PEARL: PET BASED RADIOTHERAPY TRIAL

Radiotherapy Outlining, Planning, Delivery and Quality Assurance Guidelines

V 3.0 24th July 2020

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1 Foreword

This document describes the Radiotherapy (RT) guidelines and Quality Assurance (QA) processes for treatment of patients within the PEARL trial, and should be referred to in conjunction with the main trial protocol.

Further amendments or corrections to these guidelines may be necessary. Updated versions of the guidelines will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact the PEARL Radiotherapy Trials Quality Assurance (RTTQA) group to confirm that they have the most recent version.

Any queries regarding these guidelines should be directed to the PEARL RTTQA contact PEARL.RTTQA@wales.nhs.UK.

2 Introduction

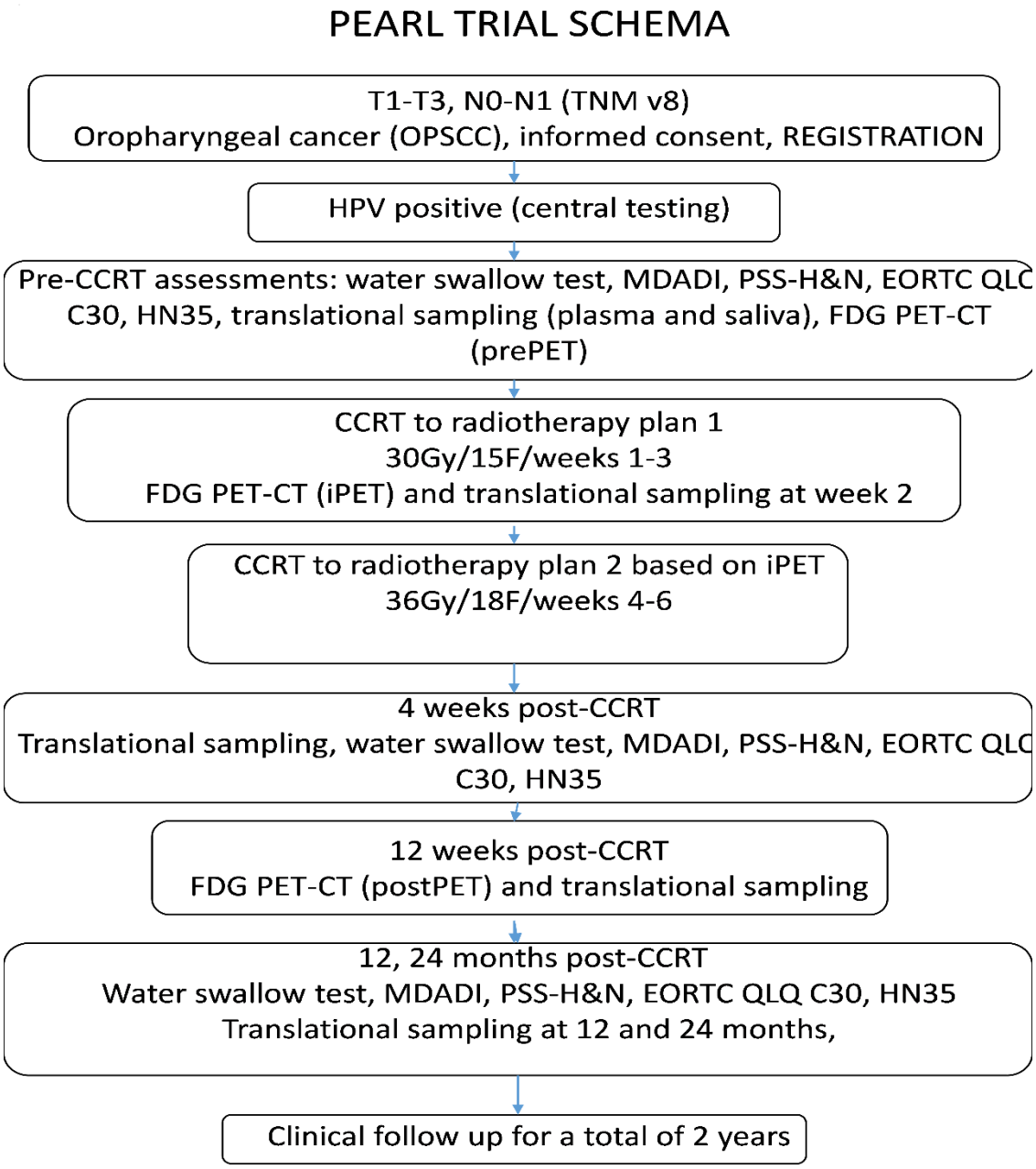
The PEARL trial aims to examine whether adapting the high dose volume midway through radiotherapy treatment based upon response on PET-CT is feasible and reduces dose to swallowing structures while maintaining low local recurrence rates in Human Papillomavirus positive Oropharyngeal Squamous Cell Carcinoma (HPV-positive OPSCC).

This guidance document describes the process for delivering Volumetric Arc Therapy (VMAT)-based treatment for OPSCC in the pre-treatment and intra-treatment setting for patients within the PEARL Trial. Investigators should refer to the main trial protocol which sets out the background to the study and explains the rationale behind some of the recommendations made with regards to target volume definition and dose prescription.

The PEARL study uses a geometric approach to define clinical target volumes.

Neck node levels are outlined according to the 2019 update of the consensus guidelines (1).

3 PEARL Trial Schema



PRIMARY OUTCOME MEASURE

2 year progression free survival

SECONDARY OUTCOME MEASURES

Swallowing panel measurements including qualitative and quantitative swallowing assessments (MDADI, PSS-H&N, water swallow test) and feeding tube dependency rate at 1 year.

Quality of life (EORTC QLQ C30, HN35 and UW-QOL questionnaires)

Acute and late toxicity (NCI CTCAE criteria v4.03)

Complete response rate on PET-CT (postPET)

4 Quality Assurance Team Overview

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RTTQA website: www.rttrialsqa.org.uk

5 Radiotherapy treatment planning

5.1 Radiotherapy Localisation

Patients should be immobilised in a thermoplastic shell with their neck in a neutral position. No mouth bite should be used. The planning PET-CT scans are to be done in the shell, reconstructed at appropriate thickness (2 to 3 mm). Use of intravenous contrast is recommended in order to facilitate accurate delineation. The PET-CT scan should include both shoulders and extend from vertex to liver as a minimum. Follow up PET-CT scan (postPET) will be carried out as per standard protocol.

5.2 PEARL 'dummy run' appointment

Depending upon the treating centre, patients may attend a 'PEARL dummy run' appointment in the radiotherapy CTSIM after the mask is made. The patient does not have a CT scan but has anterior and lateral topograms taken to check alignment on the couch and the fitting of the shell. An anterior alignment PM is given and the sagittal laser position marked down their anterior skin surface to assist in set up on the PET-CT scanner.

5.3 CT data Acquisition

Radiotherapy treatment planning (RTP) must be performed on a 3-dimensional CT dataset with axial slice separation of no more than 3mm, acquired on a PET-CT scanner. The image quality and dimensions of the CT scan should be sufficient for the production of contours specific to head and neck sites. The field of view (FOV) should encompass the entire patient outline through which the treatment beams will pass, including any immobilisation devices. Longitudinal scan limits should include 5cm of tissue beyond the superior and inferior extents of any PTV in order for the TPS to account for scatter from these regions. Where practical, planning CT parameters should be matched to local practice for radiotherapy head and neck planning CT, but care should be taken to ensure the CT dose is within that specified in the research application. The actual parameters used will likely vary between sites and scanner models; advice can be obtained from the lead site (Velindre University NHS Trust).

For all patients in PEARL as part of the PET-CT study, a separate CT for attenuation correction of the PET should be acquired. As the study involves CT contrast the acquisition sequence should be as follows:

1. Low dose CT for attenuation only

2. PET (2-3 bed positions to cover vertex to carina)

3. Planning CT with contrast

All should be done in the RT treatment position.

5.4 PET data acquisition

A 3-dimensional PET scan must be acquired on an integrated PET-CT scanner in order to improve image quality through use of CT attenuation scan. The patient must be in the radiotherapy treatment position (flat-top couch and full immobilisation setup) for both PET and CT scans. In order to get the most accurate alignment between PET and CT data the planning CT scan (used for radiotherapy dose calculation) must be acquired directly after the PET scan using an integrated PET-CT scanner. This minimises the possibility of internal and external anatomy differences between CT and PET and reduces image fusion errors. This planning PET - CT scan will be done after the AC (attenuation correction) CT. As the planning CT dataset will be acquired on the PET-CT scanner external lasers must be fitted in order to reference external patient landmarks to isocentre position at planning. Image quality will be matched between PET-CT systems at different centres. This will be done using standard phantoms. The NEMA image quality phantom will be used to assess the PET data. The recovery curve and accuracy of calibration will be investigated. The CATPHAN phantom will be used to assess the CT data acquisition with regards noise and resolution. Other phantoms may be used.

5.5 Quality Assurance

A quality assurance program must be in place to assess the quality of the CT data (geometry, image quality, electron density, etc.). To this end the CT component of the PET-CT scanner should be subject to the same rigorous testing as a conventional radiotherapy-dedicated CTSIM machine. The daily QC may be performed instead weekly (on account of less throughput of patients) but must be carried out on the day of scanning a patient in RT treatment position and it is also advised to perform the daily QC on the day prior to this as well. Monthly or bi-monthly QC testing should also be performed along with 6-monthly and annual QA. The couch sag and couch levelling on a PET-CT scanner are expected to be worse than CT scanners used routinely for radiotherapy planning scans. These parameters must be measured with and without load and the results compared with those from the centre's routine CT scanner used for planning. The PET to CT alignment must be checked at least annually and after gantry separation. The PET-CT scanner must be accredited by the NCRI PET Core Lab.

5.6 Planning PET-CT process QA

On the day of each scanning session, local treatment centre pre-treatment radiographers must check with the PET-CT operators at the PET-CT centre that the PET-CT scanner is in clinical use. Position the radiotherapy hard couch top with the minimum of two staff. The input of all patient data and scanning parameters is the responsibility of the PET-CT staff. In the scanner room turn on the radiotherapy

lasers and set the couch X,Y and Z to zero. Place the ISIS phantom on the bed at H1 and align with the LAP lasers in all directions. Move the central axis of the phantom to the position of the internal lasers and check indicated position.

5.7 Other planning PET-CT QA

Actual machine checking and calibration are carried out by PET centre staff and PET-CT physicists. If out of tolerance then it is the responsibility of the PET-CT physicists to inform the PEARL trial team at the treating centre, and advise in terms of suitability for clinical use. On a quarterly basis a QA check shall be commissioned by a member of medical physics from the treating centre, and it is the responsibility of medical physics at the treating centre to liaise with PET-CT staff to ensure suitable access to the scanner. The Infusion pumps, maintenance, and any service agreement are the responsibility of the PET-CT centre. The LAP lasers, maintenance, and any service agreement is the responsibility of the PET-CT centre. RAW data of all PET scans (i.e. data before image reconstruction) must be saved and made available with the reconstructed PET scans as part of standard trial data collection.

6 Target Volume Delineation

6.1 Primary Tumour Categorisation

Prior to target volume delineation, the investigator must categorise the primary tumour as lateralised or non-lateralised, based on the site of primary, T-stage and the extent of involvement of midline structures. We recommend that this categorisation is based on clinical examination findings and imaging.

Lateralised Tumour

Tumour confined to the tonsillar fossa/lateral pharyngeal wall extending onto or into the adjacent base of tongue and/or soft palate by <1 cm and with >1cm clearance from midline

Non-lateralised Tumour

Tonsillar/lateral pharyngeal wall tumour that involves the adjacent base of tongue and/or soft palate by ≥1 cm or with ≤1cm clearance from midline

OR

A tumour that arises from a midline structure (base of tongue, soft palate or posterior pharyngeal wall primary tumour)

6.2 Treatment of Neck

The trial protocol requires that all patients with lateralised tumours should undergo unilateral neck RT, regardless of the nodal stage of the ipsilateral neck and all patients with non-lateralised tumours should undergo bilateral neck RT.

6.3 Definition of Treatment Volumes

Diagnostic imaging, clinical findings including pan-endoscopy reports, and pathology information should be used to delineate target volumes. Outlining will be carried out using a geometric approach as per the current international consensus guidelines (1). Co-registration of the diagnostic CT and/or MRI scans with the first planning PET CT scan (prePET) is recommended.

Treatment will be prescribed in 2 phases. Phase 1 includes #1 – 15 (week 1 to 3 of treatment) and will be prescribed prior to the start of treatment. Phase 2 includes #16 – 33 and will be prescribed after the radiotherapy plan has been adapted based on iPET.

Treatment of the nodes will not be adapted based on biological tumour activity seen on iPET. However, the nodal volumes should be transferred across from prePET to iPET and edited for

anatomical change, or may be re-outlined de novo on the CT component of iPET without reference to avidity.

6.4 Primary tumour target volume delineation

6.4.1 First Phase

Primary biological Gross Tumour Volume (bGTV_preP)

Defining the bGTV_preP:

The region of the GTV_P that is avid on baseline PET-CT (bGTV_preP) will be defined by a nuclear medicine radiologist and a clinical oncologist. They should review the PET and CT scans with any relevant clinical information to inform review of the bGTV_preP e.g. to distinguish tumour uptake from physiological uptake or causes for increased FDG uptake such as any infective/inflammatory causes. Both bGTV_preP and bGTV_iP (below) will consist of the high FDG uptake volume based upon suitable windowing levels. Any differences in contouring will be settled either by the two doctors reaching a consensus, or by a third doctor if differneces between the first two cannot be resolved.

Definition of bGTV_preP may also be informed by the automatic delineated volume created by ATLAAS software (bGTV_preP_ATLAAS) if available. All volumes delineated by ATLAAS must be reviewed and if required, modified by the nuclear medical expert and clinical oncologist (see below). It will then be re-named bGTV_preP.

Defining bGTV_preP_ATLAAS

Automated contouring with the Automatic Decision Tree-based Learning Algorithm (ATLAAS) should be used. This will take place using CERR software and will be transferred to Velocity within 24 hours. See the SOP for ATLAAS structure creation and transfer (Appendix A) for more information regarding this.

This will then be reviewed by a clinical oncologist and/or nuclear medicine consultant:

1. Open PET and accompanying planning CT images on Velocity

2. All PET images must be displayed in SUV. The display settings for the PET should be:

a. Zoom: 150-200%

b. SUV scaling: 0 - 10

c. Colour scale: Inverse Linear

3. Review the PET and CT scans with any relevant clinical information to inform review of the bGTV_preP e.g. to distinguish tumour uptake from physiological uptake or causes for increased FDG uptake such as any infective/inflammatory causes.

4. Review the ATLAAS generated bGTV_preP_ATLAAS and check it corresponds to the visible tumour on the PET-CT. It is the FDG uptake on the PET that directs the drawing of the bGTV_preP_ATLAAS, not the CT abnormality. If there is a discrepancy (i.e. the tumour is not well visualised on the CT scan) the volume to be defined as the bGTV_preP_ATLAAS will remain the metabolically active volume.

5. The bGTV_preP_ATLAAS should not include areas of soft tissue/tumour on CT that have low grade FDG uptake or are not FDG avid. The bGTV_preP_ATLAAS may sometimes include areas which do not contain tumour e.g. the airway because of scatter. This will be adjusted by the Clinical Oncologist or nuclear medicine consultant in the radiotherapy treatment planning system where the volume will be edited out of bone (unless involved) and/or air. The zoom tool can also be used to better define the bGTV_preP but it is important to be aware that increasing the zoom too much means that larger regions are likely be outlined, which may overestimate the metabolic volume.

Primary Gross Tumour Volume (GTV_P)

This volume includes the primary tumour. It will be delineated taking into consideration all the information available from the diagnostic CT (and MRI if available) as well as the bGTV_preP generated from the prePET scan, and findings from clinical examination including the panendoscopy report.

Primary Clinical Target Volume 1 (CTV1_P)

This volume includes the primary tumour (GTV_P) with an isotropic margin of 5mm, edited for anatomical barriers e.g. air, fascia and bone. The editing for platysma is permissible. The CTV margin allows for potential microscopic spread around the primary tumour.

Primary Clinical Target Volume 2 (CTV2_P)

This volume includes the primary tumour (GTV_P) with an isotropic margin of 1cm, edited as above.

6.4.2 Second Phase

Phase 2 will commence at #16.

Primary biological Gross Tumour Volume (bGTV_iP)

Defining the bGTV_iP:

The region of the GTV_P that remains avid on PET-CT after 10# of radiotherapy will be created by a nuclear medicine radiologist and a clinical oncologist and named bGTV_iP. Definition of the bGTV_iP may also be informed by the automatic delineated volume created by ATLAAS software (bGTV_iP_ATLAAS) if available. All volumes delineated by ATLAAS must be reviewed and if required, modified by the nuclear medical expert and clinical oncologist (the same procedure as for bGTV_preP_ATLAAS). It will then be re-named bGTV_iP.

NB - If there is a complete metabolic response (CMR) at this time point, ATLAAS will not generate a bGTV_iP_ATLAAS and there will not be a bCTV1_P. If this there is clinical concern about any residual avidity in this scenario, the decision to include a bGTV_iP defined by the nuclear medicine consultant and the clinical oncologist will need to be made at the treating clinician's discretion.

Primary biological Clinical Target Volume (bCTV1_P)

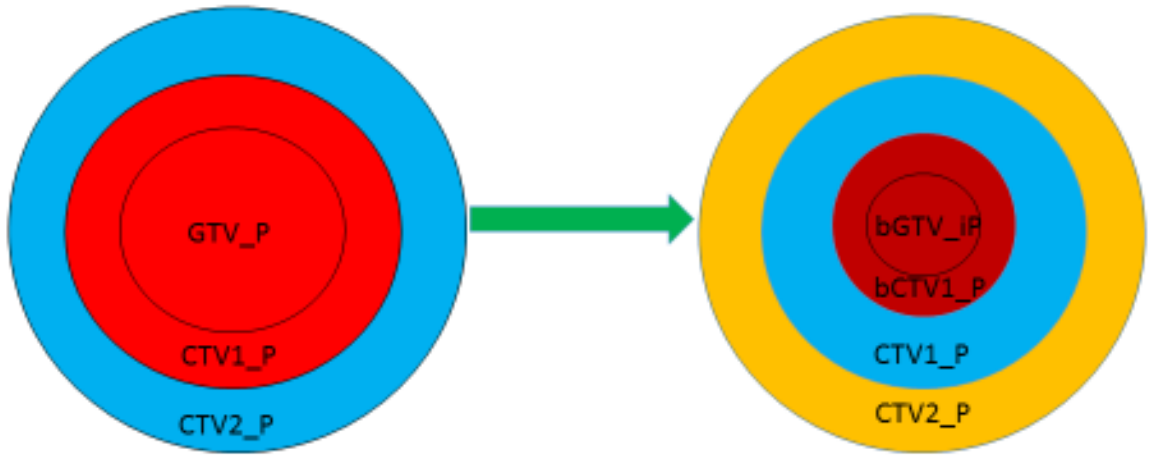
This volume includes the bGTV_iP with an isotropic margin of 5mm edited for anatomical barriers.

Primary Clinical Target Volume 1 (CTV1_P) and Primary Clinical Target Volume 2 (CTV2_P)

This volume includes the primary tumour (GTV_P) transferred from the prePET and rigidly registered with the iPET. It can then be re-grown on iPET with a geometric expansion of 5mm and 10mm to create CTV1_P and CTV2_P respectively, edited for anatomical barriers. The CTV margin allows for potential microscopic spread around the primary tumour.

Fig 1. Comparison of final primary dose levels and volumes in standard treatment (a) and PEARL (b)

a) STANDARD TREATMENT b) PEARL



CTV1_P RECEIVES 66GY
CTV2_P RECEIVES 60GY

bCTV1_P RECEIVES 66GY
CTV1_P RECEIVES 60GY
CTV2_P RECEIVES 54GY

The volume of the GTV_P remaining avid on the iPET will be boosted in phase 2 to receive a final dose of 66Gy. The original CTV1_P receives at least 60Gy (intermediate dose), the original CTV2_P receives at least 54Gy (prophylactic dose).

7 Nodal target volume delineation

In the scenario where there is concern about contralateral pathological nodes on the prePET or iPET, these should be outlined as GTV_N_CONTRALAT or GTV_iN_CONTRALAT respectively and grown with margins as for the ipsilateral GTV_N. Although the presence of contralateral pathological nodes deems the patient ineligible for PEARL, the patient's data will be included in the intention-to-treat analysis of results.

Nodal Gross Tumour Volume (GTV_N)

This volume includes the involved nodes. It will be delineated taking into consideration all the information available from the diagnostic CT (and MRI if available), USS and FNA/core biopsy as well as the prePET scan (bGTV_preP_nodes) and findings from clinical examination.

Nodal Clinical Target Volume (CTV1_N)

This volume includes the GTV_N with a 5mm margin in all directions edited for anatomical barriers as detailed above. The CTV margin allows for potential microscopic spread around the involved nodes.

Nodal Clinical Target Volume (CTV2_N)

This volume includes the GTV_N with a 10mm margin in all directions edited for anatomical barriers.

Prophylactic Nodal Clinical Target Volume (CTV3_N)

This volume includes the rest of the involved nodal level(s) and all at risk non-pathological nodal levels appropriate for prophylactic irradiation as defined by the updated consensus guidelines and atlas (1). The contours for CTV3_N should include the entire level regardless of any overlap with CTV1_N or CTV2_N.

NB The nodal volumes can either be transfered from the phase 1 scan (prePET) to the phase 2 scan (iPET) and edited, or they can be re-contoured on the CT component of the iPET de novo. CTV1_N and CTV2_N may become smaller. The definitions and nomenclature of all the nodal target volumes will remain the same.

	Nodal status	CTV3_N
Lateralised tumour	Node negative	Ipsilateral (1b)[2], II, III, IVa[3] + VIIa*
	Node positive	Uninvolved ipsilateral 1b, II, III, IVa, Va+b Ipsilateral VIIa at the level of the oropharynx Ipsilateral VIIb (when II involved) Ipsilateral IVb+Vc (when IVa or V is involved)
Non-lateralised tumour	Node negative	Ipsilateral II, III, IVa, IIVa 1b[2] Contralateral II, III, IVa, VIIa
	Node positive	Uninvolved ipsilateral Ib, II, III, IVa, Va+b Ipsilateral IIVa at the level of the oropharynx Ipsilateral VIIb (when II involved) Ipsilateral IVb +Vc (when IV or V is involved) Contralateral II, III, IVa

		Contralateral VIIa at the level of the oropharynx

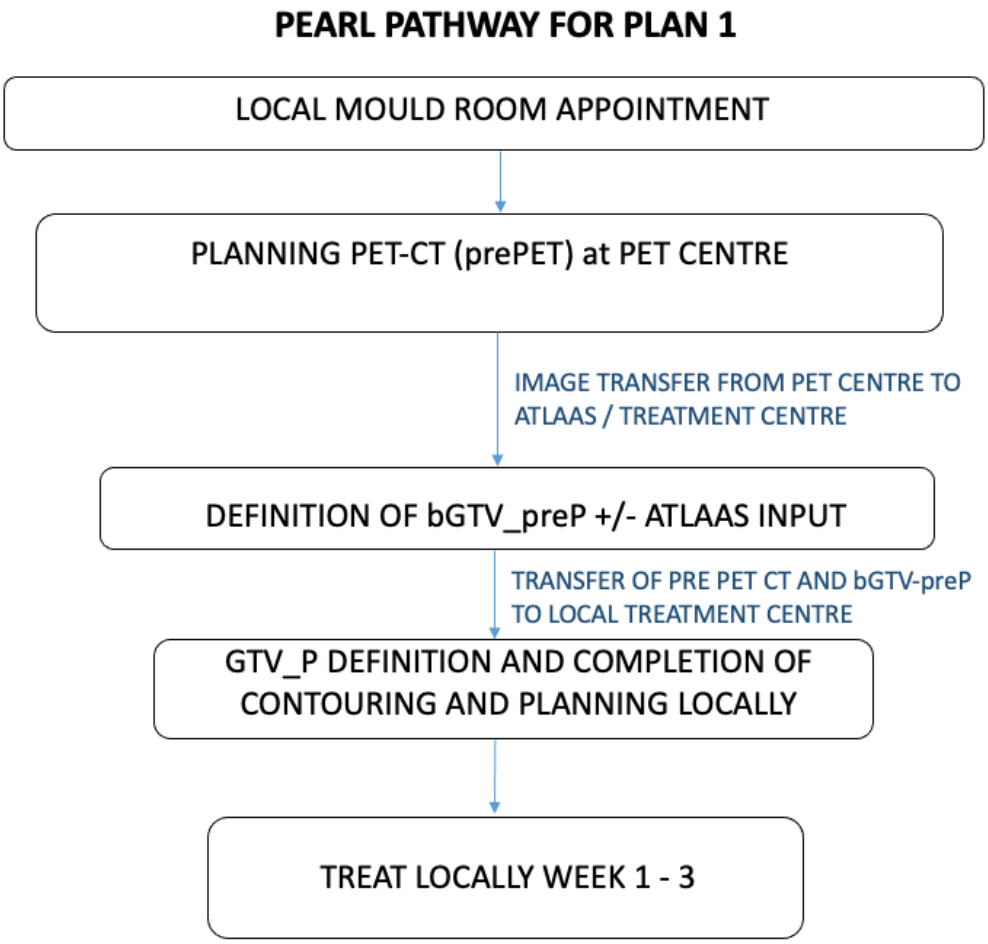
1 Unilateral treatment is recommended for N0 – N1 tonsillar fossa tumour not infiltrating the soft palate nor the base of tongue.

2 Any tumour with extension to the oral cavity and/or the anterior pillar of tonsil and/or in the case of anterior involvement of level II.

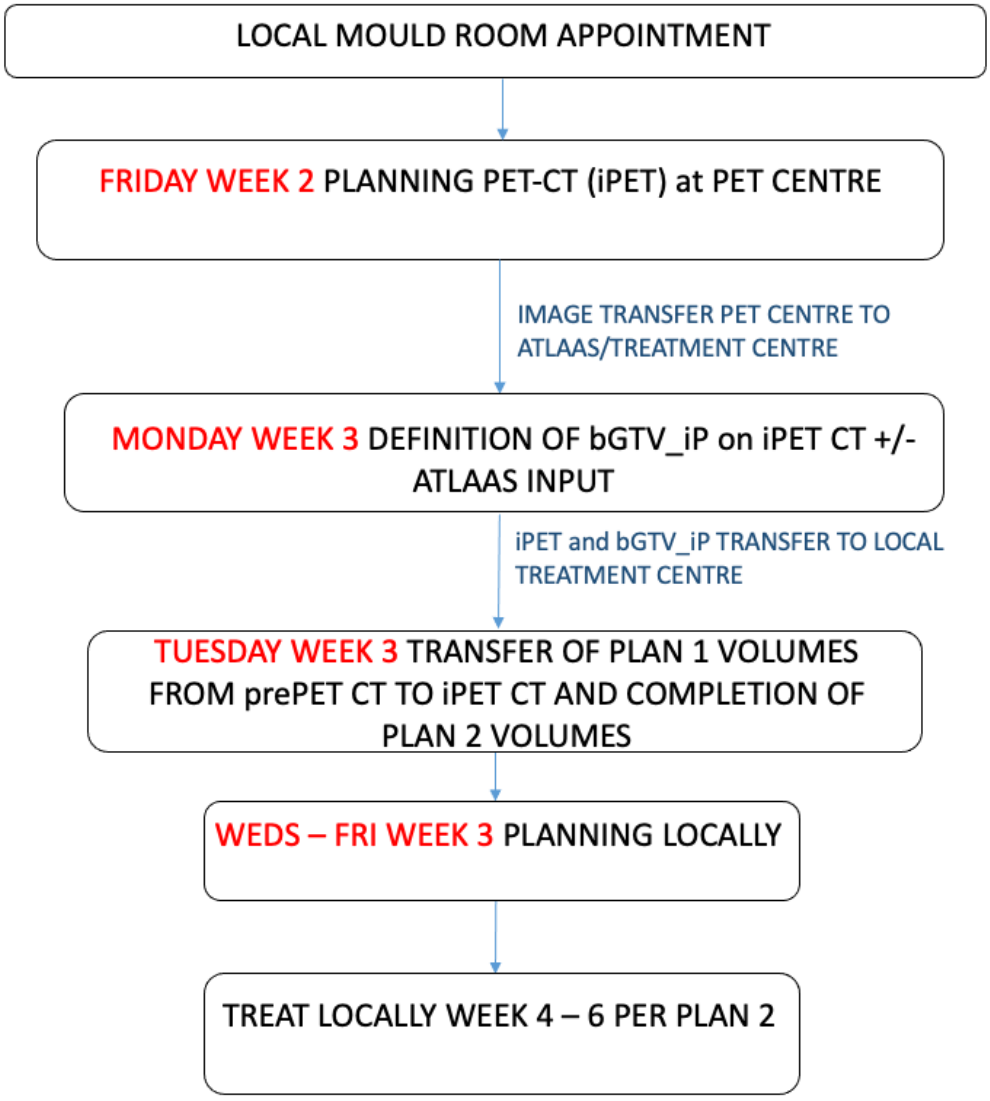
3 Level IVb should be included in case of involvement of level IVa

*In PEARL, we recommend that the cranial border of the retropharyngeal nodal level (level VIIa) is defined as the upper edge of the body of C1 or the upper extent of the hard palate, whichever is more cranial.

Planning pathways



PEARL PATHWAY FOR PLAN 2



8 Example case

8.1 Pre-outlining requirements

The required preparation for PEARL oropharyngeal plans will standardly include:

- A contrast-enhanced planning PET-CT

- Access to diagnostic information:

Diagnostic CT

Diagnostic MRI

USS neck

Panendoscopy

NB For the benchmark case you will be provided with an outline of the GTV_P and GTV_N, and only basic clinical and radiological information. We acknowledge that in practice, more information will be at your disposal to assist with GTV and CTV definition.

8.2 Example Case Information

Clinical information: 52 year old man presenting with a 2 month history of soreness and a feeling of fullness in the back of the throat

Diagnostic CT: Soft tissue in the right tongue base measuring 3.8cm in maximal axial dimension. Extends inferiorly into the right side of the vallecular, crosses the midline in the region of the lingual tonsils which are involved. Superiorly it appears to involve the right palatine tonsil and right lateral pharyngeal wall which are bulky. Does not appear to involve the extrinsic tongue muscles but does appear to invade the tongue base. The mass abuts the right submandibular gland although a faint fat plane is visible. No extension into the parapharyngeal fat, no involvement of the pterygoid muscles. Two right level II nodes.

Diagnostic PET-CT: An area of avidity, maximum SUV 11.9, in the tongue predominantly on the right side but extends across the midline into the left tongue base and right vallecular. Tumour measures 4.1cm in longest axis. Two adjacent FDG avid right level II lymph nodes.

Interim PET-CT: Since baseline there has been a reduction in size and metabolic activity within the primary tumour in the right base of tongue. This now measures 2.9cm in the longest axis and has a maximum SUV of 9.1.

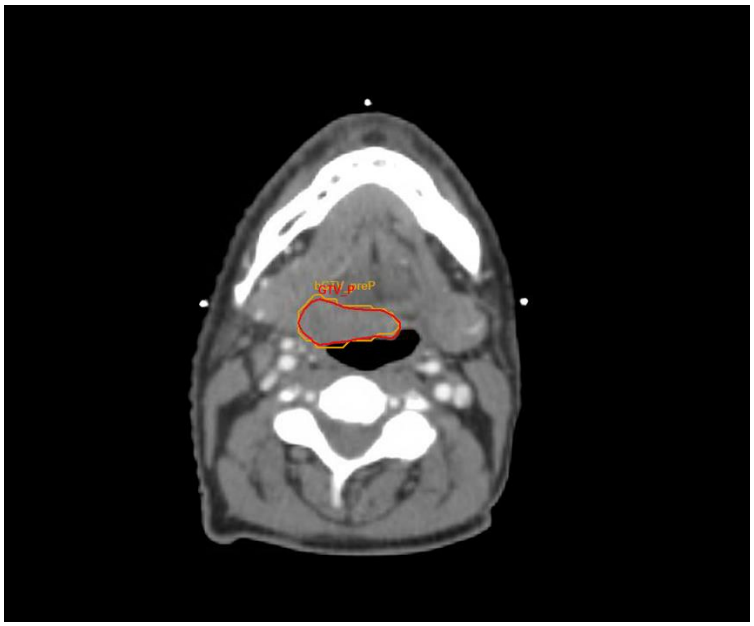
8.3 Primary tumour target volume delineation

Colour code: Red = GTV Green = High dose Pink = Intermediate dose Blue = prophylactic dose

FIRST PHASE

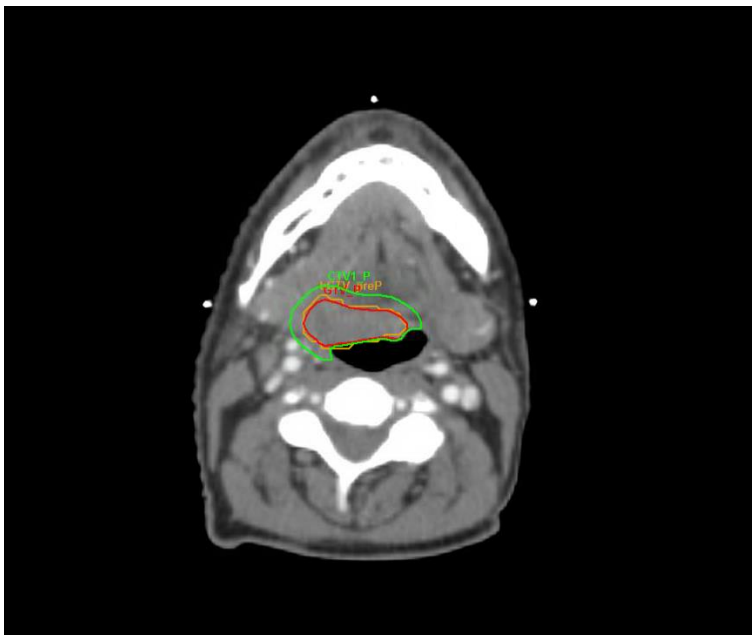
Step 1 Definition of Primary Gross Tumour Volume (GTV_P) (red)

This volume includes the primary tumour. Delineation should take into consideration all the information available from the clinical examination, panendoscopy, diagnostic CT and MRI, as well as the avid volume on the prePET scan (bGTV_preP in orange) as defined by a nuclear medical expert and a clinical oncologist. In some cases, the bGTV_preP will also be informed by the volume automatically defined by ATLAAS software (bGTV_preP_ATLAAS).



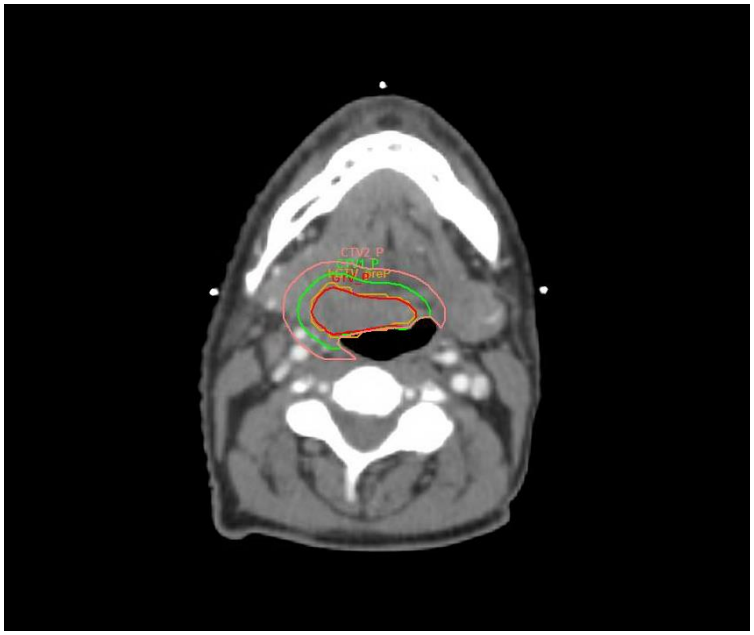
Step 2 Definition of CTV1_P (Green)

This volume includes the primary tumour (GTV_preP) with a margin of 5mm, edited for anatomical barriers.



Step 3 Definition of CTV2_P (Pink)

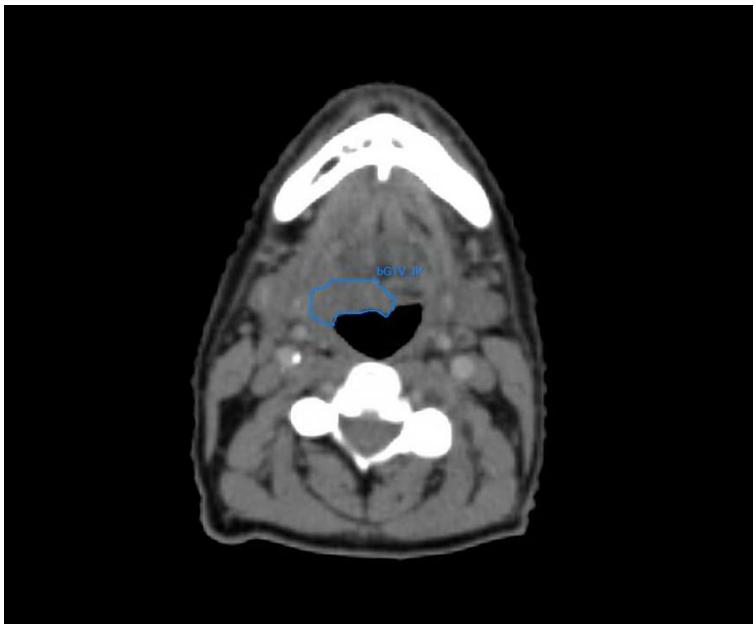
This volume includes the primary tumour (GTV_P) with a margin of 10mm, edited for anatomical barriers.



SECOND PHASE

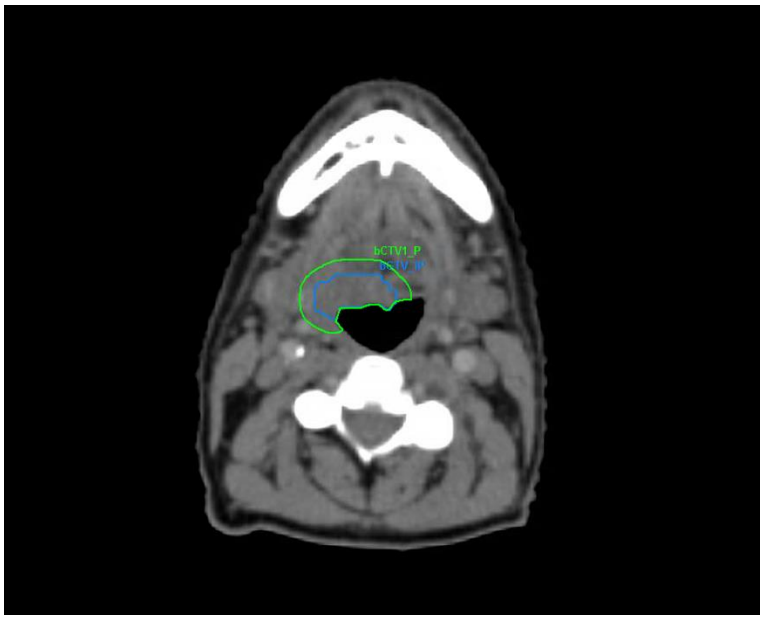
Step 1 Definition of primary biological Gross Tumour Volume (bGTV_iP)

The region of the GTV_P that remains avid on PET-CT after 10 fractions of radiotherapy will be defined by a consultant clinical oncologist, and a consultant of nuclear medicine, to create the bGTV_iP (dark blue). bGTV_iP incorporates the avid and macroscopic primary tumour disease. In some cases, it may be informed by the contour defined by ATLAAS (bGTV_iP_ATLAAS).



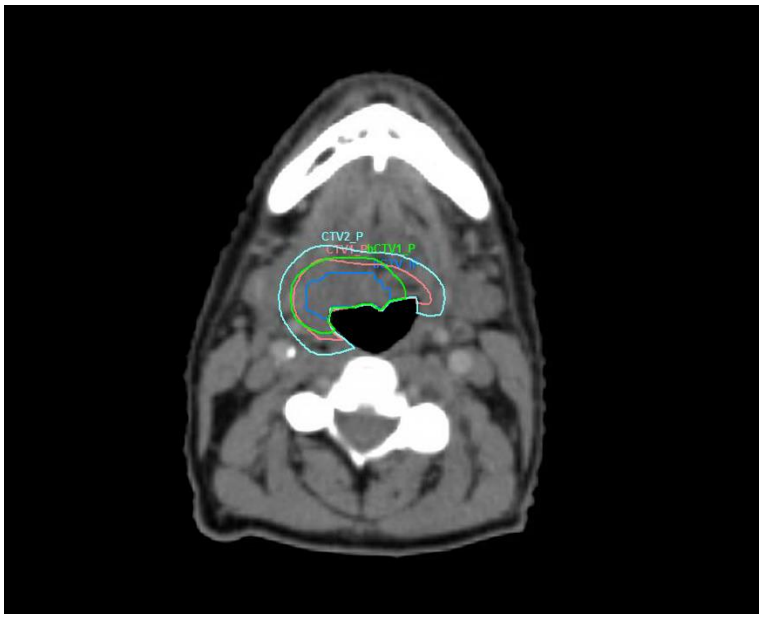
Step 2 Definition of primary biological Clinical Target Volume (bCTV1_P) (Green)

This volume includes the bGTV_iP with a margin of 5mm edited for anatomical barriers.



Step 3 Phase 1 volumes brought over to become phase 2 volumes

The GTV_P is transferred from the pre_PET onto the iPET using rigid fusion. It is re-grown to CTV1_P and CTV1_P and edited as before. However, CTV1_P is now treated to an intermediate dose and CTV2_P to a prophylactic dose so the colours will change accordingly. bCTV1_P will be treated to the high dose.



8.4 Nodal Target Delineation

Colour code: Red = GTV Green = High dose Pink = Intermediate dose Blue = prophylactic dose

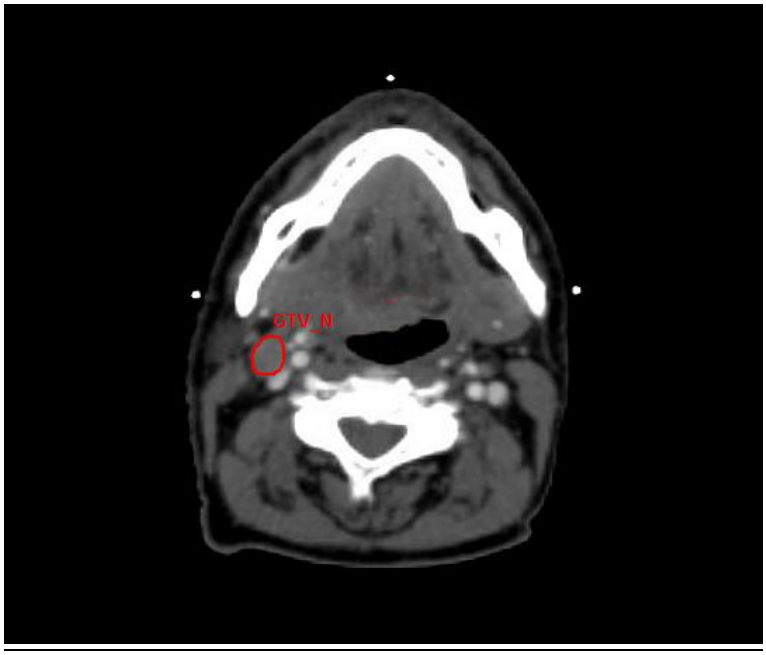
The nodal volumes are outlined on the phase 1 scan. They can then either be transferred to the phase 2 scan and edited as necessary, or re-outlined de novo on the phase 2 scan.

NB The nodal volumes will only be edited to match the CT component of the phase 2 scan and not be adapted based upon any biological response on the PET.

FIRST PHASE

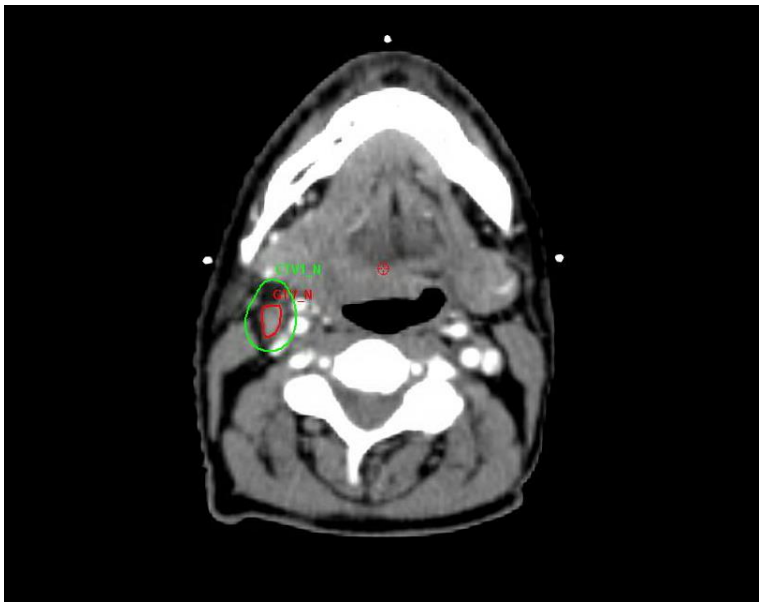
Step 1 Definition of Nodal Gross tumour Volume (GTV_N) (red)

This volume includes the pathological lymph nodes and delineation should take into account all the information available from the diagnostic CT and MRI as well as the avid volume on the prePET scan (bGTV_preP_nodes), and findings from clinical examination.



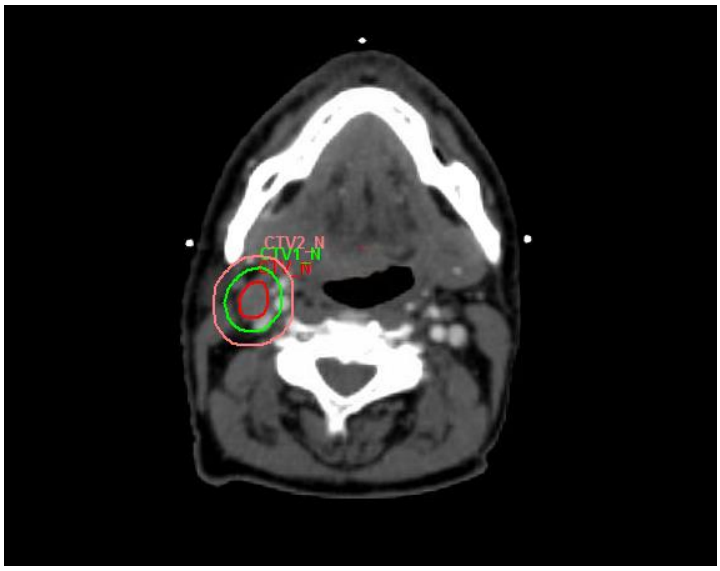
Step 2 Definition of CTV1_N (Green)

This volume includes the pathological nodes (GTV_N) with a margin of 5mm, edited for anatomical barriers.



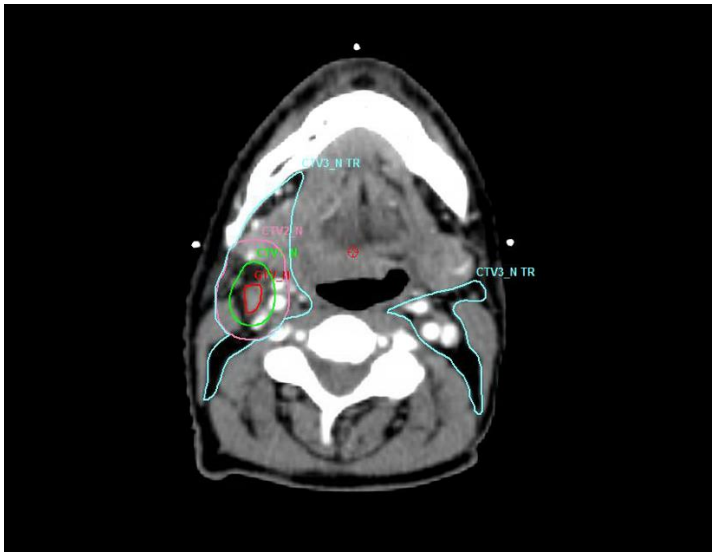
Step 3 Definition of CTV2_N (Pink)

This volume includes the pathological nodes (GTV_N) with a margin of 10mm, edited for anatomical barriers.



Step 4 Definition of CTV3_N (Light blue)

This volume includes all the prophylactic nodal levels to be included as per the PEARL trial requirements and should be outlined to include the entire level regardless of whether this overlaps with CTV1_N or CTV2_N.



8.5 Conversion of Clinical Target Volume (CTV) To Planning Target Volume (PTV)

A margin will be added to each CTV in all directions, to produce the corresponding Planning Target Volumes (PTV), in line with IRCU50, 62 and 83. The PTV margin allows for day-to-day variations in patient anatomy and positioning. The magnitude of this margin (typically 2 – 5mm) should reflect the geometric accuracy of the immobilisation system used by the treating centre. Radiotherapy dose is prescribed to the PTV and minimum standards for PTV coverage are given in the Dose prescription and Fractionation section.

9 Organs at Risk (OARs) outlining

OARs will be outlined on prePET CT and can be transferred by deformable fusion methods onto iPET CT for phase 2 planning. They can then be modified on iPET CT by the consultant clinical oncologist as appropriate. Alternatively, the OARS for phase 2 can be outlined de novo on the iPET CT if this is felt to be a more accurate method of maintaining consistency between the 2 phases.

The following normal tissue structures should be delineated:

9.1 Spinal cord

Outline the spinal cord (not the spinal canal) from the lower border of foramen magnum to 2.5 cm inferior to PTV. Isotropic expansion of 3-5mm (depending on local practice and immobilisation) to create the PRV. Please contact the RTTQA team if your centre wishes to create a PRV volume outside of 3-5mm.

9.2 Brainstem

Outline the entire brainstem up to the lower border of foramen magnum. Isotropic expansion of 3-5mm (depending on local practice and immobilisation) to create the PRV. Please contact RTTQA team if your centre wishes to create a PRV volume outside of 3-5mm.

9.3 Parotid glands (contralateral and ipsilateral)

Both superficial and deep lobes should be included. When blood vessels (external carotid artery and retromandibular vein) are encased by the gland, these should be included. If there is an accessory lobe to the parotid, this should be included in the volume. Outline the visible parotid glands with reference to the diagnostic MRI if available.

9.4 Submandibular glands (contralateral and ipsilateral)

Outline the visible submandibular glands with reference to the diagnostic MRI if available.

9.5 Swallowing-Related Structures

The following swallowing related structures (SWOARS) will also be outlined for every patient according to published guidelines and the PATHOS atlas for contouring swallowing related structures. These structures include the pharyngeal constrictor muscles (superior PCM, middle PCM and inferior PCM), supraglottic/glottic larynx, cricopharyngeus, oesophageal inlet, cervical oesophagus and oral cavity. The superior and middle pharyngeal constrictor muscles will often be in the treated volume but the other SWOARs can all be used for treatment plan optimisation.

Comprehensive guidelines for outlining the swallowing-related structures in PEARL are included in Appendix B based on those published by Christianen et al (2) and Schwartz et al (3).

The dose constraints for OARs and PRV are given below. No constraint is given for the ipsilateral parotid gland as it often overlaps or abuts the PTV; this should be kept as low as possible but not at the expense of PTV coverage.

NB All doses to OARs must be within tolerance for both phases, as though each phase iss being planned for the entire 33 fractions.

Structure	Volume Constraint	Optimal Dose Constraint
Spinal cord	Max	<48Gy*
	$1cm^3$	<46Gy*
Spinal cord PRV	$1cm^3$	<48Gy*
Brain stem	Max	<55Gy*
	$1cm^3$	<54Gy*
Brain stem PRV	$1cm^3$	<55Gy*
Contralateral Parotid (Lateralised Tumour)	Mean	<14Gy
Contralateral Parotid (Non-lateralised Tumour)	Mean	<24Gy
Ipsilateral Parotid	Mean	ALARP
Contralateral Submandibular Gland	Mean	<35Gy
Supraglottic Larynx	Mean	<55Gy

Glottic Larynx	Mean	<45Gy
Superior Pharyngeal Constrictor Muscles	Mean	<50Gy
Middle Pharyngeal Constrictor Muscles	Mean	<50Gy
Inferior Pharyngeal Constrictor Muscles	Mean	<20Gy
Cricopharyngeus/oesophageal inlet	Mean	<20Gy
Cervical oesophagus	Mean	<20Gy
Oral Cavity (low priority for optimisation)	Mean	<30Gy

*Mandatory dose constraint

10 Dose prescription and Fractionation

10.1 Primary tumour radiotherapy dose and fractionation

PHASE 1	DOSE (Gy)	FRACTIONATION
PTV1_P	27.3	15
PTV2_P	24.5	15

PHASE 2	DOSE (Gy)	FRACTIONATION
bPTV1_P	38.7	18 (Total 66Gy/33F)
PTV1_P	32.7	18 (Total 60Gy/33F)
PTV2_P	29.5	18 (Total 54Gy/33F)

10.2 Nodal radiotherapy dose and fractionation

PHASE 1	DOSE (Gy)	FRACTIONATION
PTV1_N	27.3	15
PTV2_N	27.3	15
PTV3_N	24.5	15

PHASE 2	DOSE (Gy)	FRACTIONATION
PTV1_N	38.7	18
PTV2_N	32.7	18
PTV3_N	29.5	18

The dose is prescribed to the median of the respective volumes (ICRU 83). Centres unable to prescribe to the median dose due to their planning system capabilities should ensure that the median dose lies within 1Gy (aim for within 0.5Gy) of the prescription dose. The median dose should be reported on the plan assessment form. D50 must be within 1Gy of the prescription value for PlanPTV5400 (aim for within 0.5Gy). Centres with any issues regarding the median dose prescription should contact the QA group. The minimum and maximum doses to the PTV should be within 95 –107% of the prescription dose. Less than 2% of the volume outside the PTV should receive >107% of the prescription dose. In those areas where the PTV and PRVs overlap, under-dosage of the PTV will be permitted in order to fulfil the constraints for the OARs. Plan assessment will follow ICRU 83 guidance and report doses to the PTVs and CTVs.

Dose volume constraints for volumes of interest

	DOSE (%)					
VOLUME (%)	bPTV1_P	PTV1_P	PTV2_P	PTV1_N	PTV2_N	PTV3_N
99	>90	>90	>90	>90	>90	>90
98	Unspecified but must be reported	Unspecified but must be reported	Unspecified but must be reported	Unspecified but must be reported	Unspecified but must be reported	Unspecified but must be reported
95	>95	>95	>95	>95	>95	>95
50	= 100	= 100	= 100	= 100	= 100 +/- 1Gy	= 100 +/- 1Gy
5	<105	<105	<105	<105	As low as possible	As low as possible
2	<107	<107	<107	<107	As low as possible	As low as possible

11 Planning guidelines and treatment delivery

The trial protocol mandates that all patients within the PEARL study will undergo swallowing and saliva-sparing RT, delivered using Volumetric Arc Therapy (VMAT) (RapidArc), which the UK DARS clinical trial team demonstrated reduced RT dose to the pharyngeal constrictors more effectively than IMRT. Each participating trial centre must detail their method of treatment planning and delivery in their radiotherapy process document. The Velindre planning process is detailed in Appendix C as an example.

11.1 Treatment verification

The PEARL protocol mandates daily imaging with online cone beam CT for the majority of fractions (a minimum of 30) for on treatment verification.

11.2 Field arrangement

A partial-arc VMAT technique is recommended.

11.3 TPS Dose modelling

Dose distributions should be calculated and corrected for inhomogeneities and undeliverable beams. Normalisation should be to the median/mean dose of the PlanbPTV1, PlanPTV1, PlanPTV2 or PlanPTV3 (ICRU 83). Normalisation to the uncropped PTV may be accepted on a case by case basis.

11.4 Plan evaluation

A Dose Volume Histogram (DVH) should be produced to show as a minimum: For all treatment arms: bPTV1, PlanbPTV1, PTV1, PlanPTV1, PTV2, PlanPTV2, PTV3, PlanPTV3, spinal cord, spinal cord PRV, brainstem, brainstem PRV, contralateral parotid gland and ipsilateral parotid gland. Dose reporting should also include the CTVs.

If volumes are to be edited away from the skin surface for purposes of planning and maintaining skin sparing, then this should be noted on the plan assessment form. Both edited and unedited volumes should be recorded in the relevant columns of the plan assessment form. The treatment plan along with the plan assessment form (PAF), preferably filled in electronically, need to be submitted. Plans should be inspected on each and every slice to ensure conformal coverage of the PTVs resulting in sufficient target coverage as well as normal tissue and OAR sparing. There should be no avoidable low and high dose regions inside the PTVs, as well as no high dose regions in normal tissue.

Planning aims should be prioritised in the following order:

Meeting critical organ constraints (spinal cord and brainstem)

bPTV1 (phase 2 only)

PTV1

PTV2

PTV3

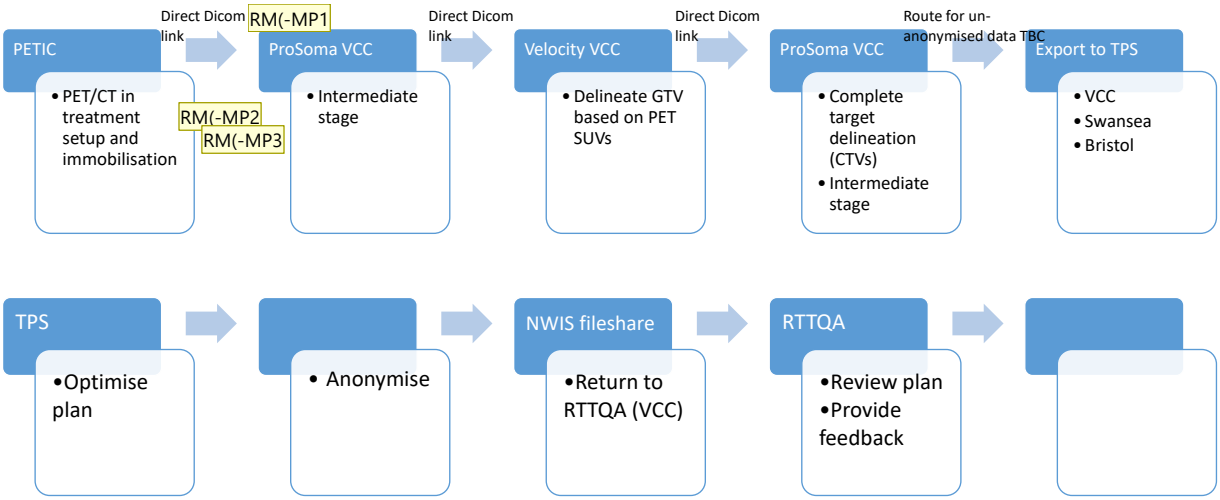
Non-critical organ constraints (e.g. parotids)

Other non-specified normal tissue

Please note, meeting specified DVH criteria alone may not be sufficient to ensure that an optimal plan has been produced. A plan may still need to be resubmitted if it is not compliant with the above as well as ICRU reports 50, 62 and 83.

If a centre feels unable to meet the trial requirements, please contact the RTTQA team for further guidance.

11.5 Treatment Plan Patient-Specific QA



Once the treatment plans have been accepted by the QA team, the accepted plans must undergo patient specific QA, and the QA data sent to the QA team. This should be obtained by following the standard local procedure for VMAT per-patient QA for PEARL trial patients.

No extra forms are included for this data as all centres will have created their own documentation.

This is required for completion of the planning benchmark cases. It is recommended that this is carried out once the plans have been accepted to avoid the centre carrying out QA unnecessarily.

11.6 Monitor Unit checking

Monitor units should be checked by measurement for a minimum of one dose point in an appropriate homogeneous region of the high dose volume for each plan. Independent calculation programs may be used in place of measurements, provided the centre has a previous high level of experience in measurement QA and has a system in place for verifying errors found by the independent calculation.

11.7 Treatment verification

Centres should follow their local protocols for on-treatment verification. This should be detailed in the process document.

The use of volumetric imaging (CBCT or MVCT) matched to planning PET-CT scans is strongly recommended within the PEARL study.

Daily imaging is recommended for an acceptable minimum of 30 fractions.

11.8 Radiotherapy Delays

Patients in the PEARL trial are managed as category 1 patients. Radiotherapy must be completed on time as planned: 6 weeks (42 days) to receive 66Gy in 33 fractions as per the Royal College of Radiologists best practice guidelines.

Planned interruptions (machine servicing, bank holidays) should be managed by delivering fractions on other days of the week and unplanned interruptions should be managed as per the Royal College of Radiologists guidelines.

12 Radiotherapy quality assurance

12.1 Pre-Trial Requirements

Prior to opening the trial at a participating centre a programme of pre-trial RT trials QA must be completed. Details of these requirements are outlined below.

12.2 VMAT Credentialing

Centres must have achieved VMAT credentialling from the RTTQA group in order to enter patients into the PEARL trial. An overview of the complete credentialing programme, along with the associated data and documentation, is given on the RTTQA website (www.rttrialsqa.org.uk). The VMAT credentialing programme consists of the following steps:

12.3 Pre-Accrual Target Delineation Benchmark Case

The aim of the outlining benchmark cases is to ensure consistency of outlining across study centres. The outlining benchmark cases must be done or reviewed by the Principal Investigator before submission.

All participating centres are required to outline both phase 1 and phase 2 of the benchmark case as below:

- ZPEARLDelineationPh1Z-1
- ZPEARLDelineationPh2Z-1

Clinicians will be provided with clinical information on the benchmark cases to assist them in establishing whether or not the tumour is lateralised and what nodal levels should be included in CTV3_N. In all cases primary and nodal GTV delineation will be completed by the RTTQA centre using all clinical and radiological information available and the automated delineation on PET-CT scan using ATLAAS software followed by manual checking. Investigators at each centre should follow the guidance in section 9 and section 10 of the RT guidance document for target volume delineation and organ at risk outlining respectively. The GTVs should not be edited, but used as provided to create the CTVs as per the guidance in section 9.

The following OARs should be outlined:

1. Ipsilateral parotid
2. Contralateral parotid
3. Submandibular glands
4. Spinal Cord
5. Brainstem
6. Superior Pharyngeal Constrictor Muscle
7. Middle Pharyngeal Constrictor Muscle
8. Inferior Pharyngeal Constrictor Muscle
9. Cricopharyngeus
10. Oesophageal Inlet
11. Cervical Oesophagus
12. Supraglottic Larynx
13. Glottic Larynx
14. Oral Cavity

The structures should be labelled according to the nomenclature below:

bGTV_preP_ATLAAS	ATLAAS defined biological primary GTV in phase 1
bGTV_preP	Clinician defined biological (avid) primary GTV in phase 1.
GTV_P	Gross primary tumour volume
CTV1_P	CTV to receive a dose of 60Gy
CTV2_P	CTV to receive a dose of 54Gy
bGTV_iP_ATLAAS	ATLAAS defined biological primary GTV in phase 2
bGTV_iP	Clinician defined biological primary GTV in phase 2
bCTV1_P	CTV to receive a dose of 66Gy
bGTV_preP_nodes	Clinician defined biological nodal GTV in phase 1

GTV_N	Gross nodal tumour volume
CTV1_N	CTV to receive a dose of 66Gy
CTV2_N	CTV to receive a dose of 60Gy
CTV3_N	CTV to receive a dose of 54Gy
SpinalCord	Spinal cord
BrainStem	Brainstem
Parotid_IL	Ipsilateral Parotid
Parotid_CL	Contralateral Parotid
SMG_IL	Ipsilateral Submandibular Gland
SMG_CL	Contralateral Submandibular Gland
PCM_Superior	Superior Pharyngeal Constrictor Muscle
PCM_Middle	Middle Pharyngeal Constrictor Muscle
PCM_Inferior	Inferior Pharyngeal Constrictor Muscle
Cricopharyn	Cricopharyngeus Muscle
Oeso_Inlet	Oesophageal Inlet
Cervical_Oeso	Cervical Oesophagus
Larynx_SG	Supraglottic Larynx
Larynx_G	Glottic Larynx
Oral_Cavity	Oral Cavity

Benchmarking of participating centre target (CTV) delineation will be achieved through test case delineation and either submission to the RTTQA centre for review, or through discussion at the RTTQA workshop.

The local PI at participating centres will be required to complete the target delineation benchmark case and should be involved in completion of all on-trial cases by non-credentialled clinicians in their centres.

12.3.1 PEARL Target Delineation Benchmark Case

T2N2M0 Squamous cell carcinoma right base of tongue

Clinical Information

62 year old man presents with a fullness in the back of his throat and a right neck lump. No other symptoms. No co-morbidities.

Panendoscopy: Right posterior tongue base mass. Biopsy confirmed squamous cell carcinoma. P16 strongly positive. Extends inferiorly into the right side of the vallecular and crosses the midline at the lingual tonsils which are involved.

CT: Soft tissue mass in the region of the right tongue base measuring 3.8 cm in maximum axial dimension. This extends inferiorly into the right side of the vallecula, crosses the midline in the region of the lingual tonsils which are involved. Superiorly it appears to involve the right palatine tonsil and right lateral oropharyngeal wall which are bulky. Within the limits of the CT this this does not appear to involve the extrinsic tongue muscles but does appear to invade the tongue base. The mass abuts the right submandibular gland although a faint fat plane is visible. No definite extension into the para pharyngeal fat with no involvement of the pterygoid muscles. No involvement of the hyoid bone or lingual surface of the epiglottis. Conclusion: Tumour centred in the region of the right base of tongue as described above with likely involvement of the tongue base, lingual tonsils and possibly the right palatine tonsil with extension across the midline. Radiologic stage of T2 N2b M0.

PET-CT: Base of tongue is FDG avid with a maximum SUV of 11.9. This is predominantly right sided but extends across the midline into the left base of tongue and inferiorly to involve the right vallecula. The tumour measures 4.1 cm in longest axis. No overt invasion into surrounding structures. There are two adjacent FDG avid right level II nodes, the largest measures 16 mm in short axis and has a maximum SUV of 9.5. No contra-lateral cervical or distant nodal disease demonstrated. The remainder of FDG uptake is unremarkable. No other significant abnormality demonstrated. Conclusion: FDG avid right base of tongue tumour with ipsilateral nodal disease (T3 N2b M0).

12.4 Pre-accrual Planning Benchmark Cases

Participating centres will be required to submit two planning benchmark cases – one for each phase of treatment. A plan is to be optimised on a pre-outlined case (targets and OARs) provided by the RTTQA group. Centres should grow the PTVs and PRVs using their own margins as determined by their local immobilisation and set up techniques. This will be returned to the RTTQA group to assess adherence to protocol, suitability of the planning technique and plan quality.

A plan assessment form must be completed and submitted to assess agreement of dose/volume recording between participating centre and RTTQA group.

12.4.1 PEARL Planning Benchmark Case

T2N2M0 Squamous cell carcinoma right base of tongue

Clinical Information

57 year old man presents with right neck lump. No other symptoms or co-morbidities.

Panendoscopy: Subtle abnormality in the right tongue base. Biopsies confirm moderately differentiated squamous cell carcinoma.

MRI: Multiple enlarged right level 2/3 nodes which are cystic with peripheral rim enhancement. These measure up to 14mm in short axis. No further significantly enlarged jugular chain nodes identified. Irregularity of the mucosa region of the right lingula tonsil and right sided vallecula which shows some asymmetric increased enhancement. No apparent involvement of the structures deep to the mucosa or the tongue base. There is also slight asymmetry of the soft tissues in the right lateral oropharynx although there is no increased enhancement in this region. No further abnormality identified within the tongue base, pharynx or larynx. Normal appearances of the major salivary glands. Conclusion: The features are highly suspicious for neoplastic infiltration of the right level 2/3 nodes. Abnormalities within the region of the right lingual tonsil, vallecula and oropharynx as described above should be directly visualised as potential sites of a primary lesion

PET-CT: The known primary tumour within the right side of the base of the tongue is marked FDG avid with a maximum SUV of 14.8. This measures 2.6 cm in long axis and there is no invasion into surrounding structures. There is ipsilateral, necrotic right cervical lymphadenopathy at level II/III with the largest node measuring 16 mm in short axis. The maximum SUV of the nodes on the right side is 5.7. There are shotty nodes in the left neck at level II/III, none of which are enlarged by size criteria, however one of the nodes at level II demonstrates abnormal FDG uptake with an SUV of 3.2 (8 mm short axis) and this is suspicious of nodal infiltration. The remainder of FDG uptake is unremarkable, in particular there is no evidence of distant disease. Conclusion: FDG avid primary tumour within the right base of tongue with bulky right and probable small volume left cervical nodal disease (T2 N2 M0).

12.5 Trial Specific Facilities Questionnaire

Participating centres will be required to complete a facilities questionnaire during credentialing for a new trial. This will be sent directly from the RTTQA contact.

12.6 Verification of Electronic Transfer of Data

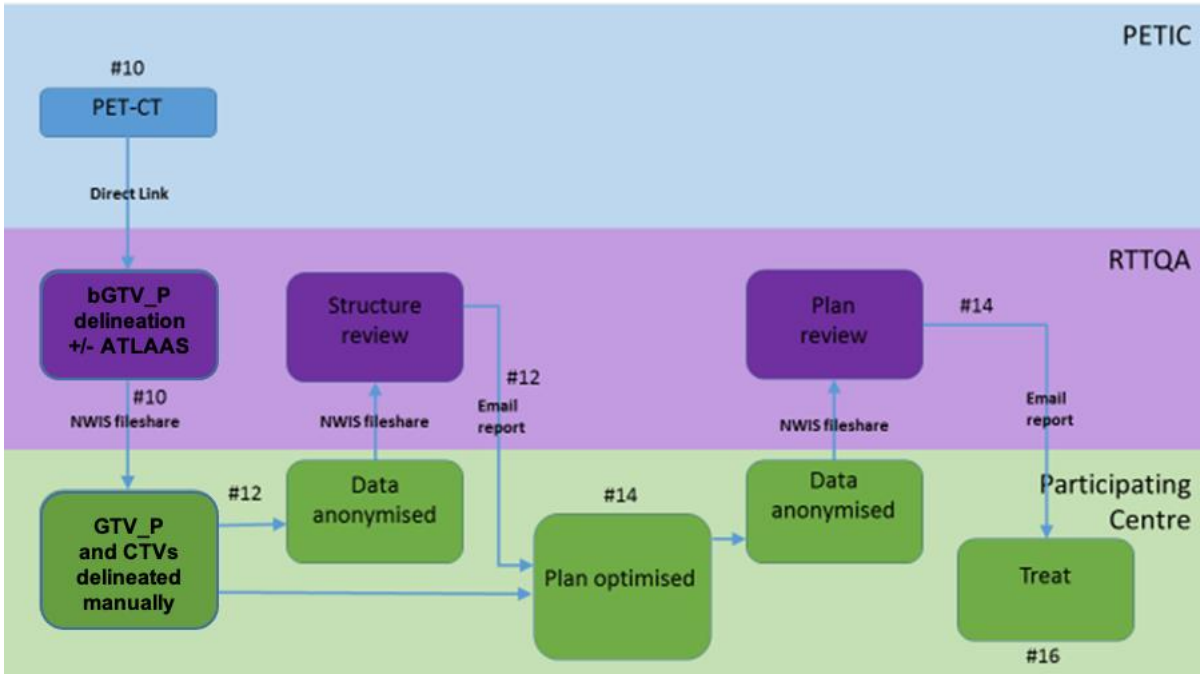
During the typical patient pathway, data shall be transferred both anonymised and non-anonymised. As such, transfer between participating centres and the RTTQA group will be undertaken via the NWIS Fileshare Service. The data transfer method is outlined below:

1. Patient PET-CTed at PET centre
2. Data transferred directly to RTTQA group for bGTV_P delineation
3. Data transferred to participating centre via NWIS FileShare (where participating centre is remote from RTTQA Centre).
4. Anonymised delineated / planned data returned to RTTQA centre for review

The intended transfer method between RTTQA and participating centre will be followed using a test case in the trial setup stage to ensure this transfer can be successfully achieved and to identify any issues that require resolution prior to commencing on-trial cases.

12.7 Map of the real time review process

A map of the real-time review process for phase II is shown below. Next to each stage is shown the latest fraction day (assuming no breaks) at which each task should be concluded to achieve the overall process within the intended timescale.



12.8 Dosimetry Audit

Consists of an output measurement and dosimetric measurement of a representative treatment plan. Audits are carried out either by the RTTQA group in person (with participating centre support) or via a postal audit using RTTQA equipment and performed by the participating centre. Centres may start entering and treating patients into the trial prior to the dosimetry site visit. However, the dosimetry audit should be completed as soon as possible following general pre-trial QA approval.

12.9 Streamlining of Outlining, Planning and Audit process

There is no streamlining of target delineation or planning from having completed credentialing for other H&N trial(s). Ph1 and Ph2 delineation must be completed and submitted for structure baseline case (Ph2 structures are partially generated through transfer from Ph1). However, as Ph2 is the more complex it is only required to submit a baseline planning case for Ph2, and standardly, only the first Ph2 cases will undergo real-time target delineation and planning QA.

A dosimetry audit is required per technique, not per-trial. As such, completion of a dosimetry audit for the purposes of a previous trial within an appropriate timescale will suffice for credentialing for subsequent trials. This will be checked by the RTTQA centre.

12.10 On-Trial Prospective Case Review

It is intended that all trial cases will undergo a real-time QA of target delineation prior to plan optimisation. Itis intended that independent review will be conducted by any available TMG clinician. To allow for this, the delineation and submission must be completed in a timely manner, especially in the case of the more tightly time-bound phase 2 turnaround, and sufficient clinical history must be submitted to include as a minimum:

- Site of primary disease
- Categorisation of primary tumour
- Involved nodal levels on pathology
- TNM stage
- Treatment start date

Review will be organised by the RTTQA centre to ensure that timescales and communication method are agreed in advance of submission to allow for maintenance of required trial planning timescales.

Following successful completing of target delineation QA, real-time plan QA will be completed through submission of optimised plan and completed plan assessment form and review by RTTQA. This must be successfully completed prior to patient commencing RT.

12.11 Trial Data Collection

Data will be collected by the RTTQA centre for all patient treated in the PEARL trial. Data must be appropriately anonymised and transmitted to the RTTQA using the NWIS FileShare – a named trial contact at the participating centre will require user privileges to be setup for this. Please submit in DICOM format the following:

- PET-CT images. MRIs, if used, may be collected.
- Structures, ensuring conformance with agreed trial nomenclature.
- Plan.
- Dose cube.
- Electronically completed plan assessment for (in .xlsx format)

Data associated with any re-plans for PEARL patients during radiotherapy must also be submitted to the RTTQA group. This data may not be subject to prospective review given the further shortened timescales for re-plans.

12.12 Data Anonymisation

All data collected by the RTTQA centre must be anonymised prior to being sent; data that has not been anonymised will not be accepted. Any anonymising software may be used; DICOMpiler is available at http://itc.wustl.edu/DICOMpiler/index.htm. It is required that the trial number and initials are used to identify the patient. It may be of use to keep your own list of names and IDs as well.

13 References

1. Biau, J et al *Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 update* Radiotherapy and Oncology 134 (2019) p.1 - 9
2. Christianen, M et al *Delineation of organs at risk involved in swallowing for radiotherapy treatment planning* Radiotherapy and Oncology 101 (2011) p.394 - 402
3. Schwartz, D et al *Adaptive radiotherapy for head and neck cancer – Dosimetric results from a prospective clinical tria*l Radiotherapy and Oncology 106 (2013) p.80 - 84

14 Appendix A: ATLAAS structure creation and transfer SOP

14.1 Importing patient scans into Velocity from Prosoma

1. In Prosoma, find the patient to be exported.
2. Double-click to open the PET scan.
3. Register the patient if necessary, and ensure that the yellow exclamation mark is not present.
4. Select 'Export' from the DICOM RT menu.
5. Select the network destination as ''DICOM_FOLDER_DUMP''. Select 'Send images', but not 'Sent RT structures' or 'RT plan'. Press 'Send'.
6. Repeat this for the CT scan.
7. In Velocity, go to the atient Import Inbox. Browse to \\rqfh5srvpukkaj5\folderdump\study.
8. Select the patient study, making sure the pET and CT scans are selected.
9. Select 'Delete source files'.
10. Import the scans.
11. Check that the patient details including Patient ID are correct.

14.2 Setting the Matlab path

1. Open Matlab 2018b and under the home tab select 'set path'. Remove any files listed which are located in the T drive.
2. Select 'Add with Subfolders'.
3. Browse to T:\Working roups\DBIT\ and then choose the pet-stat, cerrt and custom-functions directories in turn.
4. Select 'close'.

14.3 Importing DICOM Scans into the CERR environment

1. Find the patient in Velocity using the search tools. Ensure that the PET scan has been interpolated to match the CT scan. If this has not been performed, open the patient. Select the CT scan as the primary dataset and the PET scan as the secondary dataset. Right-click on the PET scan and select 'create resampled'. A new interpolated PET scan will be inserted.

2. In the main Velocity menu, right click on the patient and select "export''. Browse to the directory T:\TrialsQA\PEARL\OnTrial\ and create a folder with the nomenclature 'PatientID_pre' or 'PatientID_interim' for a PET-CT acquired pre-treatment and mid-treatment respectively. Select the scan(s) to be exported (i.e. the interpolated PET, original PET scan and CT scan). Press 'export'.

3. Open Matlab and type "CERR" into the command line.

4. In the CERR control panel (Figure 1) ensure that "DICOM" is selected from the drop-down menu. Click "import".

5. Browse to the relevant folder where the exported patient data was saved. Click "select folder".

6. Once CERR has finished scanning for files, click "Import All".

7. Select “No" if asked whether you want to append the scans.

8. Save the new CERR files with the nomenclature ‘PatientID_pre’ or ‘PatientID_interim’ in the directory T:\TrialsQA\PEARL\OnTrial\PatientID_pre (or PatientID_interim)\CERR_data\ If asked whether you want to zip the file, select ‘no’. If it is not possible to save directly onto the T drive, save onto the local drive and then manually move to the correct directory on the T drive.

Figure 1: The CERR control panel.

14.4 Performing the ATLAAS segmentation

1. If not already done so, open Matlab and type “CERR" into the command line to open the CERR control panel (Figure 1).

2. Click on “Viewer" to open the CERR viewer.

3. Click on “File" and select “open". Browse to the location of the patient CERR file which you previously created. Select this file.

14.5 Creation of the segmentation boundary box

1. Click on “scan" and select the interpolated PET image from the drop-down menu.

2. Scroll through the image set to find the approximate location of the bGTV. It should be noted that Velocity slice numbering is lower by 1 than CERR slice numbering.

3. From the PET-STAT drop-down menu, select “step 2: Start segmentation". This will open the segmentation GUI (figure 2)

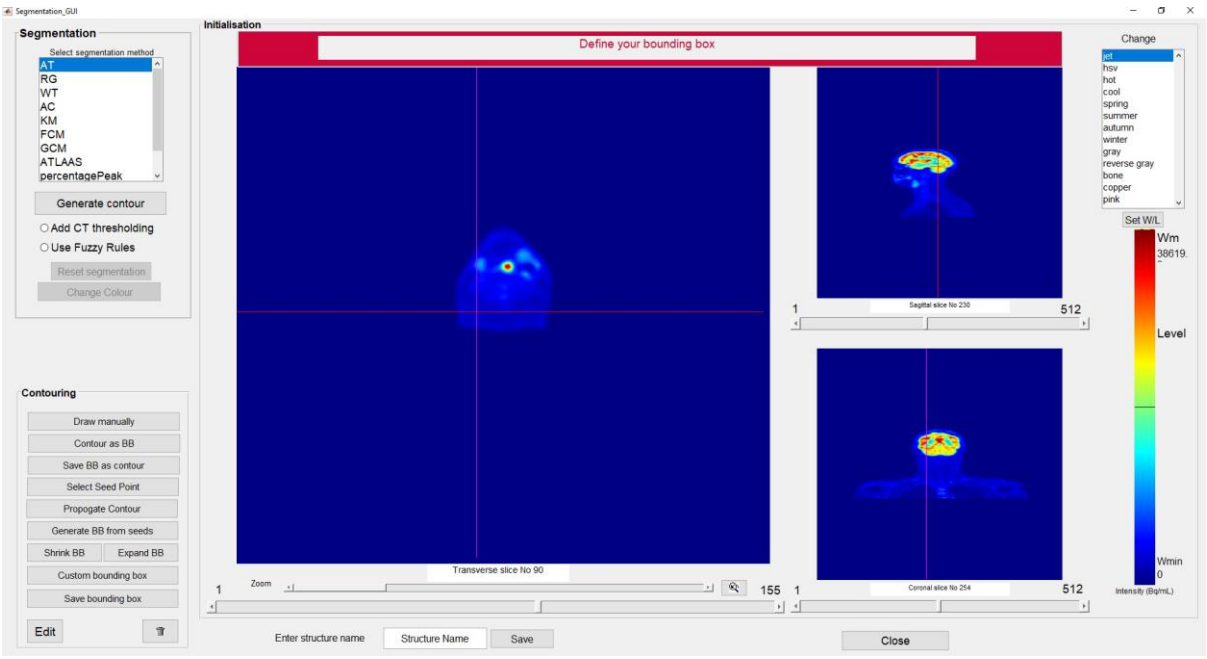


Figure 2. The segmentation GUI

4. Select the appropriate colour map and the window level and width by using the windowing tool (Figure 3) in the upper right hand corner of the segmentation GUI.

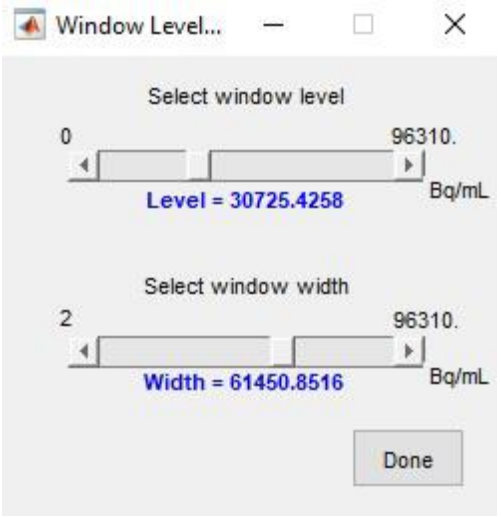


Figure 3: The adjustable window level and width tool.

5. Create a boundary box demonstrating the location of the tumour. This should be attempted in the first instance using the “seed method" described in Section 2.2.1. If this method fails, the boundary box should be created manually using the method described in Section 2.2.2.

14.6 Creation of a boundary box using the “seed method"

1. Within the segmentation GUI, move through the transverse slices to find the extremity of the primary tumour volume. Once the extremity slice is chosen, left click “Select Seed Point" in the contouring box (Figure 4) and then left click on the approximate location of the extremity of the primary tumour. Press the enter key ( ) after placing the seed point on the PET image.

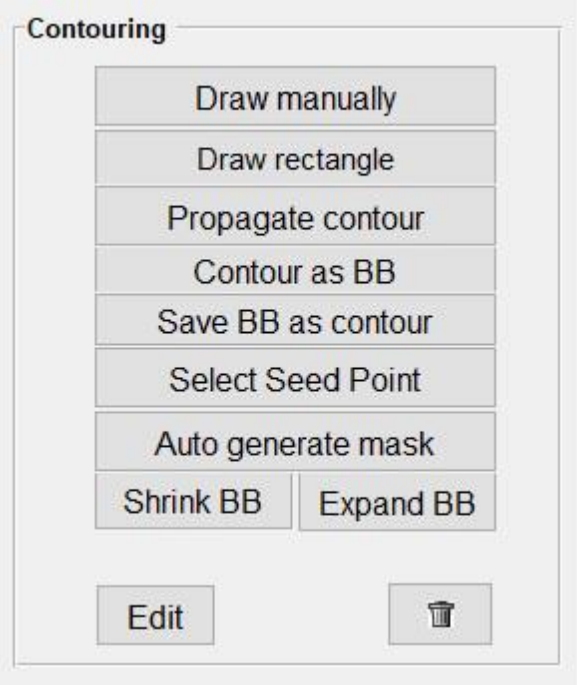


Figure 4: The contouring box within the segmentation GUI.

2. Repeat for the extremity of the tumour in the opposite transverse direction.

3. Seeds should also be placed indicating the tumour extent on an approximately central/ high uptake slice of the tumour (Figure 5). A maximum of 4 seed points should be placed on this slice.

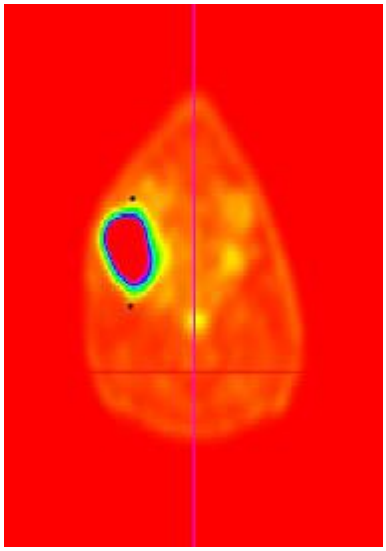


Figure 5: Placement of seed points (the black dots) to mark the extent of the boundary box.

4. Scroll through the slices and check that the positions of the seeds are correct. If any seeds are in the incorrect position, the GUI should be closed and re-opened and the above process repeated. In the event of repeat incorrect seed placement, the bounding box should be created using the manual method (see section).

5. Select 'Generate BB from seeds' to create the bounding box.

6. Check visually that the generated boundary box (drawn in purple) is in the correct location, covers the full extent of the tumour and does not include any other regions of avid uptake. If the boundary box appears poorly located, close and re-open the segmentation GUI and use the manual boundary box creation method described in Section 2.2.2.

14.7 Creation of a boundary box using the "manual method"

This method should be attempted if an acceptable boundary box cannot be produced using the seed method.

1. The extent of the boundary box can be defined manually by clicking the 'draw manually' button (Figure 4). On each slice, left click around the shape to define the area to run the ATLAAS segmentation on (Figure 6). When finished right click to complete the shape.

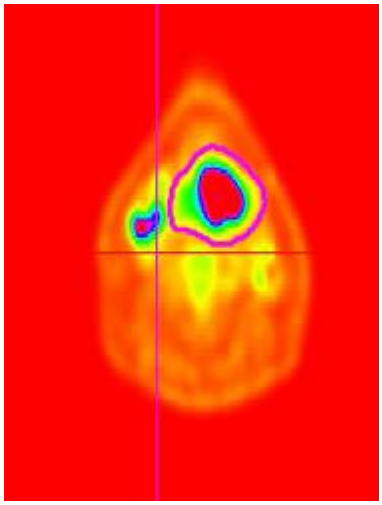


Figure 6: A boundary box created using the “draw manually" function. The boundary box is displayed in purple.

2. The boundary box on individual slices can be propagated onto adjacent slices using the propagate contour function. After drawing the boundary box on a slice, click the “Propagate contour" button (Figure 4).Enter the slice number of the contour you wish to propagate and the first and last slice numbers you wish to copy the boundary box onto. The slice number can be found above the slice in the segmentation GUI. Click “ok" and check that a matching boundary box has been copied onto the correct slices.

3. In order to delete the boundary box on an individual slice, click on the rubbish bin icon (Figure 4).

14.8 Saving the segmentation bounding box

1. Once the bounding box has been created, it should be saved by clicking ‘Save bounding box’. The nomenclature ‘PatientID_bb_pre’ or ‘PatientID_bb_interim’ should be used for PET scans acquired pre-treatment and mid-treatment respectively. The saved bounding box should be moved from the Matlab working directory to the directory T:\TrialsQA\PEARL\OnTrial\PatientID_pre (or PatientID_interim)\CERR_data\
2. It is also useful to visualise the bounding box in the CERR viewer. This can be achieved by selecting ‘Save BB as contour’ in the contouring section of the GUI (Figure 4).

14.9 Performing the ATLAAS segmentation

1. To delineate the primary bGTV_preP-ATLAAS or bGTV_iPET_ATLAAS after the boundary box has been delineated, select the ATLAASv1 segmentation from the left hand side of the segmentation GUI (Figure 7). Click the “Generate contour" button.

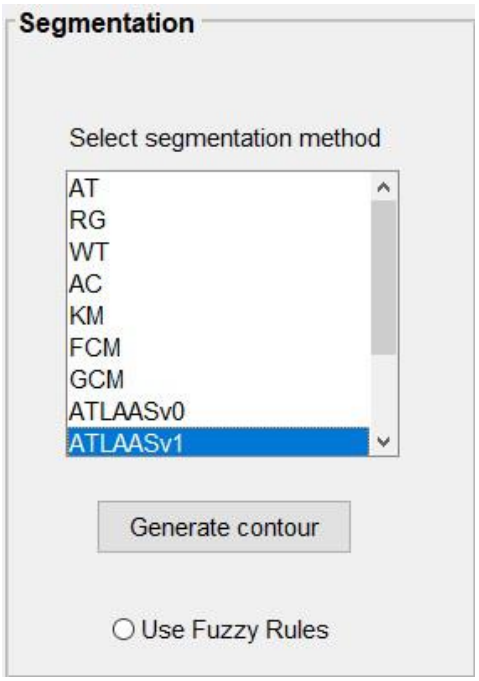


Figure 7: The segmentation selection box within the segmentation GUI. The ATLAASv1 segmentation method has been selected.

2. Check that the contour is ticked in the results box. Name the structure using the structure name box as as “bGTV_preP_ATLAAS" if the PET was acquired pre-treatment or ‘bGTV_iP_ATLAAS’ if the PET was acquired mid-treatment.Click “Save".
   Check that the ATLAAS segmentation and bounding box look as expected in the CERR viewer.
3. Check in the Matlab command window that no errors have been generated.Close the segmentation GUI.
4. Find the volume of the structure by typing ‘vol structure [ATLAAS structure number]’ into the command box in the CERR viewer. (The structure number can be found by selecting the relevant PET image under the structures menu in the viewer and finding the number to the left of the contour name). Make a note of the volume.
5. Delete the bounding box as a structure in the viewer by using the command ‘del structure [BB structure number]’ in the CERR viewer command box.
6. Save the CERR file.

14.10 Exporting the ATLAAS segmentation

1. Click on “PET-STAT" and then select “Step 3: Export Structures". Export the structures to T:\TrialsQA\PEARL\OnTrial\PatientID_pre (or PatientID_interim)\CERR_data\. Separate folders will be created in the directory for each scan which has contours associated with it.
2. Exit CERR.

14.11 Importing the ATLAAS segmentation into Velocity

1. In Velocity, find and open the patient.

2. Right-click on the PET scan, make the scan the primary dataset and select 'attached objects'. Browse to the folder containing the ATLAAS contour associated with the CT scan and click on import.

3. Click on "ST" to view the ATLAAS segmentation.

4. Right click on the ATLAAS structure and select it. Right click again and select 'Primary volume histogram'. Click on 'Graph Statistics'. Note down the volume of the structure and check that this agrees with the volume recorded in CERR.

5. Ensure that visual interpolation in Velocity is turned off.

6.The ATLAAS contour should be assessed.An inverse grey colour map should be used for this assessment on the PET scan, with an SUV window setting of 0 - 10.

7. A new structure should be delineated which should be named 'bGTV_preP_ATLAAS for a pre-treatment structure and 'bGTV_iP_ATLAAS' for a mid-treatment structure.

8. The final bGTV structure should be exported to Prosoma. In the structure menu, right click on the structure sset containing the bGTV. Export to T;\TrialsQA\PEARL\OnTrial\PatientID_pre (or patientID_interim)\bGTV\. The 'Use Velocity Patient Details' box should be ticked on export.

14.12 Exporting from Velocity to Prosoma

1. Load the Prosoma database.
2. Import the bGTV structres files using 'Select DICOM files'. Browse to T:\TrialsQA\PEARL\OnTrial\PatientID_pre (or PatientID_interum)\bGTV\ and select the structure file.

15 Appendix B: Swallowing structures atlas

The swallowing structure outlining guidelines for PEARL are based on those published by Christianen et al (2) and Schwartz et al (3). The table below details the anatomical borders of the structures.

Organs at Risk	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Cervical Oesophagus	1 cm caudal to lower edge of the cricoid cartilage	Sternal notch				
Supraglottic Larynx	Tip of epiglottis	First slice cranial to the upper edge of the arytenoid cartilages	Hyoid bone; Pre-epiglottic space; Thyroid cartilage	Pharyngeal lumen; Inferior PCM	Thyroid cartilage	Pharyngeal lumen (lumen excluded)
Glottic Larynx	Upper edge of arytenoids cartilages	Lower edge of cricoid cartilage if soft tissue is present	Thyroid cartilage	Inferior PCM; Pharyngeal lumen/ Cricoid cartilage	Thyroid cartilage	Pharyngeal lumen (lumen excluded)
Oral Cavity (to include mucosal surface of hard palate, oral tongue, gingiva, buccal mucosa and floor of mouth)	Upper edge of hard palate	First slice cranial to superior border of Level 1a/ Insertion of Platysma muscle to mandible anteriorly/ First slice where hyoid seen on axial sections	Buccal surface of maxilla, mandible and teeth	Anterior to soft palate up to bottom of C1 in the upper half and Anterior to tongue base from below C1 in the lower half	Medial edge maxillary sinus superiorly Medial edge of buccinator muscle Buccal surface of mandible/ maxilla/ teeth	

Organ at risk	Anatomic borders					
	Cranial	**Caudal**	**Anterior**	**Posterior**	**Lateral**	**Medial**
Superior PCM	Caudal tip of the pterygoid plates (hamulus)	Lower edge of C2	Hamulus of pterygoid plate; Mandibula; Base of tongue; Pharyngeal lumen	Prevertebral muscle	Medial pterygoid muscle; Para-pharyngeal space	Pharyngeal lumen
Middle PCM	Upper edge of C3	Lower edge of hyoid bone	Base of tongue; Hyoid	Prevertebral muscle	Greater horn of hyoid bone	Pharyngeal lumen
Inferior PCM	First slice caudal to the lower edge of hyoid bone	Lower edge of arytenoid cartilages	Soft tissue of supraglottic/ Glottic larynx	Prevertebral muscle	Superior horn of thyroid cartilage	
Cricopharyngeal Muscle	First slice caudal to the arytenoid cartilages	Lower edge of the cricoid cartilages	Posterior edge of cricoids cartilage	Prevertebral muscle	Thyroid cartilage; Fatty tissue; Thyroid gland	
Oesophageal Inlet Musde	First slice caudal to lower edge of cricoid cartilage	1 cm caudal to the superior border of oesophageal inlet muscle	Tracheal lumen	Prevertebral muscle	Fatty tissue; Thyroid gland	

16 Appendix C: VELINDRE CANCER CENTRE PLANNING PROCESS

The PEARL planning process at Velindre Cancer Centre (VCC) uses RayStation (RS))

16.1.1 Standard practice

Standard practice at VCC uses three dose levels at 54, 60 & 66Gy. Once targets (GTV and CTV) are delineated in Prosoma the OARs are added (spinal cord, brainstem, mandible and parotids). Swallowing structures are not current standard practice.

CT, targets and OARs are exported to Raystation. An in-house script will then generate optimisation structures, grow PTV and PRVs, apply the initial plan and initial plan objectives.

Optimisation structures include:

Dummy PTVs – these are a small growth of the PTV used to ensure the plan covers targets adequately. They avoid primary OARs and higher dose target volumes by defined amounts based on dose fall off estimations

OAR/PTV overlap structures – these are used to control hotspots in OARs where within higher priority target volumes (e.g where Mandible PRV overlaps target).

OAR avoiding PTV – used to optimise to an OAR without causing target compromise (e.g. parotids outside target)

Conformality max dose volumes – for each dose level there are two one avoiding that dose level by 3mm and another at 5mm. These will also avoid all other targets, abutting lower dose targets and avoiding higher dose by larger margins. Objectives are applied at 95% of the relevant dose level, with a higher weight on the more retracted structure.

Conformality dose fall off volumes – one for each PTV, based on a 1.5cm margin around the target and avoiding all other target structures. Highest dose volumes are created first, lower dose volumes also avoid higher dose fall off structures. A dose fall off objective is applied to each at 95% to 75% of the relevant dose level.

“Sup” and “Inf” conformality volumes – these control dose fall off beyond the ends of the PTVs, where optimiser can be too generous with field size.

PTV/air regions – these have defined density of 0.6, used to ensure optimiser doesn’t falsely increase dose to air, risking hotspots.

16.1.2 Phase 1

Plan largely follows standard practice, however needs introduction of swallowing structure volumes to minimise dose. The plan is completed as if to be used for full 33 fractions. Target coverage and OAR doses are planned for full course, to ensure adequate coverage and overall plan safety.

Process is:

- CT, targets and OARs imported to RS.
- Standard H&N script used to produce optimisation structures and applies plan
    - Includes all PTV and PRV growths
    - Includes annulus type structures to drive conformality
    - Dummy target volumes, retracted from higher dose structures and primary OARs
    - Overlap structures (e.g. parotid/target overlap region) and exclusions (e.g. parotid outside target)
    - Adds plan and all DVOs
- Initial coarse optimisation (fluence mode) used to determine objectives for parotids and conformality (this step is standard practice)
- At this stage objectives are applied for all swallowing structures (PRVs for all except oral cavity), drawing DVH curve down
- Fluence mode repeated, to assess impact to new DVOs. DVOs are adjusted to further draw down DVH.
- Plan optimised fully and reviewed for coverage, OAR doses, conformality and feasibility

16.1.3 Phase 2

Planned as if to be used for full 33 fractions. Initial process follows similar to phase 1, however significant adjustments to resulting volumes is required. At a future point this will be scripted to improve efficiency.

Process is:

- CT, targets and OARs imported to RS.
- VCC scripts currently setup to deal with 3 dose levels (54, 60 and 66). New dose levels are therefore not automatically incorporated. To run initial script, the new volumes are labelled as if for 54Gy, will expectation of editing these post scripting.
- Standard H&N script used to produce optimisation structures and applies plan
    - Includes all PTV and PRV growths
    - Includes annulus type structures to drive conformality
    - Dummy target volumes, retracted from higher dose structures and primary OARs
    - Overlap structures (e.g. parotid/target overlap region) and exclusions (e.g. parotid outside target)
    - Adds plan and all DVOs
- Modifications are now required as the scripts are based on 3 dose levels only

    - Dummy target volumes avoid higher dose levels by a specified distance, adjustments are therefore required to these
    - Dummy targets volumes also avoid primary OARs by defined distance (based on approximation of dose fall off at 2Gy/mm)
    - Conformality structures to be adjusted, again based on dose fall off estimations
    - Creation of new conformality structures to represent new dose levels
- Modifications to DVOs, to introduce new dose levels
- Initial coarse optimisation (fluence mode) used to determine objectives for parotids and conformality (this step is standard practice)
- At this stage objectives are applied for all swallowing structures (PRVs for all except oral cavity), drawing DVH curve down
- Fluence mode repeated, to assess impact to new DVOs. DVOs are adjusted to further draw down DVH.
- Plan optimised fully and reviewed for coverage, OAR doses, conformality and feasibility

16.1.4 Plan merging

To assess phase one plan on phase two scan, a route to calculate a plan on different scans is required. In RS it is not possible to directly calculate a plan on a different scan as the UIDs are linked. It is possible to recalculate on a different data set after fusion, but this does not give any flexibility in plan positioning.

Alternative route to positioning requires unlinking plan and CT, this can be done by taking the plan through OMP. This allows greater control over plan positioning.

Plans are summed as 15 fractions of phase one and 18 fractions of phase two.

As plans are individually safe for full treatment, there is low risk to OARs.