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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Abstract

Radiation Therapy (RT) consensus contouring guidelines in the post-operative setting for complex cutaneous squamous cell carcinoma of the head and neck (cSCCHN) 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 (HNCIG) to assist radiation oncologists involved in the management of this disease. These guidelines present a set of principles used to define post-operative RT (PORT) volumes and corresponding minimum doses following resection of all macroscopic tumour with or without microscopic residual disease.

It is anticipated they will 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.

Running title; Skin cancer radiation therapy contouring guidelines

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Abstract

Radiation Therapy (RT) consensus contouring guidelines in the post-operative setting for complex cutaneous squamous cell carcinoma of the head and neck (cSCCHN) 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 (HNCIG) to assist radiation oncologists involved in the management of this disease. These guidelines present a set of principles used to define post-operative RT (PORT) volumes and corresponding minimum doses following resection of all macroscopic tumour with or without microscopic residual disease.

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Introduction

High-risk cutaneous squamous cell carcinomas of the head and neck (cSCCHN) are those tumours deemed to be at sufficient risk of recurrence following curative surgery warranting consideration of post-operative radiation therapy (PORT). Commonly, the location and proximity to critical structures and the RT volumes required to encompass the resected disease site and 'at risk' areas make these cases complex. The clinico-pathological 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 radiation therapy (RT) contouring of these complex cases. (1-19)

Head and Neck Cancer (HNC) 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 post-operative management of complex cSCCHN.

These guidelines present a set of principles used to define PORT volumes and corresponding minimum doses following resection of all macroscopic tumour 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 post-operative 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 judgement 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 centres prior to 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 pre-defined RT protocol and a RT quality assurance program. (1) ~~In cases where induction systemic therapy has been administered prior to surgery, we recommend using the pre-chemotherapy imaging to define the High Risk Tumour Volume (HRTV). (20)~~

Methodology

These guidelines were developed under the auspices the HNCIG. This group is made up of nominated head and neck clinicians from national co-operative trial groups and selected large cancer centres that are capable of conducting large-scale phase II and III clinical trials. The aim of the organisation is to promote HNC trials globally and also endeavours to develop harmonisation of trial protocols. The authors of the manuscript were directly involved in the development of the guidelines. As 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 manuscript. Of the 18 board members, 2 felt 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 acknowledgements.

~~The guidelines were developed through the collective experience of the authors and the highest level of evidence, where available. Regional differences were acknowledged and where consensus could not be reached or there was more than one viable approach that the authors felt should be highlighted, these were included in the guidelines. The guidelines underwent a number of re-iterations until universal agreement was reached. The guidelines were then circulated to all HNCIG board members for review and any further modifications. The board is~~

~~comprised of a HNC expert representative from each of the 18 HNCIG membership groups. The membership groups are made up of collaborative trial groups, and selected cancer centres capable of conducting large-scale single institution clinical trials in HNC. Board members were asked to provide endorsement as members of the HNCIG and not necessarily on behalf of their group.~~ ~~Sixteen of the 18 members provided endorsement of the final manuscript and the board were in agreement in naming them HNCIG guidelines.~~ ~~Due to the multi-disciplinary and international nature of the board~~ ~~Two of the board members abstained from endorsing the guidelines due to their group's lack of expertise in the treatment of complex skin cancers.~~~~some members felt they were not qualified to provide endorsement of the final manuscript.~~ ~~Sixteen of the 18 members provided endorsement of the final manuscript and the board were in agreement in naming them HNCIG guidelines. Two of the board members abstained from endorsing the guidelines due to their group's lack of expertise in the treatment of complex skin cancers.~~

General radiation therapy recommendations

Technique

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

Localisation, Simulation and Immobilisation

Patients should be positioned and immobilised according to institutional policy prior to the treatment planning computerised 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 2-3mm should be

performed, preferably with intravenous contrast.

Daily treatment position

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

Treatment Planning and Target Volume Definitions

Target Volumes (TV) and OAR nomenclature and labeling are based on the AAPM TG-263 report: Standardizing Nomenclatures in Radiation Oncology. (201) 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 pre-operative diagnostic images should be co-registered with the planning CT data set. Any additional available information such as pre-operative photographs and clinical description, along with the operative findings should also be used to assist in defining TVs.

Gross and High Risk Tumour Volumes

The HRTV is defined as the pre-operative gross tumour volume (GTV) transposed onto the post-operative planning CT and modified to account for anatomic changes and pathologic findings.

For example, following surgery of an intra-parotid nodal metastasis, the external body contour may have changed from the pre-operative imaging due to the removal of the mass and the parotid gland. As a result there may be a discrepancy in the pre-operative imaging external body contour and location of tumour compared with the post-operative external body

contour on the planning CT scan. These differences need to be taken into account at the time of image co-registration and when delineating the pre-operative tumour position onto the post-operative planning CT.

In cases where induction systemic therapy has been administered prior to surgery, we recommend using the pre-chemotherapy imaging to define the High Risk Tumour Volume (HRTV). (210)

HRTV primary and HRTV nodal disease

Where applicable, there will be a HRTV defined for the primary (p) site (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 (e.g. an extensive primary lesion over the pre-auricular area with underlying intra-parotid nodal metastases).

HRTV Boost

In cases for which the pathology report has described positive or very close (<2mm) 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, pathological description and pre-operative imaging and defined as either HRTVp_Boost and/or HRTVn_Boost.

Clinical Target Volumes

In the post-operative setting, following resection of all gross primary and nodal disease, the differing TV's 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)

Below is a description of the recommended Clinical TV's (CTV) 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 5mm isotropic expansion of the HRTV for either primary disease (CTVp_HR) and/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 (e.g. uninvolved bone) and prescribed to receive 60Gy in 2.0Gy once-daily fraction, 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 harbouring microscopic disease but does not meet the criteria for CTV High Risk. These CTVs are modified to anatomic barriers (e.g. uninvolved bone) and prescribed to receive 54Gy or 56Gy in 2.0Gy once-daily fraction, 5 days per week, or a biologically equivalent dose (refer to **Dose prescription and specifications** section).

- 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_LResser Risk 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 harbouring microscopic disease (i.e. elective nodal and/or intra-parotid regions)

Refer to **Figure 1 (**supplementary) for an illustration of pattern of lymphatic draining of the HN and **Table 2 (**supplementary) for a summary of lymphatic drainage of the HN based on primary site location. **Table 3 (**supplementary) summarises 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 V et al 2014 (22), although modifications for post-operative anatomic changes will need to be made in the dissected neck.

Clinical Target Volume High Risk Boost (CTV_Boost)

This is defined as a minimum 5mm isotropic expansion of the HRTV_Boost for either primary disease (CTVp_Boost) and/or regional nodal disease (CTVn_Boost). This volume is optional and would typically be prescribed to receive a dose in the range of 66Gy in 2.0Gy once-daily fraction,

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 due to anatomical changes following surgery
- if no pre-operative imaging was performed prior to primary disease resection the CTVp_HR may be defined as a minimum 10mm isotropic expansion around the primary site surgical scar and modified to account for anatomic changes and pathologic findings. Where available, pre-operative photographs, clinical examination description and operative findings should be used to localize the primary tumour 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 the decision to include the primary site was recommended if the primary lesion had been excised within 12 months of the development of nodal metastases. Note; 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 intra-parotid (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 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 due to anatomical changes following surgery and/or disease not identifiable on pre-operative 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 employed 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: some centres opt to observe the nodal basin e.g. forehead lesion with a clinically negative parotid nodal basin and no parotidectomy.*

- refer to **Figure 1** (Supplementary) and **Table 2** (Supplementary)**.**
- where intra-parotid nodes are pathologically positive the ipsilateral undissected neck node levels Ib-III will be defined as the CTVn_LR.

  Note; some centres also include IVa/b +/- Va.
- where an upper cervical neck dissection only (e.g. levels I-III) was performed with pathological 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 it may be unclear as to what are the likely first echelon nodes, e.g. 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. *While 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. While 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 post-operative management of complex cSCCHN can often pose challenges with regards to ensuring adequate tumour coverage while achieving acceptable dose constraints of the OAR. This can be particularly challenging with target volumes that abut structures such as the optic chiasm, optic nerves and brainstem. It is beyond the scope of these

guidelines to provide a detailed discussion regarding these issues. The balancing of these two factors remains at the discretion of the treating radiation oncologist, based on the clinical scenario and patient's wishes.

Case 1- Right cheek cutaneous squamous cell carcinoma (clinical T4N0M0, pathologic T4NxM0). Figure **2**.

Case 2 - Metastatic squamous cell carcinoma of presumed cutaneous primary to right intra-parotid (VIII) and levels II, III & V cervical lymph nodes with extranodal extension (pTxN3bM0). **Figure 3.**

Case 3 - Midline lower lip vermilion border SCC (clinical T3N0M0, pathologic T3NxM0). **Figure 4.**

Case 4 - Recurrent right upper hair bearing lip squamous cell carcinoma (recurrent T2N0M0) presenting with large nerve perineural spread of ipsilateral infra-orbital nerve (V2) involving Zone 1. **Figure 5.**

Planning Target Volumes (PTV)

The recommended CTV-to-PTV expansion should be a minimum of 5mm taking into account 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.

Two PTV's may be considered for a given CTV:

1) PTV for planning, which may extend to the skin surface (when skin 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 3mm of the skin surface (when skin 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 harbouring residual disease and the technique and fractionation chosen. For example, IMRT or VMAT techniques will typically simultaneously deliver multiple dose levels over an identical number of fractions of varying fraction size through simultaneous integrated boost (SIB) technique. Non-IMRT techniques will typically deliver identical fraction size to all volumes with sequential phases of volume reduction. It must be recognised that for any given dose level there exist variations in practice within acceptable ranges for which sufficient dose-response data is unavailable.

Planning Target Volume High Risk

The recommended dose to the PTV_HR is 60Gy in 2.0Gy once-daily fraction size over 6 weeks at 5 days per week, or the equivalent dose in 2.0Gy per fraction [EQD2]. When using IMRT techniques, this should be prescribed as per the ICRU 83 recommendations, such that the median dose (D50%) is 60Gy, near minimum dose (D98%) is at least 57Gy and the near maximum dose (D2%) is no more than 64.2Gy.

Planning Target Volume Lesser Risk

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

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

For IMRT techniques the recommended dose is 56.1Gy in 1.87Gy once-daily fraction size over 6 weeks.

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

Planning Target Volume boost

The recommended dose to the PTV_HR_Boost is 66Gy in 2.0Gy once-daily fraction size, or a BED.

For an IMRT-SIB the total dose may be prescribed as 63Gy in 2.1Gy once-daily over 6 weeks.

Refer to **Table 4** for a summary of recommended minimum prescribed doses.

Special Consideration

Perineural Spread

The growth of tumour along nerve sheaths is a route of spread that is distinct from lymphatic or haematogenous dissemination. The histologic finding of tumour involving small nerves is termed incidental or pathologic perineural invasion (pPNI) whilst involvement of larger nerves, that is, named nerve *(e.g. infra-orbital nerve (V2))* involvement, is referred to as large nerve perineural spread (LNPNS). Spread can occur in an antegrade direction towards smaller more peripheral nerves where it may lead to cutaneous or subcutaneous recurrence, or in a retrograde spread towards 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 fibres to the parotid gland, and sensation to various regions on the side of the head. Because of it's 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 summarised in **Table 5** (Supplementary). (25)

Pathologic (incidental) perineural invasion

Primary Site High Risk Clinical Target Volume

This is defined as a minimum 5mm 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 modified to anatomic barriers, particularly in scenarios where there may be uncertainty in defining the HRTVp due to anatomical changes following surgery or pre-operative imaging was not performed.

Primary Site Lesser Risk Clinical Target Volume

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

Large Nerve Perineural Spread High Risk Volume

This is defined as a minimum 5mm isotropic expansion of the pathologic involved portion of the nerve (i.e. HRTVp) and the operative bed containing the involved nerve.

Optionally, the CTVp_HR may also include the entire zone harbouring the involved named nerve.

For example, if there is only Zone 1 involvement of the infraorbital nerve (V2) the

CTVp_HR may include a 5mm isotropic expansion of the involved infra-orbital nerve, operative bed and the region back to the pterygo-palatine 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 post-operative MRI is recommended in LNPNS where disease is found to be extending back to the skull base either pre-operatively 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; some institutions consider treating the uninvolved portion of the nerve (dissected or non-dissected) back to the brainstem*. 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.

Conclusion

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 post-operative RT volumes. It is hoped that they will promote the harmonization of PORT globally and help to minimise 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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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)

Abstract

Radiation Therapy (RT) consensus contouring guidelines in the post-operative setting for complex cutaneous squamous cell carcinoma of the head and neck (cSCCHN) 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 (HNCIG) to assist radiation oncologists involved in the management of this disease. These guidelines present a set of principles used to define post-operative RT (PORT) volumes and corresponding minimum doses following resection of all macroscopic tumour with or without microscopic residual disease.

It is anticipated they will 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.

Running title; Skin cancer radiation therapy contouring guidelines

Introduction

High-risk cutaneous squamous cell carcinomas of the head and neck (cSCCHN) are those tumours deemed to be at sufficient risk of recurrence following curative surgery warranting consideration of post-operative radiation therapy (PORT). Commonly, the location and proximity to critical structures and the RT volumes required to encompass the resected disease site and 'at risk' areas make these cases complex. The clinico-pathological 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 radiation therapy (RT) contouring of these complex cases. (1-19)

Head and Neck Cancer (HNC) 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 post-operative management of complex cSCCHN.

These guidelines present a set of principles used to define PORT volumes and corresponding minimum doses following resection of all macroscopic tumour 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 post-operative 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 judgement 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 centres prior to 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 pre-defined RT protocol and a RT quality assurance program. (1)

Methodology

These guidelines were developed under the auspices the HNCIG. This group is made up of nominated head and neck clinicians from national co-operative trial groups and selected large cancer centres that are capable of conducting large-scale phase II and III clinical trials. The aim of the organisation is to promote HNC trials globally and also endeavours to develop harmonisation of trial protocols. The authors of the manuscript were directly involved in the development of the guidelines. As 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 manuscript. Of the 18 board members, 2 felt 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 acknowledgements.

General radiation therapy recommendations

Technique

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

Localisation, Simulation and Immobilisation

Patients should be positioned and immobilised according to institutional policy prior to the treatment planning computerised 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 2-3mm should be performed, preferably with intravenous contrast.

Daily treatment position

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

Treatment Planning and Target Volume Definitions

Target Volumes (TV) and OAR nomenclature and labeling are based on the AAPM 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 pre-operative diagnostic images should be co-registered with the planning CT data set. Any additional available information such as pre-operative photographs and clinical description, along with the operative findings should also be used to assist in defining TVs.

Gross and High Risk Tumour Volumes

The HRTV is defined as the pre-operative gross tumour volume (GTV) transposed onto the post-operative planning CT and modified to account for anatomic changes and pathologic

findings.

For example, following surgery of an intra-parotid nodal metastasis, the external body contour may have changed from the pre-operative imaging due to the removal of the mass and the parotid gland. As a result there may be a discrepancy in the pre-operative imaging external body contour and location of tumour compared with the post-operative external body contour on the planning CT scan. These differences need to be taken into account at the time of image co-registration and when delineating the pre-operative tumour position onto the post-operative planning CT.

In cases where induction systemic therapy has been administered prior to surgery, we recommend using the pre-chemotherapy imaging to define the High Risk Tumour Volume (HRTV). (21)

HRTV primary and HRTV nodal disease

Where applicable, there will be a HRTV defined for the primary (p) site (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 (e.g. an extensive primary lesion over the pre-auricular area with underlying intra-parotid nodal metastases).

HRTV Boost

In cases for which the pathology report has described positive or very close (<2mm) 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, pathological description and pre-operative imaging and defined as either HRTVp_Boost and/or HRTVn_Boost.

Clinical Target Volumes

In the post-operative setting, following resection of all gross primary and nodal disease, the differing TV's 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)

Below is a description of the recommended Clinical TV's (CTV) 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 5mm isotropic expansion of the HRTV for either primary disease (CTVp_HR) and/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 (e.g. uninvolved bone) and prescribed to receive 60Gy in 2.0Gy once-daily

fraction, 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 harbouring microscopic disease but does not meet the criteria for CTV High Risk. These CTVs are modified to anatomic barriers (e.g. uninvolved bone) and prescribed to receive 54Gy or 56Gy in 2.0Gy once-daily fraction, 5 days per week, or a biologically equivalent dose (refer to **Dose prescription and specifications** section).

- 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_LResser Risk 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 harbouring microscopic disease (i.e. elective nodal and/or intra-parotid regions)

Refer to **Figure 1 (**supplementary) for an illustration of pattern of lymphatic draining of the HN and **Table 2 (**supplementary) for a summary of lymphatic drainage of the HN based on primary site location. **Table 3 (**supplementary) summarises 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 V et al 2014 (22), although modifications for post-operative anatomic changes will need to be made in the dissected neck.

Clinical Target Volume High Risk Boost (CTV_Boost)

This is defined as a minimum 5mm isotropic expansion of the HRTV_Boost for either primary disease (CTVp_Boost) and/or regional nodal disease (CTVn_Boost). This volume is optional and would typically be prescribed to receive a dose in the range of 66Gy in 2.0Gy once-daily fraction, 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 due to anatomical changes following surgery
- if no pre-operative imaging was performed prior to primary disease resection the CTVp_HR may be defined as a minimum 10mm isotropic expansion around the primary site surgical scar and modified to account for anatomic changes and pathologic findings. Where available, pre-operative photographs, clinical examination description and operative findings should be used to localize the primary tumour 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 the decision to include the primary site was recommended if the primary lesion had been excised within 12 months of the development of nodal metastases. Note; 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 intra-parotid (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 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 due to anatomical changes following surgery and/or disease not identifiable on pre-operative 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 employed 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: some centres opt to observe the nodal basin e.g. forehead lesion with a clinically negative parotid nodal basin and no parotidectomy.*
- refer to **Figure 1** (Supplementary) and **Table 2** (Supplementary)**.**
- where intra-parotid nodes are pathologically positive the ipsilateral undissected neck node levels Ib-III will be defined as the CTVn_LR.

  Note; some centres also include IVa/b +/- Va.
- where an upper cervical neck dissection only (e.g. levels I-III) was performed with pathological 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 it may be unclear as to what are the likely first echelon nodes, e.g. 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. *While 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. While 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 post-operative management of complex cSCCHN can often pose challenges with regards to ensuring adequate tumour coverage while achieving acceptable dose constraints of the OAR. This can be particularly challenging with target volumes that abut structures such as the optic chiasm, optic nerves and brainstem. It is beyond the scope of these guidelines to provide a detailed discussion regarding these issues. The balancing of these two factors remains at the discretion of the treating radiation oncologist, based on the clinical scenario and patient's wishes.

Case 1- Right cheek cutaneous squamous cell carcinoma (clinical T4N0M0, pathologic T4NxM0). Figure **2**.

Case 2 - Metastatic squamous cell carcinoma of presumed cutaneous primary to right intra-parotid (VIII) and levels II, III & V cervical lymph nodes with extranodal extension (pTxN3bM0). **Figure 3.**

Case 3 - Midline lower lip vermilion border SCC (clinical T3N0M0, pathologic T3NxM0). **Figure 4.**

Case 4 - Recurrent right upper hair bearing lip squamous cell carcinoma (recurrent T2N0M0) presenting with large nerve perineural spread of ipsilateral infra-orbital nerve (V2) involving Zone 1. **Figure 5.**

Planning Target Volumes (PTV)

The recommended CTV-to-PTV expansion should be a minimum of 5mm taking into account 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.

Two PTV's may be considered for a given CTV:

1) PTV for planning, which may extend to the skin surface (when skin 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 3mm of the skin surface (when skin 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 harbouring residual disease and the technique and fractionation chosen. For example, IMRT or VMAT techniques will typically simultaneously deliver multiple dose levels over an identical number of fractions of varying fraction size through simultaneous integrated boost (SIB) technique. Non-IMRT techniques will typically deliver identical fraction size to all volumes with sequential phases of volume reduction. It must be recognised that for any given dose level there exist variations in practice within acceptable ranges for which sufficient dose-response data is unavailable.

Planning Target Volume High Risk

The recommended dose to the PTV_HR is 60Gy in 2.0Gy once-daily fraction size over 6 weeks at 5 days per week, or the equivalent dose in 2.0Gy per fraction [EQD2]. When using IMRT techniques, this should be prescribed as per the ICRU 83 recommendations, such that the median dose (D50%) is 60Gy, near minimum dose (D98%) is at least 57Gy and the near maximum dose (D2%) is no more than 64.2Gy.

Planning Target Volume Lesser Risk

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

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

For IMRT techniques the recommended dose is 56.1Gy in 1.87Gy once-daily fraction size over 6 weeks.

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

Planning Target Volume boost

The recommended dose to the PTV_HR_Boost is 66Gy in 2.0Gy once-daily fraction size, or a BED.

For an IMRT-SIB the total dose may be prescribed as 63Gy in 2.1Gy once-daily over 6 weeks.

Refer to **Table 4** for a summary of recommended minimum prescribed doses.

Special Consideration

Perineural Spread

The growth of tumour along nerve sheaths is a route of spread that is distinct from lymphatic or haematogenous dissemination. The histologic finding of tumour involving small nerves is termed incidental or pathologic perineural invasion (pPNI) whilst involvement of larger nerves, that is, named nerve *(e.g. infra-orbital nerve (V2))* involvement, is referred to as large nerve perineural spread (LNPNS). Spread can occur in an antegrade direction towards smaller more peripheral nerves where it may lead to cutaneous or subcutaneous recurrence, or in a retrograde spread towards 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 fibres to the parotid gland, and sensation to various regions on the side of the head. Because of it's 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 summarised in **Table 5** (Supplementary). (25)

Pathologic (incidental) perineural invasion

Primary Site High Risk Clinical Target Volume

This is defined as a minimum 5mm 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 modified to anatomic barriers, particularly in scenarios where there may be uncertainty in defining the HRTVp due to anatomical changes following surgery or pre-operative imaging was not performed.

Primary Site Lesser Risk Clinical Target Volume

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

Large Nerve Perineural Spread High Risk Volume

This is defined as a minimum 5mm isotropic expansion of the pathologic involved portion of the nerve (i.e. HRTVp) and the operative bed containing the involved nerve.

Optionally, the CTVp_HR may also include the entire zone harbouring the involved named nerve.

For example, if there is only Zone 1 involvement of the infraorbital nerve (V2) the CTVp_HR may include a 5mm isotropic expansion of the involved infra-orbital nerve, operative bed and the region back to the pterygo-palatine 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 post-operative MRI is recommended in LNPNS where disease is found to be extending back to the skull base either pre-operatively 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; some institutions consider treating the uninvolved portion of the nerve (dissected or non-dissected) back to the brainstem*. 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.

Conclusion

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 post-operative RT volumes. It is hoped that they will promote the harmonization of PORT globally and help to minimise 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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Table 1. Summary of Target Volume Definitions

Target volume	Structure	Definition
Site of primary tumour before excision*	HRTVp	The volume that represents the pre-operative primary site GTV transposed onto the planning CT imaging data set and modified to account for post-operative anatomic changes and pathologic findings
Site of involved lymph nodes before excision*	HRTVn	The volume that represents the pre-operative regional nodal site GTV transposed onto the planning CT imaging data set and modified to account for post-operative anatomic changes and pathologic findings
Sub-site of the HRTVp likely to carry a higher burden of microscopic disease (i.e. positive or margin clearance <2mm) and warranting a boost dose	HRTVp_Boost	The sub-volume that represents the pre-operative primary site GTV transposed onto the planning CT imaging data set and modified to account for post-operative anatomic changes and pathologic findings and

		considered at particularly high risk
Sub-site of the HRTVn disease likely to carry a higher burden of microscopic disease (i.e. positive margin or extranodal extension)	HRTVn_Boost	The volume that represents the pre-operative regional nodal site GTV transposed onto the planning CT imaging data set and modified to account for post-operative anatomic changes and pathologic findings and considered at particularly high risk
Primary Site High Risk Clinical Target Volume	CTVp_HR	Minimum volume includes HRTVp + 5mm 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 + 5mm 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	CTVp_LR	The primary site operative bed

Risk Clinical Target Volume		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 tumour boost site (optional)	CTVp_HR_Boost	Minimum volume includes HRTVp_Boost + 5mm expansion and modified to anatomic barriers
Nodal site boost site (optional)	CTVn_HR_Boost	Minimum volume includes HRTVn_Boost + 5mm expansion and modified to anatomic barriers

HRTV=High risk tumour volume; p=primary; n=nodal; HR=high risk; LR=Low Risk; GTV=Gross Tumour Volume; CT=computerized tomography; CTV=Clinical Target Volume; LNPNS=large nerve perineural spread

*Where there is substantial overlap of the HRTVp and HRTVn, a single

HRTV termed HRTVp/n may be used (e.g. an extensive primary lesion over the pre-auricular area with underlying intra-parotid nodal metastases).

Table 4. Summary of recommended minimum prescribed doses*

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

* fractionation schedules are described as once-daily at 5 fractions per week

IMRT = intensity modulated radiation therapy; PTV= Planning Target Volume; p=primary site; n= nodal involvement; HR=high risk; LR= lesser risk; Gy = Gray

Figure 2. **Case 1** - Right cheek cutaneous squamous cell carcinoma (clinical T4N0M0, pathologic T4NxM0)

Right cheek squamous cell carcinoma fixed to underlying maxilla, 40mm x 40mm, 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

Figure 2a. Pre-operative axial magnetic resonance imaging (MRI)

Gross Tumour Volume (GTV) primary (p) (red contour)

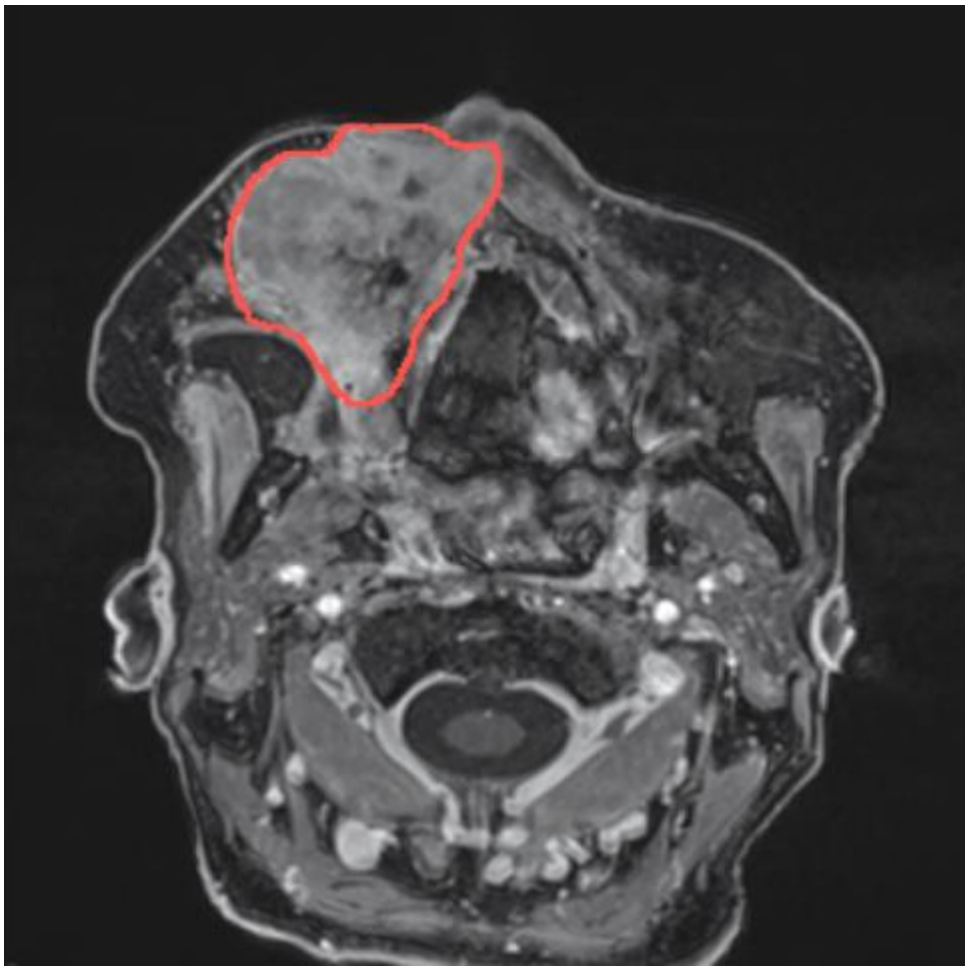

Figure 2b. Post-operative target volumes and axial post-operative planning computerized tomography (CT) at same level as pre-operative MRI

High Risk Tumour Volume (HRTVp) (red contour); GTVp modified for post-operative anatomic changes and pathologic findings

Clinical Target Volume_High Risk primary (CTVp_HR) (yellow contour); HRTVp + isotropic 5mm 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 and III, VIII, IX, nodal levels

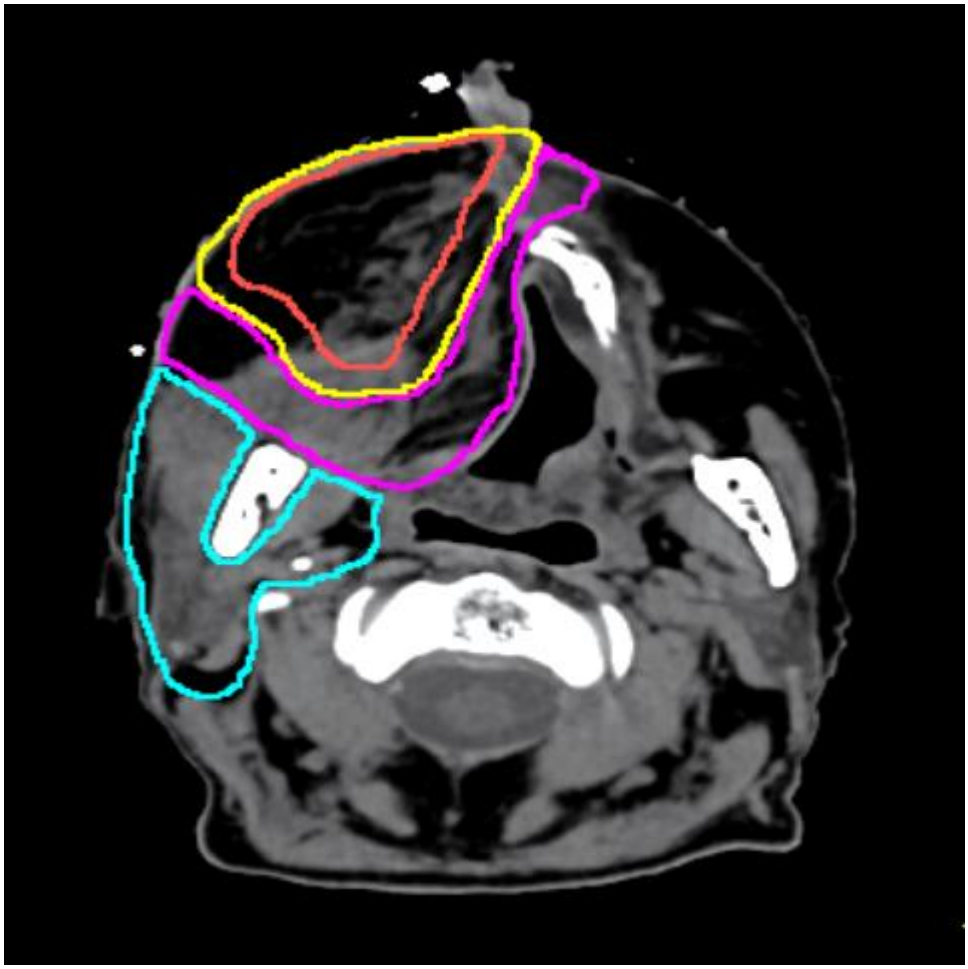

Figure 2c. Post-operative target volumes and sagittal post-operative planning CT

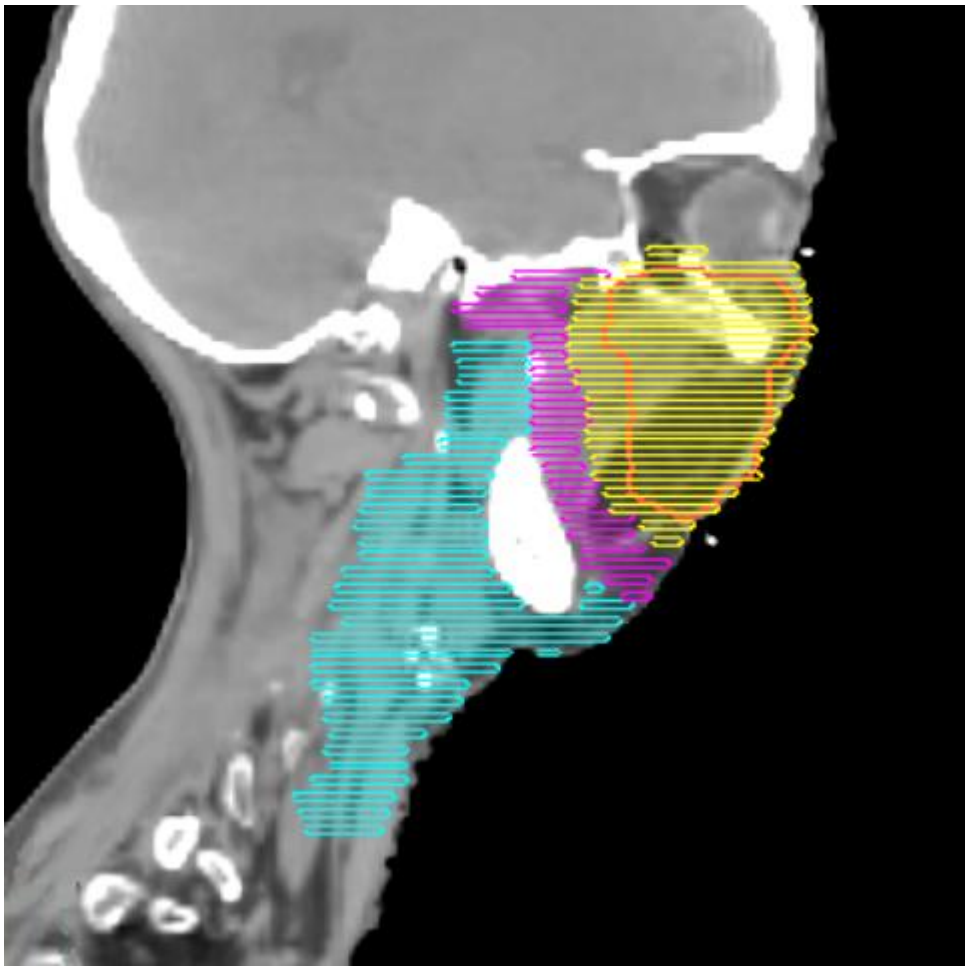

Figure 2d. Right lateral projection showing target volumes

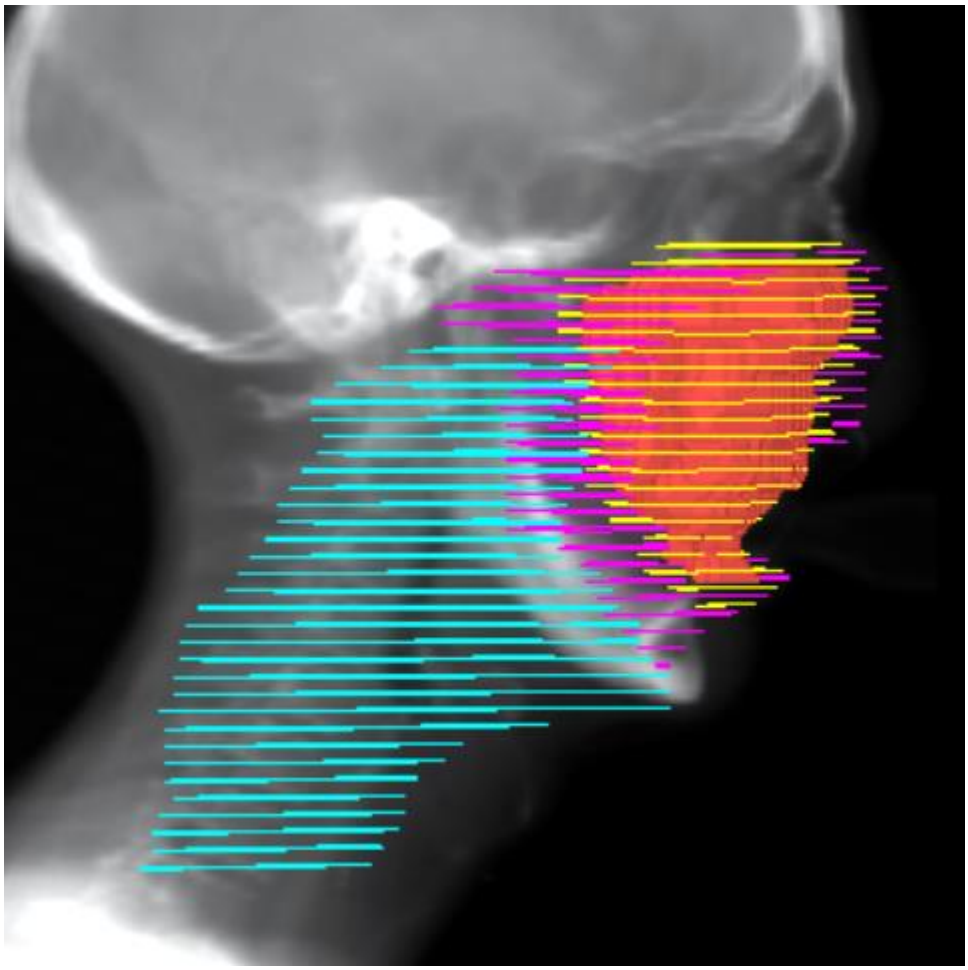

Figure 3. Case 2 - Metastatic squamous cell carcinoma of presumed cutaneous primary to right VIII (intra-parotid) and levels II, III & V lymph nodes with extranodal extension (pathologic TxN3bM0)

Right parotid mass, 35mm (height) x 30mm (width), 15mm 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 SCC involving nodal levels VIII (intra-parotid) with extranodal extension, levels II, III and Va. The intra-parotid tumour was clear (>5mm) of the facial nerve. Clear surgical margins.

Figure 3a. Pre-operative computerised tomography (CT) axial image at the level of parotid gland

Gross Tumour Volume (GTV) nodes (n) (red contour)

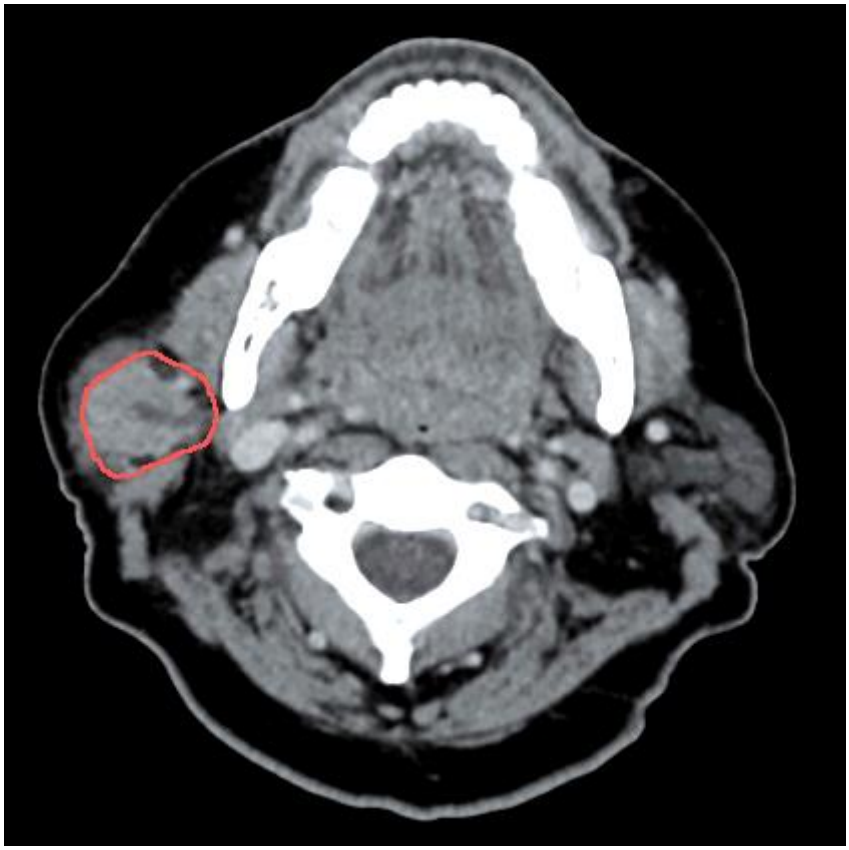

Figure 3b. Pre-operative CT axial image at the level of the cervical level II region

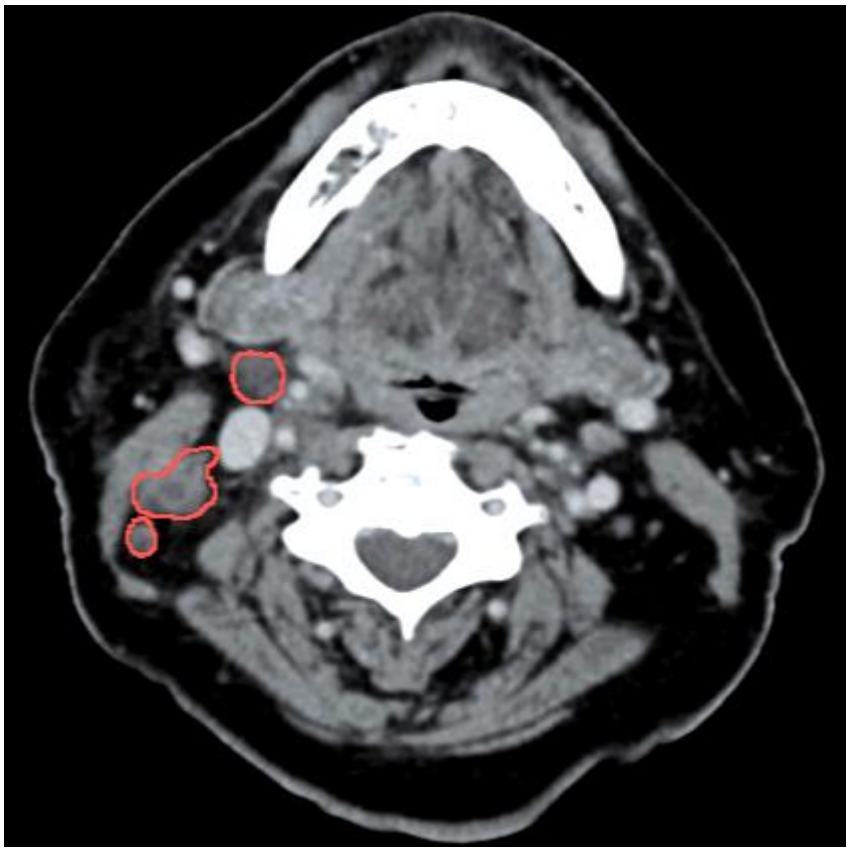

Figure 3c. Pre-operative CT axial image at the level of the cervical level III and Va region

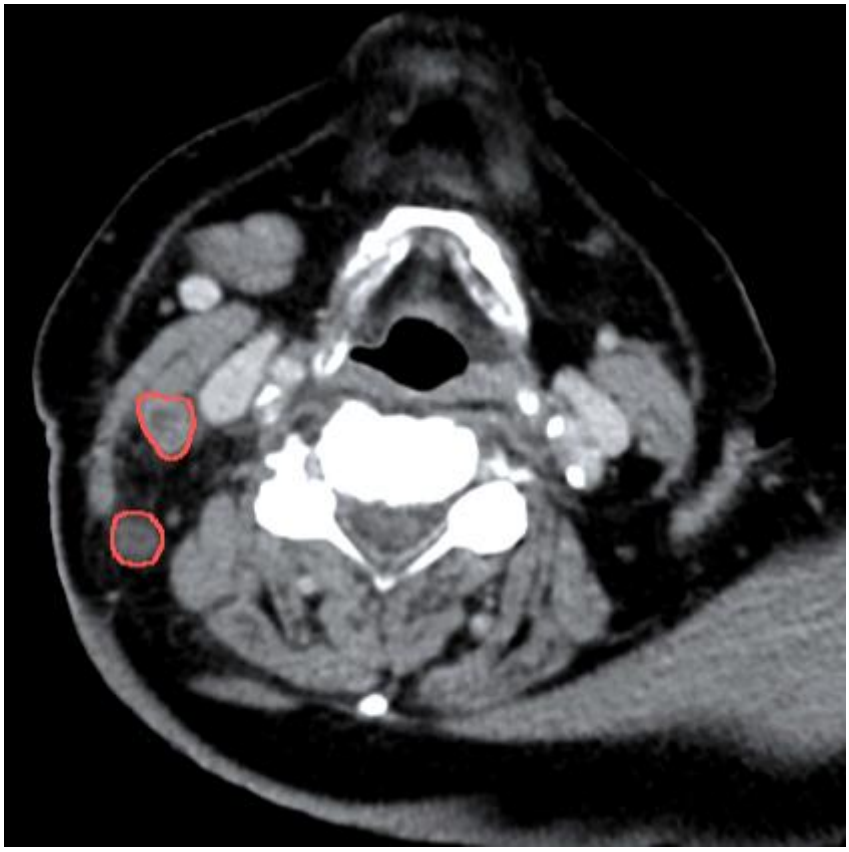

Figure 3d. Post-operative Target Volumes and CT axial image at the level of parotid gland

High Risk Tumour Volume (HRTVn) (red contour); GTVn modified for post-operative anatomic changes and pathologic findings

Clinical Target Volume_High Risk node (CTVn_HR) (yellow contour); HRTVn + isotropic 5mm margin cropped to external surface (green contour) + parotidectomy and neck dissection bed harbouring 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

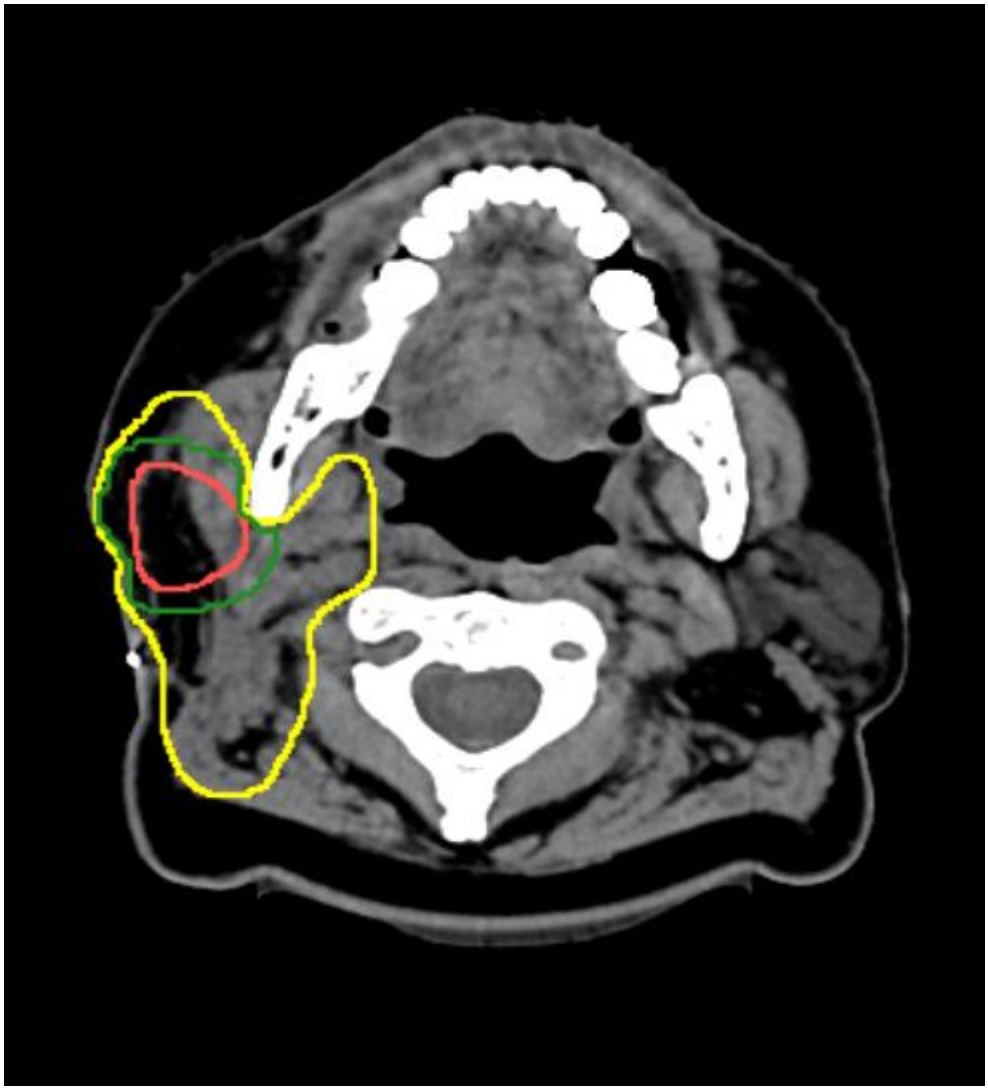

Figure 3e. Post-operative Target Volumes and CT axial image at the level of cervical level II region

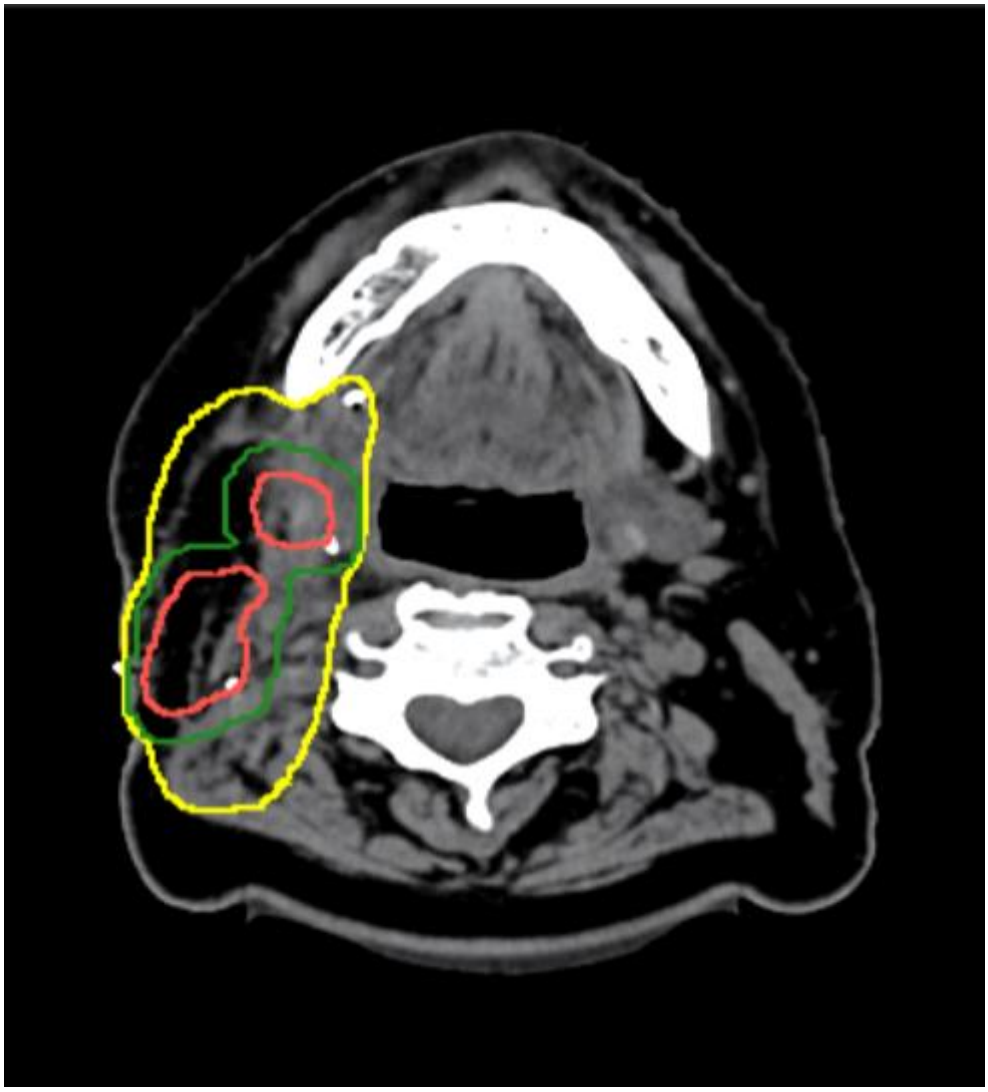

Figure 3f. Post-operative Target Volumes and CT axial image at the level of cervical levels III and V region

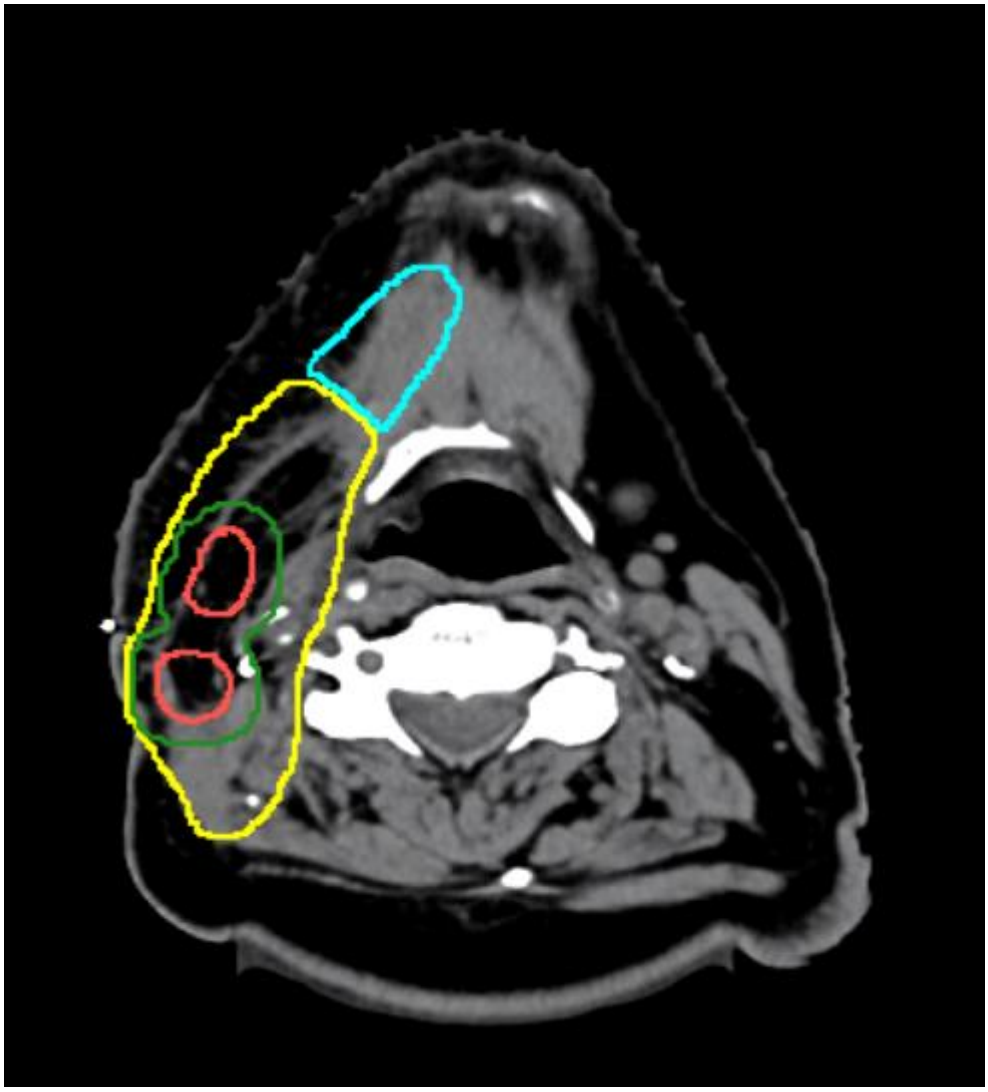

Figure 3g. Lateral projection showing target volumes

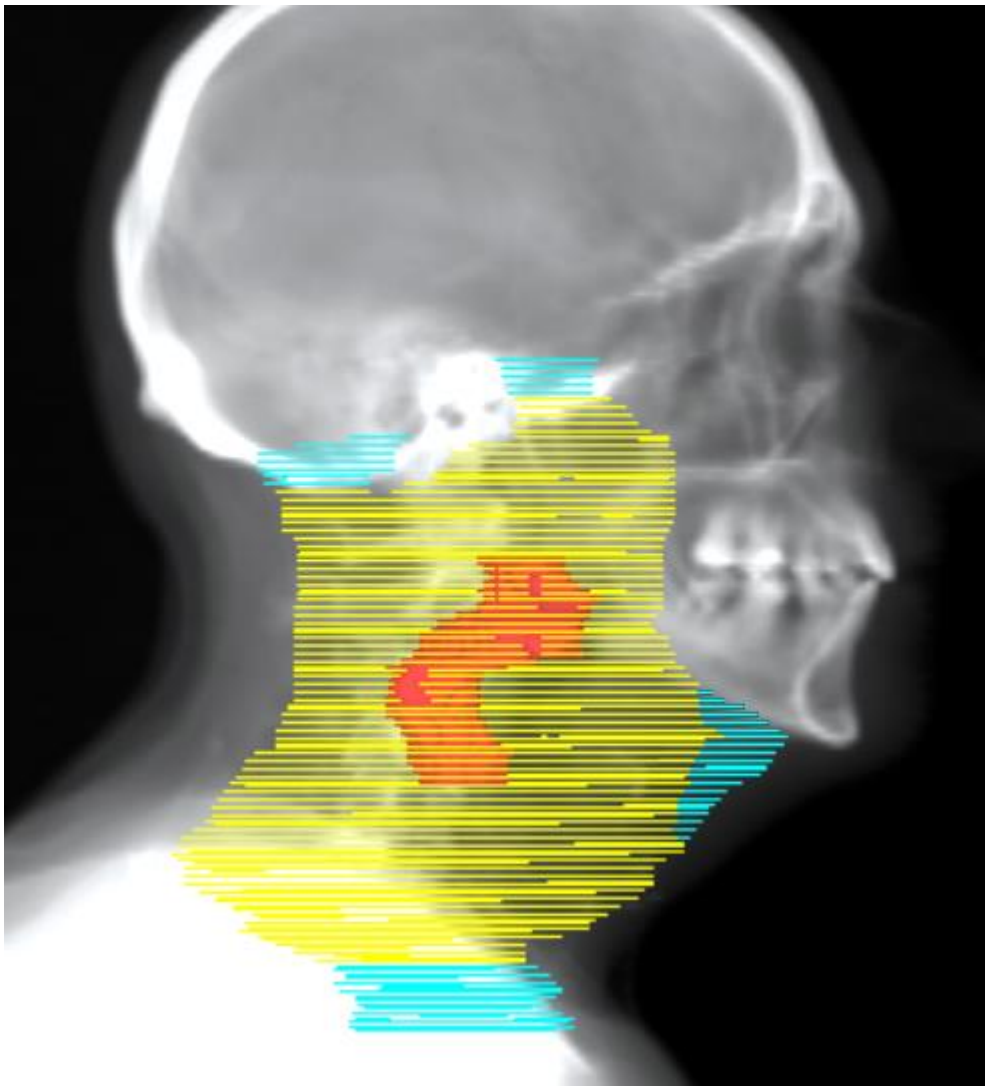

Figure 4. Case 3 – Midline lower lip vermilion border SCC

(clinical T3N0M0, pathologic T3NxM0)

Midline lower lip vermilion border squamous cell carcinoma, 15mm (width) x 10mm (height) with no palpable lymphadenopathy. Wedge excision with Abbe flap reconstruction and no neck dissection. Depth of invasion 7mm, with clear surgical margins. No pre-operative diagnostic imaging of primary lesion.

Figure 4a. Post-operative Target Volumes and axial post-operative planning computerized tomography (CT) at level of superior pole of lip scar

Clinical Target Volume (CTV) primary_High Risk (CTVp_HR) (yellow contour); scar (red contour) + minimum 10mm 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*

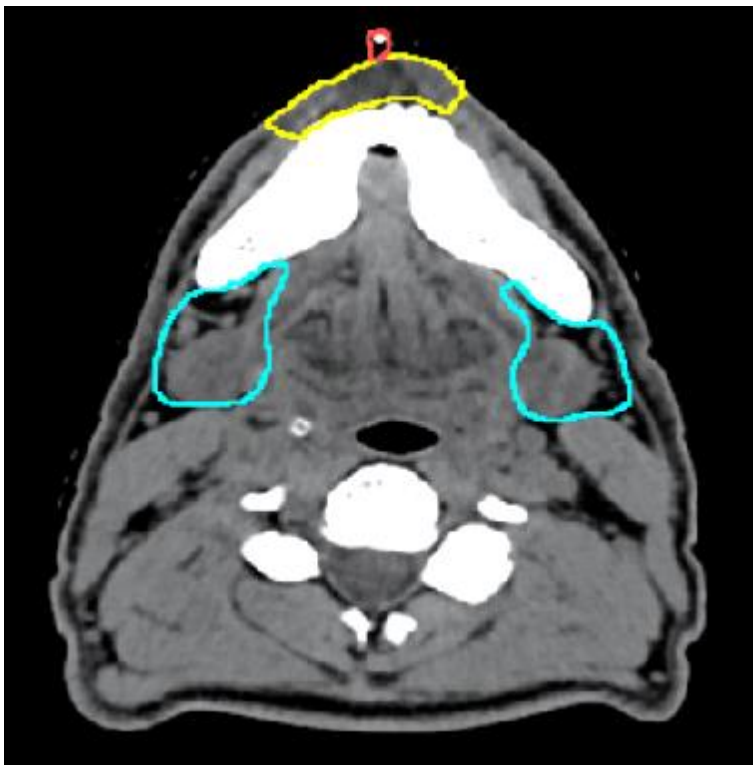

Figure 4b. Post-operative planning axial CT at level of inferior pole of lip scar

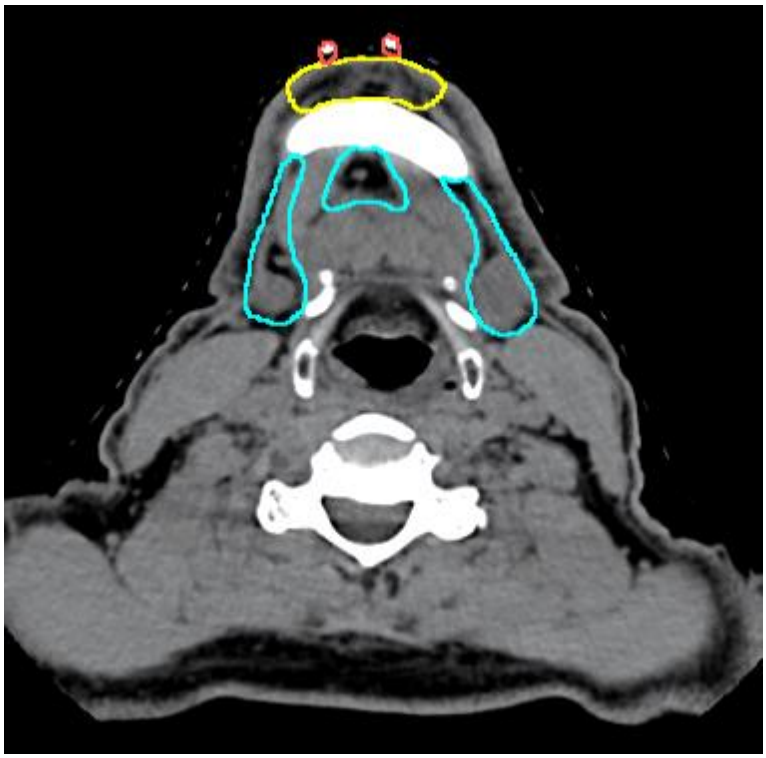

Figure 4c. Lateral projection showing scar wire, target volumes, scar volumes

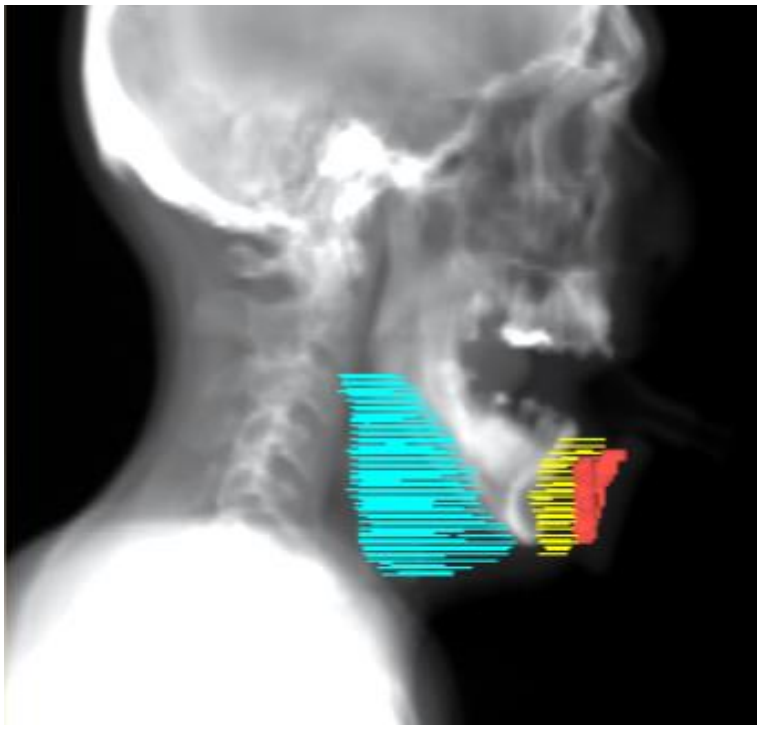

Figure 5. Case 4 - Recurrent right upper hair bearing lip squamous cell carcinoma (recurrent T2N0M0) presenting with large nerve perineural spread of ipsilateral infra-orbital nerve (V2) involving zone 1.

Progressive right upper lip scar V2 paraesthesia for 12 months following resection of right upper lip squamous cell carcinoma (SCC) T2N0M0 with pathologic multifocal (<0.1mm caliber nerves) perineural disease. No prior adjuvant treatment. Magnetic Resonance Imaging (MRI) demonstrated perineural enhancement of right infra-orbital nerve extending 17mm proximally from the lip scar (zone 1).

Resection of infra-orbital nerve from subcutis to foramen rotundum demonstrated perineural SCC extending proximally for 25mm from the cutaneous (distal) end of the specimen. Clear of proximal resection margin (zone 1 disease only). No soft tissue disease.

Figure 5a. Pre-operative axial magnetic resonance imaging (MRI) at most superior level of clinical perineural spread

Gross Tumour Volume (GTV) primary (p) (red contour); Pre-operative MRI of enhancing right infra-orbital nerve (V2)

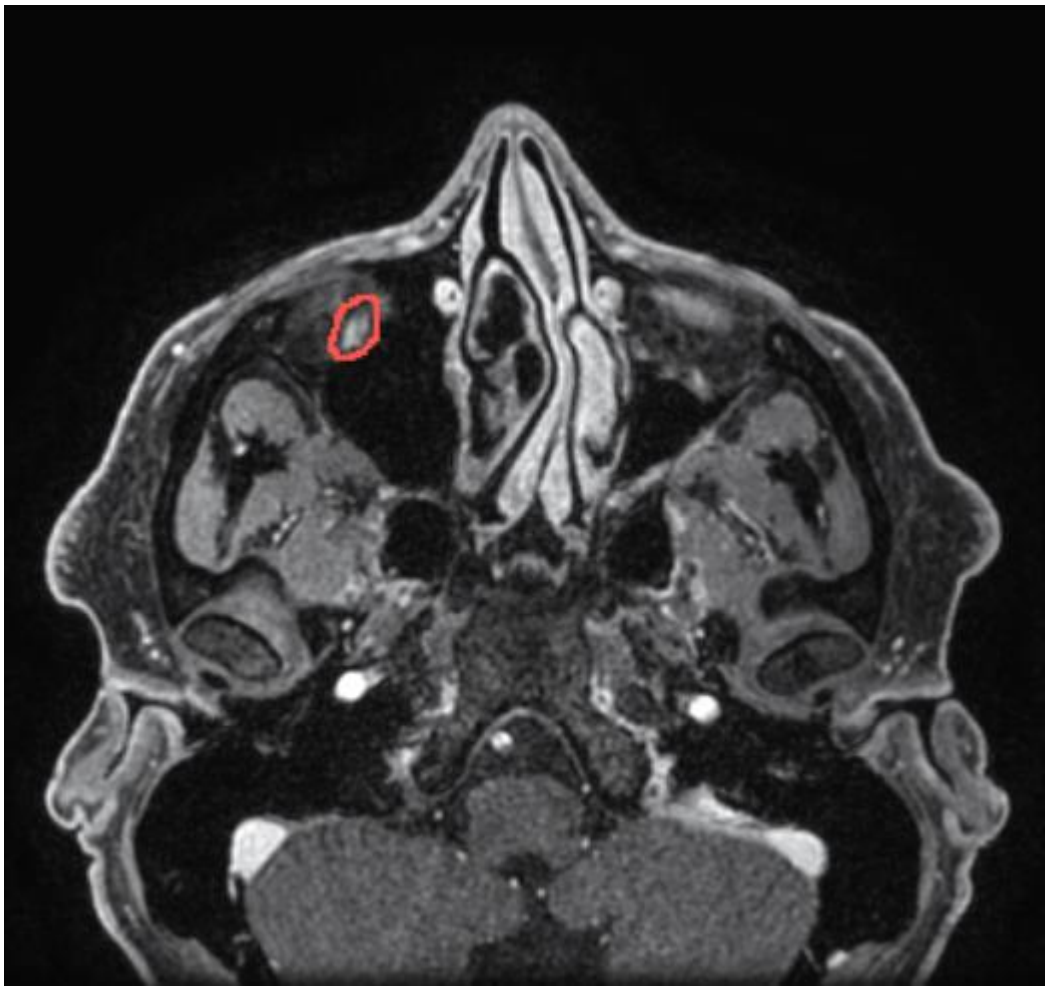

Figure 5b. Post-operative Target Volumes and axial post-operative planning computerized tomography (CT) at same level as pre-operative MRI

High Risk Tumour Volume (HRTV) p (red contour); GTVp modified for post-operative anatomic changes and pathologic findings

Clinical Target Volume primary_High Risk (CTVp_HR) (yellow contour); HRTVp + isotropic 5mm 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)

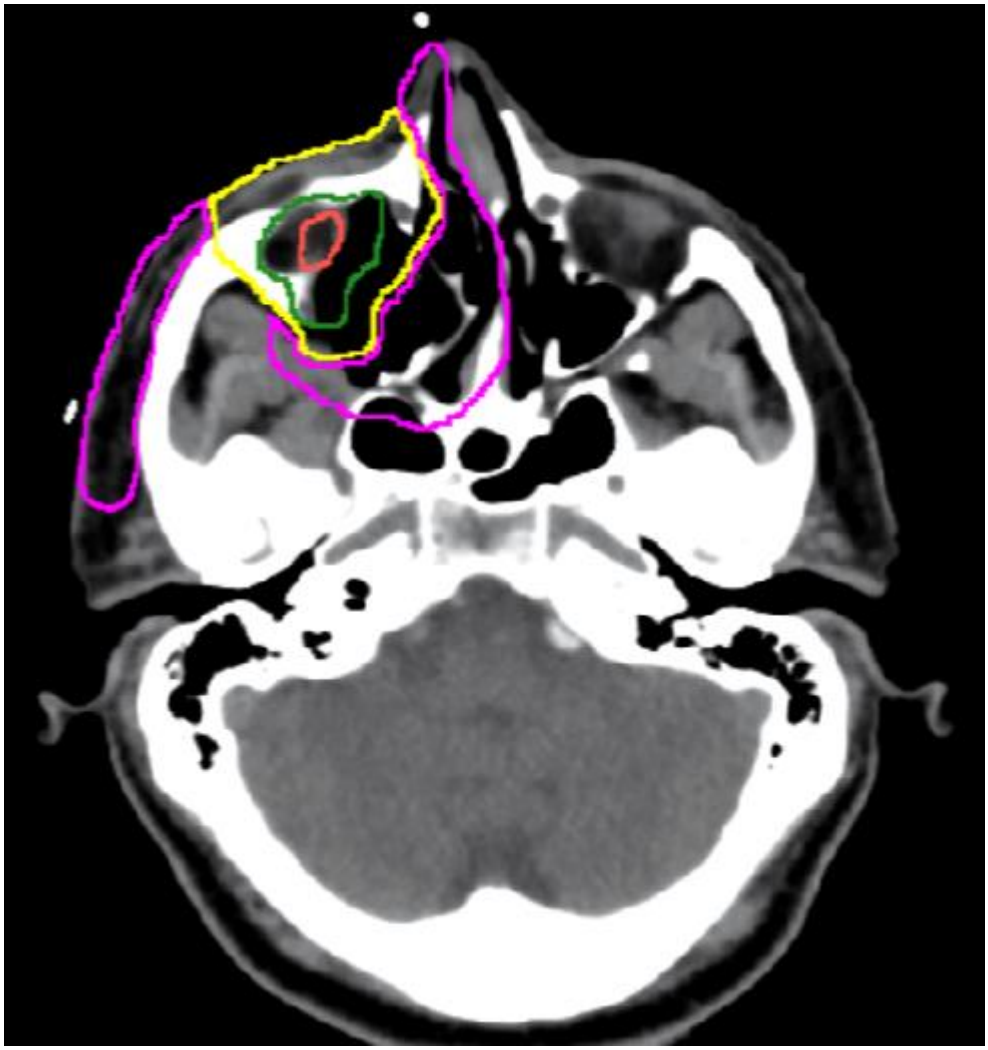

Figure 5c. Pre-operative axial MRI at level of foramen rotundum and trigeminal ganglion

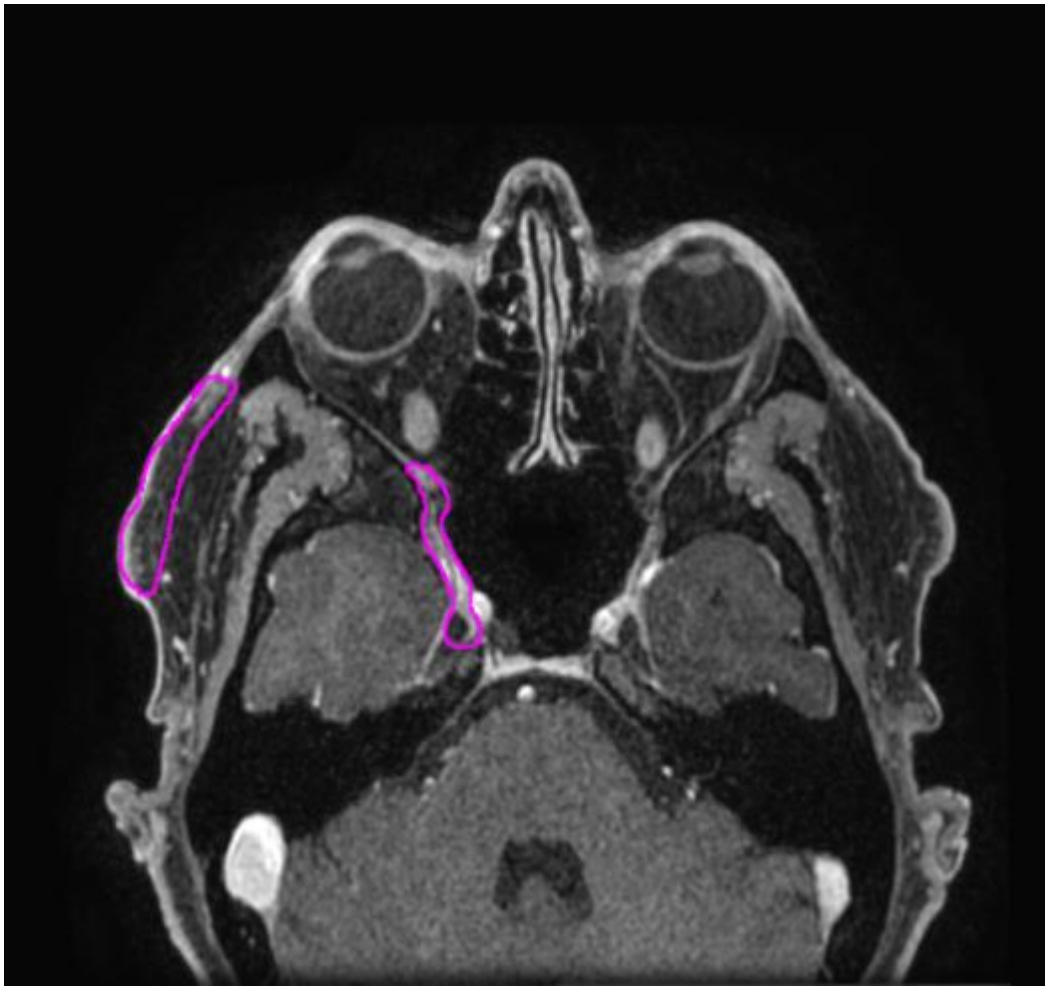

Figure 5d. Lateral projection showing target volumes