PRINCE
Radiotherapy and Quality Assurance Guidelines

Prospective, randomised, multicentre study of **first line systemic treatment and radiotherapy I**n stage IV **N**on-small **Ce**ll Lung cancer

Version: 3.0, September 2024

THIS DOCUMENT SHOULD BE USED IN CONJUNCTION WITH THE:

- PRINCE PROTOCOL
- TOURIST MASTER PLATFORM PROTOCOL

Study Sponsor	The Christie NHS Foundation Trust
TOURIST Chief Investigator (CI) PRINCE Candidate CI (CCI)	Prof Matthew Hatton ☎ 0114 226 5071 ✉ matthewhatton@nhs.net
RTTQA	Rushil Patel / Konstantinos Rizos ☎ 020 3826 2321 ✉ enh-tr.touristqa@nhs.net RTTQA website: www.rttrialsqa.org.uk
Trial Coordination Centre	Southampton Clinical Trials Unit (SCTU) Izabela Eberhart ☎ 023 8120 5154 ✉ tourist-prince@soton.ac.uk
Study Funder:	NIHR

History of Changes to PRINCE Radiotherapy and Quality Assurance Guidelines:

Current Version: Version 3.0, 06/09/2024
Previous Version: Version 2.0, 12/03/2024
Changes: ▪ Title of the document amended to "PRINCE Radiotherapy and Quality Assurance Guidelines" ▪ History of document changes table added ▪ Brachial plexus definition has been revised according to the GHG guidelines ▪ Heart+A_Pulm definition and delineation details have been introduced to replace the heart structure ▪ Lung definition has been clarified by adding that the lung contour should include all lung parenchyma and exclude hilar structures and the GTV (or ITV). ▪ Appendix added to assist in brachial plexus delineation ▪ Timings for prospective review clarified ▪ References updated
Previous Version: Version 1.0, 11/12/2023
Changes: ▪ Amend the title of the document from "PRINCE LUNG" to "PRINCE" to reflect the correct naming of the trial ▪ Definition of CTV has been clarified to differentiate 3D-CTV from 4D-CTV ▪ Definition of PTV has been amended to reflect the changes in CTV definitions ▪ Radiotherapy timings at Section 4 have been revised to improve clarity ▪ Section 5.2 has been amended to assist the streamlining process of participating centres

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Foreword

This document describes the QA processes for PRINCE trial. When used in conjunction with the PRINCE protocol and TOURIST Master protocol it provides the information necessary for entering patients into the trial.

This document should not be used as a guide for the treatment of patients outside of the trial.

Every care has been taken in drafting these guidelines but corrections or amendments may be necessary. These will be circulated to Investigators in the PRINCE trial, but centres entering patients for the first time are advised to contact the Clinical Trials Unit (tourist@soton.ac.uk) to confirm they have the most recent and approved version.

If you have any queries in regards to the content of the guidelines please contact the National Radiotherapy Trials Quality Assurance (RTTQA) group.

Trial Schema

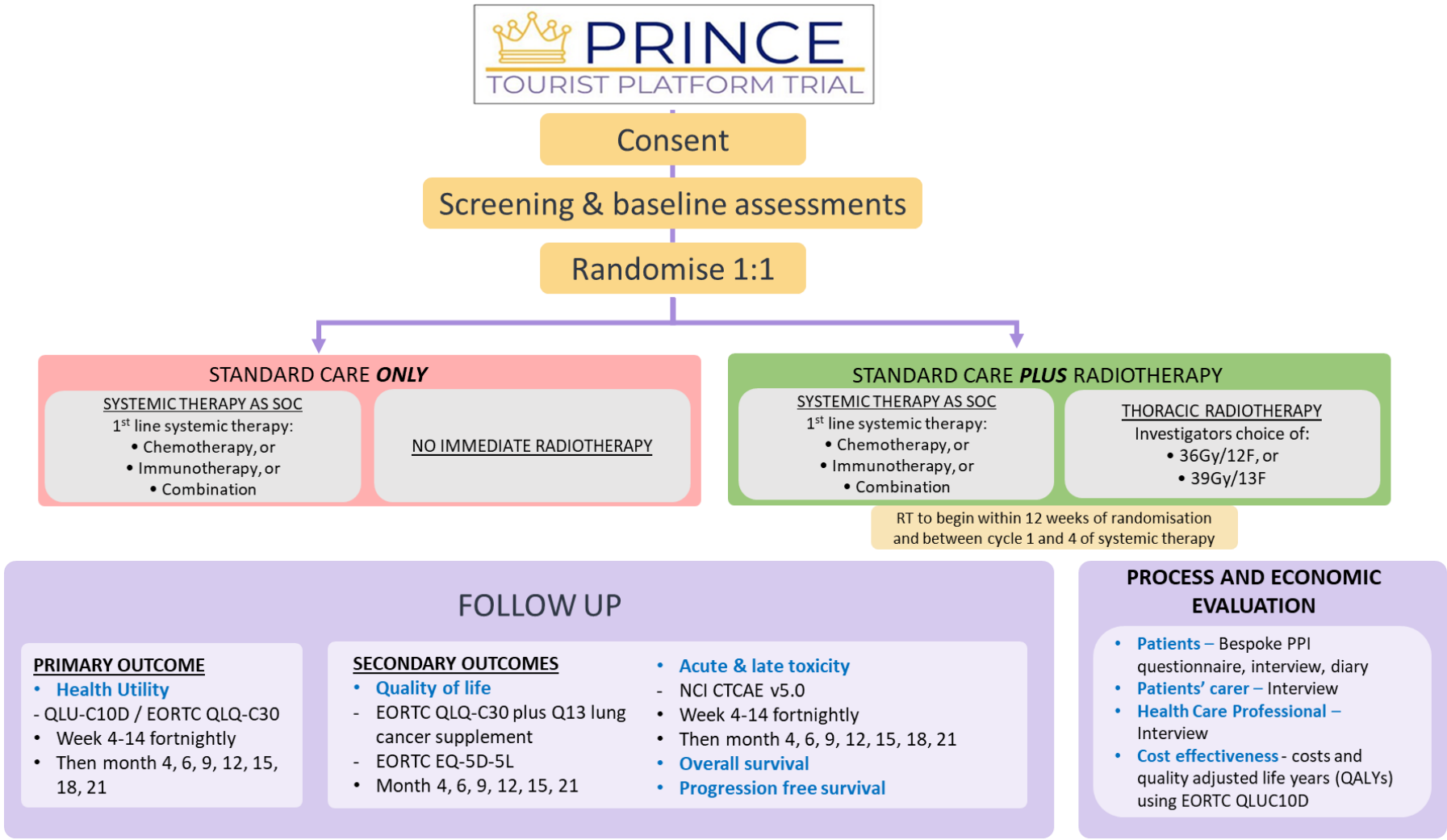


Figure 1: Trial schema

Figure key profile - Trial schema for PRINCE. Patients will be recruited on a 1:1 basis

1 Trial Summary

PRINCE is a pragmatic, parallel group, randomised controlled trial with cost effectiveness and process evaluation. ***472*** participants, recruited over a *42-month* period, will be randomised (***1:1***) to control or early high-dose palliative radiotherapy; all participants will receive first-line systemic therapy to determine the impact of the addition of early high-dose palliative thoracic radiotherapy on quality of life (QoL) in patients with stage IV NSCLC receiving first-line standard of care systemic therapy.

2 Planning and Delivery

2.1 Planning technique and dose fractionation

All patients randomised in the PRINCE trial should receive palliative high-dose thoracic CT planned, 3D conformal radiotherapy or VMAT/IMRT and Rapid Arc radiotherapy. The prescribed dose should be **36Gy in 12#** or **39Gy in 13#** (1# per day for 3 weeks). Radiotherapy will be delivered between cycles 1 and 4 of systemic therapy (or within 12 weeks of randomisation)

2.2 Patient positioning

Patients should be positioned identically for both planning and treatment: supine on the couch with arms supported above the head or a 5-point fixation shell for upper lobe tumour with arms by side. Head and knee support should also be used and a foot stop. Set up should be by reference to tattoos on stable areas of skin and bony anatomical landmarks. Other patient set-ups such as arms by sides will be considered on a centre by centre basis (Please contact RTTQA for advice).

2.3 Planning scan acquisition

The patient should be placed on a flat couch top to collect a 3mm slice thickness CT scan. The whole thorax (cricoid to L2) should be included within the planning scan to allow dose volume histograms to be calculated for the lung, heart, spinal canal, brachial plexus vessels and the oesophagus. IV contrast should be used to aid target definition and target delineation in node positive disease, unless medically contraindicated as per local practice.

Tumour motion management is fundamental in the treatment of lung cancers as it could potentially result in a geographic miss and centres are encouraged to use techniques to reduce the effect a movement could have. These include abdominal compression, deep Inspiration breath hold (DIBH), Active breathing control (ABC) and Gating could be utilised to allow tracking of the respiratory movement and assist in the treatment delivery.

4D-CT could also be used for Prince patients to account for tumour motion during the breathing cycle. A 4D-CT planning scan should be performed in the treatment position whilst the patient undertakes a normal respiration. Slice thickness should be 3mm or less.

2.4 Target volumes

The input of a thoracic radiologist is encouraged when defining the Gross Tumour Volume (**GTV)**. The primary tumour volume will be contoured on the planning scan using lung window settings and the lymph nodes on the mediastinal window settings.

2.4.1 Gross Tumour Volume (GTV)

The GTV will be segmented using any available information. These may include, but are not limited to, Diagnostic Staging CT scans, PET CT scans, bronchoscopy and EBUS.

The GTV is defined as the primary tumour mass and any involved lymph nodes. Each should be segmented using the appropriate CT windows. In the absence of direct evidence of nodal involvement from mediastinoscopy or EBUS, lymph nodes are judged to be involved if their short axis on CT is >10mm, if they are positive on PET / PET-CT, or if their appearance is suggestive of malignant involvement as judged by the specialist MDT thoracic radiologist. All non-continuous lesions comprising the GTV, i.e. primary tumour and lymph nodes, shall be segmented separately.

2.4.2 4D-GTV

Centres have the option to use a 4D-CT for patients in PRINCE in accordance with local preferences. When used to define a motion adapted **4D-GTV** a qualified radiation oncologist contours the primary target volume according to local practice as:

- Combined GTV Exhale (defined on the maximum exhale 4D-CT dataset) and GTV Inhale (defined on the maximum inhale 4D-CT dataset). The target volume should be visually

confirmed on all respiratory phases on axial, coronal and sagittal views, by playing a cine-movie of the datasets representing different phases of the respiratory cycle

- Combined GTV from all phases of the 4D-CT dataset
- GTV as defined on the Maximum Intensity Projection dataset (MIP). When delineating on the MIP, it should then be visually confirmed that the motion adapted GTV lies within the boundaries of the MIP-delineated target volume on all respiratory phases on axial, coronal and sagittal views, by playing a cine-movie of the datasets representing different phases of the respiratory cycle. These will take into account the internal motion.

2.4.3 Clinical Target Volume (CTV)

For both 3D-CTV and 4D-CTV planning scans, the Clinical Target Volume (CTV) is generated by expansion of both the primary tumour and lymph node GTVs. The 4D-GTV should be expanded by **5**mm to create the CTV. The CTV expansion includes microscopic spread and may be edited to account for anatomical barriers i.e. vertebrae but only if it is not thought to invade the structure. These will be referred to as 3D-CTV and 4D-CTV respectively. There will be no elective nodal irradiation. Manual editing of the CTV margin is allowed to account for anatomical barriers to spread.

2.4.4 Planning Target Volume (PTV)

The PTV is generated by adding a margin to the 3D-CTV or 4D-CTV:

The CTV should be expanded by **5-10**mm axially and **10-15**mm sup/inf to create the PTV.

For patients who have been scanned using 4DCT:

- If a centre is using per fraction CBCT imaging and online correction for treatment verification, the CTV should be expanded by **5**mm isotropically to create the PTV.
- If a centre is not CBCT imaging per fraction, the CTV should be expanded by **7**mm axially and **9**mm sup/inf to create the PTV.

2.5 Organs at Risk (OAR)

All Organs at Risk (OAR) should be outlined following the Global Harmonization Group consensus guidelines. For centres using the 4DCT, all OAR should be outlined on the average intensity projection (AVIP) or on a representative mid-cycle phase of the 4D-CT scan.

BrachialPlex_L *BrachialPlex_R* *BrachialPlexs*	Each brachial plexus should be contoured separately. The brachial plexus originates at the spinal nerve root foraminae C5, C6, C7, C8, and T1 and terminates at the medial limit of the second rib. Begin contouring with a 5mm diameter tool at the C5, C6, C7, C8, and T1 neural foramina and continue caudally, contouring the region from the lateral aspect of the spinal canal to the small space between the anterior and middle scalene muscles. At the levels where no neural foramina are present, contour the space or soft tissue between the anterior and middle scalene muscles. The middle scalene muscle, and therefore brachial plexus structure will terminate at the caudal border of the subclavian neurovascular bundle. This structure should be used as a surrogate for brachial plexus. The first and second ribs serve as the medial limit of the brachial plexus contour. Co-registration with MRI and/or the use of intravenous contrast can help distinguish between nerves and vessels. Be aware that patient positioning may influence the position of the underlying anatomy and the brachial plexus. BrachialPlexs is a summation of the right and left brachial plexus and may be used for dose reporting purposes.
Oesophagus	The oesophagus is contoured on mediastinal windowing to include all muscle layers out to the fatty adventitia. Contour from the lower edge of the cricoid cartilage to the gastro-oesophageal junction.
Heart + A_Pulm	The heart is contoured on mediastinal windows to include the pericardial sac. With pericarditis as the toxicity endpoint, the whole pericardium must be contoured. The pulmonary artery should, therefore, be encompassed in its entirety up to the level of the main bronchi. The cranial border is at the cranial aspect of the pulmonary artery. Please ensure the whole pericardium is included at this level, not just the pulmonary artery. The caudal extent is at the apex of the heart where the left ventricle blends with the diaphragm. Major vessels, including the inferior vena cava should be excluded. The pulmonary arteries are excluded below the main bronchi.
Lung_L *Lung_R* *Lungs*	Each lung should be contoured separately on lung windowing. The lung contour should include all lung parenchyma and exclude hilar structures and the GTV (or ITV). Contour the whole lung, from the apex to the diaphragm including all inflated and collapsed lung. Small vessels less than 10mm in diameter and vessels beyond the hilar region are included. Exclude the proximal bronchial tree and the trachea. Lungs is a summation of the right and left lung and may be used for dose reporting purposes.

SpinalCanal	The spinal canal is contoured according to the inner limits of the spinal canal using bone windows. The cranial border is at the level of the tip of the dens of the C2 vertebra. The caudal border is the most caudal slice where the spinal canal is visualized, usually at the level of the L5-S1 vertebral bodies.

2.6 Algorithms

The use of modern 'type B or C' superposition-convolution algorithms (e.g. Pinnacle and Oncentra Masterplan collapsed cone algorithms or the Eclipse AAA algorithm) is mandatory as these algorithms calculate the lung and tumour doses more accurately than older 'type A' algorithms. Centres unable to calculate PRINCE patients using a 'type B or C' algorithm should contact RTTQA for advice.

2.7 Dose distribution (target coverage)

When assessing tumour coverage, it should be noted that the dose in airways and adjacent to lung is reduced because of dose build-up. With a collapsed cone algorithm lateral electron transport is more accurately modelled than with a simpler pencil beam algorithm. This can make conforming dose to the PTV more difficult and it is therefore accepted that achieving 95% prescribed dose coverage of the PTV may not be possible even with the recommended 6-7mm margins. Thus, when using "type B" superposition-convolution algorithms the planner should aim to achieve the best possible PTV coverage, accepting that this may not be entirely within the 95% isodose. Dose stats target and OARs

PTV: D95% ≥ 95% - D90% ≥ 98% - D50% = 100% ±1 Gy - D1% ≤ 107%

OAR	Constraint	Optimal dose (Gy)	Mandatory (Gy)
Contralateral lung	<5% <50% <70%	V20 V10 V5	
Oesophagus	Dmax (0.5 cc)	30	
Spinal canal	Dmax (0.5 cc)	27	36
Heart	Dmax (0.5 cc)	36	
Ipsilateral Brachial Plexus	Dmax (0.5 cc)	36	36

Please note that PTV coverage should not be compromised in order to achieve optimal OAR dose constraints.

3. Treatment verification

Centres should follow their local protocols for on-treatment verification. This should be detailed in the facility questionnaire. Daily 2D kV or 3D imaging should be acquired and assessed off-line. Any systematic correction applied should be confirmed using imaging after being first applied. Any re-evaluation during treatment should be reported and submitted with clear documentation on the reason for change.

4. Radiotherapy timing and treatment delays

Radiotherapy will be delivered between cycles 1 and 4 of systemic therapy and will begin up to 12 weeks after the start of systemic therapy. Schedules should begin on a Monday where possible and avoid starting treatment on a Thursday or Friday to keep overall treatment time at 16 / 17 days. Radiotherapy must not be given on the same day as chemotherapy or immunotherapy.

Start radiotherapy between day 4 - 12 of a chemotherapy / immunotherapy cycle. Omission of a day 8 chemotherapy or delaying the subsequent cycle of systemic treatment by 1 – 2 weeks would be acceptable should that be needed to accommodate the radiotherapy.

Missing fractions from potential planned or unplanned interruptions (e.g. machine servicing, bank holidays) could be moved at the end of the treatment. Potential gaps in the treatment will be considered and allowed if necessary but centres should communicate with the RTTQA team.

5. Quality Assurance

5.1 Radiotherapy Quality Assurance overview

The radiotherapy quality assurance (RT QA) programme for the PRINCE trial has been designed and implemented by the National Radiotherapy Trials QA (RTTQA) Group. This will include pre-trial and on-trial components. The full details of the programme will be made available on the RTTQA group website (www.rttrialsqa.org.uk).

5.2 Pre-trial QA

All Pre-Trial QA is completed prior to centre activation for the trial and includes:

- *Facility Questionnaire (FQ)* - General and trial specific questions on equipment, software, techniques and procedures to be used for the trial. Each centre should update the Facility Questionnaire if any local changes are made to the approved technique.
- *Dosimetry Audit* - Centres must have successfully completed a relevant recent independent external dosimetry audit through the RTTQA group or another external group.
- *Benchmark case* – Centres will be streamlined through their participation in the ADSCAN clinical trial. Centres who have not participated in the ADSCAN trial will have to complete and submit the outlining and planning benchmark cases. Centres who have participated in other lung trials should contact the RTTQA team. For further information regarding the streamlining process, please contact the RTTQA team on the email enh-tr.touristqa@nhs.net.

5.3 On-trial QA

At least the first patient recruited from each centre will be subject to retrospective review. ***10%*** of the total cases recruited onto the trial will be subject to retrospective review. Further prospective and/or timely retrospective reviews may be deemed necessary at the discretion of the RTTQA group and the trial CI.

To aid efficient case review please inform the RTTQA group as soon as a patient is recruited to the trial and provide estimated dates for data submission. The DICOM data, together with the case history should be submitted once approved by the PI to allow review before the next patient is treated.

Please allow sufficient time between data submission and the start of subsequent patients as the retrospective review must be completed before additional patients can be treated at the centre. Please contact the RTTQA team if the gap is expected to be less than 1 week.

5.4 Data Export

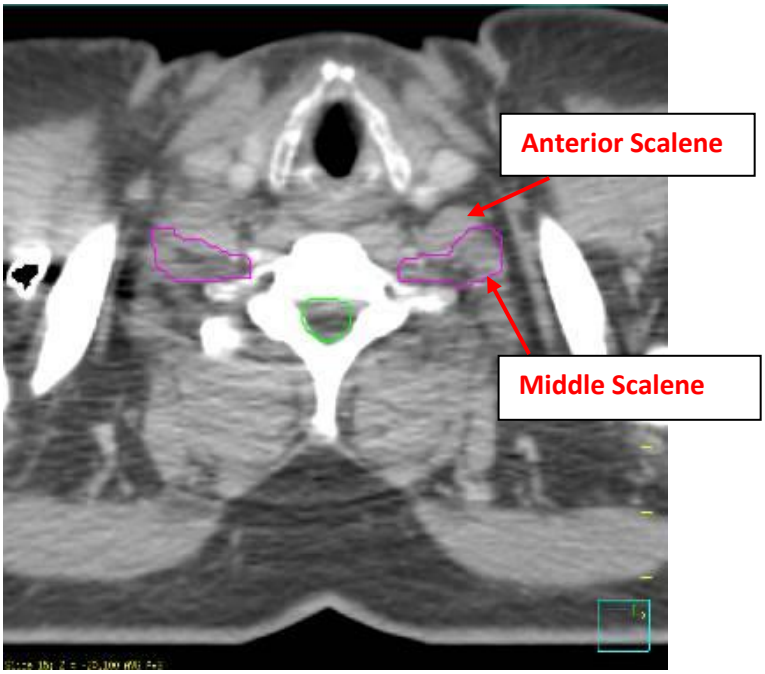
All patient data should be sent to the QA team. For each patient this must include radiotherapy data appropriate to the treatment technique, this includes the plan imaging (including 4DCT data from all phases) and plans for all patients as well as the contours and total dose cubes for 3DCRT/IMRT/VMAT patients. Please contact the RTTQA Group for further information. All data must be anonymised prior to being sent; data that has not been anonymised will not be accepted. Submissions must be labelled clearly with the trial name, patient trial ID (TNO), and the date of submission. Details of the QA programme, all required documentation and data submission can be found via the PRINCE link at www.rttrialsqa.org.uk. Please email the RTTQA contact on the PRINCE QA email enh-tr.touristqa@nhs.net with any queries.

Appendix

Use the following images as a guidance to outline the brachial plexus volume.

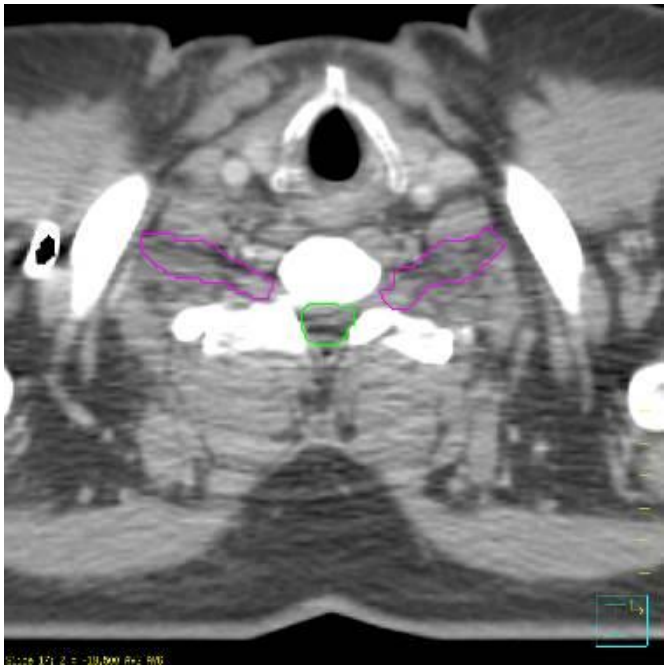
1. **Image 1**

Commence brachial plexus contours at C7 vertebral body. C8 and T1 nerve roots (starting at C7) as well as main trunk of brachial plexus will be contoured.

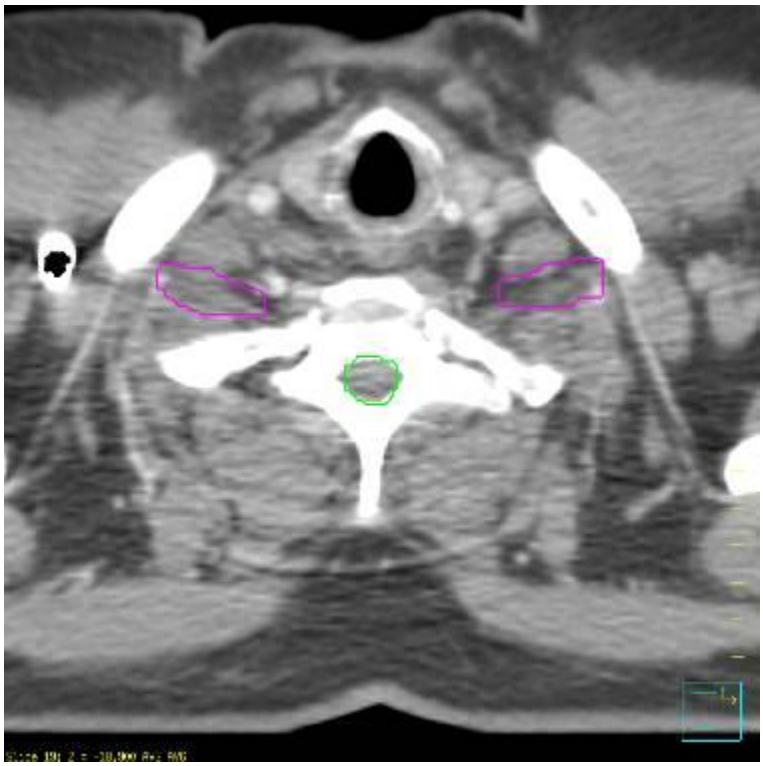


2. **Image 2**

C8 nerve roots originating from the neural foramina between C7 & T1

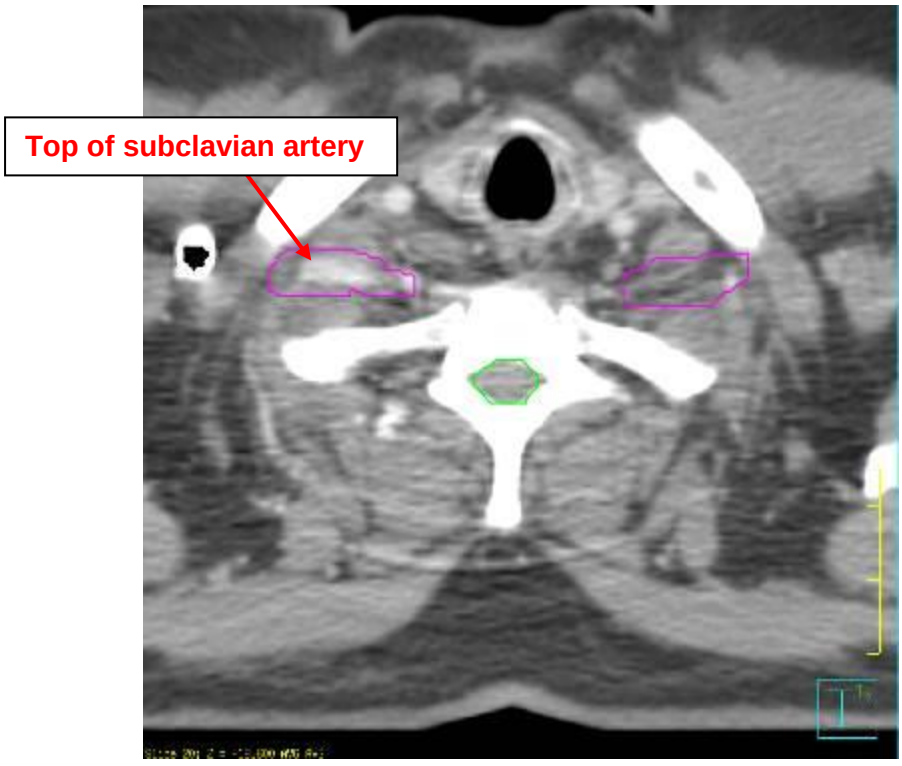


3. Image 3



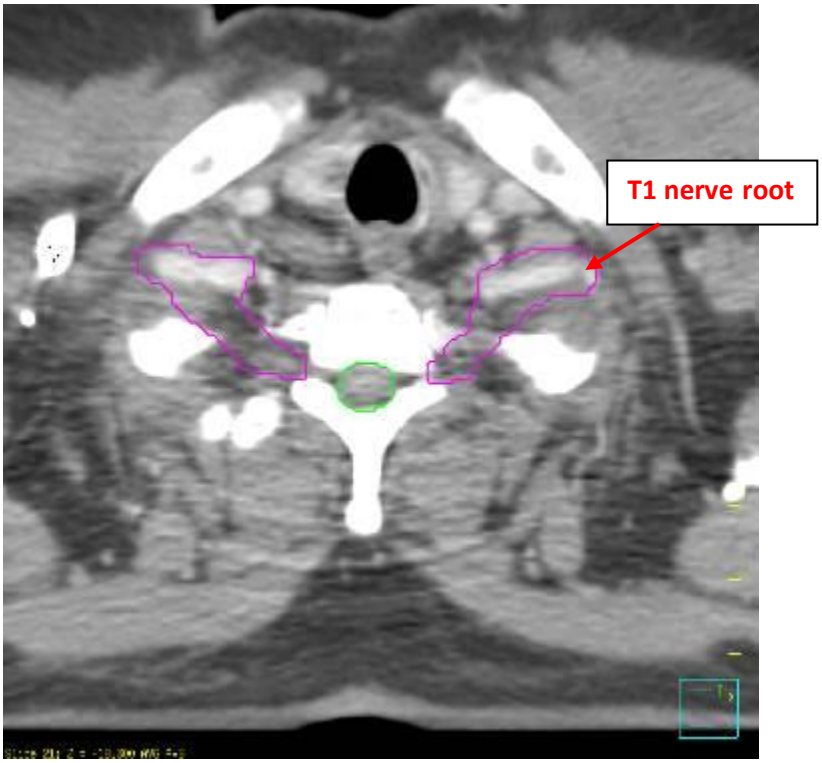
4. Image 4

Top of subclavian artery. Subclavian and axillary vessels will be used as a surrogate for identifying the location of the brachial plexus.



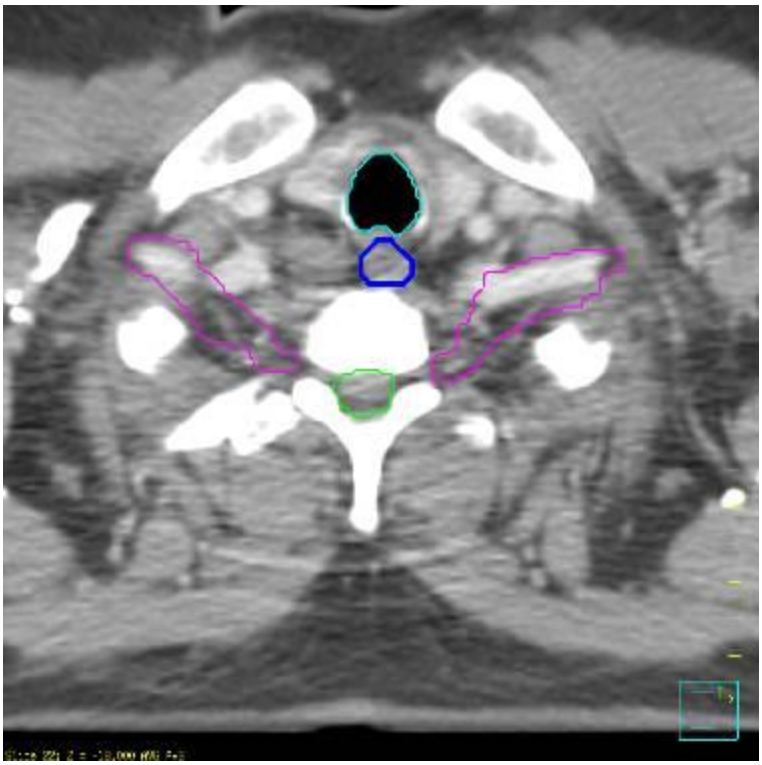
5. **Image 5**

T1 nerve root emerging between T1 and T2 vertebral bodies at the neural foramina

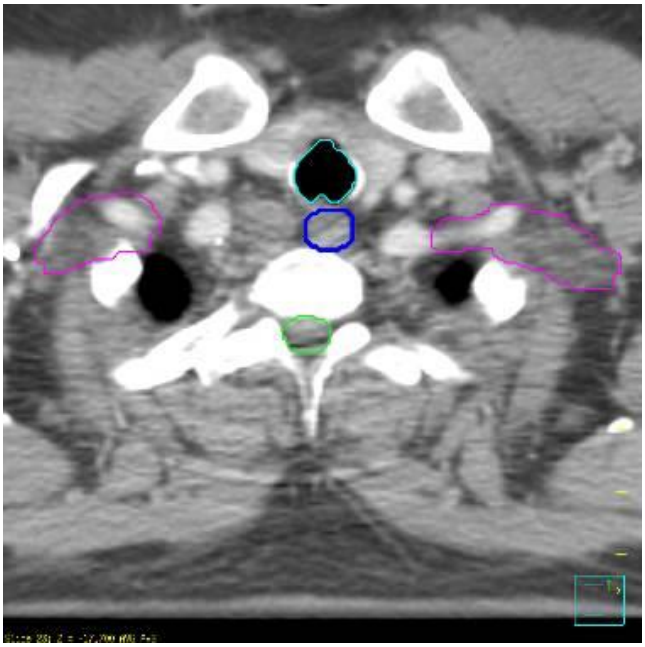


6. **Image 6**

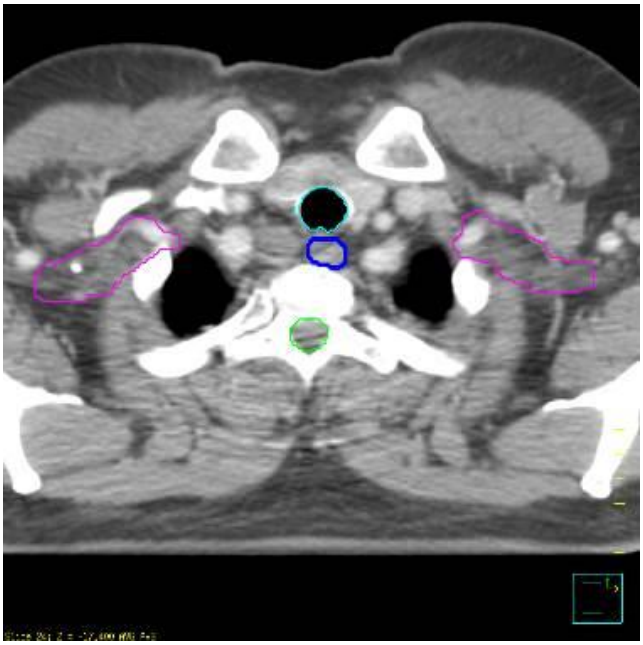
Superior extent of the trachea /oesophagus (below cricoid)



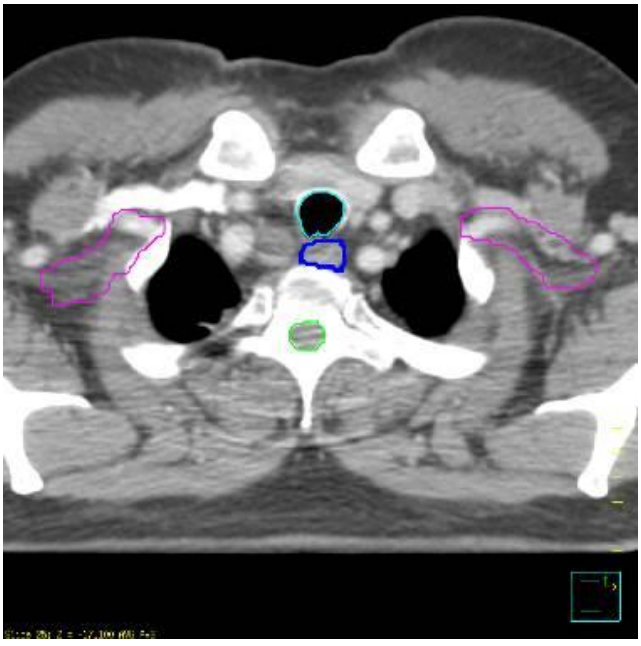
7. Image 7



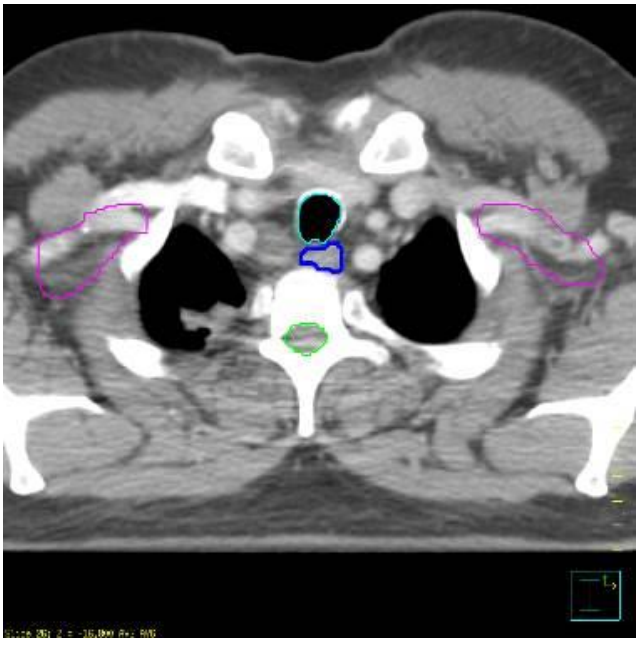
8. Image 8



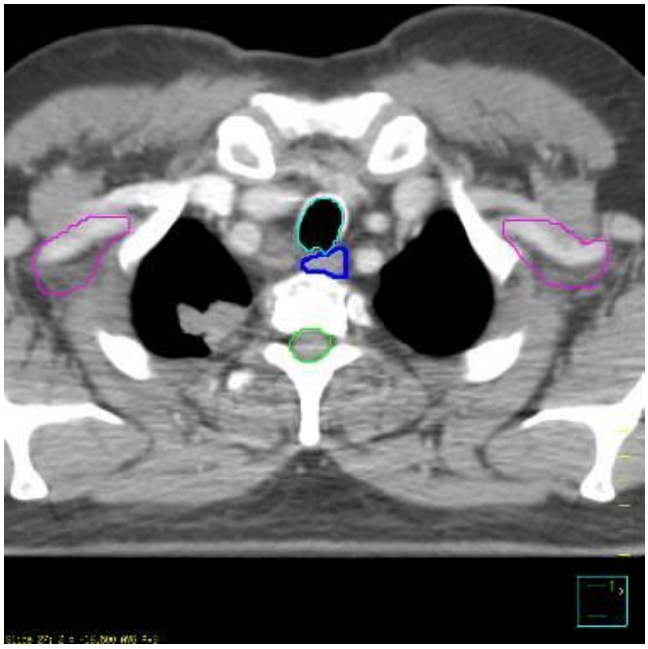
9. Image 9



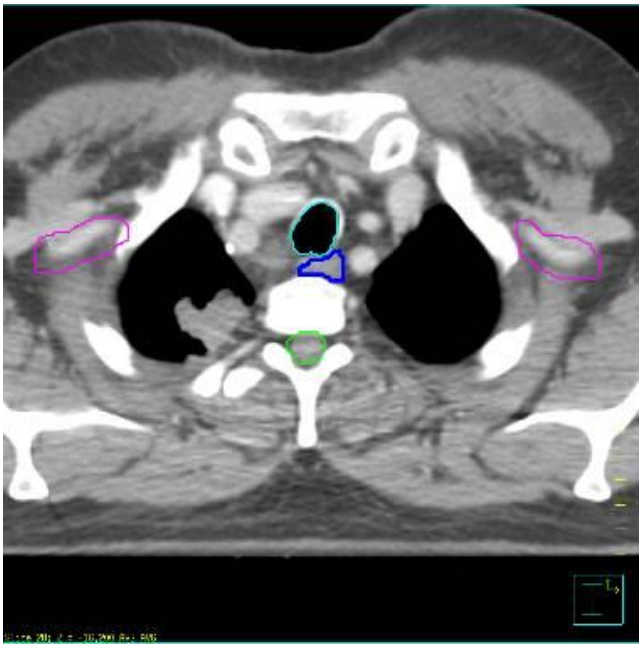
10. Image 10



11. Image 11

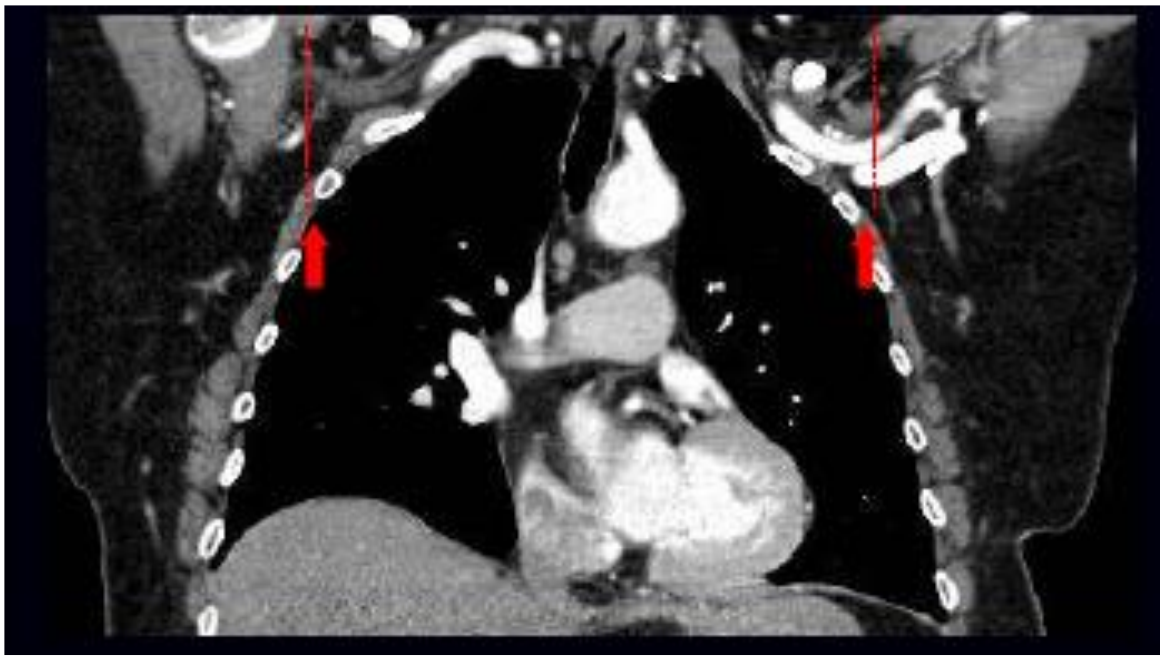


12. Image12



13. Image 13

Inferior extent of the brachial plexus, ending after the neurovascular structures across the 2nd rib



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