Thames Valley and Wessex Radiotherapy Network

Radiotherapy Protocol

Non-Small Cell Lung Cancer (NSCLC) - Radical

This document is the standardised Thames Valley and Wessex Radiotherapy Network Non-Small Cell Lung Cancer (NSCLC) Radical Treatment Protocol developed collaboratively by the Network Lung Protocol Working Group:

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1. Objective and Scope

To summarise the planning and treatment of patients with non-small cell lung cancer (NSCLC) receiving a curative dose of radiotherapy, for use in the Radiotherapy Centres within the Thames Valley and Wessex Radiotherapy Network.

2. Indications

2.1. **Stage I-IIA NSCLC** - T1N0M0 or T2N0M0: The majority of these patients should be offered surgery, SABR or radiological ablation. Where these treatments are not appropriate fractionated radical radiotherapy can be considered.

2.2. **Stage IIB NSCLC** - T3N0M0 or T2N1M0: Radical radiotherapy may be offered to patients who decline surgery or who are medically inoperable. Patients with node positive disease can be offered radical chemo-radiotherapy but are not eligible for adjuvant Durvalumab. Some patients with stage T3N0M0 by virtue of satellite nodules will be suitable for treatment with SABR.

2.3. **Stage III NSCLC** - T1N2M0, T2N2M0, T3N1-2M0, T4N0-2M0 and selected patients with N3 disease if all disease can be encompassed within a radical radiotherapy field: Concurrent chemotherapy followed by adjuvant Durvalumab should be considered for eligible patients (see section 4.6. below). In patients not suitable for concurrent chemotherapy, sequential chemotherapy without adjuvant Durvalumab or radical radiotherapy alone can be given.

2.4. **Pancoast (Superior Sulcus tumours):** Patients should be considered for trimodality therapy involving Neoadjuvant chemoradiotherapy followed by surgery withing 3-5 weeks of completion of CRT ± adjuvant chemotherapy. If surgery is unlikely to be possible, standard radical radiotherapy/chemoradiotherapy can be considered instead.

2.5. **Post-operative Radiotherapy (PORT**): Can be considered in patients with NSCLC and a positive resection margin following completion of adjuvant chemotherapy. PORT for occult pN2 disease is not routinely recommended following adjuvant chemotherapy, but can be considered following MDT discussion in the setting of extra-capsular spread.

2.6. The EORTC Phase III LungART clinical trial (LungART) reported no difference in 3 year disease free survival delivering post-op radiotherapy after a R0 resection (1) Patients were allowed to have previous neoadjuvant or adjuvant chemotherapy.

2.7. **Re-irradiation:** In very select cases/ circumstances radical re-irradiation may be considered. It depends on the expected prognosis and there being no suitable alternative treatment including SABR. The risks and benefits need to be discussed and documented within a peer group, ratified by the group and fully discussed with the patient. Time elapsed from previous treatment, the use of chemotherapy, previous surgery, associated comorbidities, lung function, BED to points of interest and evidence of radiation sequelae are all important in any decision. Consider

chemotherapy initially to reduce the treatment volume if appropriate. Dose constraints have to be determined on a case-by-case basis taking all the above into consideration and defined at the contouring stage.

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:**

- CT scan of chest, liver, and adrenal glands, with contrast unless contraindicated.
- Perform a PET-CT preferably within six weeks before commencing treatment (and ideally within four weeks) in all patients having curative-intent radiotherapy. If the time interval is greater than six weeks, consider repeating the PET-CT scan to confirm treatment and target volume.
- CT or MR brain with contrast to exclude occult metastatic disease is recommended by NICE for patients with stage II and III disease (this can be undertaken at the time of the PET-CT scan);
- MRI thorax/brachial plexus is helpful in defining the extent of Pancoast tumours and can be fused with the radiotherapy planning CT scan.
- Bronchoscopy: To determine endo-bronchial extent of central tumours.
- Offer immediate testing for PD-L1 to patients with unresectable stage III non-small cell lung cancer.

3.4. **Histological confirmation:** Undertake systematic pathological nodal staging (e.g., staging endobronchial ultrasound and biopsy) in any patient with enlarged intrathoracic lymph nodes on CT imaging (>10mm short axis) or FDG-avid intrathoracic lymph nodes on PET. Do not rely on radiological nodal staging alone.

In rare situations treatment can be undertaken in the absence of histological diagnosis following discussion in the Lung MDT on the basis of an enlarging mass on CT and increased isotope retention on PET-CT where biopsy not feasible.

3.5. **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.)

3.6. 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.

3.7. 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.

3.8. 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

Discuss all operable stage III NSCLC patients in a multidisciplinary team meeting that includes both a surgeon and a clinical oncologist. Patients being considered for preoperative treatment should ideally see a surgeon and an oncologist before starting treatment to confirm suitability for each therapy.

4.1. Chemoradiotherapy

This radiotherapy regimen can be used on its own as definitive treatment for early-stage NSCLC, or with either sequential or concurrent chemotherapy for locally advanced disease.

4.1.1. Concurrent chemoradiotherapy (CRT)

- **Inoperable stage II N1 and stage III offer** concurrent CRT as standard care to good performance status patients (WHO PS 0-1) with no significant comorbidities and with localised disease easily encompassed within a radical radiotherapy field.
- Two cycles of platinum doublet (preferably cisplatin)
- Prophylactic GCSF and antibiotics are to reduce the risk of neutropenia/neutropenic sepsis

- A diagnostic CT within a week of completion of concurrent chemoradiotherapy (CRT**) in operable patients** having preoperative treatment to exclude out-of-field progression.
- Offer adjuvant Durvalumab (see section 4.6. below) to all patients within 42 days of completing definitive CRT unless the tumour is PD-L1 negative (<1%), there is a contraindication to anti PD-L1, WHO PS has declined (≥2), side effects of CRT have not resolved or there is evidence of disease progress on a CT scan.

4.1.2. Sequential chemoradiotherapy

- Can be considered where concurrent chemoradiotherapy is not possible due to tumour size or patient co-morbidities and a radiotherapy plan and dosimetric assessment using advanced planning techniques show that OAR does are unacceptably high for a concurrent technique.
- Adjuvant Durvalumab is not funded for use following sequential chemoradiotherapy.
- Treated with 3-4 cycles of a platinum doublet (induction chemotherapy).
- Non-squamous pathology: Platinum agent plus Pemetrexed or Vinorelbine.
- Squamous pathology: Platinum agent plus either Vinorelbine or Gemcitabine.

4.1.3. Resectable trimodality treatment for Pancoast tumours

- Treatment schema is based on the SWOG 9416 phase 2 protocol and should be only used if the surgeons have reviewed the patient upfront and if there is a planned date for surgery **(2)**. Given the recent neo-adjuvant chemo/IO data prior to resection **(3)** in resectable patients careful MDT discussion is required regarding whether patients would have neo-adjuvant chemo/IO or 45/25 Gy prior to surgery.

  It is demanding, and patients should normally be of WHO performance status 0 or 1.
- 45Gy in 25# x1.8Gy fractions x5/week using 6MV photons is administered together with platinum doublet (preferably cisplatin).
- 60-66 Gy in 2 Gy / fraction or equivalent for borderline resectable or unresectable patients with Pancoast tumours.
- Prophylactic GCSF and antibiotics recommended reducing the risk of neutropenia/neutropenic sepsis. Both chemotherapy and radiotherapy should start on Day 1 which must fall on a Monday. Two further cycles of chemotherapy can be given once definitive surgery is complete.

4.2. Radiotherapy

Table 1. Dose and fractionation schedules

Clinical indications	Dose and fractionation schedules
Stage I-II NSCLC (radical radiotherapy alone)	• For use in patients not suitable for SABR. • Dose of 55-60Gy in 20 fractions of 2.75Gy per fraction delivered on consecutive days x5 per week in line with the RCR guidelines on RT dose fractionation Third Edition (2019). (4) • A more hypofractionated regime can be considered based on the RCR COVID-19 guidelines and the Canadian LUSTRE Trial of 60Gy in 15 fractions (BED10, 84Gy) (5). This can be used for node-negative tumours up to 4cm T2AN0M0 as allowed in the LUSTRE Trial. It can be considered with caution in tumours 4-5cm ie T2BN0M0 as long as the OAR constraints can be met. Consideration should be made with regard to proximity of the GTV to the oesophagus and whether the maximum dose (0.1cc) to the oesophagus of 50Gy can be met. Details of this treatment regimen are included in the Network SABR guidelines. • Alternative fractionation of 60-66Gy in 30-33 fractions of 2Gy per fraction can also be considered in selected patients particularly those with interstitial lung disease or connective tissue disorders, lung function permitting, and risks discussed with patient, or patients with borderline lung function but with small and central disease not suitable for SABR providing OAR DVH constraints are met.
Stage III NSCLC (radical radiotherapy alone)	• Dose of either 55-60Gy in 20 fractions over 4 weeks or 60-66Gy in 33 fractions over 6 ½ weeks. • The decision between the two schedules will be determined by the lead clinician based on tumour location / size, underlying lung function, comorbidities, ease of travel to the department and acceptable OAR dose constraints.
Concomitant chemo-radiation	• Treatment will be delivered on consecutive days x5 per week for 30-33 x 2Gy fractions delivering a total dose of 60-66Gy or 55 Gy in 20 fractions over 4 weeks. • The final dose is dependent on OAR DVH constraints being met.
Pancoast tumours	• With resectable disease for trimodality therapy treated using the SWOG 9416 protocol (2)

	• Treatment will be delivered on consecutive days x5 per week for 25 x 1.8Gy fractions delivering a total dose of 45Gy. • Unresectable/ borderline unresectable tumours should receive a dose of 60-66 Gy in 2 Gy/ fraction, or equivalent.
Post-operative radiotherapy (PORT)	• Treatment will be delivered on consecutive days x5 per week for 30 x 2Gy fractions delivering a total dose of 60Gy or equivalent dose following their adjuvant chemotherapy (if given). • The aim is to start radiotherapy within 6 weeks of completing any adjuvant chemotherapy.

All lung cancer staging is based on IASLC 8th edition of the TNM Classification for Lung Cancer.

4.3. Review on treatment

- Weekly review on treatment is optimal. Weekly review to be delivered by combination of clinician, specialist radiographers and/ or specialist nurses.
- To record patient's weight and manage treatment related toxicity.

4.4. 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 common and frequently troublesome. Proton pump inhibitors can help but analgesics are often needed. Escalate analgesia as required starting with soluble paracetamol 1g qds then soluble co-codamol 30/500 i-ii qds. Occasionally opiates are required. Ensure aperients are available if opiates are used. Consider sucralfate and oxecetaine with antacid.
- Hospital admission and dietician input may be required if losing weight and oral intake is poor.
- Dietician and speech and language therapy input

4.5. Category

- Classified as Category 1 in the RCR Guidelines

4.6. Adjuvant Durvalumab

- The PACIFIC trial (2018) has demonstrated that 1 year of adjuvant therapy with the immune checkpoint inhibitor Durvalumab following concurrent chemoradiotherapy improves 1-, 2- and 3-year survival. The 12-, 24- and 36-month OS rates with Durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5% (6)
- In England, 1 year of adjuvant Durvalumab was approved by NICE for NHS funding in June 2022 for patients meeting following criteria:
    - PDL1 ≥1% (or where PDL1 cannot be ascertained despite a clear and reasonable attempt)
    - Has completed concurrent chemoradiotherapy for Stage III NSCLC including 2 cycles of platinum agent within 42 days (6 weeks)
    - Has been re-staged since completing chemoradiotherapy and does not have any evidence of disease progression or metastatic spread.
    - Has an ECOG performance status of 0 or 1

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. Consider using a head and neck immobilisation for patients with superior tumours.
- The planning CT scans must include a 4DCT to capture target movement. A 3D helical scan may also be acquired with IV contrast if needed for targets and OARs definition.
- OARs should be outlined on a scan representative of the average patient position
- ITVs should be contoured using all available 4DCT information
- Optimisation and calculation may be done on 4DCT average intensity projection (AVIP) or helical scan.

- If the tumour is in the lower lobe close to the diaphragm with Superior-Inferior motion > 2cm abdominal compression, respiratory gating or breath hold should be considered with 4DCT acquisition to reduce respiratory exertion and the margins for motion.
- The extent of the planning CT scan must be sufficient to include all potential organs at risk. As a guide, contiguous axial slices of 2.0-3.0mm 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. Ensure the entire liver is scanned for lower lobe tumours.
- The extent of the 4DCT should be large enough to cover the tumour/targeted area and its motion
- Intravenous contrast may be used to help define the brachial plexus for upper lobe tumours and may be used for central tumour when they are close to or invading mediastinal structures to define the great vessels and pericardium. This will be specifically requested on the planning request form and should be given in the contralateral arm to the brachial plexus of interest.
- In the absence of 4DCT a free breathing helical CT scan will be acquired, and the treatment planned using conventional margins.

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.
- CT-MRI fusion:
    - Sometimes a diagnostic MRI may have been acquired to determine involvement of the brachial plexus and is particularly helpful when planning radiotherapy for a Pancoast tumour. This can be registered to the planning CT scan to aid planning.
- CT-PET fusion:
    - this is not done routinely but in cases of distal atelectasis making definition of the GTV difficult on a contrast enhanced CT alone the clinician may request this.

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

6. Volume Definitions

- **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 (7)*)*

- 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 (eg 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 (2) (6). 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
    - The normal lung consists of both lungs considered together as one organ but excluding the GTV. It is important to ensure the whole of both lungs are contoured from apex to base. Care should be taken to exclude the trachea and proximal bronchi, but small sized vessels (<1 cm, or vessels beyond the hilar region) should be included. All inflated lung should be contoured. When collapsed lung is present, the use of IV contrast and / or PET scans can be helpful in differentiating GTV from collapsed lung and daily CBCT to assess for re inflation during treatment should be considered. All inflated and collapsed lung should be included as this can have considerable impact on dose
- 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 ie 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 ideally 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

- For IMRT/ VMAT dose is prescribed to the median dose in PTV as per ICRU 83.
- Prescribing mean dose can also be considered.

8. Plan Evaluation

8.1. Target coverage

Tab.2. Aimed dose objectives for assessing CTV and PTV coverage (reference RTTQA):

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 or Dose	30-33#	20#
Spinal Canal	$D_{max\ 0.1cc}$	48Gy	42Gy optimal 44Gy mandatory
Non_GTV_Lung*	MLD	<20Gy	<18Gy
	V_{20}	<30% optimal <35% mandatory	<35%
	V_{17}	-	<30%
	V_{15}	-	-
Contralateral Lung	V_5	<60%	<60%
Brachial Plex_R/L	$D_{max\ 0.1cc}$	66Gy	55Gy
Heart+A_Pulm	$D_{100\%}$	<40Gy	<35Gy optimal <36Gy
	$D_{67\%}$	<50Gy	<43Gy optimal <44Gy
	$D_{33\%}$	<66Gy	55Gy optimal 57Gy
	D_{mean}	<26Gy	<22Gy
	V_{30}	46%	36%
	V_{57}		
	$D_{max\ 0.1cc}$	-	-
Oesophagus	D_{mean}	<34Gy optimal	<32Gy optimal
	V_{50}	30%	-
	V_{45}	-	105%
	$D_{max\ 0.1cc}$	-	105%
Stomach	$D_{max\ 0.1cc}$	<58Gy	<47Gy
Liver	D_{mean}	28Gy	24Gy

Great Vessels	V_{57}	-	-
	$D_{max\ 0.1cc}$	-	-
Proximal Bronchial Tree	V_{57}	-	-
	$D_{max\ 0.1cc}$	-	-
Rib (chest wall)	$D_{max\ 0.1cc}$	-	-
	V_{30}	-	-
Skin	$D_{max\ 0.1cc}$	-	-

MLD = mean lung dose; *Lung dose constraints are not acceptable for PORT or after lung surgery due to the reduced lung volumes following surgery;

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).
- **Oesophagu**s: 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. (10)
- **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 Dmean < 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

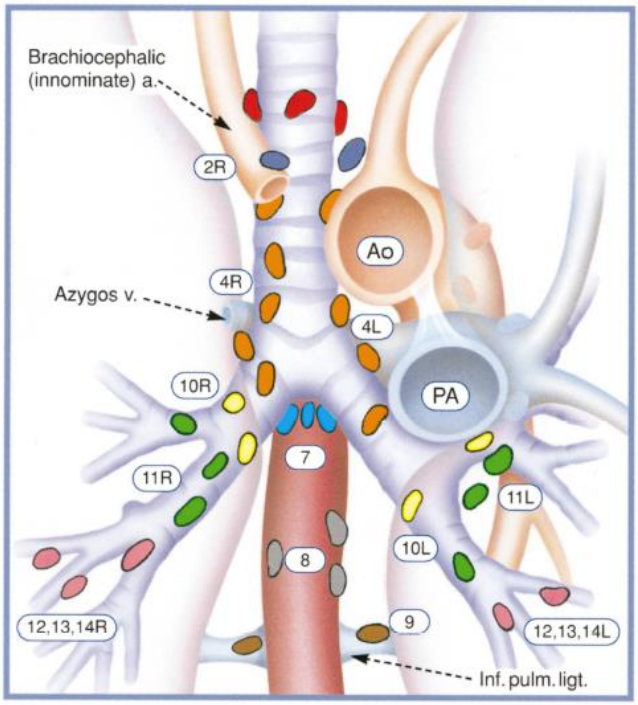
at least 2 weeks prior to starting RT. In addition, prophylactic antibiotics should be offered and started when RT starts and given a supply of emergency antibiotics.

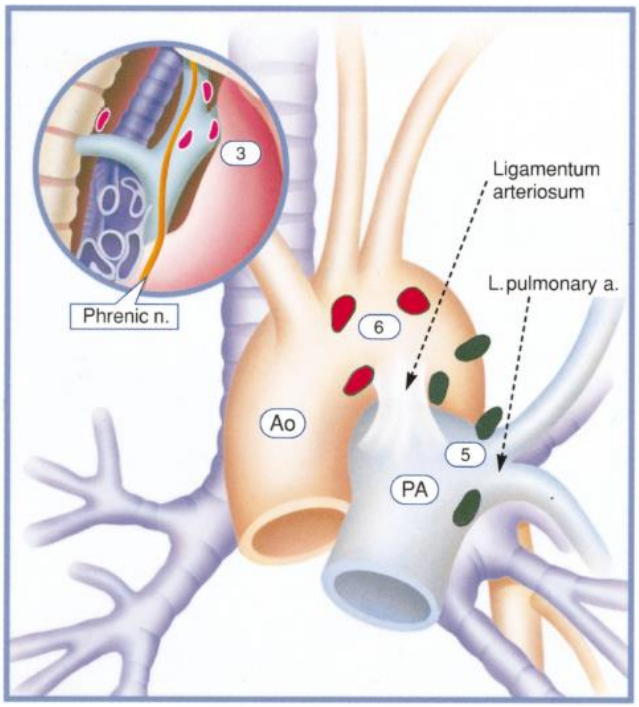
When the PTV is close to OARs, follow these priorities as a guide: Spinal canal or canal PRV Dmax, lung V20, mean lung dose, PTV coverage, oesophagus (would accept overdose to the oesophagus), Brachial plexus Dmax if it overlaps with the PTV to meet the constraint on PTV coverage.

9. Follow up after treatment

- Treating clinician should decide the follow up and cross-sectional imaging arrangements following the completion of radiotherapy treatment.
    - **Adjuvant Durvalumab**: Patients potentially eligible for adjuvant Durvalumab need to undergo a staging CT scan and start the drug within 6 weeks of completing concurrent chemoradiotherapy.
    - **Pancoast tumour:** Repeat CT within a week of completion of CRT to assess any early response. Unless surgery is clearly contra-indicated, discuss possibility of resection with thoracic surgeons in MDT meeting. Review patient at 3-4weeks to discuss results of scan and explain further treatment. Where surgery is feasible, aim for this to be done 4-6 weeks after chemo-radiotherapy. Post-operatively consider a further two cycles of chemotherapy
    - **All other patients**: Consider chest x-ray on arrival
- There is no evidence to guide frequency of subsequent follow-up, the following represents a general recommendation which can be tailored as necessary to individual patient circumstances. As an example, follow- up could be based on:
    - Year 1 – 3: 3 monthly follow-ups with 3 monthly chest x-ray and annual CT scans. More frequent CT imaging can be considered.
    - Years 3-5 years post treatment 4 monthly follow-up with 4 monthly chest x-ray and annual CT scan. Discharge to GP follow-up at 5 years if disease free.

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 (11)

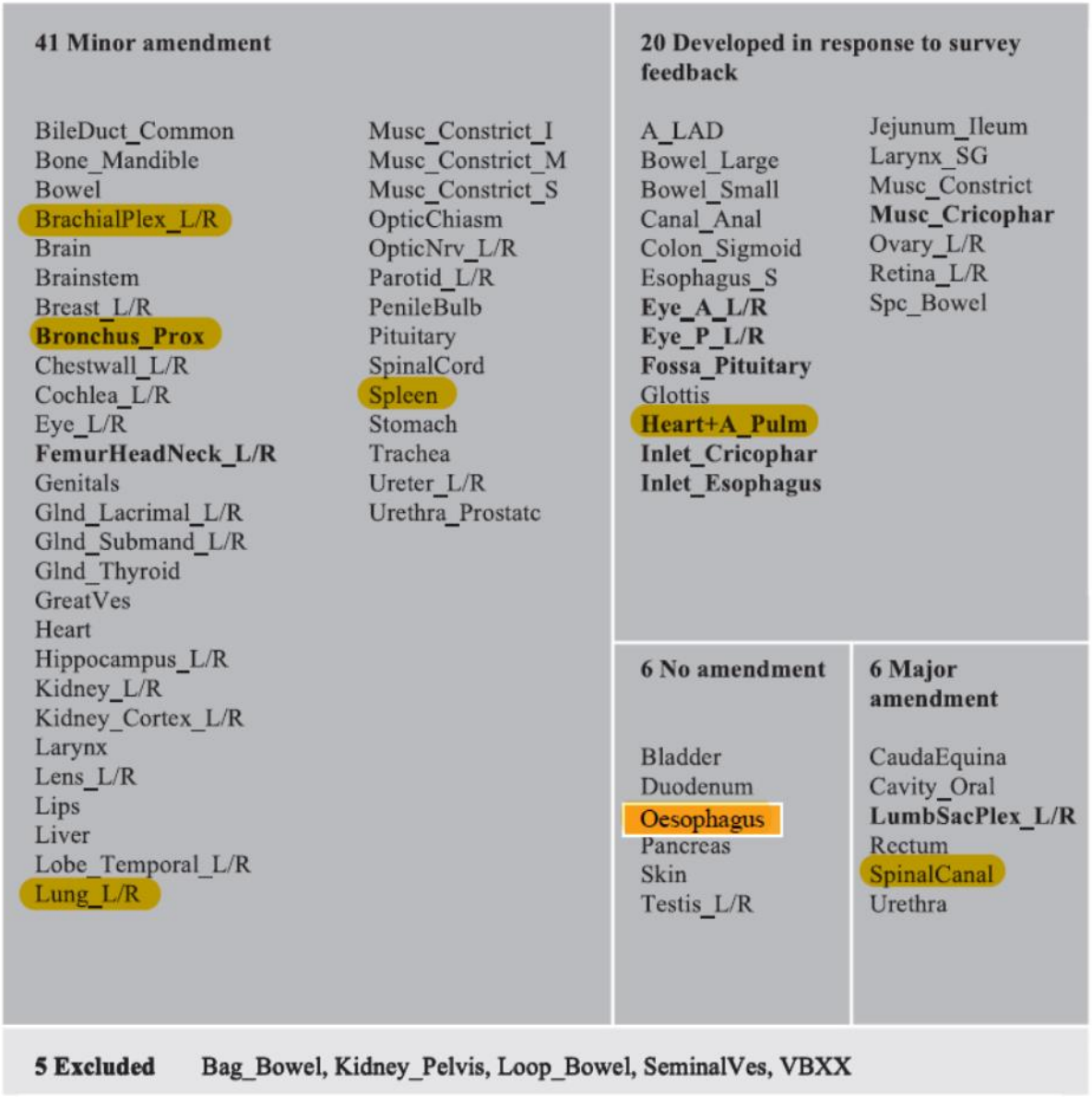
Anatomic Landmarks	Anatomic Landmarks
N2 nodes—All N2 nodes lie within the mediastinal pleural envelope	
1 Highest mediastinal nodes	Nodes lying above a horizontal line at the upper rim of the bracheocephalic (left innominate) vein where it ascends to the left, crossing in front of the trachea at its 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

Appendix 3: OAR nomenclature (7)



41 Minor amendment

BileDuct_Common
Bone_Mandible
Bowel
BrachialPlex_L/R
Brain
Brainstem
Breast_L/R
Bronchus_Prox
Chestwall_L/R
Cochlea_L/R
Eye_L/R
FemurHeadNeck_L/R
Genitals
Glnd_Lacrimal_L/R
Glnd_Submand_L/R
Glnd_Thyroid
GreatVes
Heart
Hippocampus_L/R
Kidney_L/R
Kidney_Cortex_L/R
Larynx
Lens_L/R
Lips
Liver
Lobe_Temporal_L/R
Lung_L/R
Musc_Constrict_I
Musc_Constrict_M
Musc_Constrict_S
OpticChiasm
OpticNrv_L/R
Parotid_L/R
PenileBulb
Pituitary
SpinalCord
Spleen
Stomach
Trachea
Ureter_L/R
Urethra_Prostatc

20 Developed in response to survey feedback

A_LAD
Bowel_Large
Bowel_Small
Canal_Anal
Colon_Sigmoid
Esophagus_S
Eye_A_L/R
Eye_P_L/R
Fossa_Pituitary
Glottis
Heart+A_Pulm
Inlet_Cricophar
Inlet_Esophagus
Jejunum_Ileum
Larynx_SG
Musc_Constrict
Musc_Cricophar
Ovary_L/R
Retina_L/R
Spc_Bowel

6 No amendment

Bladder
Duodenum
Oesophagus
Pancreas
Skin
Testis_L/R

6 Major amendment

CaudaEquina
Cavity_Oral
LumbSacPlex_L/R
Rectum
SpinalCanal
Urethra

5 Excluded Bag_Bowel, Kidney_Pelvis, Loop_Bowel, SeminalVes, VBXX

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