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Clinical Investigation

Head and Neck Cancer International Group (HNCIG) Consensus Guidelines for the Delivery of Postoperative Radiation Therapy in Complex Cutaneous Squamous Cell Carcinoma of the Head and Neck (cSCCHN)

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Radiation therapy (RT) consensus contouring guidelines in the postoperative setting for complex cutaneous squamous cell carcinoma of the head and neck have been developed by expert clinicians in the field of head and neck and dermato-oncology and members of the Head and Neck Cancer International Group to assist radiation oncologists involved in the management of this disease. These guidelines present a set of principles used to define postoperative RT volumes and corresponding minimum doses after resection of all macroscopic tumor with or without microscopic residual disease. It is anticipated they will promote the harmonization of postoperative RT globally and contribute to a reduction in treatment variation among clinicians, allowing for RT quality and outcomes assessment across institutions.

Introduction

High-risk cutaneous squamous cell carcinomas of the head and neck (cSCCHN) are those tumors deemed to be at sufficient risk of recurrence after curative surgery to warrant consideration of postoperative radiation therapy (PORT). Commonly, the location and proximity to critical structures and the radiation therapy (RT) volumes required to encompass the resected disease site and "at risk" areas make these cases complex. The clinicopathologic high-risk features warranting adjuvant treatment have been extensively described in the literature; however, there is a paucity of high-level evidence or consensus guidelines to assist with RT contouring of these complex cases.[1-19]

Head and neck cancer and dermato-oncology experts were assembled under the auspices of the HNC International Group (HNCIG) to assist in the development of the first international RT consensus contouring guidelines in the postoperative management of complex cSCCHN. These guidelines present a set of principles used to define PORT volumes and corresponding minimum doses after resection of all macroscopic tumor with or without microscopic residual disease. They have been written for the purpose of assisting radiation oncologists involved in the management of complex cSCCHN and the contouring of postoperative RT volumes. It is hoped they will ultimately promote the harmonization of PORT globally and contribute to a reduction in treatment variation among clinicians, allowing for RT quality and outcomes assessment across institutions.

When using these guidelines, the clinical judgment of the radiation oncologist takes primacy in deciding whether PORT is appropriate. Because of the complexity of these cases, we would also recommend assessment at major cancer centers before treatment.

The recommendations are informed by the clinical experience of the authors and the available literature on the topic, particularly the results of the Trans Tasman Radiation Oncology Group (TROG) 05.01 study, as the only reported prospective trial in cSCCHN with a predefined RT protocol and an RT quality assurance program.[1]

Methods and Materials

These guidelines were developed under the auspices the HNCIG. This group is made up of nominated head and neck clinicians from national cooperative trial groups and selected large cancer centers that are capable of conducting large-scale phase 2 and 3 clinical trials. The aim of the organization is to promote head and neck cancer trials globally; it also endeavors to develop harmonization of trial protocols. The authors of the article were directly involved in the development of the guidelines. Because the guidelines were developed under the auspices of the HNCIG and are referred to as HNCIG guidelines, all board members were provided the opportunity to endorse the guidelines and be acknowledged in the article. Of the 18 board members, 2 believed they had insufficient expertise in this area to provide endorsement. However, the board agreed the guidelines could be referred to as HNCIG guidelines. The members who provided endorsement are listed in the Acknowledgments.

General Radiation Therapy Recommendations

Technique

Techniques such as intensity modulated RT (IMRT) such as volumetric modulated arc therapy are preferable for treatment of complex volumes. Non-IMRT techniques including 3-dimensional conformal RT and electron beam therapy are acceptable, as long as adequate tumor coverage is achieved and organ-at-risk (OAR) constraints are met.

Localization, simulation, and immobilization

Patients should be positioned and immobilized according to institutional policy before the treatment planning computed tomography (CT) scan. All relevant surgical scars should be marked with radio-opaque wires and visible on the CT planning scans. A planning CT including the entire volume

of interest with slice thickness of no more than 2 to 3 mm should be performed, preferably with intravenous contrast.

Daily treatment position

Daily treatment position and patient immobilization should be replicated from planning simulation. Daily image guidance (image guided RT) is recommended for IMRT techniques and weekly verification imaging, at a minimum, for non-IMRT techniques.

Treatment planning and target volume definitions

Target volumes (TVs) and OAR nomenclature and labeling are based on the American Association of Physicists in Medicine TG-263 report: Standardizing Nomenclatures in Radiation Oncology.[20] TVs and OARs should be contoured on the planning CT scan and labeled accordingly. Refer to Table 1 for a summary of TV definitions.

To aid in TV delineation, the available preoperative diagnostic images should be coregistered with the planning CT data set. Any additional available information such as preoperative photographs and clinical description, along with the operative findings, should also be used to assist in defining TVs.

Gross and High-Risk Tumor Volumes

The high-risk tumor volume (HRTV) is defined as the preoperative gross tumor volume (GTV) transposed onto the postoperative planning CT and modified to account for anatomic changes and pathologic findings. For example, after surgery on an intraparotid nodal metastasis, the external body contour may have changed from the preoperative imaging because of the removal of the mass and the parotid gland. As a result, there may be a discrepancy in the preoperative imaging external body contour and location of tumor compared with the postoperative external body contour on the planning CT scan. These differences need to be considered at the time of image coregistration and when delineating the preoperative tumor position onto the postoperative planning CT.

In cases where induction systemic therapy has been administered before surgery, we recommend using the prechemotherapy imaging to define the HRTV.[21]

HRTV primary and HRTV nodal disease

Where applicable, there will be an HRTV defined for the primary (p) disease (HRTVp) and nodal (n) disease (HRTVn). In- transit disease may be defined as primary site disease.

Where there is substantial overlap of the HRTVp and HRTVn, a single HRTV termed HRTVp/n may be used (eg, an extensive primary lesion over the preauricular area with underlying intraparotid nodal metastases).

HRTV boost

In cases for which the pathology report has described positive or very close (<2 mm) margins or nodes with extranodal extension (ENE), these areas may be deemed at particularly high risk and considered for a boost dose. An effort should be made to specifically identify these regions on the planning CT with reference to the operative report, pathologic description, and preoperative imaging and defined as either HRTVp_Boost or HRTVn_Boost.

Clinical Target Volumes

In the postoperative setting, after resection of all gross primary and nodal disease, the differing TVs and corresponding dose levels, based on differing burden of microscopic disease, may be categorized in the following manner:

- site(s) of resected disease with clear surgical margins
- sites of resected disease with positive microscopic residual disease and/or regions of resected nodes with ENE
- surgically disrupted tissue immediately adjacent to resected primary disease and/or involved regions of resected nodes
- surgically undisrupted regions adjacent to the primary site and/or undissected neck (elective)

The following gives a description of the recommended clinical TVs (CTVs) and recommended minimum dose/fractionation schedules. The CTVs have been simplified to the following categories: high risk (HR), lesser risk (LR), and HR boost.

Clinical target volume—high risk

This is defined as a minimum 5 mm isotropic expansion of the HRTV for either primary disease (CTVp_HR) or regional nodal disease (CTVn_HR). For CTVp_HR, it may also include the entire operative bed, reconstruction flap, or graft site. For CTVn_HR, it may also include the entire involved neck node level/basin or neck dissection/parotidectomy bed. These CTVs are modified to anatomic barriers (eg, uninvolved bone) and prescribed to receive 60 Gy in 2.0 Gy once-daily fractions, 5 days per week, or a biologically equivalent dose (refer to *Dose prescription and specifications* section).

Clinical target volume—lesser risk

This is defined as the volume that is at risk of harboring microscopic disease but does not meet the criteria for CTV high risk. These CTVs are modified to anatomic barriers (eg, uninvolved bone) and prescribed to receive 54 Gy or 56 Gy in 2.0 Gy once-daily fractions, 5 days per week, or a biologically equivalent dose (refer to *Dose prescription and specifications* section).

Table 1 Summary of target volume definitions

Target volume	Structure	Definition
Site of primary tumor before excision*	HRTVp	The volume that represents the preoperative primary site GTV transposed onto the planning CT imaging data set and modified to account for postoperative anatomic changes and pathologic findings
Site of involved lymph nodes before excision*	HRTVn	The volume that represents the preoperative regional nodal site GTV transposed onto the planning CT imaging data set and modified to account for postoperative anatomic changes and pathologic findings
Subsite of the HRTVp likely to carry a higher burden of microscopic disease (ie, positive or margin clearance <2 mm) and warranting a boost dose	HRTVp_Boost	The subvolume that represents the preoperative primary site GTV transposed onto the planning CT imaging data set and modified to account for postoperative anatomic changes and pathologic findings and considered at particularly high risk
Subsite of the HRTVn disease likely to carry a higher burden of microscopic disease (ie, positive margin or extranodal extension)	HRTVn_Boost	The volume that represents the preoperative regional nodal site GTV transposed onto the planning CT imaging data set and modified to account for postoperative anatomic changes and pathologic findings and considered at particularly high risk
Primary site high-risk clinical target volume	CTVp_HR	Minimum volume includes HRTVp + 5 mm isotropic expansion and modified to anatomic barriers. May also include the entire operative bed, reconstruction flap, or graft site. Resected LNPNS
Nodal site high-risk clinical target volume	CTVn_HR	Minimum volume includes HRTVn + 5 mm isotropic expansion and modified to anatomic barriers. May also include the entire involved neck node level/basin or neck dissection/parotidectomy bed
Primary site lesser risk clinical target volume	CTVp_LR	The primary site operative bed that does not meet the criteria for CTVp_HR and modified to anatomic barriers. May also include the broader operative bed, reconstruction flap, or graft site. For LNPNS it also includes the undissected zone proximal to the involved zone
Nodal site lesser risk clinical target volume	CTVn_LR	The nodal dissection operative bed that does not meet the criteria for CTVn_HR, modified to anatomic barriers, and next echelon of surgically undisrupted clinically uninvolved nodes (elective)
Primary tumor boost site (optional)	CTVp_HR_Boost	Minimum volume includes HRTVp_Boost + 5 mm expansion and modified to anatomic barriers
Nodal site boost site (optional)	CTVn_HR_Boost	Minimum volume includes HRTVn_Boost + 5 mm expansion and modified to anatomic barriers

Abbreviations: CT = computed tomography; CTV = clinical target volume; GTV = gross tumor volume; HR = high risk; HRTV = high-risk tumor volume; LNPNS = large nerve perineural spread; LR = low risk; n = nodal; p = primary.

* Where there is substantial overlap of the HRTVp and HRTVn, a single HRTV termed HRTVp/n may be used (eg, an extensive primary lesion over the preauricular area with underlying intraparotid nodal metastases).

- For primary disease, the CTV_LR should include the broader operative bed and the reconstruction flap or graft site that has not already been included in the CTVp_HR.
- For regional nodal disease, the CTVn_LR should include any of the following:
- involved regional nodal level(s) and/or neck dissection/parotidectomy bed not included in the CTVn_HR
- surgically disrupted uninvolved regional neck dissection/parotidectomy bed
- undissected clinically negative regional nodal levels and/or parotid bed at risk of harboring microscopic disease (ie, elective nodal and/or intraparotid regions)

Refer to Figure E1 for an illustration of pattern of lymphatic draining of the head and neck and Table E1 for a

summary of lymphatic drainage of the head and neck based on primary site location. Table E2 summarizes the at-risk (elective) nodal level(s) based on clinical scenario.

The delineation of the nodal-level CTVs for the node negative (N0) undissected neck will follow those recommended by Gregoire et al,[22] although modifications for postoperative anatomic changes will need to be made in the dissected neck.

Clinical target volume high-risk boost

This is defined as a minimum 5-mm isotropic expansion of the HRTV_Boost for either primary disease (CTVp_Boost) or regional nodal disease (CTVn_Boost). This volume is optional and would typically be prescribed to receive a dose in the range of 66 Gy in 2.0 Gy once-daily fractions, 5 days per week, or a biologically equivalent dose (refer to *Dose prescription and specifications* section).

Relevant Clinical Scenarios

Primary site CTV high risk

- CTVp_HR may include the broader operative resection bed, or the entire reconstruction flap or graft site, modified to anatomic barriers, particularly where there may be uncertainty in defining the HRTVp owing to anatomic changes after surgery.
- If no preoperative imaging was performed before primary disease resection, the CTVp_HR may be defined as a minimum 10-mm isotropic expansion around the primary site surgical scar and modified to account for anatomic changes and pathologic findings. Where available, preoperative photographs, clinical examination description, and operative findings should be used to localize the primary tumor site.
- Where regional nodal disease requiring PORT develops some time after a primary lesion was excised (which remains free of recurrence), the inclusion of the primary site in the CTV is at the discretion of the clinician. In the TROG 05.01 study, inclusion of the primary site was recommended if the primary lesion had been excised within 12 months of the development of nodal metastases. Note that some institutions will include the primary site up to 24 months from the time the primary lesion was excised to the development of nodal disease.[1]

Primary site CTV lesser risk

- Where the entire operative bed, reconstruction flap, or graft site are included in the CTVp_HR, there may be no CTVp_LR
- CTVp_LR may also include the intervening dermal lymphatics between the primary site and the first echelon nodal region if it is deemed acceptable and feasible. For example, treating the intervening lymphatics between a temple lesion and the intraparotid (VIII) nodes may be considered acceptable with respect to toxicity because of its close proximity. Conversely, it may be considered unacceptable to include the intervening lymphatics from a vertex scalp lesion and level VIII nodes because of the large volume that would need to be encompassed and the resulting toxicity.

Regional nodal disease CTV high risk

- CTVn_HR may be expanded to include the entire nodal level(s) of the involved lymph node(s) and/or the entire neck dissection/parotidectomy bed, modified to anatomic barriers, particularly where there may be uncertainty in defining the HRTVn because of anatomic changes after surgery or disease not identifiable on preoperative imaging but detected on histopathology.
- Where there is substantial overlap between CTVp_HR and CTVn_HR, one volume may be created and labeled CTVp/n_HR.
- The neck dissection scar does not necessarily require full dose on the skin surface. However, where there was gross ENE extending to the subcutaneous tissues or skin, this region should be included in the CTVn_HR and appropriate bolus material used to provide adequate coverage.

Regional nodal disease CTV lesser risk

- Where a high-risk primary site resection without an elective nodal dissection was performed, the at-risk nodal level(s) (elective), based on primary site location and commonly understood patterns of lymphatic drainage, will be defined as the CTVn_LR. Note that some centers opt to observe the nodal basin (eg, forehead lesion with a clinically negative parotid nodal basin and no parotidectomy). Refer to Figure E1 and Table E1.
- Where intraparotid nodes are pathologically positive, the ipsilateral undissected neck node levels Ib to III will be defined as the CTVn_LR. Note that some centers also include IVa/b +/- Va.
- Where an upper cervical neck dissection only (eg, levels I-III) was performed with pathologic positive nodes in any of those levels, the undissected clinically/radiologically uninvolved lower neck IVa/b-Va/b will be defined as the CTVn_LR.
- Where lower neck nodes IVa/b-Va are involved, the undissected Vb-Vc neck nodes will be defined as the CTVn_LR.
- Where the likely first echelon nodes may be unclear (eg, a midline vertex scalp lesion), it may be more appropriate to observe the nodal regions rather than risk unnecessary toxicity by electively treating bilateral nodal regions. Although the utility of sentinel lymph node biopsy in cSCCHN remains unproven, some institutions use it in certain clinical scenarios.[23]

Clinical Cases

Examples of clinical cases illustrating CTVs as per the contouring guidelines are included. Although there may be clinical and regional differences in the management of these cases, they are solely presented for the purposes of highlighting the principles of the guidelines.

It is worth highlighting that the postoperative management of complex cSCCHN can often pose challenges with regard to ensuring adequate tumor coverage while achieving acceptable OAR dose constraints. This can be particularly challenging with TVs that abut structures such as the optic chiasm, optic nerves, and brain stem. It is beyond the scope of these guidelines to provide a detailed discussion regarding these issues. The balancing of these 2 factors remains at the discretion of the treating radiation oncologist, based on the clinical scenario and the patient's wishes.

- Case 1: Right cheek cutaneous squamous cell carcinoma (clinical T4N0M0, pathologic T4NxM0; Fig. 1).

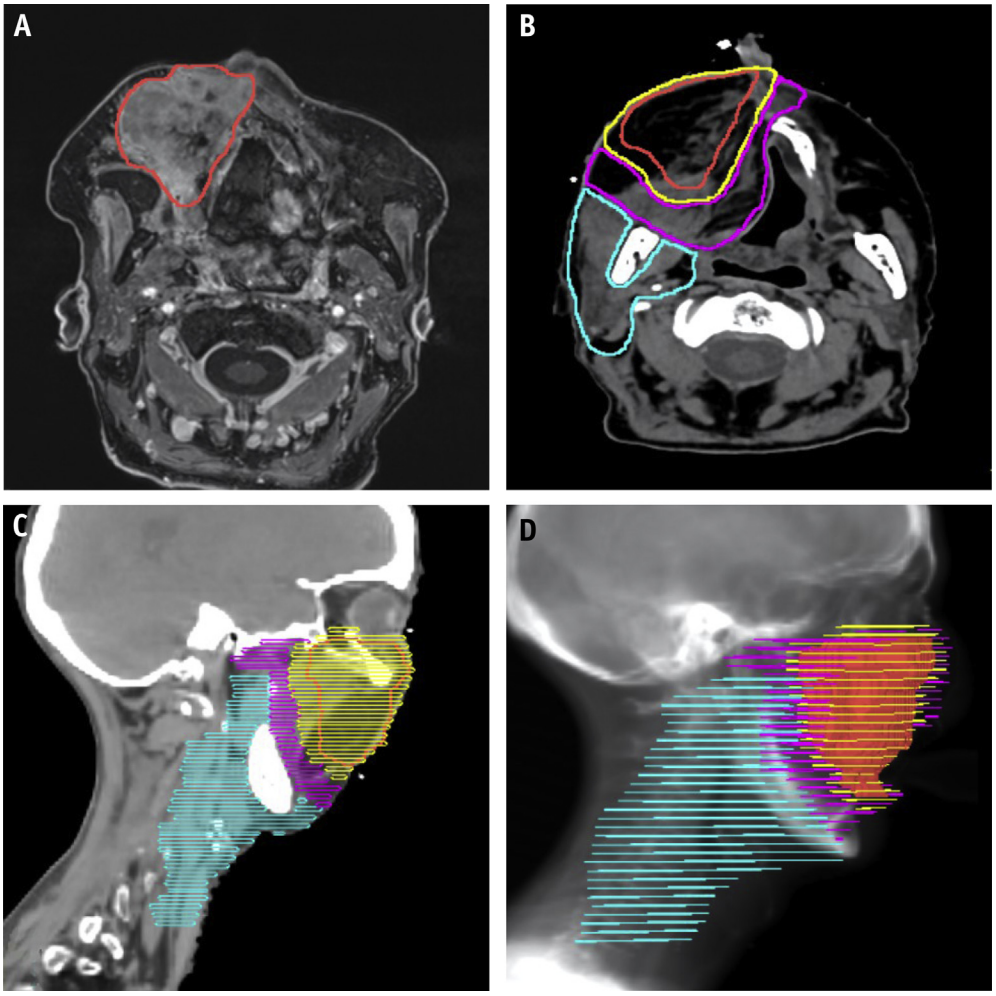

Fig. 1. Case 1: Right cheek cutaneous squamous cell carcinoma (clinical T4N0M0, pathologic T4NxM0). Right cheek squamous cell carcinoma fixed to underlying maxilla, 40 mm x 40 mm, with no palpable lymphadenopathy. Wide local excision, maxillectomy, free flap reconstruction with vertical rectus musculocutaneous flap and clear surgical margins. No involvement of resected right infra-orbital nerve (V2) − zone I. No elective neck dissection. (A) Preoperative axial magnetic resonance imaging (MRI). For figure A the color contour designates the following: gross tumor volume (GTV) primary (p) (red contour). (B) Postoperative target volumes and axial postoperative planning computed tomography at same level as preoperative magnetic resonance imaging. (C) Postoperative target volumes and sagittal postoperative planning computed tomography. (D) Right lateral projection showing target volumes. For figures B-D the color contours designate the following: high risk tumor volume (HRTVp) (red contour); GTVp modified for postoperative anatomic changes and pathologic findings, clinical target volume_high risk primary (CTVp_HR) (yellow contour); HRTVp + isotropic 5 mm margin cropped to external surface, clinical target volume_lesser risk primary (CTVp_LR) (purple contour); the broader operative bed (not included in the CTVp_HR) and reconstruction flap, clinical target volume_lesser risk nodal (CTVn_LR) (blue contour); undissected ipsilateral Ib, II, III, VIII, and IX nodal levels. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.024.)

- Case 2: Metastatic squamous cell carcinoma of presumed cutaneous primary to right intraparotid (VIII) and levels II, III, and V cervical lymph nodes with ENE (pTxN3bM0; Fig. 2).
- Case 3: Midline lower lip vermilion border squamous cell carcinoma (clinical T3N0M0, pathologic T3NxM0; Fig. 3).
- Case 4: Recurrent right upper hair-bearing lip squamous cell carcinoma (recurrent T2N0M0) presenting with large nerve perineural spread of ipsilateral infraorbital nerve (V2) involving zone 1 (Fig. 4).

Planning Target Volumes

The recommended CTV-to-planning target volume (PTV) expansion should be a minimum of 5 mm considering individual institution practice and patient set-up uncertainties. In cases where there is close approximation of CTV to OARs and concerns regarding potential toxicity, higher precision immobilization and set-up verification is recommended so that a smaller PTV expansion may be used.

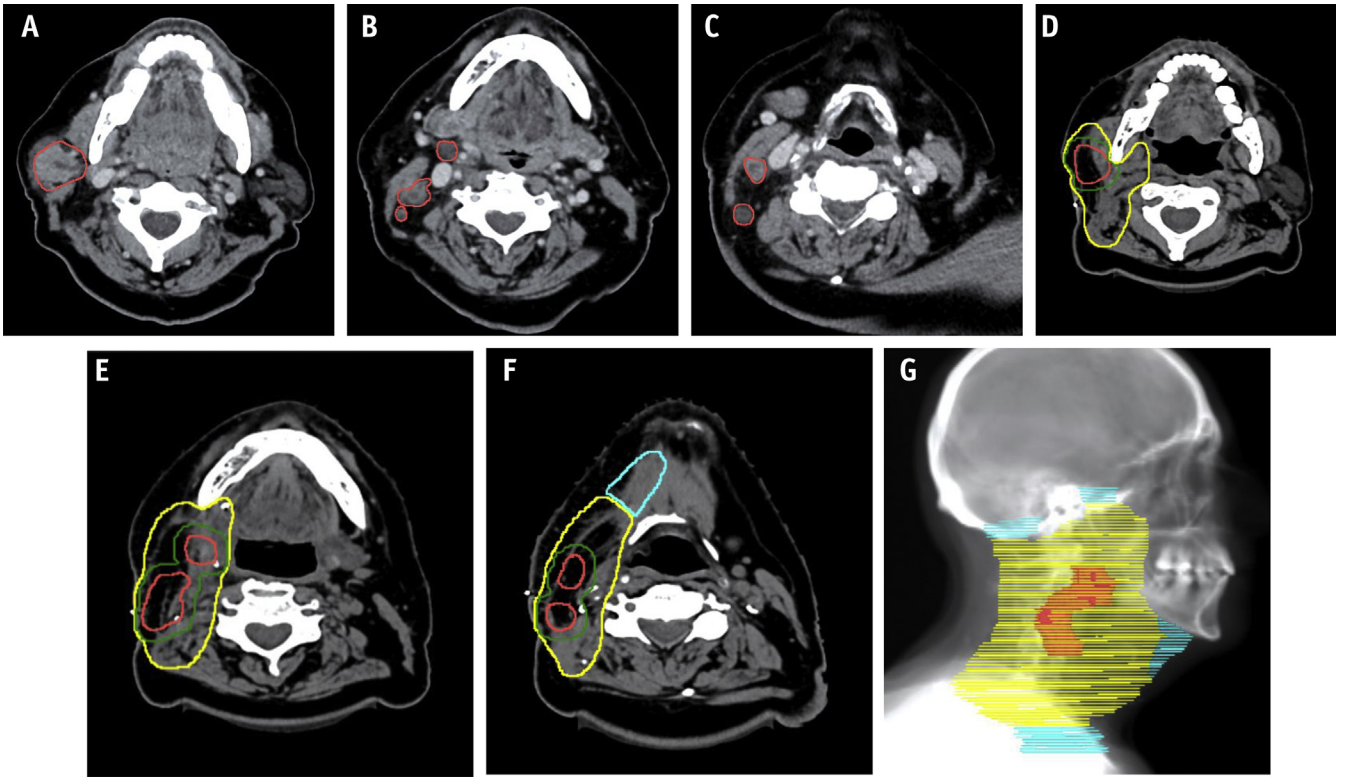

Fig. 2. Case 2: Metastatic squamous cell carcinoma of presumed cutaneous primary to right intraparotid and levels II, III, and V cervical lymph nodes with extranodal extension (pTxN3bM0). (A) Preoperative computed tomography (CT) axial image at the level of parotid gland. Right parotid mass, 35 mm (height) x 30 mm (width), 15 mm diameter palpable ipsilateral upper cervical lymph node, no overlying skin involvement and no synchronous primary skin lesion. No right facial nerve weakness. History of previously treated cutaneous squamous cell carcinomas of the head and neck. Right radical parotidectomy and ipsilateral levels I-Va neck dissection with antero-lateral thigh free flap reconstruction. Metastatic poorly differentiated squamous cell carcinoma involving nodal levels VIII (intra-parotid) with extranodal extension, levels II, III and Va. The intraparotid tumor was clear (>5 mm) of the facial nerve. Clear surgical margins. (B) Preoperative CT axial image at the level of the cervical level II region. (C) Preoperative CT axial image at the level of the cervical level III and Va region. For figures A-C the color contour designates the following: gross tumor volume (GTV) nodes (n) (red contour). (D) Postoperative target volumes and CT axial image at the level of parotid gland. (E) Postoperative target volumes and CT axial image at the level of cervical level II region. (F) Postoperative target volumes and CT axial image at the level of cervical levels III and V region. (G) Lateral projection showing target volumes. For figures D-G the color contours designate the following: high risk tumor volume (HRTVn) (red contour); GTVn modified for postoperative anatomic changes and pathologic findings, Clinical target volume_high risk node (CTVn_HR) (yellow contour); HRTVn + isotropic 5 mm margin cropped to external surface (green contour) + parotidectomy and neck dissection bed harboring involved nodes in levels II, III, Va and VIII. Facial nerve path up to styloid foramen included (see lateral projection). Clinical target volume_lesser risk (CTVn_LR) (blue contour); broader surgical (not included in the CTVn_HR) including the uninvolved dissected ipsilateral Ib and the undissected (elective) IVb nodal levels. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.024.)

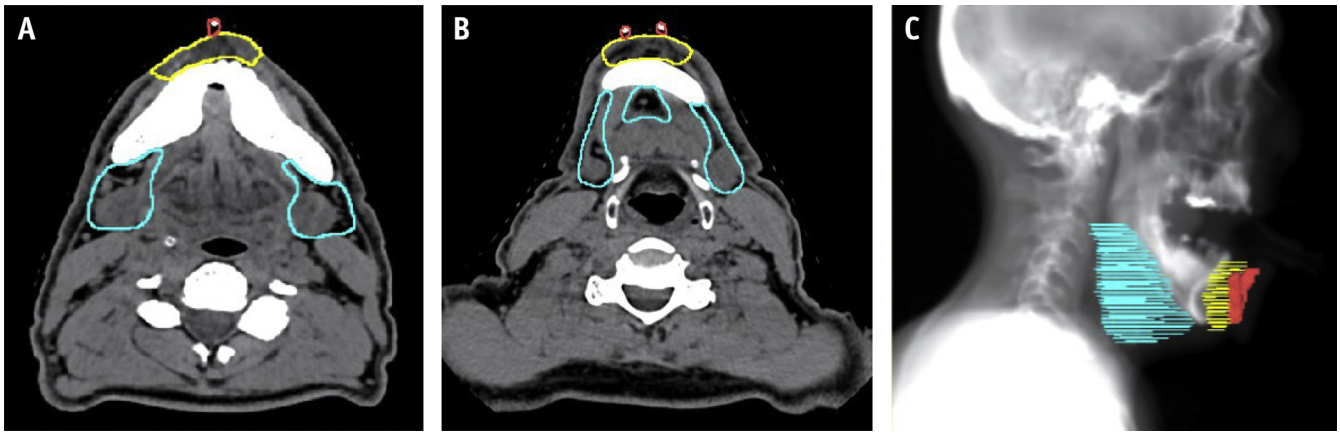

Fig. 3. Case 3: Midline lower lip vermilion border squamous cell carcinoma. (clinical T3N0M0, pathologic T3NxM0). Midline lower lip vermilion border squamous cell carcinoma, 15 mm (width) x 10 mm (height) with no palpable lymphadenopathy. Wedge excision with Abbe flap reconstruction and no neck dissection. Depth of invasion 7 mm, with clear surgical margins. No pre-operative diagnostic imaging of primary lesion. (A) Postoperative target volumes and axial postoperative planning computed tomography at level of superior pole of lip scar. (B) Postoperative planning axial computed tomography at level of inferior pole of lip scar. (C) Lateral projection showing scar wire and target volumes, scar volumes. The color contours designate the following: clinical target volume (CTV) primary_high risk (CTVp_HR) (yellow contour); scar (red contour) + minimum 10 mm isotropic margin cropped to lip surface and bone, clinical target volume (CTV) nodal_lesser risk (CTVn_LR) (blue contour); "at risk" undissected bilateral Ia (submental) and Ib (submandibular) nodes. Note: some centres would include bilateral levels II and III nodal basins. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.024.)

Two PTVs may be considered for a given CTV: (1) PTV for planning, which may extend to the skin surface (when skin is not involved and part of the CTV) and is used for planning treatment segments; and (2) PTV evaluation (PTV_Eval), which is clipped to within 3 mm of the skin surface (when skin is not involved and part of the CTV) and is used for evaluation of the PTV coverage in the dose-volume histogram.

Dose Prescription and Specifications

Doses prescribed to PTVs are derived from the potential risk of the volume harboring residual disease and the technique and fractionation chosen. For example, IMRT or volumetric modulated arc therapy techniques will typically simultaneously deliver multiple dose levels over an identical number of fractions of varying fraction size through the simultaneous integrated boost technique. Non-IMRT techniques will typically deliver identical fraction size to all volumes with sequential phases of volume reduction. It must be recognized that for any given dose level there exist variations in practice within acceptable ranges for which sufficient dose-response data are unavailable.

Planning target volume high risk

The recommended dose to the PTV_HR is 60 Gy in 2.0 Gy once-daily fractions over 6 weeks at 5 days per week, or the equivalent dose in 2.0 Gy per fraction. When using IMRT techniques, this should be prescribed as per the International Commission on Radiation Units & Measurements 83 recommendations, such that the median dose (D50%) is 60 Gy, near minimum dose (D98%) is at least 57 Gy, and near maximum dose (D2%) is no more than 64.2 Gy.

Planning target volume lesser risk

The minimum recommended dose to the PTV_LR is 54 Gy in 2.0 Gy once-daily fractions at 5 days per week, or a biologically equivalent dose.

- Some institutions, for non-IMRT techniques, elect to treat the surgically disrupted PTV_ LR to 54 Gy in 2.0 Gy once-daily fractions for 5.6 weeks and the surgically undisrupted PTV_LR to 50 Gy in 2.0 Gy once-daily fractions over 5 weeks.

For IMRT techniques, the recommended dose is 56.1 Gy in 1.87 Gy once-daily fractions for 6 weeks.

- Some institutions elect to treat the surgically disrupted PTV_ LR to 56.1 Gy in 1.87 Gy once-daily fractions and the undisrupted (elective) PTV_LR to 54.0 in 1.80 Gy once-daily fractions for 6 weeks.

Planning target volume boost

The recommended dose to the PTV_HR_Boost is 66 Gy in 2.0 Gy once-daily fractions, or a biologically equivalent dose.

For an IMRT-simultaneous integrated boost, the total dose may be prescribed as 63 Gy in 2.1 Gy once-daily fractions for 6 weeks.

Refer to Table 2 for a summary of recommended minimum prescribed doses.

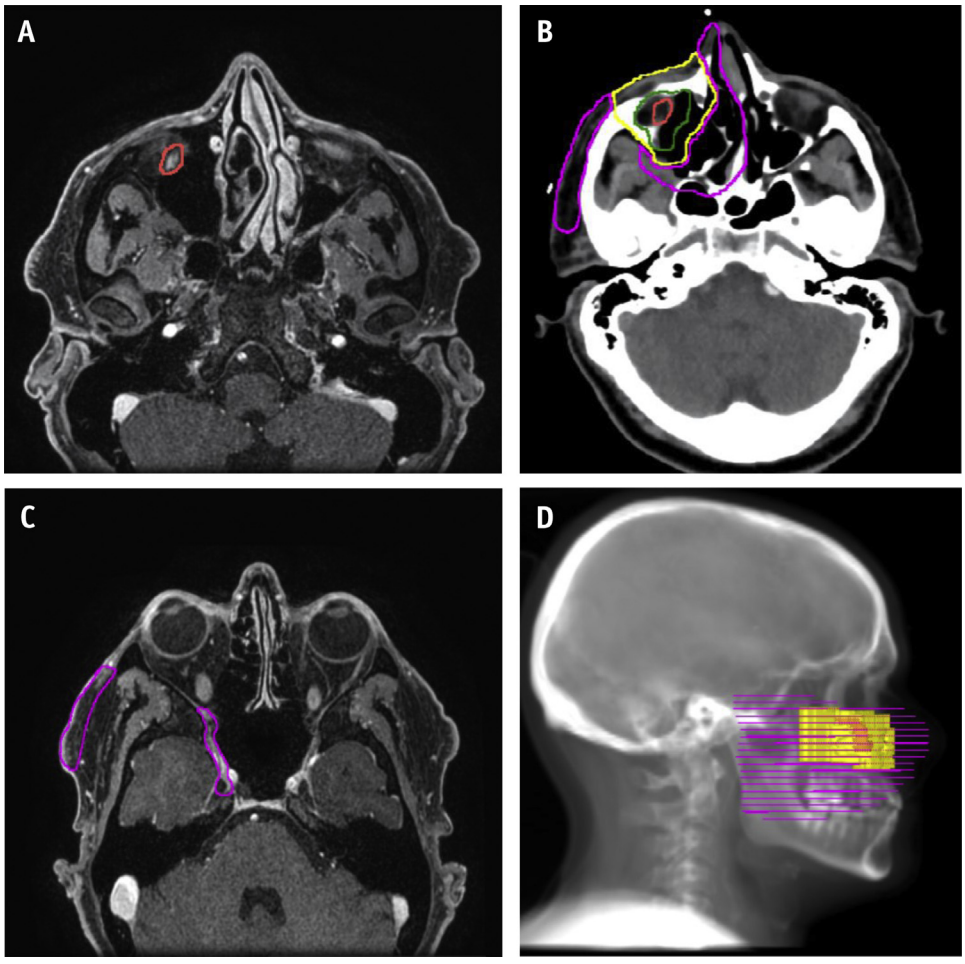

Fig. 4. Case 4: Recurrent right upper hair-bearing lip squamous cell carcinoma (recurrent T2N0M0) presenting with large nerve perineural spread of ipsilateral infraorbital nerve (V2) involving zone 1. Progressive right upper lip scar V2 paraesthesia for 12 months following resection of right upper lip squamous cell carcinoma (SCC) T2N0M0 with pathologic multifocal (<0.1 mm caliber nerves) perineural disease. No prior adjuvant treatment. Magnetic resonance imaging (MRI) demonstrated perineural enhancement of right infra-orbital nerve extending 17 mm proximally from the lip scar (zone 1). Resection of infra-orbital nerve from subcutis to foramen rotundum demonstrated perineural SCC extending proximally for 25 mm from the cutaneous (distal) end of the specimen. Clear of proximal resection margin (zone 1 disease only). No soft tissue disease. (A) Preoperative axial MRI at most superior level of clinical perineural spread. For figure A the color contour designates the following: gross tumor volume (GTV) primary (p) (red contour); Pre-operative MRI of enhancing right infra-orbital nerve (V2). (B) Postoperative target volumes and axial postoperative planning computed tomography at same level as preoperative MRI. (C) Preoperative axial MRI at level of foramen rotundum and trigeminal ganglion. (D) Lateral projection showing target volumes. For Figures B-D the color contours designate the following: high risk tumor volume (HRTV) p (red contour); GTVp modified for postoperative anatomic changes and pathologic findings, clinical target volume primary_high risk (CTVp_HR) (yellow contour); HRTVp + isotropic 5 mm expansion cropped to bone (green contour) + broader operative bed containing involved large nerve perineural spread, clinical target volume primary_lesser risk (CTVp_LR) (purple contour); broader zone 1 (not included in the CTVp_HR) and extending to the pterygo-palatine fossa, through foramen rotundum and including the trigeminal ganglion in the anterior part of Meckel's cave (zone 2) + ipsilateral cutaneous distribution of infra-orbital nerve (V2). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.024.)

Special Consideration

Perineural spread

The growth of tumor along nerve sheaths is a route of spread that is distinct from lymphatic or hematogenous dissemination. The histologic finding of tumor involving small nerves is termed incidental or pathologic perineural invasion, although involvement of larger nerves—that is, named nerves (eg, infraorbital nerve [V2])—is referred to as large nerve perineural spread (LNPNS). Spread can occur in an antegrade direction toward smaller more

Table 2 Summary of recommended minimum prescribed doses*

Target volume	IMRT technique	Non-IMRT technique
PTVp_HR and/or PTVn_HR	60.0 Gy in 30 fractions	60.0 Gy in 30 fractions
PTVp_LR and/or PTVn_LR	56.0 Gy in 30 fractions Optional: 54.0 Gy in 30 fractions for surgically undisrupted LR region	54.0 Gy in 27 fractions Optional: 50.0 Gy in 25 fractions for surgically undisrupted LR region
PTVp_boost and/or PTVn_boost (optional)	66.0 Gy in 33 fractions or 63.0 Gy in 30 fractions	66.0 Gy in 33 fractions

Abbreviations: HR = high risk; IMRT = intensity modulated radiation therapy; LR = lesser risk; n = nodal involvement; p = primary site; PTV = planning target volume.

* Fractionation schedules are described as once daily at 5 fractions per week.

peripheral nerves where it may lead to cutaneous or subcutaneous recurrence or in a retrograde spread toward larger more centrally located nerve trunks where it has the potential to involve other cranial nerves or nerve branches via known conduits. For example, the auriculotemporal nerve is a branch of the mandibular nerve (V3) that runs with the superficial temporal artery and vein and provides somatosensory fibers to the parotid gland, and sensation to various regions on the side of the head. Because of its close proximity to the facial nerve, both the auriculotemporal nerve and the mandibular branch of the trigeminal nerve (V3) are "at risk" in cases involving extensive facial nerve involvement in the parotid gland and should be included in either the high- or low-risk CTV.[24]

A zonal classification system for LNPNS has been described and summarized in Table E3.[25]

Pathologic (incidental) perineural invasion

Primary site high-risk clinical target volume

This is defined as a minimum 5-mm isotropic expansion of the primary site HRTVp. The CTVp_HR may include the broader operative resection bed or the entire reconstruction flap or graft site and be modified to anatomic barriers, particularly in scenarios where there may be uncertainty in defining the HRTVp because of anatomic changes after surgery or because preoperative imaging was not performed.

Primary site lesser risk clinical target volume

Optionally, where there is extensive pathologic perineural invasion of nerves $\geq$ 0.1 mm diameter or multifocal perineural invasion but no clinical or radiologic evidence of large nerve PNS, zone I of the nearby (within 10-20 mm) named nerve may be considered the CTVp_LR.

Large nerve perineural spread high-risk volume

This is defined as a minimum 5 mm isotropic expansion of the pathologic involved portion of the nerve (ie, HRTVp) and the operative bed containing the involved nerve. Optionally, the CTVp_HR may also include the entire zone harboring the involved named nerve. For example, if there is only zone 1 involvement of the infraorbital nerve (V2), the CTVp_HR may include a 5-mm isotropic expansion of the involved infraorbital nerve, operative bed, and the region back to the pterygopalatine fossa and foramen rotundum. In cases where there is extensive involvement of the facial nerve within the parotid bed, the auriculotemporal and mandibular nerve back to the foramen ovale may be considered part of the CTVp_HR.

It is worth highlighting that a postoperative magnetic resonance imaging is recommended in LNPNS where disease is found to extend back to the skull base either preoperatively or at surgery to exclude gross residual disease, which may require a boost dose.

Large nerve perineural spread low risk volume

This is defined as the uninvolved broader surgical bed thought to be at lesser risk than the CTVp_HR and the next most proximal (central) uninvolved zone. Note that some institutions consider treating the uninvolved portion of the nerve (dissected or nondissected) back to the brain stem. In addition, the cutaneous distribution of the involved cranial nerve (with appropriate bolus build-up) should also be considered for inclusion in the CTVp_LR.

In the absence of a synchronous primary lesion or soft tissue disease recurrence at the site of the LNPNS, elective regional nodal treatment is optional.

Conclusions

These contouring guidelines for the delivery of PORT in complex cSCCHN represent the first international consensus guidelines for this disease. They have been written for the purpose of assisting radiation oncologists involved in the management of complex cSCCHN and the contouring of postoperative RT volumes. It is hoped that they will promote the harmonization of PORT globally and help to minimize treatment variation among clinicians, facilitating RT quality and outcomes assessment across institutions. It is expected that over time there will be continuing refinement of the guidelines.

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