Thames Valley and Wessex Radiotherapy Network

Radiotherapy Protocol

Thymoma/ Thymic Carcinoma- Radical

This document is the standardised Thames Valley and Wessex Radiotherapy Network Thymic Tumours Radical Treatment Protocol 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 Dr Mike Bayne	Jonny Lee	
Portsmouth Hospitals University NHS Trust	Dr Hannah Bainbridge Dr Yoodhvir Singh Nagar	Sarah Muscat	
Royal Berkshire Hospitals NHS Foundation Trust	Dr Joss Adams	Ignacio Di Biase	
University Hospitals Southampton NHS Foundation Trust	Dr Paul Fenton Dr Andrew Bates	Mekala Chandrasekaran	

Document History

Date of Issue	Version Number	Date Approved	Responsible for Change	Nature of Change	Ratification/ Approval
5.10.2021	0.1		The Lung Protocol Working Group	1st draft	
23.11.2021	0.2		The Lung Protocol Working Group	Finalising the document	For ratification by the NOG
24.11.2021	1.0	10.12.2021		Ratified by the RT NOG	
10.05.2023	2.0		The Lung Protocol Working Group	Document updated in line with the latest clinical evidence	

1. Objective and Scope

To summarise the planning and treatment of patients with thymic carcinomas receiving a curative dose of radiotherapy, for use in the Radiotherapy Centres within the Thames Valley and Wessex Radiotherapy Network.

2. Indications

2.1. **Thymomas and thymic tumours: Surgery remains the mainstay of treatment but there may be a role for radiotherapy for these radiosensitive tumours in certain settings.** These tumours are rare so there is a paucity of data from prospective randomised controlled trials so the recommendations here are derived from retrospective series, the ESMO Guidelines 2015 [1] and NCCN Guidelines 2019 [2]. The role of adjuvant RT for mixed pathological types of tumours requires a review of the proportion of high-grade pathology within the resected specimen, the presence of extracapsular extension and the relationship to the high-grade tumour to the resection margin. A discussion about the risks and benefits of adjuvant RT needs to consider and balance all these risk factors for recurrence.

Reference to staging is in line with IASLC 8th Edition of the TNM Classification for Lung Cancer:

- **Stage II B3 disease:** Consider post-operative adjuvant radiotherapy following a complete resection (no survival advantage but small series suggest a decreased rate of local recurrence) [3].
- **Stage III - IVA disease:** These patients should be offered post-operative radical radiotherapy to improve local control [4]. If disease is unresectable consider trimodality therapy sequentially or definitive radiotherapy. In view of the anterior location of thymic tumours and relationship to the heart treat using IMRT with RapidArc/ VMAT to reduce the risk of late cardiac toxicity is recommended.
- Tumours of mixed histology: treatment should be considered based on the more aggressive histological type.

2.2. **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.

3.4. Histological confirmation:

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

4.1. Chemoradiotherapy

For the Stage IVA or unresectable disease, chemoradiotherapy may be considered; please refer to the Thames Valley and Wessex Radiotherapy Network NSCLC Protocol limiting the dose to 60Gy in 30 fractions and platinum- etoposide.

Where induction chemotherapy is given, and tumour is unresectable or undergoes R1/R2 resection consider radiotherapy sequentially. If R1 resection, give 45-50Gy and if R2 rection or unresectable give 60Gy.

4.2. Radiotherapy

Table 1. Dose and fractionation schedules

Clinical indications	Dose and fractionation schedules
Thymoma [1, 2]:	• Stage I (with extracapsular extension) B3 resected (R0) thymoma to be considered for adjuvant radiotherapy 45-50Gy in 25# • Stage I R1 resection to receive 50-54 Gy in 25-30# • Stage IIA B3 resected (R0) disease to consider adjuvant RT to 45-50 Gy in 25# with a boost to areas of concern. If R1 incomplete resection, for post-operative RT 50-54Gy in 25-30#. • Stage IIB B2-B3 R0 disease consider adjuvant RT 45-50Gy in 25#. If R1 incomplete resection for post-operative RT 50-54Gy in 25-30#. • Stage III-IVA resected R0 disease for adjuvant RT 45-50Gy with a boost to areas of concern. Unresectable Stage III-IVA disease should be considered for trimodality treatment with primary chemotherapy followed by surgery if they become resectable. R0 resections should receive post operative RT 45-50Gy in 25# with a boost to areas of concern. Incompletely resected (R1) Stage II-IVA disease to receive 50-54Gy in 25-30# x5 per week. • Incompletely resected (R2) or if disease remains unresectable after primary chemotherapy to be considered for definitive RT 60Gy in 30#.
Thymic carcinoma	• Stage I R0 resection adjuvant postop RT 45-50Gy in 25# • Stage I R1 resection postop RT 50-54 Gy in 25-30# • Stage II-IIIA resection (R0) post-operative RT 45-50 Gy in 20-25# with a boost to areas of concern. • Unresectable Stage IIIA-IVA disease should be considered for trimodality therapy with primary chemotherapy followed by surgery if they become resectable. R0 and R1 resections should receive post-op RT 45-50Gy in 25# with a boost to areas of concern. • Incompletely resected (R2) or unresectable disease to receive definitive RT 60Gy in 30#.

4.3. Review on treatment

- Consider weekly review from week 3 onwards (or more often if specified by doctor).
- 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 uncommon.
- Consider neurologist input in myasthenia

4.5. Category

- Classified as Category 2 in the RCR Guidelines.

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

- **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.
- No CTV used in the LUSTRE-Trial of 60Gy/15#.
- **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 (5))

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) (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
    - 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.
- If using 60Gy/15# regime, must also contour:
    - Great vessels: To include the mediastinal envelop above the Heart+A_Pulm contour.
    - Trachea and Large Bronchus
    - Rib (define chest wall)
    - Stomach
- 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 or Dose	Number of Fractions		
		30-33#	20#	15#
Spinal Canal	Dmax 0.1cc	48Gy	42Gy optimal 44Gy mandatory	36Gy
Non_GTV_Lung*	MLD	<20Gy	<18Gy	-
	V20	<30% optimal <35% mandatory	<35%	<15%
	V17	-	<30%	
	V15	-	-	<30%
Contralateral Lung	V5	<60%	<60%	<60%**
Brachial Plex_R/L	Dmax 0.1cc	66Gy	55Gy	<50Gy
Heart+A_Pulm	D100%	<40Gy	<35Gy optimal <36Gy	-
	D67%	<50Gy	<43Gy optimal <44Gy	-
	D33%	<66Gy	55Gy optimal 57Gy	-
	Dmean	<26Gy	<22Gy	-
	V30	46%	36%	-
	Dmax 0.1cc	-	-	66Gy
Oesophagus	Dmean	<34Gy optimal	<32Gy optimal	-

	V50	30%	-	-
	Dmax 0.1cc	-	105%	48Gy
Stomach	Dmax 0.1cc	<58Gy	<47Gy	<48Gy
Liver	Dmean	28Gy	24Gy	-
Great Vessels	Dmax 0.1cc	-	-	66Gy
Trachea_Large Bronchus	Dmax 0.1cc	-	-	66Gy
Rib (chest wall)	Dmax 0.1cc	-	-	66Gy
Skin	Dmax 0.1cc	-	-	45Gy

MLD = mean lung dose; *Lung dose constraints are not acceptable for PORT or after lung surgery due to the reduced lung volumes following surgery; **taken from 15# conversion from the I-START 20# schedule [7]

If the dose constraints cannot be met with 60Gy/15# regime you can drop the dose to 55/15# (BED10, 70Gy which is equivalent to 55Gy/20# BED10, 70.1Gy. Isotoxic for late complications with BED3)

For the more hypofractionated regime of 60Gy /15# we need to evaluate the plans based on data from the Canadian Group also used is the RCR Covid paper, Table 4 [8].

Table 4. Dose Constraints for Hypofractionated RT of 50-60Gy/15#

Dose (Gy)	**Volume**	**RT only 50-60Gy/15#**
Spinal Cord	Max 0.1cc	36Gy
Oesophagus	Max 0.1cc	48Gy
	Vol	V45 <10cc
Brachial Plexus	Max 0.1cc	<50Gy
Heart A_Pulm	Max 0.1cc	66Gy
	Vol	V57 <10cc
Great Vessels	Max 0.1cc	66Gy
	Vol	57Gy <10cc
Trachea and Large Bronchus	Max 0.1cc	66Gy
	Vol	V57 <10cc
Rib (chest wall)	Max 0.1cc	66Gy
	Vol	V30 <30cc
Skin	Max 0.1cc	<45Gy
Stomach	Max 0.1cc	<48Gy
	Vol	V45 <10cc
Lung-GTV	Vol	V20<15% and V15 <30%
	Dose	MLD <20Gy
Contralateral Lung	Vol	V5<60Gy *

If the dose constraints cannot be met with 60Gy/15# regime you can drop the dose to 55/15# (BED10, 70Gy which is equivalent to 55Gy/20# BED10, 70.1Gy. Isotoxic for late complications with BED3)

**taken from 15# conversion from the I-START 20# schedule [7]*

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

  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 [3, 4].

- **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 [9] 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 [10].

- **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 [11]. Similarly in a Japanese study D_{max} > 60Gy resulted in a 46% incidence of acute RTOG ≥G3 toxicity [12]. QUANTEC data recommendations in Table 3 [13].

- **Brachial plexus**: recent systematic review and meta-analysis of radiation induced brachial plexopathy and the associated radiation doses to the brachial plexus suggest that the current brachial plexus dose constraints of 60-66Gy in 2Gy per fraction or less daily are safe with ≤ 5% incidence of brachial plexopathy [14] We therefore do not need to compromise PTV for brachial plexus but try to meet $D_{0.1cc}$ constraint.

- **Stomach**: Optimal dose constraints V50Gy <5cc and V_{45}<75cc AND $D_{0.1cc}$ <54Gy.

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

- **Spleen:**

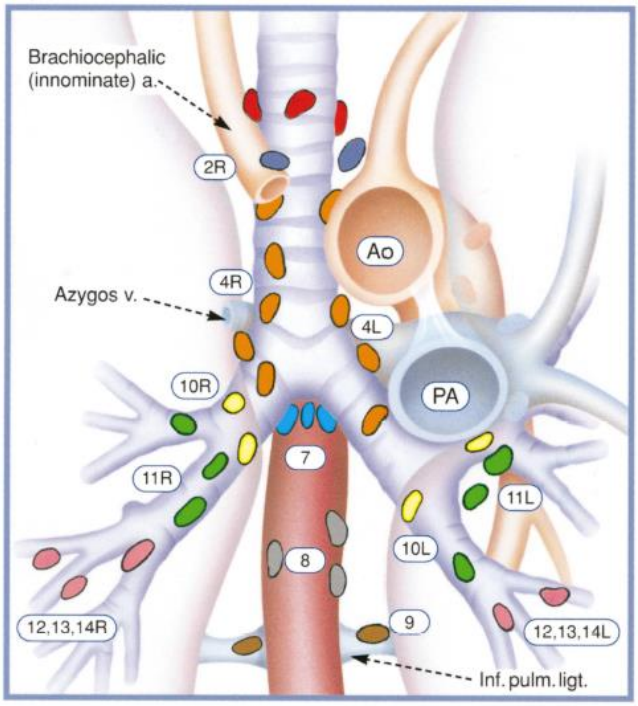
  Special consideration needs to be taken with tumours in the base of the left lower lobe where there may be overlap of dose with the spleen, particularly where prognosis is > 1 year. The spleen is very radiosensitive and low dose RT may impact on splenic function. Patients with a dysfunctional spleen 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

- **Thymic tumours** follow-up is recommended for a total of 10 years with CT scans annually for 5 years and then every 2 years up to 10 years:
  Consider more frequent scanning for Stage III and IV or after R1 and R2 resection.

Appendix 1: Surgical Nodal Stations



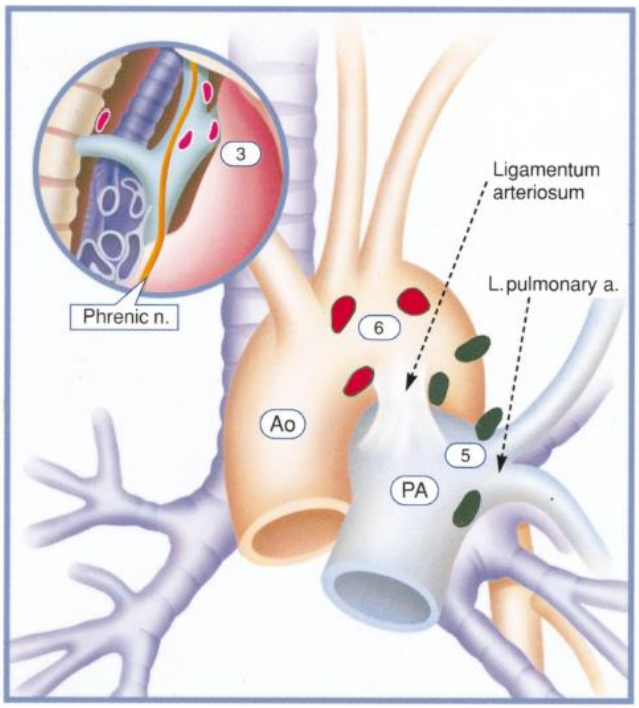
Superior Mediastinal Nodes

- **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 [15]

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

[1] Girard N, Ruffini E, Marx A et al. Thymic Epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 26(Supplement 5):v40-55,2015.

[2] National Comprehensive Cancer Network (NCCN) Guidelines, Version 2.2019: Thymomas and Thymic carcinomas.

[3] Fernandes AT, Shinohara ET, Guo M et al. The Role of radiation therapy in malignant thymoma. A surveillance, epidemiology, and end results database analysis. J Thorac Oncol 2010;5:1454-1460.

[4] Eng TY, Thomas CR. Radiation therapy in the management of thymic tumours. Semin Thorac Cardiovasc Surg 2005;17:32-40.

[5] Mir R, Kelly SM, Xiao Y, et al. Organ at risk delineation for radiation therapy clinical trials: Global Harmonization Group consensus guidelines. Radiother Oncol. 2020;150:30-39. doi:10.1016/j.radonc.2020.05.038

[6] Hall WH, Guiou M, Lee NY, Dublin A, Narayan S, Vijayakumar S, Purdy JA, Chen AM. Development and Validation of A Standardized Method for Contouring THE Brachial Plexus: Preliminary Dosimetric Analysis Among Patients Treated with IMRT for Head-and-Neck Cancer. Int J Radiat Oncol Biol Phys. 2008;72;1: S385.

[7] Lester JF, Courtier N, Eswar C, Mohammed N, Fenwick J, Griffiths G, Nixon LS Initial results of the phase ib/II, I-START trial: Isotoxic accelerated radiotherapy for the treatment of stage II-IIIb NSCLC. Meeting Abstract. Journal of Clinical Oncology 2018; 36 (15_Sup), e20551.

[8] Swaminath A, Wierzbicki M, Parpia S, et al. Canadian Phase III Randomized Trial of Stereotactic Body Radiotherapy Versus Conventionally Hypofractionated Radiotherapy for Stage I, Medically Inoperable Non-Small-Cell Lung Cancer - Rationale and Protocol Design for the Ontario Clinical Oncology Group (OCOG)-LUSTRE Trial. Clin Lung Cancer. 2017;18(2):250-254. doi:10.1016/j.cllc.2016.08.002

[9] Hatton MQF, Lawless CA, Faivre-Finn C, et alAccelerated, Dose escalated, Sequential Chemoradiotherapy in Non-small-cell lung cancer (ADSCaN): a protocol for a randomised phase II studyBMJ Open 2019;9:e019903. doi: 10.1136/bmjopen-2017-019903

[10] Marks LB, Bentzen SM, Deasy J et al. QUANTEC: organ specific paper Radiation dose-volume effects in the lung. IJROBP 2010:76:3: S70-6.

[11] Singh AK, Lockett MA, Bradley JD Predictors of radiation-induced toxicity in patients with non-small cell lung cancer treated with 3D CRT. IJROBP 2003;55:337-341

[12] Qiao w-b, Zhao Y-H, Zhao Y-B et al. Clinical and dosimetric factors of radiation-induced esophageal injury: radiation-induced esophageal toxicity. World J Gastroenterol 2005:11:2626-9

[13] Werner-Wasik M, Yorke E, Deasey J et al. QUANTEC: organ specific paper Radiation dose-volume effects on the esophagus. IJROBP 2010:76;3: s86-93

[14] Yan M, Kong W, Kerr A et al. The radiation dose tolerance of the brachial plexus: a systemic revies and meta-analysis. Clinical and Translational Radiation Oncology 18 (2019) 23-31

[15] Moutain et al., Chest 1997: Lymph Node Map Definitions