STANDARD PROTOCOL

<table>
<thead>
<tr>
<th>Document Title:</th>
<th>Radical External-Beam Radiotherapy for Non-Small Cell Lung Cancer (55Gy in 20 fractions or 60-66Gy in 30-33 fractions)</th>
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<tbody>
<tr>
<td>Document Type:</td>
<td>Clinical Guideline</td>
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<tr>
<td>Subject:</td>
<td>Standard Care Plan</td>
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<td>Author(s):</td>
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Standard care plan for radical external-beam radiotherapy for non-small-cell lung cancer

References


**Patient group**
- Stage I NSCLC not suitable for surgery or stereotactic radiotherapy
- Stage II NSCLC not suitable for surgery
• Stage III NSCLC not suitable for surgery or concurrent chemo-radiotherapy (can be given after neo-adjuvant chemotherapy)

Indications
• Stage I-III NSCLC not suitable for surgery
• Lesion not within a previous radical radiotherapy field
• Any histological subtype of NSCLC
• MDT consensus of NSCLC if not able to confirm histologically
• ECOG PS 0-2 (selected cases with PS 3)
• Radiotherapy target volume is likely to be within radiotherapy planning constraints as judged by a clinical oncologist

Cautions
• Co-morbidity preventing safe administration of radiotherapy
• Adequate lung function (typically FEV1 >40% predicted and KCO >40% predicted). However, the evidence for correlation of lung function with respiratory toxicity is poor, hence these parameters serve only as a guide. Therefore, radical treatment is not precluded with lung function below these arbitrary levels with careful patient consent and consideration of anticipated PTV and V20.

Evidence
55Gy in 20 fractions is the most commonly used regimen for radical treatment of NSCLC in the UK. Radiobiologically it is similar to the international standard of 66Gy in 2Gy per fraction, with a shorter overall treatment time. There is no randomised evidence comparing 55Gy in 20 fractions to 66Gy in 33 fractions.

Elective nodal irradiation (ENI) is now no longer practiced as evidence suggested that the risk of elective nodal elapse in the absence of local failure is only about 6-7% and the omission of ENI does not compromise overall survival. Reducing the target volume is obviously beneficial in terms of facilitating dose escalation within the context of clinical trials and minimizing toxicity to the organs-at-risk.

Outcome
Previous studies of radical radiotherapy alone (from the late 1980’s) demonstrated a median survival of 15-20 months for stage I-II NSCLC, and approximately 10-15 months for stage III NSCLC. The 55Gy in 20 fraction regimen has not been validated in a phase III trial. More recent retrospective, single centre data has demonstrated median survival of 21-24 months with 2 year overall survival of 45% and cause-specific survival of 47.8% for stage I-III NSCLC treated with 55Gy in 20 fractions. One study subdivided by stage showing 2 year overall survival of 48.2% for stage I/II disease and 26.1% for stage III.

Toxicity
Grade 2/3 rates of oesophagitis of 11% and pneumonitis of 14% were quoted in one retrospective series (using a maximum V20 of 40%). Another retrospective series demonstrated no grade 3/4 toxicity but did not report less severe acute/late effects using 55Gy in 20 fractions. The risk of grade 3/4 late effects are typically considered <5%.

1. Initial investigations and work up prior to start of treatment

1.1. **Diagnostic review and work up should usually include:**
- Pathology/Cytology confirmed diagnosis of NSCLC (MDT consensus of NSCLC diagnosis if not able to confirm histologically)
- Stage of disease determined and documented
  - CT Abdomen/thorax
  - Bronchoscopy
  - PETCT
  - EBUS/mediastinoscopy if radiologically suspicious mediastinal lymph nodes
  - Biopsy of supraclavicular lymph node if radiologically suspicious of malignancy
- Clinical assessment and documentation of current disease related symptoms
- Performance status recorded
- Co-morbidities recorded
- Smoking status recorded
- FH recorded
- Concomitant medications recorded and stopped if necessary
- Lung function test desirable but not compulsory (see above)
- Patient consented for aims, practicalities and toxicity of radical external-beam radiotherapy
- Plan confirmed with consultant oncologist if 1st seen by junior college

1.2. **MDT meeting**
Case must have been through the relevant diagnostic MDT prior to commencing treatment.


Treatment will be 3-D conformal radiotherapy, 4-D conformal radiotherapy, or intensity modulated radiotherapy (IMRT) if dose constraints cannot be met with conventional treatment planning.

2.1. Patient treatment position and set-up

http://discover/departments/radiotherapy/docs/work_instructions/LEVEL3/191.3.doc
Supine, breathing normally using an external immobilisation device with arms immobilised above the head in most cases. Exceptionally, for patients with limited arm movement or apical cancer, arms may be positioned by the patients’ side and consideration should be given to a 5 pt shell fixation to aid stability.
Set up should be by reference to anterior and lateral tattoos on stable areas of skin and bony anatomical landmarks.

2.2. Patient data acquisition

For 3-D planning, a planning CT scan should be performed in the treatment position, whilst the patient undertakes normal respiration. The whole lung (cricoid to L2) should be imaged using 0.3 cm slices to allow dose-volume histograms to be calculated. IV contrast is used if the patient has either nodal or central disease invading the mediastinum (see http://discover/departments/radiotherapy/docs/work_instructions/LEVEL3/191.3.doc)

For 4D-planning, see http://discover/departments/radiotherapy/docs/work_instructions/LEVEL3/281.3.doc

2.3. Target volume delineation

Treatment will be planned based on information from bronchoscopy, PET-CT scan if available and mediastinoscopy or thoracotomy, if performed in addition to CT findings. Target volume delineation will be done using both the mediastinal and lung windows.

For 3-D CT planning:
Gross Tumour Volume (GTV) is defined as the identifiable tumour and involved nodes (nodal involvement on CT scan is defined as nodes \( \geq 1 \) cm in short axis). PET-CT positive nodes if confirmed histologically should be included in the GTV. Elective nodal irradiation should not be employed.

The planning target volume (PTV) comprises the CTV with a 1.3 cm margin superiorly and inferiorly, and 1 cm margin laterally. Reduction of the CTV to PTV expansion is not permitted.

For 4D-CT planning, see http://discover/documents/default.aspx?Details=Y&Doc_ID=5979

In those patients responding to induction chemotherapy, the CTV should aim to encompass the pre-chemotherapy tumour volume and the nodes where possible, providing the V20 constraints are not breached.

2.4. Organs at risk (delineation and dose constraints)

Critical normal structures are the spinal cord, lung, heart and oesophagus. Dose volume histograms (DVH) for the normal lung tissue and spinal cord and will be calculated. The oesophagus and heart should also be contoured if using intensity-modulated radiotherapy.
Lungs: contour all inflated right and left lung as one structure using lung windows. The V20 should be <35% in conventional fractionation (i.e. <35% of the volume of “normal” lung, excluding PTV, should receive a dose of ≥20Gy).

Spinal cord: contour based on the bony limits of the spinal canal. Delineation of the spinal cord should extend at least 10cm beyond the superior and inferior extent of the PTV. Maximum radiation dose to spinal cord should not exceed 48Gy in conventional fractionation. With hypofractionated regimens of 55Gy in 20 fractions a maximum dose of 39Gy to the sc+0.5cm is specified.

Oesophagus: contoured using mediastinal windows from cricoid cartilage to the gastro-oesophageal junction. Planning should aim (not mandatory) to limit the length of treated oesophagus to 120 mm within the PTV and aim to limit the volume treated with doses ≥50Gy. Due to lack of clear evidence regarding toxicity correlation with oesophageal dose volume histogram data, if these parameters are exceeded the clinician may proceed with radiotherapy at their discretion.

Heart: contour along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the superior aspect of the left atrium and extend inferiorly to the apex of the heart. The heart can receive the total dose (TD) to < 30% of its volume. For > 50% of cardiac volume, dose < 50% of TD is recommended.

If dose constraints cannot be met using 3D-conformal radiotherapy, intensity-modulated radiotherapy (IMRT) should be considered to optimise the dose distribution.

2.5. Dose prescription

The dose will be specified at the ICRU reference point according to ICRU 50 and 62 and fully corrected for inhomogeneity. A DVH for the PTV should be calculated. The dose distribution within the PTV should ideally be within ±5% of the prescribed dose, and no more than ±7% of the prescribed dose. Wedges, tissue compensators or multi-leaf collimators may be used to achieve homogeneity of dose.

Radical Radiotherapy doses: 55Gy in 20 daily fractions over 28 days; 60-66Gy in 30-33 fractions over 42-45 days.

2.6. Verification:

Standard departmental policy dictates consecutive imaging on days 1-3 of radiotherapy to confirm set-up accuracy and once weekly thereafter. If a discrepancy of ≥ 5 mm is found then set-up should be corrected and re-imaged as above. All patients treated with 4D-RT and/or IMRT should receive image-guided radiotherapy using cone-beam imaging.

2.7. Treatment Delays:

Every effort should be made to deliver the prescribed dose of radiotherapy within the standard timeframe. 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 on a subsequent day, with a minimum interval of six hours between fractions, or
- treating on a weekend day, or
- if conventional fractionation – adjustment of fraction size (ensuring remains <2.5Gy) to deliver the total prescribed dose within 33 days. Not applicable to hypofractionated regimens

3. On treatment assessments

3.1. Weekly clinical assessment by medical team including
- Graded documentation of toxicity
- Assessment of disease related symptoms
- Performance status recorded

3.2. Management of treatment related toxicity

3.2.1 Radiation oesophagitis
- Grade 2 oesophagitis – optimise analgesia (consider sucralfate suspension, paracetamol mucilage, codeine phosphate liquid, oromorph, fentanyl patch). Advise soft diet/oral dietary supplements if required
- Grade 3 oesophagitis - treat as for grade 2 oesophagitis but also consider admission to The Christie/dietician input/parenteral nutrition if required. Every effort should be made to continue radiotherapy. Avoid placement of nasogastric tubes
- Grade 4 oesophagitis – As for grade 3 oesophagitis but radiotherapy should be stopped.

3.2.2 Radiation Pneumonitis
- Grade 2 pneumonitis - Consider oral steroids/antibiotics/antifungals
- Grade 3 pneumonitis – consider admission to The Christie for high dose IV steroids/oxygen/antibiotics/antifungals. Alert critical care team. Consider stopping radiotherapy
- Grade 4 pneumonitis – as for grade 3 but will require admission to critical care and consider ventilatory support if appropriate. Stop radiotherapy.

3.2.3 Radiation dermatitis
- Topical treatment with aqueous cream/1% hydrocortisone cream if required
Post treatment follow-up

- 6 week post-treatment review with clinical assessment for residual treatment related toxicity and appropriate investigations at discretion of clinician.
- Further follow-up with chest physician or oncologist as appropriate.
**Appendices**

### ECOG PERFORMANCE STATUS*

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
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<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
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### CTCAE v4.0 Skin and Subcutaneous Tissue Disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagitis</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; altered eating/swallowing; oral supplements indicated</td>
<td>Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated</td>
<td>Life-threatening consequences; urgent operative intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL; oxygen indicated</td>
<td>Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)</td>
<td>Death</td>
</tr>
<tr>
<td>Rash: dermatitis associated with radiation</td>
<td>Faint erythema or dry desquamation</td>
<td>Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema</td>
<td>Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion</td>
<td>Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Shortness of breath with moderate exertion</td>
<td>Shortness of breath with minimal exertion; Limiting instrumental ADL</td>
<td>Shortness of breath at rest; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue relieved by rest</td>
<td>Fatigue not relieved by rest; limiting instrumental ADL</td>
<td>Fatigue not relieved by rest; limiting self-care ADL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chest wall pain</td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self care ADL</td>
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<td>-</td>
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<tr>
<td>Cough</td>
<td>Mild symptoms; nonprescription intervention indicated</td>
<td>Moderate symptoms, medical intervention indicated</td>
<td>Severe symptoms; limiting instrumental ADL</td>
<td>-</td>
<td>-</td>
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