Standard care plan for post operative adjuvant radical external-beam radiotherapy for non-small-cell lung cancer

References


**Patient group**

- Stage I-III NSCLC following an R1 resection (microscopic residual tumour tissue at the bronchial resection margin)

**Indications**

- Stage I-III NSCLC post R1 resection where further surgery not possible
- No previous high dose radiotherapy in planned radiation field
- Any histological subtype of NSCLC
- ECOG PS 0-2
- Radiotherapy target volume likely to be within radiotherapy planning constraints as judged by a clinical oncologist
- Radiotherapy should ideally start within 6 weeks of surgery
- If adjuvant chemotherapy is recommended then this should usually precede the adjuvant radiotherapy.

Post operative radiotherapy is not routinely indicated for complete resection of non small cell lung carcinoma.

**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 adjuvant treatment is not precluded with lung function below these arbitrary levels with careful patient consent and consideration of anticipated PTV and V20.

**Evidence**

**Following complete resection (R0):**

The most important surgical goal during potentially curative surgery for non-small cell lung cancer (NSCLC) is a macroscopic and microscopic radical resection (R0-resection). The PORT Meta-analysis Trialists group performed a systemic review and meta-analysis of individual patient data from nine randomized trials exploring the use of PORT in completely resected NSCLC. Results showed a significant adverse effect of PORT on survival with an absolute detriment of 7% at 2 years (reducing overall survival from 55% to 48%). Exploratory subgroup analyses suggested that this detrimental effect was worst for patients with stage I/II, N0-N1 disease, whereas for
stage III, N2 patients there was no clear evidence of an adverse effect. Hence, within the UK, PORT is not routinely indicated following complete resection of NSCLC. However, given that the detrimental effect of PORT on survival may be in part due to sub-optimal radiotherapy techniques and dosages used at that time, PORT especially for the N2 subgroup merits further investigation. Zou et al, 2009, demonstrated a survival benefit using adjuvant chemoradiotherapy compared to chemotherapy alone in patients with completely resected Stage III–N2 nodal disease in NSCLC. In the SEER analysis, PORT did not significantly impact on survival. However, subgroup analysis revealed a significant survival benefit in N2 patients, but a decrease in survival for N0 and N1 patients. Although, the results of such a retrospective study using a large database should be interpreted with caution, the end points in the PORT meta-analysis and the SEER study are remarkably similar. This highlights the need for a randomized trial to evaluate the role of PORT further in N2 disease. Lung ART, an adjuvant radiotherapy trial (Lung ART), is now underway to compare 3D conformal PORT to no PORT, and will include patients who have proven N2 disease and a complete resection irrespective of whether adjuvant or neo-adjuvant chemotherapy was used.

Following incomplete microscopic resection (R1)

R0 resection is established when all resection margins are microscopically tumour free, when there is no extra-capsular extension of positive lymph nodes and no lymph node metastases in the highest resected mediastinal lymph node. However, there is limited data on incidence, treatment and prognosis of patients with microscopic residual tumour tissue at the bronchial resection margin (R1-resection). According to stage, survival of patients with stage I and II NSCLC and an R1-resection of the bronchial resection margin is significantly worse as compared to stage corrected survival after a radical resection. In these patients, survival is limited due to local recurrence with 75-85% having mediastinal lymph node metastasis. The negative effect of an R1-resection of the bronchial margin in stage III NSCLC is limited, as these patients often die due to disseminated disease before local recurrence occurs. Hoffman et al [7] demonstrated significant differences in survival between patients with extrabronchial vs. bronchial infiltration and N0/N1 vs. N2 using univariate analysis. The evidence for survival benefit especially in R1 N2 disease is extremely limited.

Given the current evidence, the clinical oncology lung team here recommends that PORT should be considered following an R1 resection, where further surgery is not possible, provided that the patient is fit (PS 0-2) to start within a reasonable time frame (ideally starting within 6 weeks of surgery). If adjuvant chemotherapy is indicated, this should usually precede radiotherapy (see later). Patients should ideally have repeat post-operative pre-radiotherapy full lung functions tests.
1. Initial investigations and work up prior to start of treatment

1.1. Diagnostic review and work up should be completed pre initial surgery and 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
- Pre operative Lung function test and repeated post operatively if possible
- Patient consented for aims, practicalities and toxicity of radical external-beam radiotherapy
- Plan confirmed with consultant oncologist if 1st seen by junior colleague

1.2. MDT meeting

Case must have been through the relevant diagnostic MDT prior to surgery and desirable but not mandatory to be discussed post resection.


Treatment will be 3-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

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. [http://discover/departments/radiotherapy/docs/work_instructions/LEVEL3/191.3.doc](http://discover/departments/radiotherapy/docs/work_instructions/LEVEL3/191.3.doc)

2.3. Target volume delineation

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

In the vast majority of cases there is no residual tumour and so a CTV only should be outlined. The surgeon usually marks the tumour bed with large clips to aid accurate localisation of the subsequent post operative radiotherapy. This should be discussed with the surgeon prior to radiotherapy planning.

Clinical target volume (CTV) is defined using all the information above and aims to cover the positive margin(s) and tumour bed where possible. It will take into account possible microscopic spread. The CTV can be is adjusted to reduce dose to the spinal cord for example, when disease is adjacent to a structure such as a vertebra but is not thought to invade the structure.

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.

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 (50-55Gy 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 adjuvant Radiotherapy doses: 50-55Gy in 20 daily fractions over 28 days.

2.6. Verification:

Standard departmental policy dictates consecutive portal 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. Alternatively, patients may be verified using cone-beam imaging with the same frequency and tolerance.

http://discover/departments/radiotherapy/docs/work_instructions/LEVEL3/231.3.doc  
http://discover/departments/radiotherapy/docs/work_instructions/LEVEL3/229.3.doc

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

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 shared between thoracic surgeon and oncologist. If the patient had previous adjuvant chemotherapy followup may be with the medical oncologist.
## Appendices

### ECOG PERFORMANCE STATUS*

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<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>
</tbody>
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### CTCAE v4.0 Skin and Subcutaneous Tissue Disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>Rash: dermatitis associated with radiation</td>
<td>Faint erythema or dry desquamation</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Shortness of breath with moderate exertion</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue relieved by rest</td>
</tr>
<tr>
<td>Chest wall pain</td>
<td>Mild pain</td>
</tr>
<tr>
<td>Cough</td>
<td>Mild symptoms; nonprescription intervention indicated</td>
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