Thames Valley and Wessex Radiotherapy Network

Radiotherapy Protocol

Small Cell Lung Cancer

This document is the standardised Thames Valley and Wessex Radiotherapy Network Treatment Protocol for treatment of small cell lung cancer developed collaboratively by the Network Lung Protocol Working Group:

Trust	Clinician	Physicist	Radiographer
Oxford University Hospitals NHS Foundation Trust	Dr Niki Panakis	Sriram Padmanaban	
University Hospitals Dorset NHS Foundation Trust	Dr Mark Noble		
Portsmouth Hospitals University NHS Trust	Dr Hannah Bainbridge Dr Yoodhvir Singh Nagar	Sarah Muscat	
Royal Berkshire Hospitals NHS Foundation Trust	Dr Joss Adams		
University Hospitals Southampton NHS Foundation Trust	Dr Paul Fenton Dr Victoria Wood Dr Andrew Bates	Stephen Thompson	

Document History

Date of Issue	Version Number	Date Approved	Responsible for Change	Nature of Change	Ratification/ Approval
26.9.2023	1.0		The Lung Protocol Working Group	-	

1. Objective and Scope

To summarise the planning and treatment regimes used in the treatment of limited and extensive stage small cell lung cancer (SCLC) with concomitant [3] or sequential chemotherapy [1, 2] and prophylactic cranial irradiation (PCI), for use in the Radiotherapy Centres within the Thames Valley and Wessex Radiotherapy Network.

2. Indications and Selection Criteria

Combining chemotherapy and radiotherapy is now regarded as a standard treatment for limited stage small cell lung cancer.

2.1. Radical radiotherapy- thoracic irradiation with concurrent chemotherapy [3, 7]

Radical thoracic radiotherapy improves overall survival and local control in patients with stage I-III small cell lung cancer. The CONVERT trial confirms optimal results with either a twice a day fractionation schedule or daily fractionation schedule, however there was a trend to improved survival with the twice a day schedule, and this should be the standard of care in patients with limited disease [6].

Suitable patients should fulfil the following criteria:

a) Patients with limited stage disease (Veterans Administration Lung Cancer Study Group) i.e., patients whose disease can be encompassed within a single radical radiotherapy portal and the radiotherapy target volume is felt to be acceptable for radical treatment by the clinician in charge of the case.
b) Patients should normally have an adequate pulmonary reserve with FEV1 >1.0 litre or >40% predicted, TLCO >40% of predicted. Small volumes may be treated in patients with lung function below these limits at the clinician's discretion.
c) Normal serum creatinine and calculated GFR ≥ 50ml/min according to the Cockcroft-Gault formula. If calculated GFR <50ml/min then EDTA GFR should be performed
d) Adequate haematological function with neutrophils ≥1.5 x 109 /platelets >100 x 109/l.
e) Adequate liver function with ALT and AST ≤2.5 x ULN.

2.2. Thoracic consolidation radiotherapy- thoracic irradiation following induction chemotherapy in <u>limited</u> stage SCLC

If the disease is too extensive or PS / comorbidities preclude primary concomitant chemoradiation, but the disease is confined to the hemithorax and there has been tumour shrinkage with first line chemotherapy, then consolidation with thoracic radiotherapy should be considered delivering 40.05 Gy in 15x 2.67 Gy x5/week fractions [7] or 50 Gy in 25#.

Suitable patients should fulfil the following criteria:

a) Patients with limited stage disease (Veterans Administration Lung Cancer Study Group) i.e., patients whose disease can be encompassed within a single radical radiotherapy portal. The RT target volume is acceptable for radical treatment by the clinician in charge of the case.
b) Patients should normally have an adequate pulmonary reserve with FEV1 >1.0 litre or >40% predicted, TLCO >40% of predicted. Small volumes may be

treated in patients with lung function below these limits at the clinician's discretion.

Patients should also be considered for prophylactic cranial irradiation (PCI) at the same time as receiving thoracic radiotherapy.

2.3. **Thoracic consolidation radiotherapy- thoracic irradiation following induction chemotherapy in <u>extensive</u> stage SCLC.**

Suitable patients should fulfil the following criteria:

a) Extensive stage SCLC
b) Performance status (PS): 0-2
c) Any response after 4-6 cycles of platinum etoposide chemotherapy
d) Thoracic treatment volume considered acceptable is judged by a clinical oncologist
e) No clinical evidence of brain, leptomeningeal or pleural metastases
f) No previous radiotherapy to the brain or thorax.

Patients within Impower133 were allowed to receive PCI (although we note that only approximately 10 % patients did have PCI), but not thoracic radiotherapy, therefore the use of radiotherapy in these situations should be carefully considered regarding the risks versus benefits. Where the bulk of disease is thoracic with small numbers of metastatic deposits and patients have good lung function it would not be unreasonable to consider consolidation radiotherapy with immunotherapy.

2.4. **Prophylactic cranial irradiation (PCI)**

Patients with both limited [11,12] and extensive stage SCLC [13] with a performance status of 0-2 who have evidence of disease response to 1st line chemotherapy should be considered for PCI no later than 6 weeks after the final cycle of chemotherapy.

Patients with a history of cerebrovascular disease are at higher risk of radiotherapy toxicities and should be approached with caution with regards to PCI.

In patients who are unsuitable for PCI consider MRI Brain. In the Japanese extensive stage SCLC study [10], MRI brain 3 monthly in year 1 and 6 monthly in year 2 was non-inferior to PCI. Median OS 11.6 months in PCI cohort vs 13.7 months in those undergoing MRI surveillance. Caution, however, should be exercised with this approach as the study population and treatment regimes differ in this study compared to the UK population.

2.5. **Re-irradiation**

Palliative re-irradiation may be considered in symptomatic patients. It depends on the expected prognosis and the patient's symptoms. The risks and benefits of re-irradiation need to be discussed between the treating clinician and the patient and ideally within the peer group. Time elapsed from previous treatment, use of chemotherapy, previous thoracic surgery, comorbidities, lung function, dose to organs at risk and evidence of late radiation sequelae are all important in the decision making.

Dose to organs at risk need to be determined on a case-by-case basis taking all the above into account.

3. Pre-Radiotherapy Investigations

3.1. **History:** Including any pre-existing lung disease and weight loss over 10%.

3.2. **Clinical examination:**

- Include patient's height, weight, and performance status (PS).
- Advice about physical activity including referral to dedicated activity programmes where possible.
- Screening for malnutrition and dietetic advice as appropriate.
- Advice for smokers, e.g., 'Very brief advice', the offer of medication to treat tobacco addiction and referral to a specialist team for more intensive support.

3.3. **Diagnostic imaging:**

- Staging CT chest and upper abdomen

3.4. **Histological confirmation**

3.5. **Pleural aspiration if patient has pleural effusion:** Pleural effusion should normally be regarded as an exclusion criterium for radical radiotherapy of SCLC, unless cytologically negative and thought to be unrelated to lung cancer.

3.6. **Lung function tests** form part of an assessment of a patient's ability to tolerate radical radiotherapy.
Spirometry and diffusion capacity testing within six weeks of radiotherapy.
FEV1 >1 litre or 40% of predicted value
KCO (DLCO/VA) > 40% predicted value
TLCO > 40% predicted value
As per NICE guidelines, patients with small tumours (PTV<150ml) can be treated with an FEV1 ≥ 0.7 litres.
(Patients with lung function outside these ranges may still be suitable for radical radiotherapy which should be considered on a case-by-case basis taking into account tumour size, position, degree of movement, and functional assessment. In some cases, the final decision regarding suitability for radical radiotherapy can only be made on review of the radiotherapy plan and assessment of the organ at risk doses.)

3.7. Be aware that patients who have had radical radiotherapy are at risk of fragility fractures of the vertebrae which may be visible on routine post-treatment imaging. Consider referral to a fracture liaison service or rheumatologist.

3.8. Assess patients for relevant co-morbidities (e.g., lung fibrosis, auto-immune conditions, use of radio-sensitising medication) and liaise with the relevant specialist team to assess the impact on the feasibility of treatment and the potential for increased toxicities.

3.9. Consider all patients receiving radical radiotherapy for prophylactic treatment of pneumocystis jiroveci pneumonia (PJP) during or after their treatment if they are thought to be at risk, e.g., lymphocyte count <0.6x109/L, patients on steroids for more than four weeks, patients having combined-modality treatment.
Treatment should continue until lymphocyte count >0.6x109/L or for a minimum of six weeks post radiotherapy.

4. Therapeutic Schemata

Table 1. Dose and fractionation schedules

Clinical indications	Dose and fractionation schedules
Concurrent chemoradiotherapy (stages I-III)	Concurrent chemoradiotherapy with cisplatin and etoposide should be delivered with either: • 45 Gy in 30 fractions treating twice daily over 3 weeks • 66 Gy in 33 fractions over 6.5 weeks
Sequential chemoradiotherapy	• 40 Gy in 15 daily fractions over 3 weeks
Prophylactic cranial irradiation (PCI) (stages I-III)	Selected patients with locally advanced metastatic SCLC who respond to primary chemotherapy should be offered PCI. Recommended schedules are: • 20 Gy in 5 fractions over 1 week • 30 Gy in 10 fractions over 2 weeks • 25 Gy in 10 fractions over 2 weeks • 30 Gy in 12 fractions over 2.5 weeks
Prophylactic cranial irradiation (PCI) (stage IV)	Selected patients with metastatic SCLC who respond to primary chemotherapy should be offered PCI: • 20 Gy in 5 fractions over 1 week • 30 Gy in 10 fractions over 2 weeks • 25 Gy in 10 fractions over 2 weeks • 30 Gy in 12 fractions over 2.5 weeks

4.1. Review on treatment

- Consider weekly review from week 2 onwards (or more often if specified by doctor).
- To record patient's weight (if severe weight loss occurs referral to a dietician arranged) and manage treatment related toxicity.

4.2. Supportive care

- Skin toxicity is usually not severe – see Skin Care Guidelines for advice and topical creams which can be used.
- Chest wall discomfort may require simple analgesics.
- Oesophagitis is uncommon.
- Consider neurologist input in myasthenia

4.3. Category

- Classified as Category 1 in the RCR guidelines: The timely delivery of radical radiotherapy.

5. Pre-Treatment

5.1. Pre-planning

- Patients will receive an explanation of the radiotherapy process and expected side effects and outcome
- They will consent to the treatment and be given the patient information sheets

5.2. Patient simulation and immobilisation

- Assess physical disability that may affect treatment position and employ strategies to enable the delivery of radiotherapy (e.g., physiotherapy, alternative treatment position such arms down, analgesia)
- Patients will be positioned on the CT couch using appropriate immobilisation preferably in the supine position with arms supported above their head. If the patient is unable to raise their arms above their head, or has a superior tumour, the patient should be planned supine with arms by sides in a vac-bag to raise the arms up to the mid-axillary line.
- The planning CT will be conducted in the RT department; a free-breathing helical radiotherapy planning (RTP) CT image will be acquired for target/OAR delineation and dosimetry planning, followed by a free-breathing 4DCT.
- The extent of the helical planning CT scan must be sufficient to include all potential organs at risk. As a guide, contiguous axial slices of 2.5mm will be obtained from the upper cervical spine to the lower edge of the liver, taking care to include all lung parenchyma on the planning scan.
- The extent of the 4DCT should be equivalent to the helical planning CT scan.
- Intravenous contrast is normally used for help to define mediastinal structures. Department may consider administering contrast during 4DCT acquisition if technical capabilities allow rather than undertaking a separate 3D scan with contrast. This will be specifically requested on the planning request form and given at the time of the helical radiotherapy planning scan.
- In the absence of 4DCT a free breathing helical CT scan will be acquired, and the treatment planned using conventional margins.
- The radiographers will review the 4DCT scan and label the maximum exhale and maximum inhale datasets.

5.3. Image Fusion

- CT-CT fusion:
    - In the absence of appropriate IV contrast enhanced CT Simulation; diagnostic images may be registered to the planning CT scan.
    - If delivering RT after induction chemotherapy or PORT, pre-chemotherapy or pre-operative diagnostic CT scan images may be registered to the planning CT scan.

All registrations are to be reviewed and approved by the treating consultant.

6. Volume Definitions

(ICRU 50, 62 [4, 5])

- **4D_ GTV** generated from 4DCT data set using either the maximum intensity projection or extremes of tumour motion.
- No 4D GTV if scanned with a DIBH or 4DCT unavailable
- Following induction chemotherapy, the GTV is the post-chemotherapy extent of disease in the primary and pre-chemotherapy nodes involved. With PORT there is no GTV just a CTV to include all the margins at risk and surgical clips taking into consideration the pre-operative extent of disease with respect to the change in anatomical boundaries following surgery.
- **4D_CTV**=ITV: A margin is added to the 4D_GTV to treat subclinical or microscopic disease which must be treated to achieve cure. This recommended margin is 5mm - 8mm which can be based on the histological sub-type or radiological appearances of the tumour. The CTV can be edited to exclude anatomical boundaries that limit microscopic spread such as bone and chest wall evaluated on the 4D imaging.
- Elective nodal irradiation: There is no role for elective nodal irradiation.
- Following induction chemotherapy: The CTV should include all lymph node stations involved prior to chemotherapy irrespective of disease response. Where induction chemotherapy has been given to shrink the primary tumour and make the disease encompassable within a radical RT portal it is appropriate to treat the post-chemotherapy extent of disease in the primary (GTV) with a margin for CTV. If, however pre-chemotherapy primary tumour size is acceptable consider treating the pre-chemotherapy extent of disease in the primary with respect to anatomical boundaries.
- In the postoperative setting: the CTV should include all the margins at risk taking into consideration the pre-operative extent of disease with respect to the change in anatomical boundaries following surgery
- **PTV**: A set-up margin will be added to the 4D_CTV to account for variations in set-up with the immobilisation technique employed and corrected for by using daily image guided kV CBCT. With daily online CBCT imaging and repositioning a 5 mm margin should be sufficient to account for setup variability. The CTV-PTV margin should not be edited.
- Conventional CTV-PTV margins are defined below where a 4DCT was not possible:
    - Conventional margins (non 4DCT)
    - **CTV to PTV**

    axial 5mm-10mm sup-inf 10mm-15mm depending on tumour location.

(OAR nomenclature as per Mir et al [15])

In general, any OARs which are traversed by the treatment beam should be contoured. Where OAR constraints are based on the dose received by the whole organ (e.g., lung, liver, spleen) the whole organ should be contoured. Otherwise, a volume of OAR should be outlined, sufficient to show that the OAR constraints have been met, with particular care paid to the volume receiving the highest doses. OARs should be contoured at least ≥20mm superiorly and inferiorly to the PTV for coplanar techniques. The body contour should be contoured wherever the beams traverse it. The skin

should be inspected to ensure that the beams do not overlap, producing excessive skin dose, especially where there is a skin fold.

- Consider for the upper lobe tumours close to Brachial Plex_L/R
  - The ipsilateral brachial plexus is defined as originating from the spinal nerves exiting the neural foramina on the involved side from C5 to T2. Only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus (1) (5). Use of a contrast enhanced CT may assist with outlining with contrast administered in the contralateral arm to the tumour.
- Heart+A_Pulm
  - Heart will be contoured along with the pericardial sac. Defined superiorly as superior aspect of the pulmonary artery (as seen in a coronal reconstruction of the CT scan) and inferiorly to the apex of the heart.
- Oesophagus
  - Contoured using the mediastinal window setting from the thoracic inlet to the gastro-oesophageal junction and to include the mucosal, submucosa and all muscular layers out to the fatty adventitia at least 20mm above and below the PTV.
- Non_GTV_Lung
  - Both lungs segmented as a single structure using pulmonary windows. GTV, trachea and ipsilateral bronchus shall be excluded.
- Spinal_Canal
  - Contoured at least for 20mm above and below the PTV based on the bony limits of the spinal canal.
- For left lower lobe tumours the spleen should be contoured.
- Any other structures deemed appropriate by the consultant.

When non-coplanar beams are used additional organs may be irradiated i.e., bowel, stomach, or liver. Allowances should be made for this. It is recommended that the entire liver is scanned and segmented for lower lobe tumours and tolerances for these organs are defined.

All contours shall be reviewed and signed-off by the prescribing clinician.
Each centre should have a peer-review programme for lung cancer radiotherapy. Peer review should involve assessment of contours and may involve review of plans.

7. Treatment Planning

- 6 MV photons to be used for planning. For RA or VMAT dose is prescribed to the median dose in PTV as per ICRU 83.

8. Plan Evaluation

8.1. Target coverage

Table 2. Aimed dose objectives for assessing CTV and PTV coverage

Target Volume	**Goal Doses**	**Importance**
PTV	V 95% > 90%	Mandatory
	V 95% > 95%	Optimal
	V 90% > 98%	Mandatory
	V 85% > 99%	Optimal
	V 80% > 99%	Optimal
	D5% ≤ 105%	Mandatory
	D2% ≤ 105%	Optimal
	D2% ≤ 107%	Mandatory
CTV	V 95% > 99%	Mandatory

*In some situations, the mandatory constraints will not be possible to achieve.

8.2. Dose limitation to organs at risk (OAR)

Table 3. Summary OAR dose constrains

Organ	Volume	Fractionation Scheme		
		45 Gy / 30 # (BD) From CONVERT protocol [6]	2.67 – 2.75 Gy per fraction (OD) [14]	1.8 – 2 Gy per fraction (OD)
Spinal Canal/ Spinal Canal PRV	$D_{max\ 0.1\ cc}$	42 Gy	42 Gy (optimal) 44 Gy (mandatory)	48 Gy
Brachial Plexus**Invalid source specified.**	$D_{max\ 0.1\ cc}$	45 Gy	55 Gy	66 Gy
Heart/ Pericardium	D_{mean}		< 22.5 Gy (optimal)	< 26 Gy (mandatory)
			V_{30} < 36 % (mandatory)	
Oesophagus	D_{mean}	< 34 Gy (optimal)	< 29 Gy (optimal)	< 34 Gy (optimal)
Lung-GTV / iGTV	D_{mean}	< 18 (optimal) < 20 Gy (mandatory)	< 15 Gy (optimal) < 18 Gy (mandatory)	< 18 Gy (optimal) < 20 Gy (mandatory)
			V_{18} < 30 % (optimal)	
		V_{20} < 30 % (optimal)	V_{20} < 30% (optimal) < 35 % (mandatory)	V_{20} < 30 % (optimal)

		< 35 % (mandatory)		< 35 % (mandatory)
Lung contralateral		V_5 < 60 % (optimal)	V_5 < 60 % (optimal)	V_5 < 60 % (optimal)

Organ at risk (OAR) dose constraints are mainly empirical and have for the most part not been validated vigorously. Therefore, the recommendations here are not prescriptive but are the useful reference doses that have been used in international clinical trials. These constraints represent doses that generally should not be exceeded. Because the risk of toxicity increases progressively with dose to normal tissues, a key principle of radiation treatment planning is to keep normal tissue doses "as low as reasonably achievable" while adequately covering the target. The doses to any given OAR should be typically lower than these constraints, approaching them only when there is close proximity to the target volume.

After surgery, lung tolerance to RT is much less than for patients with intact lungs; therefore, more conservative constraints should be used for postoperative RT (PORT). It is also recommended to use more conservative lung dose limits in patients with interstitial lung disease / UIP. The tolerance of these patients is low although not well characterised.

- **Non-GTV lung**: uninvolved lung at the same craniocadual level as the PTV may receive up to full dose subject to the following provisos summarised in Table 3 [3].

  If these limits are exceeded the plan should be discussed with the consultant.

  V_{18} is radiobiological equivalent of V_{20} for hypofractionated regimes (20 fractions) with radiation fibrosis as the end point, $\alpha/\beta = 3$.

  These dose limits are not acceptable for PORT due to the loss of lung volume following surgery and should be reviewed in the peer review meeting as there is little evidence to guide us on acceptable dose limits post-operatively. The experience of lung toxicity in mesothelioma patients treated with Extra-Pleural Pneumonectomy suggest that the V_{20} should be <4-10%, V5 <60% and MLD < 8Gy [4, 5].

- **Spinal canal or PRV_CANAL**: A D_{max} of 50 Gy EQD2 to the full cross section spinal cord is associated with a 0.2% risk of myelopathy and may be an acceptable dose to spinal canal or PRV_CANAL if the PTV is closely related to the spinal cord. This must be approved by the clinician and the peer review group. The trade-off between risks and benefits of radical treatment must be fully discussed with the patient.

- **Heart**: ADSCAN used the Emami data T/D 5/5 the entire heart should not exceed 40 Gy. Up to 30% of the heart if closely associated with the CTV may receive 66 Gy. Up to 67% of the heart may receive 50 Gy. This data is historical and more up to date QUANTEC data is recommended (see Table 3).

- **Oesophagus:** current lack of data means that absolute limits cannot be imposed. The aim is to keep the D_{max} less than the treatment dose if possible (not practical if the PTV overlaps with the oesophagus). In a study using a similar treatment regime to our own, the incidence of acute RTOG ≥G3 oesophageal toxicity was increased once the D_{max} exceeded 58Gy with chemotherapy (induction or concomitant) and 69Gy with no chemotherapy [12]. Similarly in a Japanese study D_{max} > 60Gy resulted

in a 46% incidence of acute RTOG ≥G3 toxicity [13]. QUANTEC data recommendations in Table 3 [14].

- **Brachial plexus**: Damage to the brachial plexus can arise following surgery or radiation. Brachial plexopathy manifests clinically as neuropathic pain, paraesthesia, or motor weaknesses of the upper extremities, and can cause significant morbidity. Radiation induced brachial plexopathy (RIBP) is a late toxicity that can present months to years following a course of radiotherapy.

  Classically, the dose tolerance as defined by Emami for the brachial plexus is 62 Gy, 61 Gy, and 60 Gy to one third, two thirds, and the whole plexus volume respectively, for a 5% risk of RIBP at 5 years.

  In Emami's recent update, the dose tolerance for the brachial plexus remained at 60 Gy but is now defined as a maximum point dose to reflect the serial nature of the plexus as an organ. Modern RTOG constraints vary between 60 Gy (RTOG 0412, 0435,0522) and 66 Gy (RTOG 0615, 0617) maximum point doses. The supporting evidence for these recommendations is scarce however and is derived from a small number of observational studies that comprise the basis of these widely accepted clinical guidelines. **Invalid source specified.**

- **Stomach**: Optimal dose constraints V50Gy <5cc and V_{45}<75cc AND d0.1cc <54Gy.

- **Liver**: Emami TD5/5 for whole organ irradiation > 30Gy. D_{mean} for 2 Gy/ fraction < 28 Gy.

- **Spleen:**

  Special consideration needs to be taken with tumours in the base of the left lower lobe where there may be overlap of dose with the spleen, particularly where prognosis is > 1 year. The spleen is very radiosensitive and low dose RT may impact on splenic function. Patients with a dysfunctional spleen are at risk of overwhelming sepsis from encapsulated bacteria, which can potentially be life-threatening.
  For patients with a PTV on the same level as the spleen, mean splenic dose and V10 should be considered and recorded. Aim to keep the spleen D_{mean} < 10Gy. If the mean splenic dose is >10Gy the patient should be considered at high risk for functional hypo-splenism and managed based on national guidelines from the British Committee for Standards in Haematology. This should include pneumococcal, haemophilus influenza type B conjugate vaccine, meningococcal conjugate vaccine at least 2 weeks prior to starting RT. In addition, prophylactic antibiotics should be offered and started when RT starts and given a supply of emergency antibiotics.

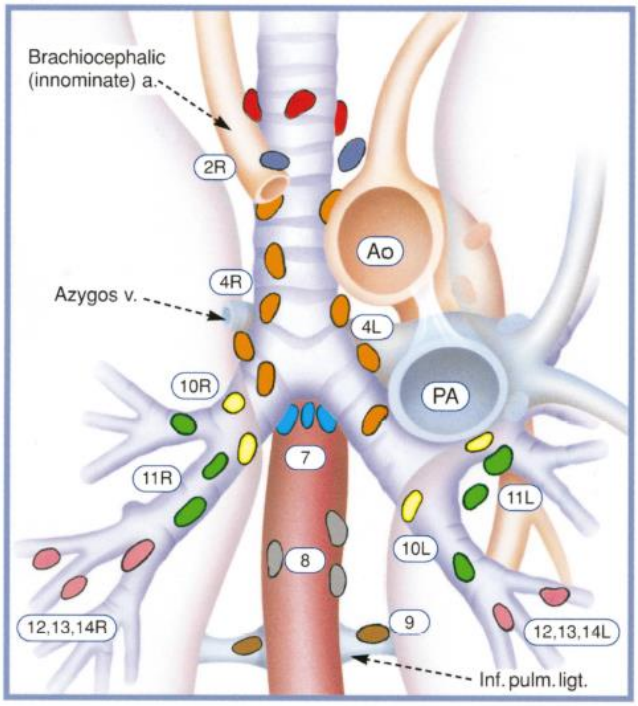
  When the PTV is close to OARs, follow these priorities as a guide: Spinal canal or canal PRV D_{max}, lung V_{20}, mean lung dose, PTV coverage, oesophagus (would accept overdose to the oesophagus), Brachial plexus D_{max} if it overlaps with the PTV to meet the constraint on PTV coverage.

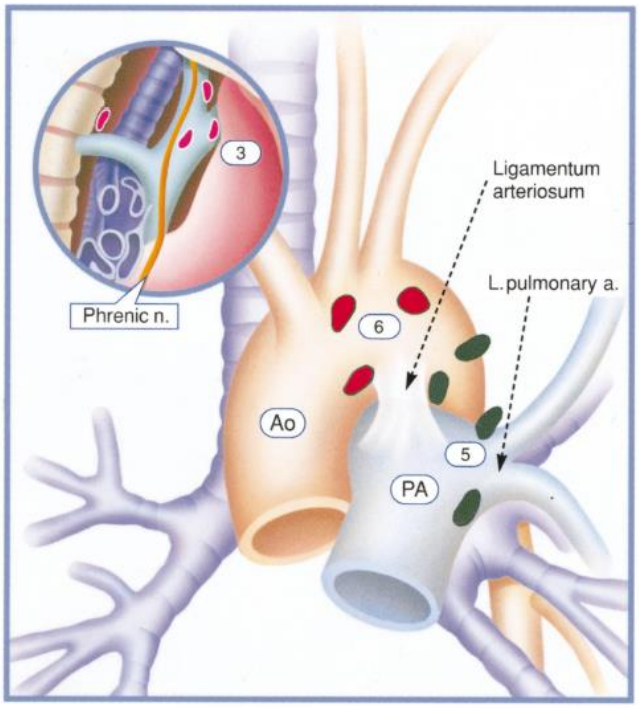
9. Follow up after Treatment

Patients should be seen in out-patients in line with the need for pre-chemotherapy assessment (aim to give further cycles of chemotherapy post radiotherapy to a total

of 4-6 cycles) or 3-4 weeks after completing radiotherapy with a chest X-ray on arrival.
Patients should be considered for PCI to start within 6 weeks of their last cycle of chemotherapy.
A baseline CT thorax/abdomen should be requested 8-10 weeks after completing concomitant chemoradiotherapy to the thorax.
A further CT scan may be requested at 12 months.
Clinic reviews should be 3 monthly for two years, 4-6 monthly thereafter.

Appendix 1: Surgical Nodal Stations





Superior Mediastinal Nodes

- **1** Highest Mediastinal
- **2** Upper Paratracheal
- **3** Pre-vascular and Retrotracheal
- **4** Lower Paratracheal (including Azygos Nodes)

N_2 = single digit, ipsilateral
N_3 = single digit, contralateral or supraclavicular

Aortic Nodes

- **5** Subaortic (A-P window)
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- **7** Subcarinal
- **8** Paraesophageal (below carina)
- **9** Pulmonary Ligament

N_1 Nodes

- **10** Hilar
- **11** Interlobar
- **12** Lobar
- **13** Segmental
- **14** Subsegmental

(Mountain/Dresler modifications from Naruke/ATS-LCSG Map)

Appendix 2: Lymph Node Map Definitions

Lymph Node Map Definitions [16]

Anatomic Landmarks	Anatomic Landmarks
N2 nodes—All N2 nodes lie within the mediastinal pleural envelope	
1 Highest mediastinal nodes	Nodes lying above a horizontal line at the upper rim of the bracheocephalic (left innominate) vein where it ascends to the left, crossing in front of the trachea at its midline
2 Upper paratracheal nodes	Nodes lying above a horizontal line drawn tangential to the upper margin of the aortic arch and below the inferior boundary of No. 1 nodes
3 Prevascular and retrotracheal nodes	Prevascular and retrotracheal nodes may be designated 3A and 3P; midline nodes are considered to be ipsilateral
4 Lower paratracheal nodes	The lower paratracheal nodes on the right lie to the right of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the right main bronchus at the upper margin of the upper lobe bronchus, and contained within the mediastinal pleural envelope; the lower paratracheal nodes on the left lie to the left of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the left main bronchus at the level of the upper margin of the left upper lobe bronchus, medial to the ligamentum arteriosum and contained within the mediastinal pleural envelope Researchers may wish to designate the lower paratracheal nodes as No. 4s (superior) and No. 4i (inferior) subsets for study purposes; the No. 4s nodes may be defined by a horizontal line extending across the trachea and drawn tangential to the cephalic border of the azygos vein; the No. 4i nodes may be defined by the lower boundary of No. 4s and the lower boundary of No. 4, as described above
5 Subaortic (aorto-pulmonary window)	Subaortic nodes are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope
6 Para-aortic nodes (ascending aorta or phrenic)	Nodes lying anterior and lateral to the ascending aorta and the aortic arch or the innominate artery, beneath a line tangential to the upper margin of the aortic arch
7 Subcarinal nodes	Nodes lying caudal to the carina of the trachea, but not associated with the lower lobe bronchi or arteries within the lung
8 Paraesophageal nodes (below carina)	Nodes lying adjacent to the wall of the oesophagus and to the right or left of the midline, excluding subcarinal nodes
9 Pulmonary ligament nodes	Nodes lying within the pulmonary ligament, including those in the posterior wall and lower part of the inferior pulmonary vein
N1 nodes—All N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura	
10 Hilar nodes	The proximal lobar nodes, distal to the mediastinal pleural reflection and the nodes adjacent to the bronchus intermedius on the right; radiographically, the hilar shadow may be created by enlargement of both hilar and interlobar nodes
11 Interlobar nodes	Nodes lying between the lobar bronchi
12 Lobar nodes	Nodes adjacent to the distal lobar bronchi
13 Segmental nodes	Nodes adjacent to the segmental bronchi
14 Subsegmental nodes	Nodes around the subsegmental bronchi

From Moutain et al., Chest 1997

Appendix 3: References

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