, no pENE. Images show: A) and B) Involved levels II and III included in CTV-N1 (green, post-operative dose, EQD_2 60 Gy); C) level Ia and ipsilateral levels Ib, IVa, Va and Vb included in CTV-N2 (cyan, 'prophylactic' dose, EQD_2 50 Gy); D) and E) contralateral undissected levels Ib, II and III included in CTV-N2 as elective treatment (cyan, 'prophylactic' dose, EQD_2 50 Gy); F) coronal projection showing CTV-N1 and CTV-N2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

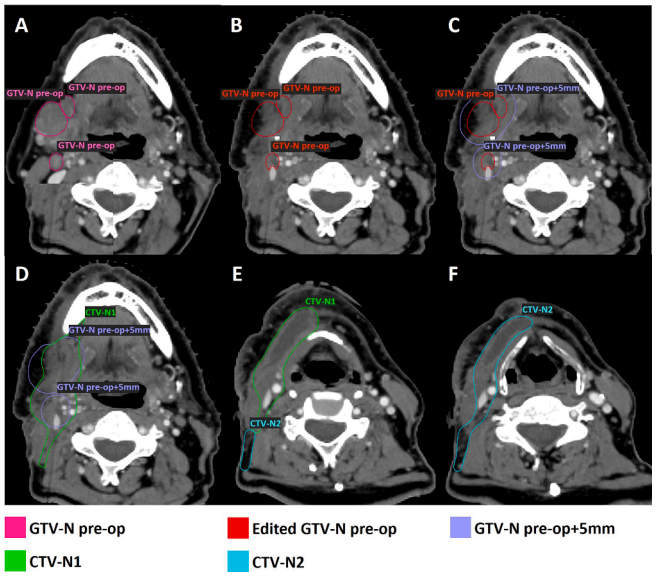

Fig. 11.1. Example outlining of a case with a well lateralized SCC of the right retromolar trigone. Primary tumour resection and right (ipsilateral) level I-IV neck dissection was carried out (36 nodes dissected). Histology showed a pT4apN2b (UICC/AJCC TNM8th edition) moderately differentiated SCC; out of 36 dissected nodes, 2 right level Ib nodes and 1 level II node were positive, with no pENE. Images show: A) Diagnostic CT fused with planning CT scan at the level of the involved level Ib and II nodes with GTV-N pre-op re-created on diagnostic CT (dark pink); B) GTV-N pre-op re-created as a surrogate volume on the planning CT (red); C) a 5 mm isotropic margin added to GTV-N pre-op (purple) to ensure coverage of the pre-op nodal tumour bed; D) GTV-N pre-op + 5 mm is edited for skin, subcutaneous tissues (platysma is not breached in this case), floor of mouth and scalene muscles and extended to include the involved nodal levels (Ib and II) and post-operative changes to create CTV-N1 (green, post-operative dose, EQD_2 60 Gy); E) level II and adjacent post-operative seroma included in CTV-N1; F) level Ia and ipsilateral levels III, IVa, Va and Vb and adjacent post-operative changes are included in CTV-N2 (cyan, 'prophylactic' dose, EQD_2 50 Gy).

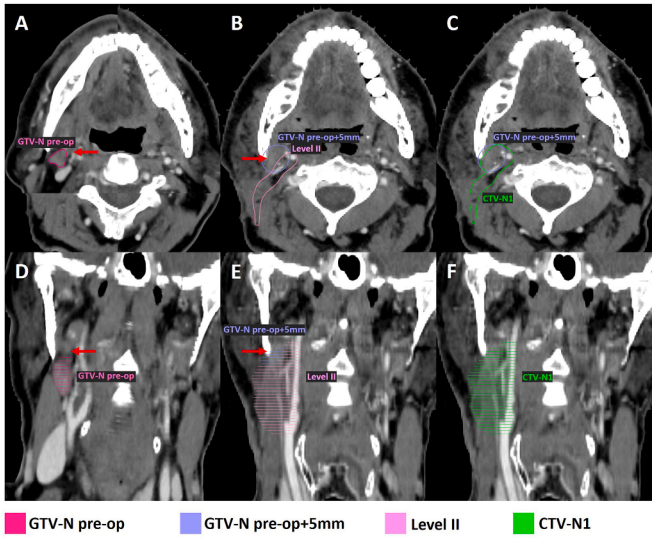

Fig. 11.2. Images show: A) Pre-operative involved level II node (dark pink) abutting the digastric muscle (red arrow); B) delineating level II as per standard guidelines (pink) would provide insufficient coverage of the at-risk area, whereas GTV-N pre-op + a 5 mm isotropic margin (purple) can encompass this area; C) CTV-N1 created using GTV-N pre-op + a 5 mm isotropic margin ensures adequate coverage of the at-risk area; D-F) corresponding coronal images of A-C.

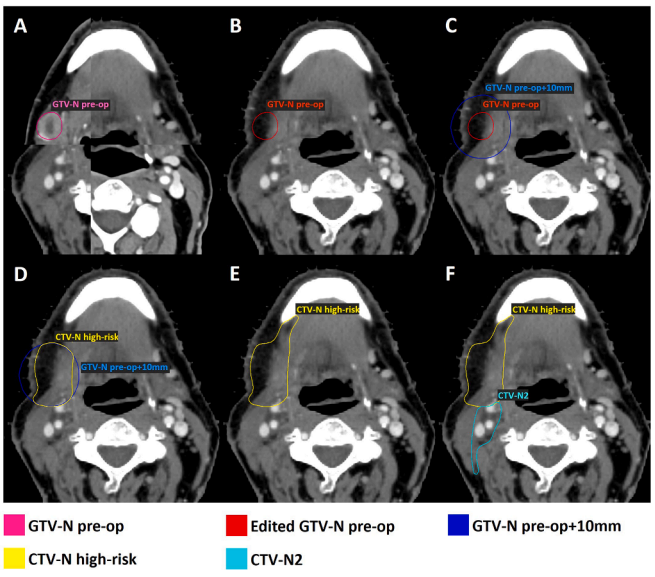

Fig. 12.1. Example outlining of a case with a SCC of the right buccal mucosa. Primary tumour resection and right (ipsilateral) level I-IV neck dissection was carried out. Histology showed a pT2pN2a (UICC/AJCC TNM8th edition) moderately differentiated SCC; out of 22 dissected nodes, 1 right level Ib node was positive, measuring 20 mm with pENE. Images show: A) Diagnostic CT fused with planning CT scan at the level of the involved level Ib node (which disrupts/involves platysma) with GTV-N pre-op re-created on diagnostic CT (dark pink); B) GTV-N pre-op re-created as a surrogate volume on the planning CT (red); C) a 10 mm isotropic margin added to GTV-N pre-op (navy) to encompass microscopic spread of cells radially from the involved node which had a disrupted capsule (pENE); D) GTV-N pre-op + 10 mm is edited for skin and floor of mouth to create CTV-N high-risk (yellow, high dose, EQD_2 64–66 Gy); E) CTV-N high-risk is then extended to include the remainder of level Ib (there is no dosimetric benefit of including the rest of the nodal level in CTV-N1 in this case); F) level Ia and ipsilateral levels II, III and IX are included in CTV-N2 (cyan, 'prophylactic' dose, EQD_2 50 Gy).

Where the pathologically involved nodes cannot be identified on pre-operative imaging, and/or when co-registration of the pre-operative images and the planning CT scan is not accurate or cannot be done, then it is recommended that the involved nodal level(s) are all delineated in the CTV-N1, along with any adjacent post-operative changes (seroma and/or surgical clips), as demonstrated in Fig. 10. The remaining 'at-risk' levels are delineated in the prophylactic CTV (CTV-N2), according to Table 2. Such a process could also be done when there are too many lymph nodes to outline individually.

Note that if one or more of the involved levels in this case harboured a node with pENE which was not identifiable on pre-op imaging, the entire level could be included in CTV-N high-risk (EQD_2 64–66 Gy), rather than in CTV-N1 (EQD_2 60 Gy).

Delineating the CTV-N for nodes that can be identified on pre-operative imaging:

In the absence of a GTV-N (which has been removed at surgery), the use of a surrogate volume can aid definition of the post-operative CTV-N. The pre-operative GTV-N (GTV-N pre-op) defines the size and position of the involved node(s) prior to surgery, providing the involved node(s) can be reliably identified on the pre-operative CT or MRI scan, and can be accurately re-created on the post-operative planning CT scan. Where co-registration is not accurate or cannot be done, the pre-operative anatomical position of the involved node(s) may be used to re-create the GTV-N pre-op, which is then used as a basis for creating the CTV-N. Re-creating the pre-operative GTV-N will ensure an adequate margin of 'at-risk' tissue receives PORT and, in cases with pENE, can potentially reduce the volume of tissue receiving a higher dose of radiotherapy.

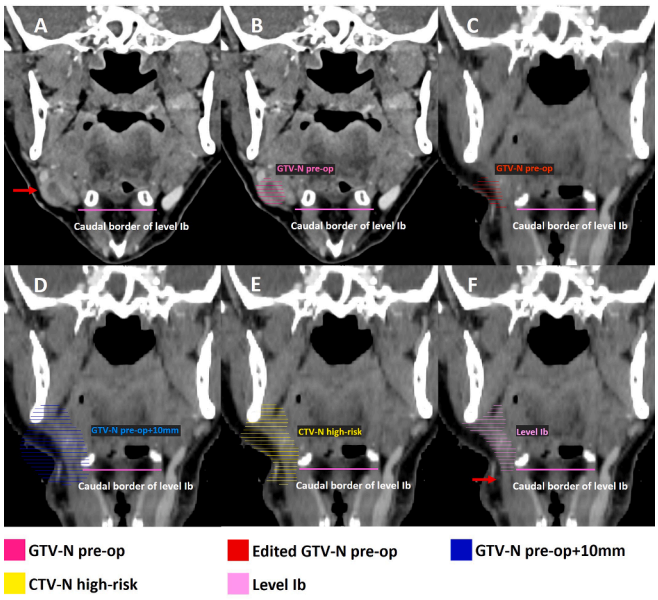

Fig. 12.2. Coronal images of the clinical case depicted in Fig. 12.1. A) and B) Pre-operative location of involved level Ib node with pENE (red arrow, dark pink) is close to the caudal border of level Ib (caudal border of the hyoid bone); C) GTV-N pre-op (red) created as a surrogate volume on the planning CT scan identifies the high-risk area; D) GTV-N pre-op + a 10 mm isotropic margin (navy); E) is edited to create CTV-N high-risk (yellow) ensuring adequate coverage of the at-risk area; F) in contrast, delineating level Ib as per standard guidelines (pink) would provide insufficient coverage of the at-risk area.

- In cases without pENE, a **5 mm** isotropic margin added to GTV-N pre-op is recommended to ensure coverage of the pre-op nodal tumour bed. The CTV-N1 is a composite volume, which includes GTV-N pre-op + 5 mm, the involved nodal level(s) and the adjacent post-operative changes.
- In cases with pENE, a **10 mm** isotropic margin, which accounts for microscopic spread from the involved node with disrupted capsule, is added to GTV-N pre-op to create the CTV-N high-risk. The rest of the involved nodal level(s) and the adjacent post-operative changes can either be included in the CTV-N high-risk, or where there is likely to be a dosimetric advantage to doing so, can be included in CTV-N1.

The following examples outline the principles of CTV-N delineation in the post-operative setting, in cases where involved nodes can be identified on pre-operative imaging. The first case has no evidence of pENE in the neck dissection specimen (Figs. 11.1 and 11.2), whereas the last two cases (Figs. 12.1 and 12.2 and Figs. 13.1 and 13.2) do.

Case 11.1 illustrates how to include post-operative changes in the CTV-N by extending the adjacent CTV to include them, either in CTV-N1 (EQD_2 60 Gy) or CTV-N2 (EQD_2 50 Gy) depending on the dose being delivered to the adjacent nodal level. The case also demonstrates the potential benefit of re-creating a GTV-N pre-op as a surrogate volume to guide post-operative CTV-N delineation (see Fig. 11.2). In this case, the involved level II node was abutting the digastric muscle and delineating level II alone according to standard landmarks/guidelines would not have adequately covered the soft tissue above that level (Fig. 11.2 A-B and D-E). Re-creating a surrogate volume to represent the pre-operative GTV-N and adding a margin to this ensures the involved nodal tumour bed is included in CTV-N (Fig. 11.2 C and F). In the absence of pENE, a 5 mm margin is sufficient, providing the clinician is confident about image co-registration and localisation of the surrogate GTV-N pre-op.

The case in Fig. 12 also shows the benefit of re-creating the GTV-N pre-op as a surrogate volume to guide post-operative CTV-N delineation (see Fig. 12.2). The involved level Ib node with pENE in this case was close to the caudal border of level Ib (caudal edge of the hyoid bone)

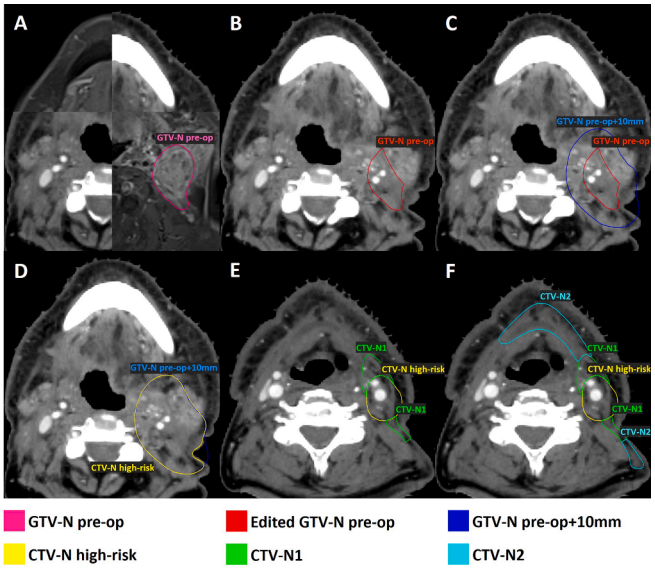

Fig. 13.1. Example outlining of a case with a SCC of the left floor of mouth. Primary tumour resection and bilateral neck dissections have been carried out, including a left level I-V modified radical neck dissection with removal of the sternocleidomastoid muscle (36 nodes dissected), and right level I-IV selective neck dissection (18 nodes dissected). Histology showed a pT1pN3b (UICC/AJCC TNM8th edition) poorly differentiated SCC with one nodal deposit in left level II extending into the upper border of level III, measuring 48 mm with extensive pENE. Images show: A) Diagnostic MRI fused with planning CT scan at the level of the involved level II node (which abuts but does not invade into the parotid gland) with GTV-N pre-op re-created on MRI (dark pink); B) GTV-N pre-op re-created as a surrogate volume on the planning CT and edited away from the parotid (red); C) a 10 mm isotropic margin added to GTV-N pre-op (navy) to encompass microscopic spread of cells radially from the involved node which had extensive pENE; D) GTV-N pre-op + 10 mm is edited for skin to create CTV-N high-risk (yellow, high dose, EQD_2 64–66 Gy); E) remainder of level III is included in CTV-N1 (green, post-operative dose, EQD_2 60 Gy); F) level Ia, ipsilateral levels Ib, IVa, Va, Vb and VIIb and adjacent post-operative changes are included in CTV-N2 (cyan, 'prophylactic' dose, EQD_2 50 Gy). No radiotherapy is given to the contralateral pN0 neck in this case because an adequate neck dissection has been carried out.

(Fig. 12.2 A-B), therefore delineating level Ib alone according to standard landmarks/guidelines would not have provided an adequate soft tissue margin below the resected node to prevent recurrence. Re-creating a surrogate volume to represent the pre-operative GTV-N and adding a 10 mm margin to this ensures an adequate soft tissue margin around the resected node (Fig. 12.2 C-F).

As previously mentioned, where diagnostic imaging cannot be co-registered and/or where nodes cannot be reliably identified on diagnostic imaging, the whole involved nodal level(s), adjusted for the post-operative situation (e.g. seroma, clips and other post-operative change), can be delineated in CTV-N high-risk (EQD_2 64–66 Gy). Uninvolved nodal levels are treated in CTV-N2 (EQD_2 50 Gy) as outlined in Table 2.

The case in Fig. 13 once again illustrates the benefit of re-creating the GTV-N pre-op as a surrogate volume to guide post-operative CTV-N delineation (see Fig. 13.2). The involved node in this case abuts the parotid gland and post-operatively, the soft tissues lying deep to the parotid are at high-risk of recurrence. Outlining this area free-hand in 3D may be difficult and inconsistent, whereas re-creating the GTV-N pre-op as a surrogate volume on the planning scan, and adding a 10 mm isotropic margin, reproducibly encompasses the area at highest risk of recurrence within CTV-N high-risk. Level II is almost entirely included in CTV-N high-risk, therefore there is no advantage of creating a CTV-N1 at this level. However, the involved node only extends into the cranial aspect of level III, thus treating the rest of level III in CTV-N1 (EQD2 60 Gy) is likely to be dosimetrically beneficial, and could reduce toxicity. In

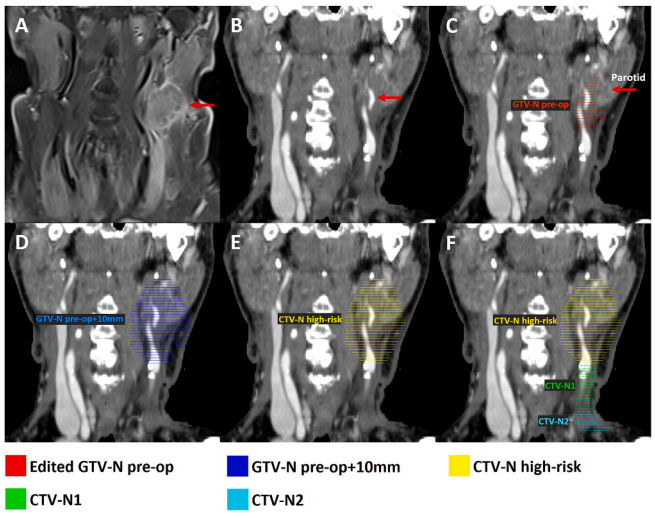

Fig. 13.2. Images show: A) Pre-operative location of involved node on diagnostic MRI (red arrow); B) high-risk region on planning CT scan lies deep to the (unresected) parotid gland (red arrow); C) GTV-N pre-op re-created as a surrogate volume on the planning CT scan and edited from the parotid (red) identifies the high-risk area; D) GTV-N pre-op + a 10 mm isotropic margin (navy); E) is edited to create CTV-N high-risk (yellow) ensuring adequate coverage of the at-risk area; F) coronal view of planning CT scan showing CTV-N high risk (EQD_2 64–66 Gy), CTV-N1 (EQD_2 60 Gy) and CTV-N2 (EQD_2 50 Gy). Note that only the cranial part of level III is treated with CTV-N high-risk, while most of level III is encompassed by CTV-N1.

this case with extensive pENE, the prevertebral and scalene muscles have not been edited out of the CTV-N high-risk because of risk of invasion, but it is acknowledged that treatment to EQD_2 of 64–66 Gy may be limited by the dose constraint placed on the spinal cord PRV.

Combining the post-operative primary tumour and nodal CTVs

Most patients receiving PORT for OCSCC will require treatment to both primary and nodal target volumes. Whereas the principles of delineating post-operative CTVs for the primary and nodes have been described separately above, in practice clinicians are likely to delineate both together, such that CTV-P post-op and CTV-N1 are combined into a single post-operative CTV to receive a dose EQD_2 60 Gy. Where high-risk features occur at the primary site and in the neck, CTV-P high-risk and CTV-N high-risk may be combined into a single high-risk CTV to receive a dose EQD_2 64–66 Gy. Electively treated nodes (selected from Table 2) can be combined into a single CTV-N2 to receive EQD_2 50 Gy. The last example below (Fig. 14) demonstrates how the post-operative primary and nodal CTVs can be combined to generate final CTVs for treatment planning.

A word of caution

These guidelines have been developed to aid delineation of target volumes for PORT in patients with OCSCC. They are not valid for tumours of other histopathologies in the oral cavity for example minor salivary gland tumours, sarcomas, lymphomas, or mucosal melanomas, as they do not share the same pattern of infiltration or recurrence as SCC. The guidelines cover cases who have undergone primary surgery with clear and/or microscopic positive resection margins. Extrapolating the guidelines to cases with macroscopic residual disease (R2 resections) and/or loco-regionally recurrent disease is considered inappropriate.

The proposals for post-operative CTV delineation in these guidelines rely heavily on accurate co-registration of pre-operative diagnostic imaging with the planning CT, and identification of at-risk regions, surgical defect, reconstruction flap and other post-operative changes based on clinical, radiological, and pathological information. Appropriate interpretation of these sources of information is essential when applying these guidelines in clinical practice. Since surgical treatment of OCSCC involves complex resection, with or without flap reconstruction,

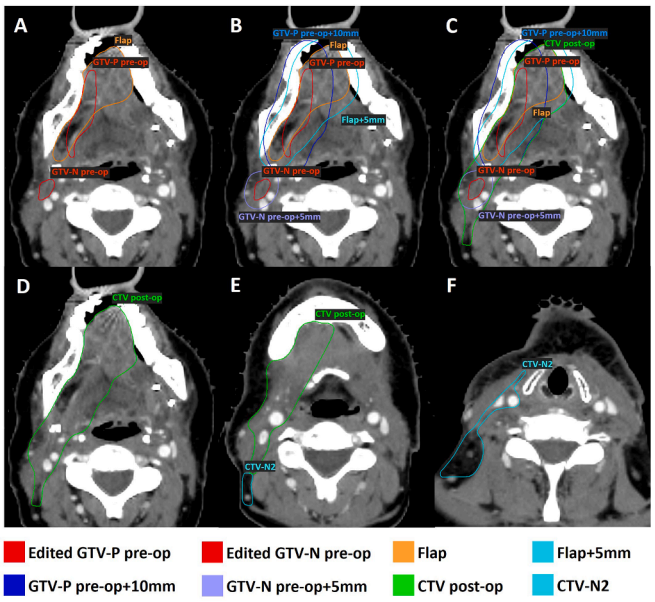

Fig. 14. Example outlining of a case with a SCC of the right oral tongue that underwent right hemi-glossectomy, bilateral level I-IV neck dissection (32 nodes dissected on the right, 21 nodes dissected on the left), with a RFFF reconstruction. Histology showed a pT3pN2b (UICC/AJCC TNM8th edition) moderately differentiated SCC with a 2.2 mm mucosal resection margin, and a 1.3 mm deep resection margin; 2 right level II nodes were positive, with no pENE. Images show: A) GTV-P pre-op and GTV-N pre-op re-created and edited as a surrogate volume on the planning CT (red) and RFFF is delineated (orange); B) a 10 mm isotropic margin added to GTV-P pre-op (navy) plus a 5 mm margin added to the RFFF (cyan) and a 5 mm isotropic margin added to GTV-N pre-op (purple); C) CTV post-op (green, post-operative dose, EQD_2 60 Gy) is a composite volume delineated by combining GTV-P pre-op + 10 mm, flap + 5 mm and GTV-N pre-op + 5 mm and extended to include the rest of the involved level II. D-F) the final CTV volumes at different levels of the planning CT. The CTV post-op (green) is edited for bone, teeth, skin, subcutaneous tissues, and scalene muscles. Ipsilateral level Ib is already covered by CTV post-op after delineating the composite volume. Ipsilateral levels III, IVa, Va and Vb and adjacent post-operative changes are included in CTV-N2 (cyan, 'prophylactic' dose, EQD_2 50 Gy).

significant anatomical changes may occur, which can affect accurate co-registration of pre-operative diagnostic imaging and/or re-creation of pre-operative primary and nodal GTVs. Clinicians need to exercise caution when relying on pre-operative imaging to re-create pre-operative GTVs as surrogate volumes. The proposed registration method, which involves matching to the C1-C3 vertebrae and/or other bony structures in close proximity to the primary tumour, serves only as a starting point for optimal co-registration, and the treating clinician must use their discretion to decide whether the location of the pre-operative GTVs is well matched to the post-operative at-risk regions. Co-registration may need to be adjusted during delineation to optimise the matching of different anatomical areas. Metallic dentures and implants can produce artefacts which degrade image quality and add to the uncertainties. When there are significant uncertainties about co-registration, the pre-operative surrogate GTVs may be delineated based on clinical information, and reference to pre-operative imaging, without co-registration. Regardless of whether accurate co-registration can be performed to assist delineation of the CTVs, it is of paramount importance that treating oncologists use their professional judgement, armed with all the available clinical information, to minimise geographical miss. Professional discretion is needed to decide whether modifications are needed when applying these guidelines to ensure that ultimately, regions which are at risk of recurrence are adequately and safely encompassed by the delineated target volumes.

In cases with flap reconstruction, the flap-native tissue interface is

the region at highest risk for tumour recurrence. These guidelines, which include the flap + 5 mm within CTV-P, ensure that the flap-native tissue interface receives an adequate dose of PORT. However, the entire body of the flap, which theoretically does not contain tumour cells, will also receive the same radiation dose. As previously discussed, there is currently a lack of evidence and consensus on the value of reducing the radiation dose to the central flap structures [13]. Due to the significant anatomical changes that occur in the post-operative setting, accurate delineation of the reconstruction flap can be challenging, and reducing radiation dose to areas of the flap could risk suboptimal dosing of the operative bed, unless this is done with caution. Editing areas of the flap which are not at risk from the CTV-P (e.g. those lying outside the oral cavity) can be done carefully on individual basis, as illustrated in the examples above (Figs. 5.1 and 5.2 and Figs. 8.1 and 8.2). Furthermore, in high-risk cases where a positive margin can be accurately localised, there is an option of delineating a flap avoidance structure as described (Fig. 9) to spare part of the flap from receiving the highest dose of radiation.

Finally, neoadjuvant +/− adjuvant immunotherapy is emerging as an important adjunct to standard of care surgery and adjuvant radiation-based treatment for patients with locally advanced HNSCC, including OCSCC [20,21]. To date, no data exist to suggest that use of immunotherapy should change the principles of post-operative CTV delineation set out above, and we recommend using the same step-by-step guidelines, pending the emergence of any new data to the contrary. In cases with a major pathological response to neoadjuvant immunotherapy, imaging after induction treatment may not be truly representative of "the true" pre-operative GTVs and thus should be used with caution; baseline diagnostic imaging prior to any treatment should be favoured instead (see Fig. 14).

Disclaimer

These guidelines outline the principles for delineating post-operative target volumes for OCSCC. They aim to assist oncologists to accurately outline the at-risk regions after surgical resection. In view of the high complexity and anatomical variability associated with post-operative OCSCC cases, these guidelines may not be applicable to every single clinical scenario. Quality assurance processes and audits are required to evaluate these guidelines in clinical practice. The authors of the guidelines are not responsible for any misuse of the material by any third parties.

Summary and conclusions

These guidelines aim to establish principles to promote consistency in the delineation of post-operative CTVs in patients with OCSCC, facilitating multi-institutional audits and clinical trials including Radiation Therapy Quality Assurance (RTQA). They assume that the oncologist has collated information from the diagnostic imaging, surgical procedure and post-operative histology. They also advocate creating surrogate volumes for the GTV-P and GTV-N as a guide to delineation, but where this is impractical, or cannot be done reliably because of suboptimal co-registration of diagnostic imaging then they can be adapted as described in the manuscript. Margins of 5 mm to 10 mm around the surrogate volumes are recommended, however where uncertainties exist then wider margins will be required, and need to be determined on an individual basis for each patient. Prospective audits of practice and of outcomes will help establish these guidelines as a standard of care, and provide a rationale for their future refinement. It is anticipated that these guidelines will form the basis for future guidelines aiming to standardise post-operative CTV delineation in other head and neck subsites.

CRediT authorship contribution statement

Mererid Evans: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Pierluigi Bonomo:** Writing – review & editing. **Po Chung Chan:** Writing – review & editing, Writing – original draft. **Melvin L.K. Chua:** Writing – review & editing. **Jesper Grau Eriksen:** Writing – review & editing. **Keith Hunter:** Writing – review & editing. **Kenneth Jensen:** Writing – review & editing. **T.M. Jones:** Writing – review & editing. **Sarbani Ghosh Laskar:** Writing – review & editing. **Roberto Maroldi:** Writing – review & editing. **Brian O'Sullivan:** Writing – review & editing. **Claire Paterson:** Writing – review & editing. **Luca Tagliaferri:** Writing – review & editing. **Silke Tribius:** Writing – review & editing. **Sue S. Yom:** Writing – review & editing. **Vincent Gregoire:** Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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