West Midlands Radiotherapy
Operational Delivery Network

West Midlands Radiotherapy Clinical Protocol

Lung Cancer - Non Small Cell

Revision history

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0.1	01.10.2020	Initial draft Linda Farthing
0.2	06.01.2021	Updated by Dr A Siva and Dr A Jegannathen
0.3	08.03.2021	Addition of Dose Constraint table
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1.0	27.11.23	Accepted changes and amended documentation dates
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Purpose

To provide a standardised protocol for planning and delivery of external beam radiotherapy, for patients with Non-Small Cell Lung Cancer (NSCLC) within the West Midlands. This protocol is aligned with the Royal College of Radiologists (RCR) Dose Fractionation Guidance Version 3 March 2019.

Information & Consent

- Each patient should be consented with individualised information of planned treatment, risks / benefits and toxicities
- Booking form and consent completed by IR(ME)R practitioner
- Patients should also receive a local patient information sheet or MacMillan information booklets

Responsibility

- To comply with the Ionising Radiation (Medical Exposure) Regulations 2017 the following roles are defined:
- Referrer & Practitioner: The consultant clinical oncologist is responsible for the care of the patient including correct referral for treatment consent, justification prescription and treatment authorization as defined in departmental protocol but in accordance with this regional protocol.
- Operators: Radiographers, physicists, technologists, Consultant clinical Oncologists and other medical staff are responsible for individual tasks associated with the plan production, verification and treatment delivery as per departmental protocols but in accordance with this regional protocol and are undertaken on the auspices of the practitioner.
- It is the responsibility of department management teams to ensure departmental protocols are consistent with this regional protocol and that any disagreement with the content of this protocol is raised through the West Midlands EAG.

1. Radical Radiotherapy for Non-Small Cell Lung cancer (NSCLC)

1.1 Indications: Stage I

Stereotactic Ablative Radiotherapy (SABR) should be considered for patients with medically inoperable T1/T2 (< 5cm) disease which is node negative and in a suitable location (1, 2). Potentially suitable are clinical stages of T1 N0 M0 or T2 (≤ 5 cm) N0 M0 or a subset of T3 (by virtue of chest wall invasion only) (≤ 5 cm) not suitable for surgery because of medical co-morbidity, lesion which is technically inoperable or patient declines surgery after surgical assessment: See National SABR Consortium guidelines.

Patients with medically inoperable stage I-II or stage III NSCLC should be considered for radical radiotherapy (RT) +/- chemotherapy, concurrently or sequentially, provided they have an adequate performance status (PS) 0-1 and their disease can be encompassed by a radical radiation field. Concurrent chemo-radiotherapy (CRT) is the preferred approach for patients with stage III disease and good PS. Meta-analyses have demonstrated absolute survival benefit of 5.7% at 3 years for concurrent treatment compared with sequential chemo-radiotherapy or radiotherapy alone (3). Concurrent treatment is associated with worse acute side effects, namely oesophagitis (4, 5).

Adjuvant Durvalumab should be offered to all patients within 42 days of completing definitive CRT unless the tumour is PD-L1 negative (<1%), there is contraindication to anti PD-L1 treatment, a decline in WHO PS (>_2), unresolved CRT toxicities or disease progression (16)

In some cases trimodality treatment would be appropriate with surgery after chemoradiotherapy. For this group Durvalumab would not be offered.

Induction chemotherapy followed by RT in sequence should be considered for patients whose performance status is inadequate for concurrent chemo-RT or patients with a large tumour volume which would be difficult to irradiate unless down staged by chemotherapy. Radical radiotherapy should commence ideally 4weeks following the final cycle of chemotherapy.

Pre-operative concurrent chemo-radiotherapy as part of a tri-modality approach is recommended for superior sulcus (Pancoast's) tumours and may be considered for selected patients who would be at risk of positive margins after upfront surgery (6). Radiotherapy alone should be considered where chemotherapy is contraindicated.

For patients of good performance status, there is evidence that local control improves with increased treatment intensity such as CHART (7-8), but this is not currently available in the West Midlands.

Consider patients for suitable trials. See WM Trials Research & Trials - West Midlands Cancer Alliance (wmcanceralliance.nhs.uk)

1.2 Patient Selection:

1. ECOG performance status 0-1. PS2 may be considered for RT alone.
2. Histologically confirmed NSCLC. In rare cases where attempts at histological confirmation have not been successful, patients may be treated with radical intent after MDT discussion.
3. No evidence of distant metastases. Supraclavicular nodes can be included if they can be safely encompassed within the primary volume.
4. No evidence of pleural effusion unless it can be attributed to a recent surgical intervention, histologically proven to be benign or is small and felt to not be related after MDT discussion.
5. The volume and site of the tumour within the thorax should be such that a radical course of radiotherapy can be given without prejudicing vital structures such as the spinal cord, heart or lung.
6. All patients being considered for radical chemoradiotherapy should have had a PET scan and brain imaging (preferably MRI brain) within 6 (ideally 4) weeks of the start of radiotherapy. For RT alone this is advised but not obligatory.
   If full mediastinal staging (cervical mediastinoscopy or EBUS) has been performed within four weeks of the start of radiotherapy it may not be necessary to repeat the PET. Consider pathological nodal sampling in patients with enlarged nodes on CT (>10mm short axis) or with FDG avid nodes.
7. Pulmonary function tests: (within 6 weeks prior to starting treatment)
   a) FEV1 >1 litre (0.8litre is acceptable only if other criteria are favorable or > 40% of predicted value)
   b) FVC >1.5 litres
   c) Gas transfer (KCO or TLCO) ≥ 40% of predicted
8. Informed consent.

9. For patients receiving cisplatin based chemotherapy, adequate renal function (eGFR) >50 - 60ml/min is required. Consider formal EDTA assessment for patients with low BSA or eGFR < 50 - 60ml/min. Alternatively a 24hr creatinine clearance can be used. Patients being considered for concurrent Cisplatin based chemo with a GFR < 60ml/min could be considered for carboplatin based regimens as an alternative. See local chemotherapy protocols.
10. For concurrent chemotherapy, adequate marrow function (Hb >10, ANC>1.5, platelets >100).

Exclusion Criteria:

1. Patients who have lost more than 10% of their body weight in the preceding 3 months.
2. Clinically significant interstitial lung disease.
3. Co-existing disease prejudicing survival.

1.3 Radical radiotherapy

Table 1.0	**Radical Radiotherapy Concurrent / Sequential**
Energy / modality	6MV photons
Patient immobilisation, set up	Supine with both arms up with locally agreed immobilisation technique For apical tumours, consider immobilisation and the use of H&N BDS to encompass shoulders, with arms by the side.
Localisation	4DCT Scan with IV contrast if no contraindications, especially if mediastinal disease Slice thickness ≤3 mm To include whole of the lung volume (typically cricoid to L2) using additional 3DCT where necessary. Refer to local guidelines for superior and inferior scan levels
Planning technique	4D CT with VMAT IMRT For a limited number of patients conformal 3D planning may give better dose constraints
Target definition	**Gross tumour Volume (GTV)** GTV is defined using planning CT and all diagnostic imaging and investigations including PET to identify tumour and involved nodes. Primary tumour volume will be contoured on the planning scan using lung and mediastinal window setting and lymph nodes on the mediastinal window setting. GTV post induction chemotherapy will include post chemotherapy tumour volume and pre chemotherapy nodal volume (10) For 4D CT GTV is determined either in all phases of respiratory cycle to create an ITV or by contouring the maximum inspiratory phase (0%), the maximum expiratory phase (50%) and as defined on the maximum intensity projection dataset (MIP) **Clinical target volume (CTV)**

	CTV includes areas at risk of microscopic spread. This is usually at least 5mm beyond the radiologically visible tumour taking into account anatomical direction of spread. The whole of the involved nodal station may need to be included. The CTV should be created throughout motion **Planning Target Volume(PTV)** The appropriate CTV/ITV-PTV margin is dependent on the respiratory motion management, local image guidance strategy, guidelines and audits. PTV expansion should be as per locally established margins. 4DCT – ITV/CTV is expanded typically by 5-10mm axially and 5-10mm cranio-caudally to form the PTV as per local approved and agreed margins If 4DCT is not possible, the CTV is expanded by 10mm margin in the axial plane, and by 15mm in the cranio-caudal plane to form the PTV.
Dose / fractionation & overall treatment time	**Radical radiotherapy** 55Gy in 20 fractions over 4 weeks. 50Gy in 15 fractions over 3weeks (COVID fractionation) **Concurrent chemo-radiation** 60 - 66Gy in 30 – 33 fractions over 6 weeks. 55Gy in 20 fractions over 4 weeks. Use SOCCAR protocol for small tumour volumes and frail / elderly (COVID) **Sequential chemo-radiotherapy** 55Gy in 20 fractions over 4 weeks aiming to start within 4 weeks of last cycle of chemotherapy
Dose Specification	For IMRT/VMAT the dose is prescribed according to ICRU 83. For 3Dconfromal the dose will be specified at the ICRU 62 reference point. The dose distribution within the PTV should ideally be within +/- 5% of the prescribed dose, and no more than +7% of the prescribed dose.
Onset verification	Plan is verified at the first fraction using cone beam CT (CBCT). Ideally daily on line CBCT imaging should be performed to confirm CTV /PTV coverage, and monitor intra thoracic anatomy, dependent on tumour site and OAR. CBCT imaging verification on 1-3# then weekly is adequate but not recommended.

Organ at risk	66Gy/33#	60Gy/30#	ADSCaN 55Gy/20#	40Gy/15#	39Gy/13#	36Gy/12#	30Gy/10#
Spinal Cord (Max dose)	0.1cc < 48Gy	0.1cc < 48Gy	0.1cc < 47Gy	0.1cc < 40Gy	0.1cc < 37.6Gy	0.1cc < 36.5Gy	0.1cc < 34Gy
α/β=2Gy *EQD2*	*41.5Gy*	*43.2Gy*	***EQD2 51.1Gy***	*46.8Gy*	*46.0Gy*	*46.0Gy*	*46.0Gy*
	If Adscan is taken as the reference, when comparing EQD2 values, it may be possible to increase the Spinal Cord dose tolerance for fractionations as below. But this should be at Clinician's discretion.						
Spinal Cord max dose	***53.2***	***51.6***		***43.2***	***40***	***38.4***	***36.2***
EQD2 Gy	***51***	***51***		***51***	***51***	***51***	***51***
Combined Lung - CTV **α/β=10Gy** for early effects Radiation Pneumonitis. (EQD2 17.8-18.3 Gy)	V20Gy < 30-35%	V20Gy < 30-35%	V20Gy < 30-35% **(EQD2 18.3 Gy)**	V20Gy < 30-35%	V18Gy < 30-35%	V18Gy < 30-35%	V18Gy < 30-35%
Heart **α/β=2.5Gy** Equivalent to Adscan EQD2 Doses	D100% < 41.3Gy D67% < 51.2Gy D33% < 67.3Gy	D100% < 40.3Gy D67% < 49.7Gy D33% < 65.3Gy	**D100% < 36.0Gy EQD2 34.4Gy** **D67% < 44.0Gy EQD2 46 Gy** **D33% < 57.0Gy EQD2 67.8 Gy**	D100% < 33.0Gy D67% < 40.0Gy D33% < 51.4Gy	D100% < 31.5Gy D67% < 38.1Gy D33% < 48.8Gy	D100% < 30.7Gy D67% < 37.0Gy D33% < 47.3Gy	D100% < 28.8Gy D67% < 34.7Gy D33% < 44.0Gy
Oesophagus (Max dose) **α/β=3Gy** (Assuming PEG/RIG fitted)(Max 10-12cm in 95-100% isodose)	**0.1cc < 60 -67.5** EQD2 max 68 Gy	**0.1cc < 60-65.6** EQD2 max 68 Gy	**0.1cc < 57.8Gy EQD2 68Gy**	-	-	-	-

Brachial Plexus (Max dose) **α/β=2Gy**	**0.1cc < 65.5 Gy** EQD2max 65.3	**0.1cc < 63.5Gy** EQD2max 65.3	**0.1cc < 55.0Gy EQD2 65.3 Gy**	-	-	-	-

D100% = Dose to 100% of the volume.
† = EQD2 values (shown in red) have been calculated for Spinal Cord for each fractionation and suggest that the tolerance dose could be higher than that quoted here for some fractionations, if ADSCaN is used as the reference. However, this should be at the Clinician's discretion. * = Tolerance doses for each fractionation have been derived from EQD2 values based on ADCSaN tolerance doses.

1.4 Pancoast tumour being treated with trimodality therapy

Treatment decision at MDT

For definitely resectable tumours offer 45- 50Gy in 25 fractions over 5 weeks with Cisplatin based chemotherapy (according to local protocols) concurrently followed by surgery (6).

For possibly resectable tumours consider delivering a full radical dose with concurrent chemotherapy as for NSCLC (1.3 above).

Radiotherapy to start on a Monday and surgery should be within 3- 5 weeks after completion of CRT with restaging CT in between. Every effort should be made to deliver the prescribed dose of radiotherapy without avoidable delays or interruptions.

2 further cycles of consolidation chemotherapy (at the discretion of the clinicians) can be given post-surgery (6)

In rare cases or borderline resectable tumours **re**staging CT should be performed at 4 weeks of CRT. If there is progression or surgery not feasible phase II should be planned with 16-20 Gy in 8-10 fractions (6).

2.0.POST-OPERATIVE RADIOTHERAPY (PORT)

2.1 Indications:

A meta-analysis showed that following complete resection, radiotherapy has a detrimental effect in stage I and II disease (13). There is no role for radiotherapy in resected N2 disease (14).
PORT is recommended for patients following R1 resection based on improved outcomes seen in non-randomised studies (15). Patients with macroscopic residual disease (R2) should receive a full radical dose of (chemo) radiotherapy.

2.2 Patient Selection:

1. ECOG performance status 0-1
2. Incomplete resection or positive chest wall or bronchial margin (R1/R2 resections)
3. Adequate postoperative pulmonary function tests - FEV1 ≥0.8litre

Table 2	PORT
Energy / modality	6MV photons
Patient immobilisation / set up / planning	Refer to Table 1.0.
Target definition	CTV to included areas felt to be at risk of local recurrence PTV Refer to Table 1.0
Dose / fractionation & treatment duration	50-55Gy in 20 fractions over 4 weeks
Dose specification	Refer to Table1.0. In addition, in cases of pneumonectomy, treatment beams should be delivered through the pneumonectomy cavity to minimise dose to the remaining lung
Onset verification	Refer to table 1.0

3.0 Category 1, Treatment compensation in Radical Treatment

Interruptions of < 1 week due to intercurrent illness or radiation toxicity will be recorded and treatment should be completed as planned. If the radiation schedule is interrupted for more than 1 week due to intercurrent illness consideration should be given to discontinuing treatment. Treatment should definitely be discontinued if there is a delay of 3 or more weeks. Further treatment will depend upon the clinical situation and is at the discretion of the responsible clinician.

If unavoidable delays occur, that could increase the overall treatment time beyond the specified period, e.g. due to machine breakdown, compensation should if possible be made by one of the following mechanisms:

- giving two fractions a day, with a minimum interval of six hours between fractions
- treating on a weekend day
- adjusting fraction size to deliver the total prescribed dose within the recommended days but fraction size should remain <2.5Gy
- For patients on 55Gy in 20# (2.75Gy/#) schedule, 2 fractions a day is not routine practice but may be delivering for individual cases, at the clinician's discretion, following a risk / benefit analysis.

4.0 PALLIATIVE RADIOTHERAPY

In minimally symptomatic locally advanced NSCLC, there is no evidence to indicate immediate thoracic radiotherapy improves quality of life, symptom control and survival compared to treating at the onset of more significant symptoms.
However, historic evidence has shown that for patients with good performance status (ECOG PS 0-2) and without extra-thoracic metastases, there is a small survival benefit to a higher palliative dose.

4.1 Indications for Thoracic radiotherapy:

Shorter courses of palliative radiotherapy produce as effective palliation as longer courses (17Gy in 2 fractions over 1 week compared to 30Gy in 10 fractions over 2 weeks) (18-19).
For those with poor performance status (WHO PS 2-3) a single 10Gy fraction is as effective as 17Gy in 2 fractions one week apart (20). For patients with good performance status (ECOG PS 0-2) and without extra-thoracic metastases, there is a small survival benefit to a higher palliative dose (36 – 39Gy) at the expense of a small increase in toxicity (19).

See Dose fractionation schedules below.

4.2 Patient Selection:

Patients with poorly controlled local symptoms attributable to their cancer:

- Haemoptysis
- Chest pain
- Cough
- Dysphagia caused by tumour compression
- Shortness of breath - central tumours

In some patients it may be appropriate to give palliative radiotherapy without a histological diagnosis.

4.3 Palliative Radiotherapy

Table 3	**Palliative**
Energy / modality	6MV photons
Patient immobilisation, set up	Patient position and immobilisation to be determined by planning technique and patient ability. Arms by side is often sufficient. Refer to local immobilisation techniques
Localisation	CT scan IV contrast as clinically indicated
Planning technique	Technique as clinically appropriate
Target definition	**Gross tumour Volume (GTV)** Visible disease in the planning CT and correlate with symptoms **Planning Target Volume(PTV**) 10- 15mm margin is added to GTV to form PTV Patients receiving high dose palliative radiotherapy can be planned using 3D conformal or IMRT as appropriate, with delineation of GTV, CTV (5mm margin), PTV (10mm radial and 15mm sup and inf) and OARs.

Dose/ fractionation &treatment duration	30-39Gy in 10-13 fractions over 2-3 weeks (max.36Gy if spinal cord is in radiation field). 30Gy in 10 fractions over 2 weeks 10Gy in single fraction in 1 day 16-17Gy in 2 fractions, one week apart 20Gy in 5 fractions over 1 week 8-10Gy for Bone involvement
Organ Tolerances	Spinal cord 36Gy (3Gy per fraction)
On set verification	Verification method dependent on planning method **IMRT/3DCRT** Plan is verified at the first fraction using cone beam CT (CBCT). Ideally daily on line CBCT imaging should be performed to confirm CTV /PTV coverage, and monitor intra thoracic anatomy, dependent on tumour site and OAR. CBCT imaging verification on 1-3# or 1-5# then weekly is adequate but not recommended. **Vsim** Image using 2D image verification (EPID or KV) on 1-3# or 1-5# then weekly

4.4 Brain Metastases

Consider stereotactic radiosurgery or surgery in all suitable patients according to National guidelines. There is no randomised controlled trial evidence that whole brain radiotherapy (WBRT) is superior to steroids alone in symptomatic patients with brain metastases from NSCLC (Quartz trial)(23). However, it may be considered in selected patients for eg: mutation positive patients with good performance status 0-1 with multiple cerebral metastases, patients who are ineligible for SRS or surgery, patients who require brain disease to be 'controlled' prior to treatment with systemic therapy i.e. chemo-immunotherapy or targeted therapy.

Consider hippocampal sparing in patients with good prognosis if clinically appropriate (22).

Table 4	Whole brain
Energy / modality	6MV photons
Patient immobilisation, set up	To be treated in a thermoplastic beam directional shell (BDS) in neutral position. For further immobilisation refer to the local guidelines.
Localisation	CT Scan
Planning technique	Conformal or virtual simulation Conformal volumes CTV = brain, outlined to C2/C3 PTV = CTV + 5mm This provides improved conformity, reduced hotspots and provides accurate reporting of lens doses
Target definition	Whole brain
Organs at risk	Lens <6Gy
Dose/Fractionation & treatment duration	30Gy in 10 fractions over 2 weeks 20Gy in 5 fractions over 1 week
On set verification	Verification method dependent on planning method I**MRT/3DCFRT** Plan is verified at the first fraction using cone beam CT (CBCT). Ideally daily on line CBCT imaging should be performed to confirm CTV /PTV coverage, and monitor intra thoracic anatomy, dependent on tumour site and OAR. CBCT imaging verification on 1-3# then weekly is adequate but not recommended. **Vsim** Image using 2D image verification (EPID or KV) on fractions 1-3

4.5 Retreatment

Re-irradiation may be considered in symptomatic patients who achieved a symptomatic and radiological response following a course of radiotherapy, more than six months previously.
All patients with expected life span of more than 6 months should have radiobiological dose calculations taken into consideration for re-irradiation schedules and to limit additional spinal cord irradiation. This BED calculation should be recorded in patients' notes for future reference.

Different treatment techniques should be considered eg tilted /oblique parallel pair vs IMRT to further reduce OAR toxicity

5.0 PATIENT CARE FOR ALL LUNG PATIENTS

5.1 Patient care:

Radical patients receiving concomitant CRT-, radical RT alone should have FBC, U&E and LFTs checked frequently.
Patients should be offered a transfusion if Hb <10.00 g/dl with the aim of maintaining Hb >12 g/dl during treatment.
All radical patients need to be reviewed weekly by the medical team.
If G3/4 pneumonitis occurs discontinue treatment
Patients should be considered for PJP (pneumocystis jiroveci pneumonia) prophylaxis if thought to be at risk eg. lymphocyte count <0.6, patients on steroids for more than 4 weeks, patients on concomitant CRT(21). Treatment should be continued until lymphocyte count >0.6 or for a minimum of six weeks post concomitant CRT.
For management of additional side effects for either radical or palliative treatments refer to the local guidelines.
See COVID-19 Vaccine Guidelines

5.2 Follow Up:

A GP end of treatment letter should be sent out automatically on completion of treatment.
Concomitant CRT patients need to be seen 1-2 weekly until ongoing acute toxicities resolve. CT scan should be performed at 3 months to assess response (or sooner if they are being considered for adjuvant Durvalumab).
Individualised follow up, including surveillance imaging, dependant on patient criteria.
Good clinical practice would be to follow up for spinal collapse or fracture. Consider referral to fracture liaison service or rheumatologist, if symptomatic.

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