Greater Manchester & Cheshire Cancer Network

Lung Clinical Sub Group

GUIDELINES FOR THE NON-SURGICAL MANAGEMENT OF LUNG CANCER

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This document will be a work in progress and will be added to and updated regularly.

The document is intended for clinical use only and should not be quoted by non-clinical staff other than in consultation with thoracic oncologists.

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INTRODUCTION

Primary lung cancer is the commonest form of malignant disease in the western world. In the UK there are about 33,000 new cases every year and more than 10% of those occur in the North West of England. Uncommon under the age of 45 years, it remains the most prevalent form of cancer amongst men over 65 years. The overall trend is for a reduction in lung cancer mortality but it continues to rise in the over 75's and in women.

Rational treatment of lung cancer depends on accurate histological diagnosis and staging. For practical purposes the disease has until recently been divided into non-small cell and small cell carcinoma. Due to the development of treatments that are specifically indicated for non-squamous cell NSCLC, it is now necessary to provide a histological subtype for NSCLC whenever possible. Prompt diagnosis, particularly in small-cell carcinoma, can have a significant impact on management and outcome. Where the diagnosis is suspected, early referral to a thoracic physician or surgeon and then to an oncologist is desirable.

The departments of clinical and medical oncology aim to provide a multi-disciplinary approach to patient management in association with thoracic physicians, surgeons, pathologists and radiologists at the Christie and Wythenshawe Hospitals and through the Cancer Unit Clinics. Agreed treatment protocols are used, in line with national clinical guidelines and patients are regularly cross-referred where appropriate. The clinical and medical oncologists also aim to provide a 'next available' system for new patients and although there are referral pathways based on the postal address of the patient, individual oncologists will frequently refer patients to each other in order to avoid delays and/or for optimal or complex treatments.

BASELINE INVESTIGATIONS and STAGING

General:

A diagnosis of lung cancer can be achieved using the following methods. Histology is preferable to cytology. All patients with a confirmed or suspected diagnosis of Lung cancer should be discussed at a fully accredited Lung cancer Multi-disciplinary team (MDT) meeting before referral.

- Bronchoscopy: fibreoptic bronchoscopy under local anaesthesia should yield a histological diagnosis in the majority of patients. If biopsy is hazardous, rigid bronchoscopy should be considered. In the absence of an endobronchial lesion, one of the following may be required:
- Percutaneous needle biopsy under CT scan control for peripheral tumours.
- Mediastinoscopy/otomy.
- Thoracotomy or Video Assisted Thoracic Surgery.
- Supraclavicular node, skin or liver biopsy.

Physical well-being or performance status is a prognostic factor for both small cell and non-small cell lung cancer patients. Either the Karnofsky Performance (KP) or World Health Organisation (WHO) Performance Scores are used. (appendix 1). Non-small cell Lung cancer is staged using the TNM staging system (appendix 2) but the latest version is also applicable to small cell lung carcinoma (SCLC). However SCLC is usually divided into limited and extensive stage based on extent of disease (appendix 3) which dictates current treatment.

Non-small cell lung cancer (NSCLC):

Investigations:

- A chest x-ray,
- Bronchoscopy,
- Full blood count and biochemical profile and liver profile including albumin
- Contrast enhanced CT scan of the thorax and upper abdomen. The staging CT scan should be according to accepted protocols with a slice thickness of no more than 5mm in the chest and 10mm in the upper abdomen and the TNM stage should be reported.
- For potentially radically treatable patients an FDG-PET scan should be requested
- Mediastinoscopy may be necessary after scanning to exclude false positive PET CT results particularly where surgery (or radical radiotherapy) is being considered.
- Other scans (bone scan or CT brain) should only be requested if symptoms or clinical examination raise the possibility of metastatic spread or for selected protocols such as concurrent chemoradiation.
- Magnetic resonance Imaging (MRI) should be performed, where necessary to assess the extent of disease, for patients with superior sulcus tumours.

Where possible, patients should undergo pulmonary function tests (including lung volumes and transfer factor) if radical radiotherapy or surgery is to be attempted.

The results of investigations should, where possible, be available to the oncologist at the first patient visit to allow a timely decision on management.

Small-cell lung cancer (SCLC):

Investigations:

- As for NSCLC except an FDG PET is not recommended routinely at present.
- CT/MRI brain recommended
- Lactase Dehydrogenase to calculate Manchester Prognostic index (see appendix 3)

TREATMENT

The Manchester Lung Group has a large portfolio of open trials and wherever possible all patients should be offered entry into an appropriate clinical trial if one is available. For further information contact Sharon Woolley: Lead Research Nurse sharon.woolley@christie.nhs.uk, and telephone 0161 918 7478 or Kirsty Stirling: Clinical Trials Support Manager kirsty.stirling@christie.nhs.uk and telephone 0161 446 8284.

Non Small Cell Lung Cancer (NSCLC):

Surgery is the curative treatment of choice for stage I, II and highly selected stage III patients. Any potentially operable patients identified at the MDT meeting should be assessed by a thoracic surgeon.

Radiotherapy: After discussion at the MDT meeting a patient will be channelled into the specialist lung teams for further assessment and treatment which might include radiotherapy and chemotherapy.

Post-Operative Radiotherapy (PORT).

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 [1] 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 [2], PORT especially for the N2 subgroup merits further investigation. Zou et al, 2009 [3], 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 [4], 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 [5].

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)

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 [6]. 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.

For radiotherapy technique see appendix 5.

Radical Radiotherapy.

Radical or curative radiotherapy is indicated where surgery is not possible due to

- tumour stage (stage 3b and most 3A (N2)) rendering it inoperable or
- medical co-morbidities rendering the patient medically inoperable despite early stage disease (1 & 2)
- patient declining surgery

All fit patients with stage 1-3 NSCLC should be considered for radical radiotherapy, if the potential radiotherapy target volume is likely to be within radiotherapy planning constraints as judged by a clinical oncologist at the MDT (see appendix 5)

Patients should be/have

- a reasonable WHO PS 0-1 (PS-2 and very occasionally stable PS3 at clinician's discretion)
- 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. The radiotherapy technique is described in detail in appendix 5.

Evidence base:

Although, the ideal rate for radical radiotherapy would seem to be around 30% of all NSCLC [8], in practice within the UK rates are lower than this [9]. There is no direct randomized evidence comparing the effectiveness of radical radiotherapy versus palliative radiotherapy given at the time of symptoms in medically inoperable stage I/II NSCLC. However, given the absence of such trials, radical radiotherapy appears to result in a better survival than might be expected had treatment not been given [10].

In the UK, the National Institute for Health and Clinical Excellence (NICE) guidelines suggest that continuous hyperfractionated accelerated radiotherapy (CHART) or its radiobiological equivalent should be used, following the study by Saunders et al. [11], which showed a 2-year survival of 29% with the CHART regimen using 54Gy in 36 (1.5Gy) fractions over 12 days compared with 20% in the conventional arm using 60Gy in 30 (2Gy) fractions over 6 weeks. However, in the UK, there are a wide variety of regimens, with the accelerated hypofractionated regimen of 55Gy in 20 daily fractions over 4 weeks

being the most common. Both regimens, 55Gy in 20 daily fractions over 4 weeks and CHART, by virtue of acceleration, shorten the overall treatment time, which is felt to be important radiobiologically in combating tumour repopulation [12]. Doses of 64-66Gy in 32-33 conventional 2Gy fractions over 6.5 weeks would be an internationally accepted standard [13]. However, the optimal radiotherapy regimen remains uncertain.

There is evidence that dose escalation can improve local control is accumulating for a number fractionations and schedules [14-17] and is best seen by the application of stereotactic radiotherapy treatments, which are reporting local control rates of up to 80% [18].

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 [19-22]. 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.

Concurrent Chemoradiation (CTRT)

Concurrent chemo-radiotherapy should be considered in very fit patients with inoperable stage III NSCLC with disease that can be encompassed in a radical radiotherapy volume. Patient selection is paramount for this regimen, and patients must have a good performance status. The tradeoff for improved local control is the increased risk of toxicity, mainly oesophagitis. No long-term oesophageal strictures have been reported in the literature so far. Higher rates of pneumonitis have not been reported with concurrent chemoradiation therapy in randomized controlled trials comparing sequential with

concurrent regimens [23-25]. **Patients selected for concurrent chemo-radiotherapy should ideally be entered into a clinical trial**.

Baseline Investigations

As in section 1a but patients being considered for concurrent CTRT should always undergo

- Lung function tests including FEV1 and DLCO (transfer factor)
- Brain scan (CT or MRI)

Patient Selection

- Histologically confirmed NSCLC
- Inoperable stage IIIa/IIIb disease that can be encompassed within a radical radiotherapy volume (patients with malignant pleural effusions should **not** undergo concurrent CTRT).
- Patients should be clinically fit with a WHO performance status 0-1 and no significant co-morbidities that might impact on tolerability and toxicity of treatment.
- FEV1 and DLCO ≥ 50% of predicted.
- Adequate renal function for platinum chemotherapy - defined by GFR > 50 ml/min. The Cockcroft and Gault formula should be used to estimate GFR, but if < 60 ml/min then an EDTA should be performed.

Treatment

All patients undergoing concurrent chemo-radiotherapy should have a Treatment Plan completed at the outset, detailing the proposed treatment dates (see appendix 7).

Chemotherapy

Two cycles of chemotherapy are given concurrently with radiotherapy. The first cycle of chemotherapy and first fraction of radiotherapy should start on the same day (preferably a

Monday). All concurrent chemo-radiotherapy should be delivered at The Christie. The concurrent chemotherapy regimen used is:

- Etoposide 50 mg/m2 iv: day 1-5 and 29-33
- Cisplatin 50 mg/m2 iv: day 1, 8, 29, 36

Prophylactic antibiotics such as ciprofloxacin or levofloxacin are recommended to start on day 1 cycle 1 of chemotherapy and continue for 10 days then again from day 1 cycle 2 of chemotherapy for 10 days to minimize the risk of neutropenic sepsis and respiratory infection especially in the presence of bronchial obstruction.

When dose modifications are required, the aim should be to delay and give at full dose rather than reducing the dose. The need for dose modification should be based on clinical judgement and the recommendations in appendix 6.

Thoracic Radiotherapy

For full radiotherapy technique including verification see appendix 5. Concurrent chemo-radiotherapy should be delivered at 2 Gy per fraction, to a total dose of 66 Gy in 33 fractions over 6 ½ weeks.

On-Treatment Assessments

During concurrent chemo-radiotherapy patients should be assessed at least on a weekly basis as per agreement between the medical and clinical oncologist and should include:

- Clinical assessment including performance statue
- FBC/Biochemical profile
- CXR if worsening dyspnoea

Pancoast tumours

Tumours of the superior sulcus should be discussed in detail at a fully accredited Lung MDT and patients should be assessed for surgical suitability by a Thoracic Surgeon. Gold standard treatment is pre-operative concurrent CTRT followed by resection where possible +/- adjuvant chemotherapy.

Baseline Investigations

As for Concurrent CTRT but the following tests should be considered:

- MR thorax may be helpful to the surgical team to assess chest wall and brachial plexus involvement
- Mediastinoscopy after completion of the induction CTRT to confirm N0 status

Patient Selection

- As for CTRT *but:*
- T3-4 pN0 M0 (pN0 status to be confirmed by a mediastinoscopy).
- Patients considered technically and medically operable.
- Patient considered able to tolerate platinum based chemotherapy and radical radiotherapy.
- Patients with the following characteristics are not eligible: medically unstable (e.g. unstable diabetes, uncontrolled arterial hypertension, infection, untreated hypercalcaemia or ischaemic heart disease) or any other condition that would limit the ability to tolerate concurrent chemoradiotherapy.

Treatment

All patients undergoing concurrent chemo-radiotherapy should have a Treatment Plan completed at the outset (see appendix 7) and a summary of the treatment is included in appendix 8.

Chemotherapy

Patients will be managed jointly by the clinical oncology and medical oncology teams. Two cycles of chemotherapy are given concurrently with weeks 1 and 5 of radiotherapy. All concurrent chemo-radiotherapy should be delivered at The Christie. The concurrent chemotherapy regimen used is

- Etoposide 50 mg/m2 iv: day 1-5 and 29-33
- Cisplatin 50 mg/m2 iv: day 1, 8, 29, 36

Prophylactic antibiotics such as ciprofloxacin or levofloxacin are recommended as per CTRT.

When dose modifications are required, the aim should be to delay and give at full dose rather than reducing the dose. The need for dose modification should be based on clinical judgement and the recommendations in appendix 6

Thoracic Radiotherapy

For full radiotherapy technique including verification see appendix 5. Radical radiotherapy should start on day 1 of the first cycle of chemotherapy. Every effort should be made to start concurrent chemoradiotherapy on a Monday. The total dose of radiotherapy will be 45 Gy in 25 daily fractions of 1.8 Gy, prescribed at the ICRU reference point.

On-Treatment Assessments

During concurrent chemo-radiotherapy patients should be assessed at least on a weekly basis as per agreement between the medical and clinical oncologist and should include:

- Clinical assessment including performance statue
- FBC/Biochemical profile
- CXR if worsening dyspnoea

Surgical Assessment

Patients to be reviewed as soon as the CTRT is completed for surgical assessment. If surgery felt not to be possible for technical or medical reasons, the radiotherapy is to be continued to the dose of 60-66 Gy in 2Gy fractions.

Consolidation Chemotherapy

Patients will be reassessed after surgery by the treating oncologist. Based on the level of fitness after surgery, patients may be offered two additional cycles of Cisplatin/Etoposide

Etoposide 50 mg/m^2 iv: day 1-5 and 29-33

Cisplatin 50 mg/m^2 iv: day 1, 8, 29, 36 with hydration

Follow up post radical RT:

Patients should be seen by ideally by the treating clinical oncologist 6 weeks post completion of radiotherapy. Thereafter, follow-up is as per local agreement between the respiratory physicians and oncologists. A typical schedule may be 3 monthly in the 1st year, 4 monthly within the 2nd year, 6 monthly in the 3rd year and annually in the 4th and 5th year of FU.

Serial CXRs are recommended if primary visible originally on CXR. A CT scan post-radiotherapy at 3 months may be helpful as a baseline in patients for whom further treatment would be appropriate should they relapse but recurrence can be difficult to diagnose.

ILT (Intra-Luminal Radiotherapy)

The Christie has been at the forefront in developing this modality of treatment [26, 27]. ILT may be used if there is visible tumour in a large airway resulting from intrinsic endobronchial disease or extrinsic submucosal infiltration from an adjacent lung parenchymal lesion or lymph node. However for patients with a good performance status and stage III NSCLC, External Beam Radiotherapy (EBR) (with or without chemotherapy) is preferred to intraluminal radiotherapy as the primary treatment, giving better symptom control, a longer duration of response and a small survival gain [28].

Indications :

As an alternative to EBR:

- To relieve symptoms such as dyspnoea, post-obstructive pneumonitis, haemoptosis and intractable cough due to endobronchial tumour in a large airway
- In selected cases ILT can be used to radically treat small predominantly endobronchial tumours in patients who are not fit for surgery or radical EBR (treatment fractionated weekly over 3 visits)

With EBR to try and improve local tumour control.

ILT is given as a single treatment 4-6 weeks before EBR (palliative or radical). Advantages of combining approaches:

- Re-expansion of the collapsed lung can help achieve better tumour definition.

- smaller tumour volume for subsequent EBR, which gives better re-oxygenation of tumour during irradiation and allows assessment of radiosensitivity when deciding further management.

After failed radical or palliative EBR.

For palliation if significant bronchial component to relapse.

Contra- Indications :

- Not fit for bronchoscopy.
- Fistula between bronchus and adjacent structure.
- Major airway embarrassment judged too extensive and at risk of airway oedema. An urgent thoracic surgical opinion should be sought to consider laser de-bulking or bronchial/ tracheal stent by rigid bronchoscopy.
- Tumour invasion is contiguous with a major blood vessel.

Radiotherapy Technique:

See Appendix 9 for ILT RT technique.

Patients who may be suitable should be identified early via local or sector MDTs and triaged on to the next available brachytherapy list (contact Dr Burt/Dr Sheikh) where a bronchoscopic re assessment proceeding to treatment will take place. A detailed bronchoscopy report including any photo or video images is helpful.

Stereotactic Radiotherapy: The Christie will be offering this treatment for selected patients later in 2010 and further guidance will be included at a later date.

Palliative Radiotherapy:

Cranial Irradiation:

Patient selection

Most patients with inoperable brain secondaries and NSCLC have a very poor prognosis (<3 months median survival) and steroids with active supportive care is often the best management strategy. However some patients – particularly younger patients with a good performance status and controlled extra-cranial disease - may benefit from a short course of whole brain radiotherapy [29, 30].

Radiotherapy Technique

Patients are simulated and treated supine and immobilized in a thermoplastic shell of the head.

Field Arrangement: Radiotherapy is given using a lateral parallel opposed pair and 4-8MV photons.

Field definition: inferior – bony landmarks of the base of the skull (Riedel's Baseline) and superior, anterior and posterior – 1cm beyond the bony skull. Field projection is checked to ensure eyes are spared and adjusted accordingly.

Dose: The mid plane dose prescribed ranges from 20Gy/5 daily fraction to 30Gy/10 fractions.

Assessments

Patients with brain secondaries symptoms may worsen in the first few days of treatment due to increasing cerebral oedema and steroids are often started or temporarily increased to try prevent this.

Side effects

Alopecia, scalp skin reaction and photosensitivity, lethargy and somnolence, mild nausea and headache.

Thoracic irradiation:

A number of MRC trials regarding palliative radiotherapy for NSCLC were published in the 1990s and inform our recommendations today [29, 31, 32].

Patient Selection

For those patients with a poor performance status (KP40-60) a single exposure of external beam radiotherapy is recommended to rapidly palliate thoracic symptoms ie pain, haemoptosis and dyspnoea due to tumour obstruction [32]. Frail patients without symptoms probably do not benefit from treatment. Those patients with a better performance status (KP >60) but who are not suitable, have declined or already had chemotherapy should receive a longer course of radiotherapy as their life expectancy is longer (extending occasionally beyond 5 years). For these better performance status patients, duration of response is important as well as immediate symptom relief and treatment may be even be beneficial for asymptomatic patients [29].

Radiotherapy Technique

The patients are usually treated supine with either an anterior posterior parallel opposed pair (APPOP) or a single field using megavoltage radiotherapy (4-8MV). Fields are determined by physician using pre- & post-chemo CT imaging (if available) as guidance and fluoroscopic imaging.

For poor PS patients being treated in a single fraction a Mid Plane Dose of 800-1000cGy is given if treated as a POP and 1000-1250cGy to Dmax if given as a single field. Better PS patients should receive a higher mid plane dose of 2750cGy in 8 daily fractions or 2000cGy in 4-5 fractions.

Assessments:

Patients should be seen weekly if receiving a longer course of radiotherapy. Temporary oesophagitis may occur 2 weeks after commencement of treatment and may be helped by paracetamol mucilage.

Bone metastases:

Patients with bone metastases and NSCLC usually have a poor prognosis. A single exposure of radiotherapy can be very effective for painful bony secondaries and is also recommended post surgical stabilization of a pathological fracture.

Radiotherapy Technique

Patients should be treated with an APPOP or single field to the lesion with at least a 2-5 cm margin although the whole bone is often treated. The dose given is 800-1000cGy using 4-6MV photons. Pain relief may take several days and may worsen immediately following treatment. For spinal cord compression a longer fractionation (2000cGy in 4-5 fractions) may be used and the treatment field should include at least 1 normal vertebrae above and below the affected one.

Others/miscellaneous:

Occasionally other symptomatic secondaries from NSCLC may benefit from radiotherapy i.e. skin or orbital metastases. Patients should be treated with a short fractionation (800-1000cGy in a single fraction or 2000cGy in 4-5 fractions). The energy and technique depends on the site treated.

Chemotherapy/Systemic Treatment (for detailed regimes see appendix 14)

Adjuvant Chemotherapy

The rationale for adjuvant chemotherapy in NSCLC is that recurrence following resection of primary disease can be metastatic as well as local. Evidence supporting the use of platinum based adjuvant chemotherapy comes from several large randomised controlled trials, which have shown a benefit for adjuvant chemotherapy (approx 4-15% at 5 years) [33-37]. These studies provide evidence of a survival benefit which is at least as good as that seen for adjuvant chemotherapy in other settings such as breast or colorectal cancer.

Patient selection:

Patients with completely resected stage Ib (4cm or more)-IIIa NSCLC should be referred to the Medical Oncologists at Wythenshawe for consideration of platinum based chemotherapy.

Regimen for Adjuvant Treatment of NSCLC

Vinorelbine 25mg/m^2 day 1 & 8

Cisplatin 75mg/m^2 day 1*

4 cycles

Prophylactic antibiotics with cycle 1 day 5-14

*Carboplatin AUC 5 on day 1 if cisplatin not suitable i.e if eGFR/EDTA clearance <50ml/min, serum creatinine >ULN, severe emesis despite appropriate prophylaxis or co-morbidity precluding cisplatin.

Neoadjuvant Chemotherapy

The clinical trial evidence-base for neoadjuvant chemotherapy in NSCLC is less secure than that for adjuvant treatment [38] and although there are a number of potential advantages (eg. more patients may be able to tolerate chemotherapy before surgery compared to afterwards, potential downstaging of tumour) neoadjuvant therapy is not routinely recommended.

Chemotherapy for Advanced Disease (Palliative) (see appendix 14)

Several meta-analyses have demonstrated a modest survival benefit (2-5 months) for platinum based chemotherapy compared to active supportive care alone [33] (which included radiotherapy) for patients with advanced NSCLC. There is also evidence that single agent third generation drugs also improve survival by about 2 months [39]. Perhaps more importantly, chemotherapy has been shown to improve quality of life. Furthermore, in trials examining patient reported symptoms, improvement in symptoms is higher than objective response rates in all studies, suggesting that palliation can be achieved with tumour shrinkage that does not meet the standard criteria for objective response.

The Lung Cancer Group have taken part in a variety of randomised trials at the Christie and Wythenshawe Hospitals comparing supportive care versus less toxic newly licensed active single agents and these have confirmed the findings of the meta-analysis. Consequently chemotherapy plays an important part in the primary treatment of stage III and IV disease.

Chemotherapy is offered to patients with stage III or IV NSCLC and good performance status (PS 0-2), to improve survival, disease control and quality of life. The benefit of chemotherapy in patients with a poor performance status is not proven and so is usually only considered within the context of a clinical trial.

First line therapy

Chemotherapy for advanced NSCLC is given as a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel, vinorelbine or pemetrexed) plus a platinum drug. Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with third-generation drugs. Pemetrexed is licensed to be given in combination with cisplatin for non-squamous cell NSCLC and should not be given to patients with predominantly squamous cell NSCLC.

Patients with locally advanced disease who are not eligible for concurrent treatment should receive sequential chemotherapy (regimens as for advanced disease) followed by radiotherapy.

Treatment Regimens for Advanced NSCLC (1st Line)

Gemcitabine 1250mg/m2 D1 & D8

Carboplatin AUC5 D1 or Cisplatin 75mg/m2 D1

21 day cycle

4 cycles planned.

Pemetrexed 500mg/m2 D1

Cisplatin 75mg/m2 D1

21 day cycle

4 cycles planned

Folic acid 400mcg daily commencing at least 5 days before cycle 1 D1 and to continue until 3 weeks post the last dose

Vitamin B12 1mg im every 9 weeks commencing on or before cycle 1 D1

Dexamethasone 4mg po bd commencing day before pemetrexed for 3 days

Avoid NSAIDs for 5 days before and after pemetrexed

Other platinum doublets used are Carboplatin AUC 6 D1 with Paclitaxel 200mg/m² D1 and Cisplatin 75mg/m² D 1 with Docetaxel 75mg/m²D1

Patients unable to tolerate a platinum doublet may receive Vinorelbine 30mg/m^2 IV D1 & D8 or Gemcitabine 1250mg/m2 D1 & D8

Prophylactic antibiotics with cycle 1 day 5-14 should be administered to patients with an increased risk of infection, particularly where there is major airway obstruction with pulmonary collapse/consolidation.

Second line therapy (see also appendix 14)

Docetaxel [40] or pemetrexed [41] monotherapy should be considered if second-line chemotherapy treatment is appropriate (and no trials are available) for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. Erlotinib [42] may also be considered for 2nd or 3rd line treatment.

Treatment Regimens for NSCLC (2nd Line)

Docetaxel 75mg/m2 D1

21 day cycle

4 cycles planned.

Prophylactic antibiotics with cycle 1 day 5-14

Pemetrexed 500mg/m2 D1

21 day cycle

4 cycles planned

Folic acid 400mg po daily starting at least 5 days before cycle 1

Vitamin B12 1000mcg IM before cycle 1 & every 3rd cycle

Erlotinib 150mg po continuously

Continue until disease progression or unacceptable toxicity

Dispense with loperamide for use in case of diarrhoea

May need to use aqueous cream, antibiotic/antifungal creams and oral antibiotics (tetracyclines) for rash.

All chemotherapy given for non-small cell lung cancer should ideally be given within trial protocols where results can be analysed and published in peer-reviewed journals.

Small Cell Lung Carcinoma (SCLC)

SCLC may progress very quickly but can be cured if diagnosed and treated when the stage is limited and if extensive at presentation, prompt treatment prolongs survival. Therefore prompt diagnosis and referral for treatment is essential. To avoid any delays in

assessment for chemotherapy and radiotherapy, patients may be referred directly to the Medical Oncologists at the Christie or Wythenshawe Hospital bypassing the Cancer Unit Oncology clinic. Referrals should be accompanied by a copy of relevant scans, bronchoscopy report and pathology report so that further investigations can be requested if necessary.

Different treatment regimens of differing intensity are targeted to particular groups of patients with SCLC. The separate patient groups are identified by prognostic factors determined by multivariate analysis. One of the data sets used in the overview analysis from the United Kingdom Co-ordinating Committee on Cancer Research involved the Wythenshawe and Christie Hospital information base (Appendix 3).

Several studies investigating chemotherapy for SCLC have compared two commonly used regimens: cisplatin/etoposide and vincristine/doxorubicin /cyclophosphamide. Early studies suggested that the two regimens have equal efficacy [43-45], however, a meta-analysis of 4054 patients from 19 trials showed that platinum containing regimens are superior in terms of response rates and survival [46]. Platinum/etoposide regimens are now the treatment of choice for patients who can tolerate platinum with anthracyclines based regimens reserved for those who cannot.

Limited Stage SCLC (LDSCLC)

Concurrent CTRT

Concurrent chemo-radiotherapy should be considered in patients with LDSCLC with disease that can be encompassed in a radical radiotherapy volume [47]. Patient selection is paramount for this regimen, and patients must have a good performance status (WHO PS 0-1, although consider for WHO PS2 if poor PS is likely to improve with tumour

response). **Patients selected for concurrent chemo-radiotherapy should ideally be entered into a clinical trial**.

Baseline Investigations

As in section 1a and b but patients being considered for concurrent CTRT should always undergo

- Lung function tests including FEV1, FVC and DLCO (transfer factor)
- Brain scan (CT or MRI)

Patient Selection

- Histologically confirmed SCLC.
- LDSCLC that can be encompassed within a radical radiotherapy volume (patients with malignant pleural effusions should **not** undergo concurrent CTRT).
- Patients should be clinically fit with a WHO performance status 0-1 and no significant co-morbidities that might impact on tolerability and toxicity of treatment. Patients with PS 2 whose general condition is explained by obstructive/bulky disease likely to improve after the first cycle of chemotherapy should be considered for concurrent treatment.
- FEV1 and DLCO ≥ 40% of predicted.
- Adequate renal function for platinum chemotherapy - defined by GFR > 50 ml/min. The Cockcroft and Gault formula should be used to estimate GFR, but if < 60 ml/min then an EDTA should be performed.

Treatment

All patients undergoing concurrent chemo-radiotherapy should have a Treatment Plan completed at the outset, detailing the proposed treatment dates (see appendix 10).

Chemotherapy (see also appendix 14)

Patients undergoing concurrent chemo-radiotherapy should receive 4 to 6 cycles of cisplatin/etoposide at 3 weekly intervals at the following doses:

- Etoposide 100 mg/m2 iv: day 1-3
- Cisplatin 75 mg/m2 iv: day 1

Or

- Etoposide 100 mg/m2 iv: day 1-3
- Cisplatin 25 mg/m2 iv: day 1-3

One cycle should be given prior to radiotherapy. Every effort should be made to start chemotherapy on a Monday. Radiotherapy should ideally start with day 1 of cycle 2. If this is not possible, radiotherapy can be started on day 1 cycle 3. All concurrent chemo-radiotherapy should be delivered at The Christie.

Prophylactic cranial irradiation (PCI) **must not** be given concurrently with Chemotherapy.

Prophylactic antibiotics such as ciprofloxacin or levofloxacin are recommended to start on day 8 cycle 1 of chemotherapy and continue for 7 days to minimize the risk of neutropenic sepsis and respiratory infection. Consideration should be given to continuing prophylactic antibiotics after subsequent cycles if bronchial obstruction is present.

When dose modifications are required, the aim should be to delay and give at full dose rather than reducing the dose. The need for dose modification should be based on clinical judgement and the recommendations in appendix.

Thoracic Radiotherapy

For detailed radiotherapy technique including verification, normal tissue constraints and management of treatment delays see appendix 5.

The radiotherapy planning scan should ideally be performed prior to starting chemotherapy, otherwise as soon as possible after the first cycle of chemotherapy.

Concurrent chemoradiotherapy should be delivered at a dose of 45 Gy in 30 fractions twice daily.

On-Treatment Assessments

During concurrent chemo-radiotherapy patients should be assessed at least on a weekly basis as per agreement between the medical and clinical oncologist:

- Clinical assessment including performance statue
- FBC/Biochemical profile
- CXR if worsening dyspnoea

Post-Treatment Assessment

Patients should be seen by ideally by the treating clinical oncologist 6 weeks post completion of radiotherapy. Thereafter, follow-up is as per local agreement between the clinical oncologist, medical oncologist, and respiratory physicians. Due to the high risk of recurrence in SCLC, patients should ideally be kept under review by an oncologist. A

typical schedule may be 3 monthly in the 1st year, 4 monthly within the 2nd year, 6 monthly in the 3rd year and annually in the 4th and 5th year of FU.

Sequential CTRT

Sequential chemo-radiotherapy should be considered in patients with LDSCLC who do not fulfil the selection criteria for concurrent chemo-radiotherapy

Baseline Investigations

As for concurrent CTRT but also needs:

- RT planning CT scan (with IV contrast if central disease/lymphadenopathy), prior to cycle 2 chemotherapy (patient does not need to attend sim).

Patient Selection

- Histologically confirmed SCLC.
- LDSCLC based on CT scan (patients with malignant pleural effusions should **not** undergo concurrent CTRT).
- Patients should be clinically fit with a WHO performance status 0-2 and no significant co-morbidities that might impact on tolerability and toxicity of treatment.
- Adequate renal function for platinum chemotherapy - defined by GFR > 40 ml/min. The Cockcroft and Gault formula should be used to estimate GFR, but if < 60 ml/min then an EDTA should be performed.

Treatment

All patients undergoing sequential chemo-radiotherapy should have a Treatment Plan completed at the outset, detailing the proposed treatment dates (see appendix 11).

Patients referred to medical oncology should also be referred immediately to clinical oncology for a discussion regarding radiotherapy and to book the initial RT planning scan.

Chemotherapy (see also appendix 14)

Patients undergoing sequential chemo-radiotherapy should first receive 4 to 6 cycles of cisplatin/etoposide at 3 weekly intervals at the following doses:

- Etoposide 120 mg/m2 iv: day 1-3,
- Cisplatin 80 mg/m2 iv: day 1,

  (Carboplatin AUC 6 on day 1 if cisplatin not suitable: eGFR/EDTA clearance <50ml/min, serum creatinine > ULN, severe emesis despite appropriate prophylaxis or co-morbidity precluding cisplatin)

  The regimes listed in 1st line treatment for ESSCLC below may also sometimes be used.

Prophylactic cranial irradiation (PCI) **must not** be given concurrently with radiotherapy.

If poor performance status/co-morbidity and/or proximal bronchial obstruction, prophylactic antibiotics such as ciprofloxacin or levofloxacin are recommended as for CTRT

The need for dose modification should be based on clinical judgement and the recommendations in appendices 6 and 14.

A post-chemotherapy CT scan should be requested during the penultimate cycle of chemotherapy. The patient should be referred again to clinical oncology at this time,

stating the date of the final cycle of chemotherapy, so that a second radiotherapy planning CT scan can be requested and the thoracic radiotherapy (+/- PCI) can be arranged.

Thoracic Radiotherapy

Radical radiotherapy should start 3 to 6 weeks after completing the final cycle of chemotherapy.

For detailed radiotherapy technique including verification, normal tissue constraints and management of treatment delays see appendix 5.

On completion of chemotherapy, the patient should have a second radiotherapy planning CT scan (with IV contrast if central disease/lymphadenopathy). The patient only needs to attend the simulator if planning PCI at the same time.

The pre- and post-chemotherapy planning scans should be fused. A GTV does not need to be demarcated. The CTV should be outlined on the pre-chemotherapy planning CT scan and edited on the post-chemotherapy planning CT scan taking into account the response to chemotherapy. However if possible the cranio-caudal extent of the disease on the pre-chemotherapy planning scan should be included in the CTV. The post-chemotherapy RTP will be used for treatment planning. The margins from CTV to PTV are standard as in appendix 5.

Radiotherapy should be delivered at a dose of 50 Gy in 20 fractions over 4 weeks.

On-Treatment Assessments

During chemotherapy, assessments as per appendix 14

During radiotherapy patients should be assessed at least on a weekly basis:

- Clinical assessment including performance statue
- CXR if worsening dyspnoea

Post-Treatment Assessment

As for concurrent CTRT for LSSCLC

PCI (Prophylactic Cranial Irradiation) in LD-SCLC patients

Brain metastases are a frequent problem for patients with SCLC due to limited penetration of chemotherapy drugs to this sanctuary site. There is evidence to support the role of PCI for patients with LS-SCLC. The PCI overview collaborative group meta-analysis showed that PCI in limited stage patients achieving a complete remission with chemotherapy significantly reduced the incidence of cranial relapse by more than 50% [48]. There was a 5.4% improvement in 3-year survival and a trend to improved survival in those receiving 30Gy or more. A randomised trial comparing 25Gy in 10 fractions to 36Gy (some receiving once-daily conventional 2Gy fractions, others twice-daily 1.5Gy fractions as an accelerated hyperfractionated schedule) showed no difference in the 2-year incidence of brain metastases but a lower survival in the higher radiation dose group [49]. Therefore the current standard of care is **25Gy in 10 daily fractions.**

Indications:

- Any LS-SCLC patient who has had a complete response (CR) or partial response (PR) to chemotherapy. Response confirmed on CT scan after minimum of 3 cycles of chemotherapy using RECIST measurements.
- No brain metastases on CT or MRI scan.
- Performance score (PS) of 0, 1 or 2.
- There is no upper age limit.

Contra-indications:

- Poor response to chemotherapy.
- Established cerebro-vascular disease.
- PS 3 or 4.

Technique:

- As for NSCLC cranial radiation (see above).
- Dose prescribed is 25Gy in 10 daily fractions.

Side Effects:

- See NSCLC cranial radiation

PCI may be given synchronously with a thoracic radiation schedule treating 2 sites on the same day but MUST NOT be given with chemotherapy. A minimum of 2 weeks since the last chemotherapy dose must have elapsed before commencing PCI.

There had been concerns about delayed neuro-cognitive impairment in patients receiving PCI in earlier studies but many of these used concurrent chemotherapy with PCI, large

dose per fraction of 3-4Gy and/or total dose. If prescribed as suggested, this is not a concern.

Extensive Stage SCLC (ESSCLC)

Although with current treatment the median survival of these patients is only 8 months with less than 10% survival at 2 years or more, the median survival untreated is less than 3 months. Studies comparing the quality of life of patients treated with different regimens of chemotherapy are important.

Patients with a number of adverse prognostic factors will be offered chemotherapy appropriate to their general condition, co-morbidity and Manchester Score. Where possible, this will be as part of a clinical trial examining both efficacy and quality of life.

Chemotherapy for Extensive Disease (see also appendix 14)

Treatment Protocol for 1st Line Therapy in SCLC

Cisplatin (75mg/m2) or Carboplatin (AUC 6) Day 1

Etoposide 120mg/m2 Day 1-3

4-6 cycles

21 day cycle

Prophylactic antibiotics with cycle 1 day 5-14

Single agent carboplatin may be used for patients with impaired hepatic or renal function and poor performance status.

Less frequently non-platinum containing regimens are used including:

- VAC - Vincristine (1.4mg/m2, max 2mg)/Adriamycin (50mg/m2)/Cyclophosphamide (800g/m2).
- D1 of 21day cycle.
- 4 cycles for patients unable to tolerate platinum/etoposide.

ACE - Adriamycin (40mg/m2)/Cyclophosphamide (1g/m2)/Etoposide (100mg/m2)
D1 of 21 day cycle.

4 cycles for patients unable to tolerate platinum/etoposide or VAC .

PCI (Prophylactic Cranial Irradiation) in ED-SCLC patients

The incidence of brain metastases in extensive stage disease approached 80% at 2 years in the pre-PCI era. A landmark EORTC study randomised 286 extensive stage patients with any response to chemotherapy to PCI or no further treatment [50]. The most common dose prescribed was 20Gy in 5# followed by 30Gy in 10#. This showed a significant reduction in the 1-year rate of brain metastases (14.6% versus 40.4%, $p < 0.05$). The 1-year survival rate was 27.1% in the irradiation group and 13.3% in the control group ($p = 0.03$). Since these results were published in 2007, the uptake of PCI has been rapid.

A Christie-led nationwide survey of UK radiotherapy centres showed that by December 2007, 90% of centres were routinely using PCI in patients with ED-SCLC who had responded to initial systemic chemotherapy [51].

Indications:

- A response to chemotherapy confirmed on plain radiographic assessment or CT scan.
- No brain metastases on CT or MRI
- Performance score (PS) of 0, 1 or 2
- Age <75 years

Contra-indications:

- No response to chemotherapy
- Established cerebro-vascular disease
- PS 3 or 4

Technique:

- As for NSCLC cranial radiation (see above)
- Dose prescribed is 20Gy in 5 daily fractions

Side Effects:

- See NSCLC cranial radiation

Thoracic irradiation in ED-SCLC

The use of thoracic radiotherapy has traditionally been for local palliation in extensive stage patients, and interest in its consolidative role has been low due to the systemic nature of this disease and its rapid tumour kinetics.

A single randomised study of patients who had a complete response in distant disease and at least a partial response in thoracic disease after 3 cycles of PE compared further

chemotherapy alone to accelerated hyperfractionated radiotherapy with concurrent carboplatin/etoposide [52]. The addition of consolidative radiotherapy to the treatment of this most favourable subset of patients significantly improved survival rates but this has not resulted in the universal adoption of consolidation thoracic radiotherapy in ED-SCLC. Both the RTOG and a Dutch Lung Cancer Study Group are planning a randomised controlled trial of thoracic radiotherapy versus observation for patients with ED-SCLC who have responded to chemotherapy and so we may have more evidence in future.

Possible Indications:

- Progressive disease (PD) during 1st line chemotherapy, to achieve local control of primary/ nodal disease.
- PD in thorax when further line of chemotherapy deemed inappropriate.
- Initial presentation with SVCO or central airways obstruction even if good response achieved.
- Bulky central mediastinal disease persisting post-chemotherapy where risk of local relapse of local relapse high.

Technique:

- As for NSCLC (see above).
- Typical doses are 10Gy in single fraction, 20Gy in 5 fractions or 30Gy in 10 fractions.

2nd Line Treatment of SCLC (see also appendix 14)

Chemotherapy response rates with 2nd line treatments in SCLC are significantly lower than with 1st line therapy and the balance of benefits and toxicity need to be carefully considered and discussed with each patient. Patients should always be considered for

appropriate clinical trials. Second line chemotherapy for SCLC should be reserved for those patients who have responded to 1st line treatment.

The treatment options are:

1. Re-challenging with further platinum/etoposide (regimens as for 1st line treatment – 4 cycles, usually if time to disease progression is more than 3 months)

2. Anthracycline based treatment eg.VAC (regimens as for 1st line treatment – no more than 4 cycles, usually if progression occurs within 3 months of a platinum regimen or after two platinum regimens).

3. Oral Topotecan if unfit for platinum rechallenge or VAC chemotherapy.

OTHER INTERVENTIONS for Lung Cancer:

Bronchial stents and/or laser therapy may be used to relieve significant major airway obstruction before radiotherapy when rapid relief of dyspnoea is required or in recurrent endobronchial tumours when other treatments have been exhausted. Immediate radiotherapy after stent insertion should be discussed with a clinical oncologist.

Superior vena caval stents (usually inserted by interventional radiologists) can provide effective relief of SVC obstruction and should be considered when this occurs as a presenting feature or with a relapse after previous radiotherapy.

Photodynamic therapy : see appendix 12 for guidance notes

Supportive care without recourse to radiotherapy or chemotherapy, using appropriate medication to alleviate distressing symptoms in patients with poor performance status and prognosis is frequently used with the help and expertise of the palliative care and support services (see below).

Radiofreqency ablation : see appendix 13 for guidance notes.

SPECIALIST SERVICES:

Palliative Care and Support Services

There are two Lung Cancer Clinical Nurse Specialists, (CNS) working at The Christie. They work alongside all the Doctors who offer treatment. Their role is to offer information and support to lung cancer patients throughout their treatment and care. They have a wide range of experience and knowledge on lung cancer and are able to provide help to patients when they are going through treatment. At the end of treatment the Lung Cancer Nurse Specialist can liaise with other health care professionals in the primary and secondary care setting to ensure the patient is supported well and has contact in the community setting.

One of the primary roles of the Lung cancer nurse specialist is to link with palliative care support services to provide a seamless approach to care at the end of life care setting.

The palliative care team work closely with the lung cancer nurses to provide specialist support to those patients needing assessment and support with symptom control and end of life care.

There are two Palliative Care Consultants, Four Palliative Care Specialist Nurses and One Nurse Consultant based at The Christie.

The Lung CNS's provide a link between The Christie and the lung nurses at the referring hospital to ensure continuing support to the patient on completion of their treatment. The Lung CNS will also liaise with relevant support services such as social work department, complimentary therapy department, hospices, local hospitals, and community services to provide the patient with a comprehensive structure of support during their illness.

All patients commencing treatment and continuing on treatment have access to support from a Lung Clinical Nurse Specialist and contact details are available in all departments and clinics.

The lung cancer nurse specialist can give information to any patient, relative or carers about treatment options and general information about lung cancer.

They will discuss preferred place of care for the terminal phase of illness at an appropriate time with patients and their carers.

The lung cancer nurse specialist can offer advise regarding medication, pain control and symptom control and will liaise with the palliative care team and medical staff as necessary.

The lung cancer nurse specialists will offer to help educate and help empower the ward nurses to deliver a high standard of care to all lung patients who are inpatients at The Christie.

http://www.christie.nhs.uk/pro/cancers/lung/default.aspx

http://discover/departments/lung_trials/default.aspx

FOLLOW-UP

Patients treated with palliative radiotherapy or chemotherapy outside a clinical trial are usually referred back to their referring physician and/or general practitioner when they have recovered from treatment. Supportive care can then be provided nearer the patient's home. Patients who have a better performance status may be suitable for second line treatment in the future (as above) and referral for an opinion regarding this should always be considered.

APPENDIX 1

Performance Status

Karnofsky Performance (KP)

100	Normal activity. No symptoms or signs.
90	Minor symptoms or signs.
80	Normal Activity with effort.
70	Reduced activity, self caring.
60	Needs some help.
50	Frequent medical care and help.
40	Disabled.
30	In hospital, death not imminent.
20	In hospital and supported.
10	Moribund.
0	Dead.

WHO Performance Score

Able to carry out all normal activity without restriction. (KP100)	0
Limited in physically strenuous activity but able to do light work. (KP80-90)	1
Ambulatory. Self caring. Cannot work. Rests less than half daylight hours. (KP60-70)	2
Limited self care. Rests for more than half the daylight hours. (KP40-50)	3
Completely disabled. No self care. In bed or chair all day. KP20-30)	4

APPENDIX 2

Non-Small Cell Lung Cancer: Staging. (updated version 2010). Now also applicable to Small cell lung carcinoma and broncho-pulmonary carcinoid tumours.

TNM Staging

T0 - no evidence of primary.
T1- </= 3cm tumour surrounded by lung or visceral pleural, not in main bronchus. T1a </=2cm. T1b: >2cm and </= 3cm
T2 - tumour >3cm and </=7cm, or involving main bronchus 2cm + from main carina, or invading visceral pleural, or associated with local atelectasis extending to hilar region. T2a >3cm and </=5cm. T2b >5cm and </=7cm.
T3 - tumour of any size involving chest wall, diaphragm, mediastinal pleural, pericardium, tumour within 2cms of carina (but not involving carina), atelectasis or obstructive pneumonitis of whole lung. Tumour >7cm. Separate nodule(s) in the primary lobe.
T4 - tumour of any size that invades heart, mediastinum, great vessels, trachea, oesophagus, vertebral body, carina. Separate nodule(s) in a different ipsilateral lobe.

N0 - nodes not involved.
N1 - ipsilateral peribronchial or hilar nodes involved, including direct extension.
N2 - ipsilateral mediastinal or subcarinal nodes.
N3 - contralateral mediastinal or hilar nodes, ipsilateral or contralateral scalene or supraclavicular fossa nodes.

M - Metastases. M1a – intra thoracic mets: disseminated pleural disease (contralateral nodules or malignant pleural or pericardial effusion). M1b – distant mets.

Stage Ia	T1	N0	M0
Stage Ib	T2a	N0	M0
Stage IIa	T1 or T2a	N1	M0
	T2b	N0	M0
Stage IIb	T2b	N1	M0
	T3	N0	M0
Stage IIIa	T1 or T2	N2	M0
	T3	N1/2	M0
	T4	N0/1	M0
Stage IIIb	Any T	N3	M0
	T4	N2/3	M0
Stage IV	Any T	Any N	M1

APPENDIX 3

Small Cell Lung Cancer: Staging.

TNM staging is now valid for SCLC (see appendix 2) and stratification by stage I to III should be included in trials of early stage disease. Traditional Limited vs Extensive stage is very useful for treatment and prognosis.

Limited stage disease - Includes ipsilateral malignant pleural effusion
Contralateral mediastinal nodes
Bilateral supraclavicular fossa nodes.

Extensive stage disease - More than limited, ie, intra-abdominal disease, high neck nodes.

Prognostic Factors

Therapy is based on the Manchester Prognostic Score

Variable	**Result**	**Score**
Serum sodium	<132	1
Serum LDH	>450 * see below	1
Serum Alkaline Phosphatase	>165 ** see below	1
Stage	Extensive	1
Karnofsky	<60	1

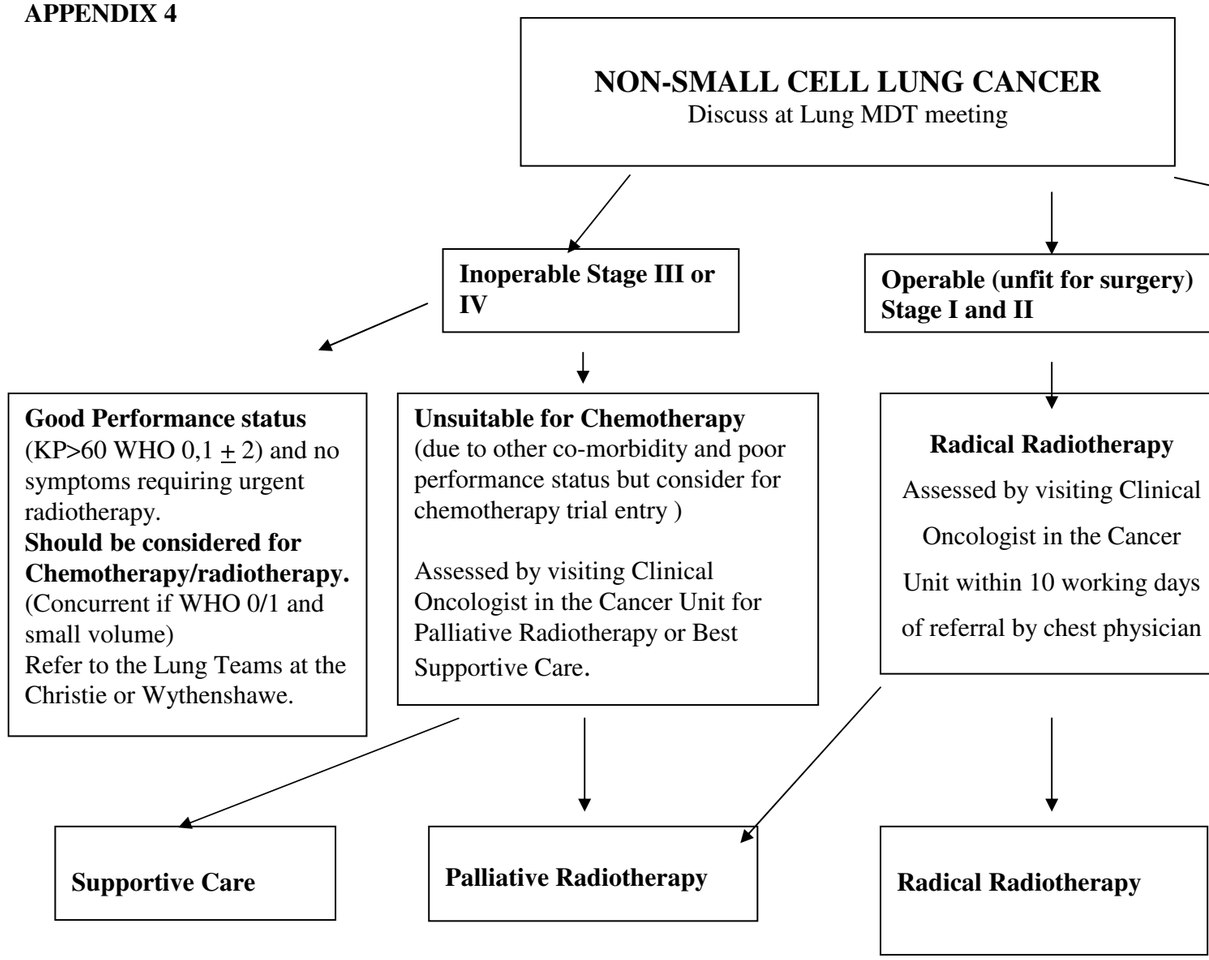
Score may be 0-5. Patients with a score of 0-1 may have extensive stage disease if other variables are normal. Age is not a prognostic factor.

* i.e > the upper limit of the normal range which may vary with different laboratories.

** the upper limit of the normal range x 1.5.

PATIENTS WITH HISTOLOGICALLY CONFIRMED LUNG CANCER

APPENDIX 4



APPENDIX 5 :

RADICAL RADIOTHERAPY TECHNIQUE for Lung Cancer (see also Senan, S., et al., Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. Radiother Oncol, 2004. 71(2): 139-46.)

Treatment will be 3-D conformal radiotherapy.

Patient treatment position and set-up

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.

Patient data acquisition

Simulation with fluoroscopic imaging is required to evaluate tumour movement during quiet respiration in superior, inferior, lateral and anterior and posterior dimensions. If tumour movement is >1cm at simulation customised margins are required.

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 0.5 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.

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.

Gross Tumour Volume (GTV) is defined as the identifiable tumour and involved nodes (nodal involvement on CT scan is defined as nodes ≥ 1 cm in short axis and 12mm for station 7). Clusters of small contiguous nodes can, in some situations, be considered as significant and contoured accordingly. Prophylactic nodal irradiation should not be employed. PET-CT positive nodes if confirmed histologically should be included in the GTV.

Clinical target volume (CTV) comprises the GTV with a 0.5 cm margin of radiologically normal tissue in all directions. It will take into account microscopic spread. Manual adjustment of CTV is permitted to reduce dose to for example the spinal cord or vascular adventitia, when disease is adjacent to a structure such as a vertebra but is not thought to invade the structure (and where the risk of involvement is low). CTV can be manually edited around a lymph node as the risk of microscopic spread beyond it is probably low and can be expanded to high risk areas (eg spicules).

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.

In those patients responding to induction chemotherapy, the CTV should encompass the post chemotherapy tumour volume but all initially involved lymph node stations where possible, providing the V20 constraints are not breached.

For postoperative radiotherapy, CTV is defined and then expanded as above. Discussion with the surgeon and operative notes are used to aid localisation of microscopic residual disease

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 may also be contoured in clinical trials.

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 44 Gy to the spinal canal is specified. For concurrent treatment of 66Gy in 33 fractions the spinal canal limit is 48Gy and for SCLC treated with twice daily RT 45/30 fractions concurrent with chemotherapy a max dose of 42 Gy 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.

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: 55Gy in 20 daily fractions over 28 days
Post-operative: 50-55Gy in 20 daily fraction over 28 days
If concurrent (part of concept trial): 66Gy in 33 fractions over 6 ½ weeks

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.

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

APPENDIX 6.
Recommendations for chemotherapy dose modifications during concurrent chemo-radiotherapy for NSCLC and SCLC.

Haematological Toxicity:

ANC x 10^9/l		Platelets x 10^9/l	Cisplatin /Etoposide
> 1.5	and	> 100	Full dose
≤ 1.5	or	≤ 100	Delay for 2 days then reassess using the same criteria.
Febrile neutropenia or grade 4 neutropenia > 7 days	or	Grade 4 platelets or ≥ grade 2 bleeding with thrombocytopenia	Recommence once ANC >1.5 and Platelets > 100 at full dose with GCSF support or at 75% dose

Hepatic Toxicity:

Raised AST/ALT		Raised Bilirubin	Cisplatin	Etoposide
< 3.0 x ULN	and	< 1.5 x ULN	Full dose	Full dose
≥ 3.0 x ULN	or	≥ 1.5 x ULN	Delay one week then reassess using the same criteria; if delayed for two weeks discontinue	

Renal Toxicity:

If estimated CrCl < 60ml/min, an EDTA should be requested prior to each cycle

CrCl/GFR (ml/min)	Cisplatin	Etoposide
≥ 60	100%	Full dose
50-59	100%	Full dose
45-49	50% or substitute with carboplatin AUC 5	75% dose
< 45	Discontinue	discontinue

Other Toxicity

Grade 2 peripheral neuropathy	Substitute carboplatin AUC 5 or 50% cisplatin dose after recovery to ≤ grade 1; 100% dose of etoposide
Any grade 3-4 toxicities except mucocitis and oesophagitis	75% previous dose of cisplatin, etoposide after recovery to ≤ grade 1

Any diarrhoea requiring hospitalisation or Grade 3-4 diarrhoea	75% previous dose of cisplatin/etoposide after recovery to ≤ grade 1
Grade 3-4 musocitis	75% previous dose of etoposide and 100% previous dose of cisplatin after recovery to ≤ grade 1
Grade 3 oesophagitis	75% previous dose of etoposide and 50% previous dose of cisplatin after recovery to ≤ grade 1

Oesophagitis

In the event of grade 3 oesophagitis, chemoradiotherapy should be suspended until resolution to ≤ grade 1. The decision to recommence treatment should be at the discretion of the clinician. In the event of grade 4 oesophagitis, chemoradiotherapy should be discontinued.

Pneumonitis

In the case of grade ≥ 3 toxicity, treatment should be discontinued.

Treatment Plan NSCLC
Concurrent Chemo-Radiotherapy

Patient label

Chemotherapy – Cisplatin & Etoposide

- Radiotherapy planning scan date……
- Provisional thoracic radiotherapy start date……..

Cycle	Chemotherapy dates		Radiotherapy dates	Comments (eg RT start date)
	Planned	Actual		
1				
2				

- Date thoracic radiotherapy delivered: ……to ……. #.....

Notes :

• When start date is given for radiotherapy please inform Medical oncologists so that they can arrange chemotherapy.
• Chemotherapy regime will be Cisplatin & Etoposide day 1, Etoposide days 2 to 5, and Cisplatin day 8.
• Both chemotherapy and radiotherapy will **start on the same day**.
• Chemotherapy is given for 2 cycles only. Cycles are 4 weekly.

APPENDIX 8

Treatment summary for PE concurrent with RT for NSCLC of the superior sulcus

Pretreatment

1. Baseline assessment, consultation and consent by clinical and medical oncologist
2. RTP scan
3. When start date is known book in patient chemotherapy ward bed (for first night if patient prefers, thereafter can administer outpatient CT)

Book CT scan for week 6 if desired (not mandatory)

↓

Week 1 – 5

Start Monday : Radiotherapy daily 1.8 Gy in 25 fractions
Week 1 and week 5- cisplatin d1 and d8 ; etoposide days 1-5 with antiemetics; consider antibiotic prophylaxis and a PPI.
Weekly review by doctor for assessment, FBC and biochemistry – check weight
CXR Week 4 before chemotherapy cycle 2

↓ ↓

Week 7

Restaging CT scan thorax / abdomen

↓

Week 8-10

Surgery

↓

Week 12-16

Consolidation chemotherapy (at the discretion of the clinicians)
2cycles of cisplatin and etoposide
Week 1 and week 5-cisplatin d1 and d8 ; etoposide days 1-5

↓

Follow up

Weekly until acute toxicities resolve
3 monthly for 1 year, 6 monthly years 2 and 3, then annually.
12 months
CT scan thorax and abdomen

Appendix 9: ILT (Intra-Luminal Radiotherapy) Patient Preparation and Technique:

- Patient admitted to ward from Oak Road Reception.
- Check when patient last had a chest x-ray if not within 6 weeks then x-ray is required.
- NBM from 9.00am following light early breakfast.
- Ensure communication check list is completed prior to theatre.
- Consent form 1 for patients who have pre-med.
- Identification wrist band prior to theatre.

Pre-med as follows:

- Omnopon 15mgm IM (½ dose if patient is frail or very old)
  Atropine 0.5mg IM
- Lidocaine 4% topical 2mls via mask, 1hr pre op
- Lidocaine 4% topical 1ml via mask, 1ml via mouthpiece ½hr pre op

Following procedure NBM for 1 hr.

Please phone Radiotherapy 3520/3523 for advice on when to give pre-med and order of the list.

Technique:

- Flexible bronchoscopy by experienced chest physician.
- Bronchoscopic exam performed and bronchial tumour suitable for ILT identified. Local anaesthetic to go beyond tumour +/- judicious use of adrenaline for bleeding tumour
- One or more applicators passed beyond tumour via bronchoscope suction port as far as comfortably tolerated. Applicator tube secured with tape to nose.
- Radiographic Marker Wire (RMW) inserted and erect CXR film taken
- Once position deemed suitable by radiotherapist, treatment planned using HDR Ir-192 source data and clinical data.
    - Treatment volume localised, start position identified, length specified
    - Dose prescribed at 10mm from source
    - Dwell times calculated for each 5mm step position of source
- Calculations checked by planning radiographer and physician
- HDR microselectron programmed and treatment delivered in theatre

Dose:

Lung Radical	Microselectron ILT	Single treatment 1750cGy
Lung Radical	" "	1000cGy weekly x3
Lung Radical	" "	Re-inflation before radical XRT 500- 1000cGy, single treatment
Lung Palliative	" "	No previous palliative XRT 1000 – 1500cGy x 1
Lung Palliative	" "	Previous palliative XRT 1000 – 1500cGy x1
Lung Palliative	" "	Previous radical XRT 500 – 750cGy

Risks:

- Bronchoscopy complications: epistaxis, laryngeal oedema, hypoxia, arrhythmias, fever, dissemination of infection
- Radiation bronchitis/ stenosis manifested by cough, wheezing days later
- Fatal haemoptysis 7-8%
- Fistula formation

  Increased risk if:
  - higher dose (20 vs 15Gy single dose)
  - Previous laser treatment
  - Repeat EBB at same site
  - Large cell histology

Appendix 10: Treatment Plan SCLC Concurrent Chemo-Radiotherapy

Patient label

Chemotherapy – Cisplatin & Etoposide

Cycle	Chemotherapy dates Planned	Actual	Radiotherapy dates	Comments (eg RT start date)
1			----------	
2				
3				
4				

- Radiotherapy planning scan date……
- Date thoracic radiotherapy delivered: ….…to ……. #.....
- Date PCI delivered: ……to …….#.....

PCI should not be given concurrently with chemotherapy

Notes :
• Chemotherapy will be started soon after the decision to treat concurrently is made. Chemotherapy must be started on a Monday.
• Chemotherapy regime will be Cisplatin & Etoposide day 1, Etoposide days 2 & 3.
• Radiotherapy will start **on day 22 of cycle 1**. (ie radiotherapy will start on this day even if cycle 2 chemo is deferred)
• Chemotherapy is given for 4 cycles only. Cycles are 3 weekly.
• **PCI should be given 3-5 weeks after final cycle of chemotherapy**

APPENDIX 11. Treatment Plan sheet for sequential chemo-radiotherapy in LDSCLC.

SCLC Treatment Plan
Sequential Chemo-Radiotherapy

Patient label

Chemotherapy Regimen ……

Cycle	Planned Date	Delivered Date	Comments (eg RT referral sent)
1			
2			
3			
4			
5			
6			

- Radiotherapy planning scan date……
- Date thoracic radiotherapy delivered: ……to …… #.....
- Date PCI delivered: ……to ……#.....

PCI should not be given concurrently with chemotherapy

Notes :
Refer to clinical oncologists for RT planning scan as soon as decision is made for sequential treatment. Re-refer on day 15 of cycle 4 (or earlier if patient is not going to receive 6 cycles).

APPENDIX 12: Photodynamic Therapy (PDT) – use for palliation in lung cancer

Background

PDT may palliate symptoms of breathlessness in patients with large airway obstruction due to intraluminal disease. A therapeutic effect may be seen within 3-5 days.

NICE guidelines on the Diagnosis and Treatment of Lung Cancer (February 2005) includes PDT. They note that the light used in PDT penetrates 5-10mm making tracheobronchial tumours well suited to this treatment. Two systematic reviews were identified together with a case series. The first review showed 60% patients had palliation of breathlessness – with 80% relief for patients with strictly endoluminal tumours (level 3 evidence). There is a 4% one month mortality rate and a 2% risk of major haemorrhage (level 3). The second review noted photosensitivity reactions in 5- 28%, haemoptysis in up to 18%. Post-treatment cough and dyspnoea were reported by many authors.

Patient selection

1) Patients with intra-luminal obstruction of large airways.
2) If trachea involved, stabilise airway with stent/surgical debulking first.
3) Patients with prior pneumonectomy must have other main bronchus stabilised with stent prior to PDT therapy.
4) Patients have received prior to external beam X-ray therapy and/or intraluminal X-ray therapy can be treated.
5) Patient able to tolerate bronchoscopy.
6) Patient able to lie semi-recumbent for 30-40 minutes.
7) Informed consent.
8) Patient understands need to avoid bright daylight for 6-8 weeks.

Contraindictions

1) Severe liver impairment.
2) Porphyria.
3) Patient not able/unwilling to comply with daylight avoidance.
4) Tracheo - or broncho-oesophageal fistula.

Information needed

Patients are to be seen by Dr Barber who needs the following:-

CXR films
CT scans and report
Bronchoscopy report (and video if performed)
Letter documenting symptoms
Documentation of patient's weight

Treatment

Patients will be seen on a Tuesday afternoon for assessment and informed consent.
Dr Barber may need to repeat the bronchoscopy.
Patient will **usually** need to be admitted for 5 days (bed must not be by window).

Procedure for PDT

1) IV photofrin 2mg/kg IV injected into injection port of slowly running IV dextrose infusion. If extravasation occurs this area will be locally photosensitive for a very long time and needs protection from light. Staff must wear gloves to administer drug. NB: If drug is spilt photofrin will stain clothes.

2) Bronchoscopy (standard procedure) at 48 hrs with application of laser light 630nm, 200 jules/cm tumour length using cylindrical diffuser over length of usually 2.5cms or micro-lens at 100 Joules/cm^2.
3) Rebronchoscopy after 48-72 hrs to debulk necrotic tumour if necessary. A further laser light treatment can be considered at this time. If neither is necessary patient may be discharged home.
4) Follow up bronchoscopy and symptom evaluation after 1-2 weeks.
5) Rebronchoscopy and biopsy after 4-6 weeks

NB: Patients can be retreated if necessary.

Complications

1) Photosensitivity – **must** wear hat, sunglasses and gloves even in ordinary daylight
2) Abnormal LFTs
3) Bronchial bleeding
4) Fibrotic stricture of treated area

In a study of 99 patients with NSCLC adverse events occurring at any time after therapy were reported as follows:-

Dyspnoea	32%
Photosensitive reaction	20%
Fever	15%
Haemoptysis	12%
Cough	17%
Pneumonia	13%
Bronchitis	11%
Massive fatal haemoptysis	10%
Increased sputum	9%
Respiratory insuffiency	7%

Reference – Product characteristics – Axcan, Dec 1998

Light avoidance

Indoor light is safe, but patients must avoid bright daylight outdoors for 6 weeks.

Patients will be shown how to patch test the skin to determine when it is safe to go out of doors without protection against light.

NB. Sunscreens are not effective for PDT.

APPENDIX 13:
RADIOFREQUENCY ABLATION (RFA) IN NSCLC OR PULMONARY METS

The aim of this emerging treatment is to provide local control for pulmonary lesions where there is no scope for further surgery or radiotherapy. Its aim is to provide local control of disease. Very beneficial in small tumours less than 3cm in size and provides control of disease in lesions up to 5cm size. It can be a useful adjunct to surgery in colorectal lung metastases. Survival benefits are not proven at this stage. Further background can be found from the RAPTURE trial (1).

Technique:

Using CT guidance, a radiofrequency electrode is directly inserted into the pulmonary lesion under general anaesthetic. The RFA aims to thermally treat the lesion and a 1cm "margin" of normal lung parenchyma resulting in coagulation necrosis. The resulting cystic cavity is usually slightly larger than the original tumour, but this generally reduces slightly over time.

Indications:

- Biopsy proven cancer (NSCLC or pulmonary metastasis).
- Conventional treatments with surgery or radiotherapy exhausted or not possible
- size <3.5cm.
- <3 lesions per lung.
- Lesion must be >1cm from heart, aorta, pulmonary artery, trachea & main bronchus.

Exclusions:

- Patients not fit for short general anaesthetic.
- Alternative oncology options of surgery, radiotherapy or chemotherapy still available to patient.
- Previous pneumonectomy.
- Obstructive pneumonitis/atelectasis .

Risks:
15-25% risk pneumothorax, 4% risk pleural effusion, 5% risk of bleeding, 2-5% risk of infection.

Referral pathway:

- Discuss patient via local sector lung MDT, oncologist to review 1st in clinic
- If suitable candidate for RFA oncologist to refer directly to MRI via Dr Rajashanker's sec with covering letter

  Dr B Rajashanker
  Consultant Radiologist
  MRI
  Fax 0161 276 4141 FAO Jane Bush
  Sec: Elizabeth Booth 0161 701 6200 or
  Email elizabeth.booth@cmft.nhs.uk

- Inform patient of referral

Reference:
1) Lencioni R, Crocetti L, Suh R et al.Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study).Lancet Oncology 2008; 9 (7):621-628

APPENDIX 14. Chemo Regimes Gemcitabine and Carboplatin

For:

Palliation or neoadjuvant treatment prior to radical radiotherapy of NSCLC

Dosages:

Gemcitabine 1250mg/m² IV day 1 & 8, Carboplatin AUC 5 IV day 1

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day 1	1	Sodium Chloride	0.9%	250ml	IVI 30 minutes
		Gemcitabine	1250mg/m²		
	2	Sodium Chloride	0.9%	100ml	IVI 30 minutes
	3	Dextrose	5%	500ml	IVI 1 hour
		Carboplatin	AUC 5		
Day 8	1	Sodium Chloride	0.9%	250ml	IVI 30 minutes
		Gemcitabine	1250mg/m²		

Number of Cycles and Scheduling:

4, q21 days

Associated medication:

- Dexamethasone 8mg IV bolus pre-chemotherapy day 1 & 8
- Ondansetron 8mg IV bolus pre-chemotherapy day 1
- Consider prophylactic antibiotics if obstructing tumour/presence of consolidation/collapse/cavitation: levofloxacin 500mg od starting on day 8 for 10 days

Expected toxicity:

Myelosuppression (particularly thrombocytopenia), nausea and vomiting, alopecia,rash, neuropathy, nephrotoxicity, ototoxicity, peripheral oedema, mucositis, diarrhoea, constipation

Required investigations pre-treatment:

- eGFR/EDTA clearance
- Staging CT – thorax/abdomen
- CXR

On-treatment assessments:

- Protocol assessment on days 1 and 8
- Toxicity assessment on day 15 of each cycle
- Consider if treatment is achieving its aims (palliation) and whether an alternative treatment such as supportive care may be more appropriate
- CXR
- eGFR, EDTA clearance if uncertain

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
2.0-2.9	0.5-0.9	50-99	Defer one week, the continue full dose, but dose reduce day 8 gemcitabine by 25%
<1.0	<0.5	<49	Defer one week then proceed with 25% dose reduction day 1 and day 8 gemcitabine (consider GCSF)

Infective

Febrile neutropaenia (1st episode)	Defer one week, then proceed with 25% dose reduction day 1 and day 8 gemcitabine (consider GCSF)
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with a further 25% dose reduction (50%) day 1 and day 8 gemcitabine

Renal: use eGFR/ EDTA clearance:

<40	Omit

Biochemistry:

Bilirubin >1.5x ULN	Omit
AST/ALT >2.5xULN (5xULN if due to liver mets)	Omit

Notes:

- A rare but important side effect is microangiopathic haemolytic anaemia: discontinue gemcitabine if haemoglobin falls with low platelets and rising bilirubin, LDH and creatinine.
- Gemcitabine-carboplatin is similar to MVP or MIC (response rates 32% vs 33%) and less resource intensive
- Gemcitabine-cisplatin is associated with a lower dependency on blood transfusions so may be considered if this may be an issue (e.g. Jehovah's witness)

References:

Rudd et al. (2005) Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. J Clin Oncol. 23(1): 142-53

Gemcitabine and Cisplatin

For:

Palliation or neoadjuvant treatment prior to radical radiotherapy of NSCLC

Dosages:

Cisplatin 35mg/m² IV and Gemcitabine 1250mg/m² IV on days 1 & 8

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day 1	1	Sodium Chloride	0.9%	1000ml	IVI 1 hour
	2	Sodium Chloride	0.9%	250ml	IVI 30 minutes
		Gemcitabine	1250mg/m²		
	3	Sodium Chloride	0.9%	250ml	IVI 1 hours
		Cisplatin	35mg/m²		
	4	Sodium Chloride	0.9%	1000ml	IVI 90 minutes
Day 8	1	Sodium Chloride	0.9%	1000ml	IVI 1 hour
	2	Sodium Chloride	0.9%	250ml	IVI 30 minutes
		Gemcitabine	1250mg/m²		
	3	Sodium Chloride	0.9%	250ml	IVI 1 hours
		Cisplatin	35mg/m²		
	4	Sodium Chloride	0.9%	1000ml	IVI 90 minutes

Number of Cycles and Scheduling:

4, q21 days

Associated medication:

- Dexamethasone 8mg IV bolus pre-chemotherapy day 1 & 8
- Ondansetron 8mg IV bolus pre-chemotherapy day 1
- Consider prophylactic antibiotics if obstructing tumour/presence of consolidation/collapse/cavitation: levofloxacin 500mg od starting on day 8 for 10 days

Expected toxicity:

Myelosuppression (particularly thrombocytopenia), nausea and vomiting, alopecia,rash, neuropathy, nephrotoxicity, ototoxicity, peripheral oedema, mucositis, diarrhoea, constipation

Required investigations pre-treatment:

- Protocol assessment on days 1 and 8
- Toxicity assessment on day 15 of each cycle
- Consider if treatment is achieving its aims (palliation) and whether an alternative treatment such as supportive care may be more appropriate
- CXR
- eGFR, EDTA clearance if uncertain

On-treatment assessments:

- Toxicity assessment with each cycle
- Consider if treatment is achieving its aims (palliation) and whether an alternative treatment such as supportive care may be more appropriate
- CXR
- eGFR

Dose modifications:

Haematological: Use FBC on day 1 of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
2.0-2.9	0.5-0.9	50-99	Defer one week, then continue full dose, but dose reduce gemcitabine by 25%
<1.0	<0.5	<49	Defer one week then proceed with 25% dose reduction on all drugs (consider GCSF)

Infective

Febrile neutropaenia (1st episode)	Defer one week, then proceed with 25% dose reduction on gemcitabine (consider GCSF)
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with a further 25% dose reduction on all drugs

Renal: use eGFR/EDTA clearance:

>60	Full dose
50-59	Give cisplatin at 75% dose. Etoposide full dose
40-49	Give cisplatin at 50% dose. Give etoposide at 75% dose.
<40	Omit

Biochemistry:

Bilirubin >1.5x ULN	Omit
AST/ALT >2.5xULN (5xULN if due to liver mets)	Omit

Neuropathy: grade 2 – reduce cisplatin by 50%, Grade 3/4 – discontinue until grade 1 or less

Ototoxicity: substitute carboplatin

Notes:

- Cisplatin based chemotherapy is associated with higher response rates than carboplatin based regimens
- A rare but important side effect is microangiopathic haemolytic anaemia: discontinue gemcitabine if haemoglobin falls with low platelets and rising bilirubin, LDH and creatinine.
- Gemcitabine-cisplatin is equivalent to gemcitabine-carboplatin in terms of efficacy and tolerability. More thrombocytopaenia and anaemia observed with gemcitabine-carboplatin. Gemcitabine-cisplatin associated with higher incidence of nausea and vomiting

References:

Ardizzoni et al. CISCA Meta-analysis Group (2007) Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst 99(11):847-57

Zatloukal et al. (2003) Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. Lung Cancer 41(3): 321-31

Scagliotti et al. (2002) Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol. 20(21): 4285-91

Cisplatin and Vinorelbine

For:

Adjuvant therapy of NSCLC

Dosages:

Cisplatin* 75mg/m² IV day 1, Vinorelbine 25mg/m² IV day 1 & 8

*Carboplatin AUC 5 on day 1 if cisplatin not suitable: eGFR/EDTA clearance <50ml/min, serum creatinine >ULN, severe emesis despite appropriate prophylaxis or co-morbidity precluding cisplatin.

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day 1	1	Sodium Chloride	0.9%	50ml	IV bolus
		Vinorelbine	25mg/m²		
	2	Sodium Chloride	0.9%	1000ml	IVI 1 hour
		Magnesium Chloride	10mmol		
		Potassium Chloride	20mmol		
	3	Mannitol	20%	200ml	IVI 20 minutes
	4	Sodium Chloride	0.9%	1000ml	IVI 1 hour
		Cisplatin	75mg/m²		
	5	Sodium Chloride	0.9%	1000ml	IVI 1 hour
		Magnesium Chloride	10mmol		
		Potassium Chloride	20mmol		
	6	Sodium Chloride	0.9%	500ml	IVI 1 hour
Day 8	1	Sodium Chloride	0.9%	50ml	IV bolus
		Vinorelbine	25mg/m²		
Alternative Day 1 if using carboplatin:					
Day 1	1	Dextrose	5%	500ml	IV 1 hour
		Carboplatin	AUC 5		

Number of Cycles and Scheduling:

4, q21 days

Associated medication:

Ondansetron 8mg IV bolus pre-chemotherapy day 1 & 8
Dexamethasone 8mg IV bolus pre-chemotherapy day 1

Expected toxicity:

Myelosuppression, nausea, vomiting,alopecia, nephrotoxicity, neurotoxicity, ototoxicity, constipation, pain at injection site
Vinorelbine is a vesicant drug – risk of extravasation injury

Required investigations pre-treatment:

- CT/PET-CT usually performed pre-operatively
- eGFR/EDTA clearance: >40ml/min (see dose modifications below)
- Post-operative chest X-ray

On-treatment assessments:

- Toxicity assessment with each cycle

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
2.0-2.9	0.5-0.9	50-99	Defer one week, the continue full dose, but give day 8 vinorelbine at 75% dose and consider G-CSF (see notes)
<1.0	<0.5	<49	Defer one week then proceed with 75% dose on all drugs and consider GCSF (see notes)

Infective

Febrile neutropaenia (1st episode)	Defer one week, then proceed with 75% dose on all drugs or consider GCSF (see notes)
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with 50% dose on all drugs and consider G-CSF

Renal: use eGFR/EDTA clearance:

>60	Full dose
50-59	Give cisplatin at 75% dose.
40-49	Use carboplatin AUC 5.
<40	Omit

Neuropathy: grade 2 – reduce cisplatin by 50%, Grade 3/4 – discontinue until grade 1 or less

Ototoxicity: substitute carboplatin

Notes:

- Try to maintain full dose rather than dose reduction, give G-CSF if only neutropenic
- Adjuvant chemotherapy with platinum based chemotherapy for resected NSCLC stages II-III has shown a clear survival benefit in 4 randomised trials (between 4-15%). Its role in stage IB patients remains uncertain

References:

Arriagada et al. (2004) Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Eng J Med. 350(4): 351-40

Pignon et al. (2006) Lung Adjuvant Cisplatin Evaluation (LACE): A pooled analysis of five randomized clinical trials including 4,584 patients. Proc Am Soc Clin Onc 24:18S (abstract)

Pemetrexed and Cisplatin/Carboplatin

For:

Palliation of mesothelioma

Dosages:

Pemetrexed 500mg/m² and Cisplatin* 75mg/m^2.

*Carboplatin AUC 5 if cisplatin not suitable: eGFR/EDTA clearance <50ml/min, serum creatinine >ULN, severe emesis despite appropriate prophylaxis or co-morbidity precluding cisplatin.

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day 1	1	Sodium chloride	0.9%	1000ml	IV 2 hours
		Magnesium sulphate	10mmol		
	2	Sodium chloride	0.9%	1000ml	IV 2 hours
		Potassium chloride	40mmol		
	3	Mannitol	20%	200ml	IV 20 minutes
	4	Sodium Chloride	0.9%	100ml	IV 10 minutes
		Pemetrexed	500mg/m²		
	5	Sodium chloride	0.9%	1000ml	IV 2 hours
		Cisplatin	75mg/m^2		
Alternative:					
Day 1	1	Sodium Chloride	0.9%	100ml	IV 10 minutes
		Pemetrexed	500mg/m²		
	2	Dextrose	5%	500ml	IV 30 minutes
		Carboplatin	AUC=5		

Number of Cycles and Scheduling:

4-6, q 21days

Associated medication:

Ondansetron 8mg IV bolus pre-chemotherapy
Dexamethasone po 4mg bd for 3 days starting the day before each cycle
Folic acid 400µg po daily starting at least 5 days before cycle 1
Vitamin B12 1000µg IM 1 week prior to cycle 1, then every 3 cycles

Expected toxicity:

Myelosuppression, nausea and vomiting (moderate-severe), diarrhoea, fatigue, nephrotoxicity, peripheral neuropathy, ototoxicity, mucositis, rash

Required investigations pre-treatment:

- Staging CT thorax/abdomen
- CXR
- eGFR/EDTA clearance

On-treatment assessments:

- Clinical assessment on day 1 and day 15
- Consider if treatment is achieving its aims (palliation) and whether alternative therapy may be more appropriate
- CXR

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
<2.9	>1.5	<99	Defer one week, then proceed with 75% dose on both drugs. If further delay then reduce dose to 50%

Nadir (Day 15)

Neut	Plt	
<0.5	>50	Reduce dose by 75%
Any	<50	Reduce dose by 50%

Infective

Febrile neutropaenia (1st episode)	Defer one week, then proceed with 75% dose on all drugs
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with 50% dose on all drugs

Gastrointestinal:
Any grade 3/4 toxicity – defer until settled and reduce dose by 75%

Renal: use eGFR/EDTA clearance:

>60	Full dose
50-59	Give cisplatin at 75% dose. Etoposide full dose
40-49	Give cisplatin at 50% dose. Give etoposide at 75% dose.
>40	Omit

Neuropathy: grade 2 – reduce cisplatin by 50%, Grade 3/4 – discontinue until grade 1 or less

Ototoxicity: substitute carboplatin

Cost:

4 cycles typically costs around £6500

Notes:

- Pemetrexed is the only licensed chemotherapy for mesothelioma and was approved by NICE in 2008
- Response rates about 40% and median survival improved from 9 months to 12 months when compared to cisplatin alone
- The addition of vitamin B12 and folic acid significantly reduces the amount of haematological toxicity experienced with this combination regimen

References

Vogelzang et al. (2003) Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma. J Clin Onc 21(14): 2636-44

Docetaxel

For:

Advanced/metastatic NSCLC (2nd line)

Dosages:

Docetaxel 75mg/m² IV

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day 1	1	Sodium Chloride Docetaxel	0.9% 75mg/m²	250ml	IVI 1 hour

Number of Cycles and Scheduling:

4, q21 days

Associated medication:

- Dexamethasone 8mg po bd for 3 days, starting 24 hours before each cycle
- Ondansetron 8mg IV bolus pre-chemotherapy

Expected toxicity:

Hair loss, fatigue, myelosuppression, nausea, vomiting, peripheral neuropathy, allergy

Required investigations pre-treatment:

- Staging CT scan
- CXR

On-treatment assessments:

- Toxicity assessment on day 15 of each cycle
- Consider if treatment is achieving its aims (palliation) and whether an alternative treatment such as supportive care may be more appropriate
- CXR

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
<2.9	<1.4	<100	Defer and continue at full dose, if further deferral reduce dose to 60mg/m^2
	<0.5		Defer and reduce dose to 60mg/m2

Infective:

Febrile neutropaenia (1st episode)	Defer one week, then proceed with 60mg/m^2
Febrile neutropaenia (2nd episode)	Consider stopping treatment

Biochemistry:

Bilirubin >1.5xULN – do not give
AST/ALT 1-2.5X ULN – give at 75% dose
AST/ALT >2.5xULN (>5XULN if due to liver metastases) – do not give

Cost:

4 cycles typically costs around £4000

Notes:

- 4 cycles of docetaxel in previously treated patients with NSCLC led to increase in survival and improved quality of life compared to best supportive care (7.5 vs 4.6 months)
- 1-year survival and survival superior to vinorelbine or ifosfamide

References:

Shepherd et al. (2000) Prospective Randomized Trial of Docetaxel Versus Best Supportive Care in Patients With Non–Small-Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy. J Clin Onc. 18 (10): 2095-2103

Fosella (2001) Docetaxel + Cisplatin (DC) and Docetaxel + Carboplatin (DCb) vs Vinorelbine + Cisplatin (VC) in chemotherapy-naïve patients with advanced and metastatic non-small cell lung cancer (NSCLC): Results of a multicenter, randomized phase III study Eur J Cancer 37 (Suppl 6): S154 (abstr)

Carboplatin Paclitaxel

For:

Treatment of stage III NSCLC (if considering sequential CTRT) or palliation of stage IV NSCLC

Dosages:

Carboplatin AUC 6, Paclitaxel 200mg/m²

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day1	1	Sodium Chloride	0.9%	500ml	IVI 3 hours
		Paclitaxel	200mg/m²		
	2	Dextrose	5%	500ml	IVI 1 hour
		Carboplatin	AUC=6		

Number of Cycles and Scheduling:

4 – 6 (6 if on trial), q21 days

Associated medication:

- Dexamethasone 20mg IV bolus, chlorphenamine 10mg IV bolus ranitidine 50mg IV bolus given 30 minutes prior to chemotherapy
- Dexamethasone 8 mg bd 2/7
- Ondansetron 8 mg bd 2/7

Expected toxicity:

Myelosuppression, nausea and vomiting, alopecia, fatigue, peripheral neuropathy, diarrhoea, nephrotoxicity

Required investigations pre-treatment:

- CT or PET-CT staging
- CXR

On-treatment assessments:

- Toxicity assessment on day 15 of each cycle
- CXR

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
<2.9	<1.4	<100	Defer and continue at full dose, if further deferral give 75% dose
	<0.5	<50	Defer and give 75% dose

Infective:

Febrile neutropaenia (1st episode) — Defer one week, then give 75% dose
Febrile neutropaenia (2nd episode) — Consider stopping treatment

Biochemistry:

Bilirubin >1.5xULN – do not give
AST/ALT 1-2.5X ULN – give at 75% dose
AST/ALT >2.5xULN (>5XULN if due to liver metastases) – do not give

Cost:

Approximate cost for 4 cycles around £7000

Notes:

- Response rates around 20-30% and median survival is around 8-10 months for stage IV disease.
- No difference in survival or time to progression when compared to cisplatin and gemcitabine but a modest improvement in overall survival is observed when combined with bevacizumab (non-squamous histology)

References:

Belani et al. (2005) Randomized phase III trial comparing cisplatin–etoposide to carboplatin–paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol. 16: 1069-75

O'Brien et al (2003) Carboplatin and paclitaxel (Taxol) as an induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer an EORTC phase II study (EORTC 08958). Eur J Cancer 39(10): 1416-22

Scagliotti et al. (2002) Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol. 20(21): 4285-91

Schiller et al. (2002) Comparisom of four chemotherapy regimens for the treatment of advanced non-small-cell lung cancer. N Eng J Med 346(2):92-8

Cisplatin and Etoposide – Concurrent Chemoradiotherapy (NSCLC)

For:

Treatment of unresectable stage IIIA/IIIB(dry) NSCLC

Dosages:

Cisplatin 50mg/m² on days 1 and 8, Etoposide 50mg/m² on days 1-5
Radiotherapy 60 Gy in 30 fractions commencing with chemotherapy

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day 1	1	Sodium Chloride	0.9%	1000ml	IVI 1 hour
		Potassium Chloride	20mmol		
	2	Sodium Chloride	0.9%		
		Magnesium Chloride	1g	1000ml	IVI 90 minutes
		Cisplatin	50mg/m^2		
	3	Sodium Chloride	0.9%	1000ml	IVI 1 hour
		Etoposide	50mg/m²		
Day 2-5	1	Sodium chloride	0.9%	500ml	IV 30 minutes
		Etoposide	50mg/m²		
Day 8	1	Sodium Chloride	0.9%	1000ml	IVI 1 hour
		Potassium Chloride	20mmol		
	2	Sodium Chloride	0.9%		
		Magnesium Chloride	1g	1000ml	IVI 90 minutes
		Cisplatin	50mg/m^2		
	3	Mannitol	20%	200 ml	IVI 20 minutes
	4	Sodium Chloride	0.9%	1000ml	IVI 1 hour
		Potassium Chloride	20mmol		

Number of Cycles and Scheduling:

2, q28 days

Associated medication:

- Ondansetron 8mg IV bolus Dexamethasone 8mg IV bolus pre-chemotherapy days 1 and 8
- Dexamethasone 8mg po bd for 3 days starting 24 hours before chemotherapy
- Consider prophylactic antibiotics if obstructing tumour/presence of consolidation/collapse/cavitation: levofloxacin 500mg od starting on day 8 for 10 days

Expected toxicity:

Emesis (severe), alopecia (total), myelotoxicity (moderate-severe), nephrotoxicity, pneumonitis, oesophagitis, ototoxicity, peripheral neuropathy, infertility

Required investigations pre-treatment:

- Full lung function including transfer factor
- Histology
- CT or PET-CT staging including brain scan
- eGFR/EDTA clearance

On-treatment assessments:

- Clinical assessment on a weekly basis during therapy – Monday am clinic
- CXR with each cycle

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
<2.9	<1.4	<100	Defer and continue at full dose, if further deferral give 75% dose
	<0.5	<50	Defer and give 75% dose

Infective:

Febrile neutropaenia (1st episode)	Defer one week, then give 75% dose
Febrile neutropaenia (2nd episode)	Consider stopping treatment

Biochemistry:

Bilirubin >1.5xULN – do not give
AST/ALT 1-2.5X ULN – give at 75% dose
AST/ALT >2.5xULN (>5XULN if due to liver metastases) – do not give

Notes:

- Complete CTRT toxicity sheet with each assessment
- Intergroup 0139 study showed that induction chemoradiotherapy plus consolidation chemotherapy was equivalent (in terms of survival) to induction chemoradiation and then surgery for resectable stage IIIA NSCLC. SWOG 9504 and EORTC 08941 have supported the role for chemoradiation in unresectable stage III NSCLC.
- The use of consolidation chemotherapy (2 further cycles of cisplatin/etoposide in 0139 and 3 cycles of docetaxel in SWOG 9504) has been questioned following recent data suggesting no difference in survival whether given consolidation docetaxel or observation alone

References:

Albain et al (2005). Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309). Proc Am Soc Clin Onc. 23(16S): 7014 (abstr)
Hanna et al (2007). Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023. Proc Am Soc Clin Onc. 25(18S): 7512 (abstr)

Cisplatin and Docetaxel

For:

Induction chemotherapy for unresectable stage III NSCLC before either surgery or radiotherapy (if unsuitable for concurrent CTRT), stage IV NSCLC if of good performance status

Dosages:

Cisplatin 75mg/m² IV, Docetaxel 75mg/m² IV

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day1	1	Sodium Chloride	0.9%	250ml	IVI 1 hour
		Docetaxel	75mg/m²		
	2	Sodium Chloride	0.18%	1000ml	IVI 1 hour
		Dextrose	4%		
		Magnesium Chloride	10mmol		
		Potassium Chloride	20mmol		
	3	Mannitol	20%	200ml	IVI 20 minutes
	4	Sodium Chloride	0.9%	1000ml	IVI 1 hour
		Cisplatin	75mg/m²		
	5	Sodium Chloride	0.18%	1000ml	IVI 1 hour
		Dextrose	4%		
		Magnesium Chloride	10mmol		
		Potassium Chloride	20mmol		

Number of Cycles and Scheduling:

4, q21 days

Associated medication:

- Ondansetron 8mg IV bolus pre-chemotherapy day 1
- Dexamethasone 8mg po bd for 3 days starting 24 hours before chemotherapy
- Consider prophylactic antibiotics if obstructing tumour/presence of consolidation/collapse/cavitation: levofloxacin 500mg od starting on day 8 for 10 days

Expected toxicity:

Fatigue, hair loss, myelosuppression

Required investigations pre-treatment:

- Histology
- CT or PET-CT staging,
- eGFR/EDTA clearance

On-treatment assessments:

- Protocol clinic on day 1
- Toxicity assessment on day 15 of each cycle
- CXR

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
<2.9	<1.4	<100	Defer and continue at full dose, if further deferral give 75% dose
	<0.5	<50	Defer and give 75% dose

Infective:

Febrile neutropaenia (1st episode)	Defer one week, then give 75% dose
Febrile neutropaenia (2nd episode)	Consider stopping treatment

Biochemistry:

Bilirubin >1.5xULN – do not give
AST/ALT 1-2.5X ULN – give at 75% dose
AST/ALT >2.5xULN (>5XULN if due to liver metastases) – do not give

Notes:

- Docetaxel and cisplatin demonstrates superior response rates to vinorelbine and cisplatin in stage IV patients (32% v 25%)
- In a phase II trial of docetaxel and cisplatin as induction therapy for stage IIIA unresectable NSCLC, an overall response rate of 45% was observed

References:

Biesma et al. (2006) Docetaxel and cisplatin as induction chemotherapy in patients with pathologically-proven stage IIIA N2 non-small cell lung cancer: a phase II study of the European organization for research and treatment of cancer (EORTC 08984). Eur J Cancer 42(10): 1399-406
Fossella et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 21(16): 3016-24

Erlotinib

For:

Second or third line therapy of NSCLC

Dosages:

Erlotinib 150mg po od given continuously

Associated medication:

Loperamide 2mg prn and metoclopramide 10mg prn

Expected toxicity:

Rash ranging from macular erythema/dryskin to generalised erythroderma/ulcerative dermatitis (76% all grades, 9% grade 3-4 – see notes below for management), nail-bed changes/paronychia, diarrhoea (55% all grades, 6% grades 3-4), nausea, fatigue, conjunctivitis, abnormal LFT, very rarely interstitial lung disease has been reported

Required investigations pre-treatment:

- CT or PET-CT staging
- CXR

On-treatment assessments:

- Clinical assessment every 2 weeks for the first 4 weeks, then every 6 weeks
- CXR

Dose modifications:

If grade 3/4 toxicity occurs, interrupt therapy until resolved and recommence with a 50mg dose reduction

Notes:

- Erlotinib must only be initiated by or on discussion with a consultant
- BR.21 study showed an improvement in overall survival of 4.7 months to 6.7 months with erlotinib over placebo in $2^{nd}/3^{rd}$ line NSCLC patients.
- Higher chance of response in: never or "modest" (<5 pack year) smokers, female, asian, adenocarcinoma histology, but no proven molecular method to select patients.
- **Rash management**

  - Rash frequently often improves within weeks of intiation of erlotinib and patients should be encouraged to persevere if possible
  - Supportive measures
    Cover up with dermatologist approved make-up (e.g.Dermablend®)
    Avoid exposure to sunlight
    Simple emollients can be used as a soap substitute and moisturiser (e.g. Oilatum®, Diprobase®)
  - Decide if interfering with daily life (grade 2B) – consider topical therapy
    Clobetasone/oxytetracycline/nystatin (trimovate®) cream and analgesia
    Agents NOT recommended are retinoids or benzoyl peroxide which may exacerbate rash
  - If secondary infection suspected
    Oral minocycline 100mg bd for 5-7 days
    Topical mupirocin applied tds if *staphylococcus aureus* infectionis suspected
  - If not improving or grade 3/4 rash (erythroderma, generalised eruption, bullous or ulcerative dermatitis) then discontinue therapy until resolved and consider restarting with a 50mg dose reduction.

References:

Shepherd et al. (2005) Erlotinib in previously treated non-small-cell lung cancer. N Eng J Med 353(2): 123-32

Pemetrexed

For:

Second or third line therapy of non-squamous NSCLC

Dosages:

Pemetrexed 500mg/m^2 IV

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day 1	1	Sodium Chloride	0.9%	100ml	IV 10 minutes
		Pemetrexed	500mg/m²		

Associated medication:

Dexamethasone po 4mg bd for 3 days starting the day before each cycle
Folic acid 400µg po daily starting at least 5 days before cycle 1
Vitamin B12 1000µg IM 1 week prior to cycle 1, then every 3 cycles

Expected toxicity:

Myelosuppression (grade 3/4 neutropaenia 5%), fatigue (34%), nausea (30%), mucositis (15%), diarrhoea (13%), rash (14%), rise in ALT (8%)

Required investigations pre-treatment:

- CXR or CT staging

On-treatment assessments:

- Protocol clinic on day 1
- Toxicity assessment on day 15 of each cycle
- CXR

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
<2.9	>1.5	<99	Defer one week, then proceed with 75% dose on both drugs. If further delay then reduce dose to 50%

Nadir (Day 15)

Neut	Plt	
<0.5	>50	Reduce dose by 75%
Any	<50	Reduce dose by 50%

Infective

Febrile neutropaenia (1st episode)	Defer one week, then proceed with 75% dose on all drugs
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with 50% dose on all drugs

Gastrointestinal:
Any grade 3/4 toxicity – defer until settled and reduce dose by 75%

Cost:

Approximate cost for 4 cycles around £1600 (discounted for Christie to £1000)

Notes:

- Pemetrexed has been shown to have equivalent efficacy in terms of survival and response rates to docetaxel in the second line treatement of NSCLC
- Haematological toxicity was much reduced in the pemetrexed group
- Concurrent use of vitamin B12 and folic acid supplementation reduces the pemetrexed toxicity

References:

Hanna et al (2004) Randomized phase II trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Onc 22(9): 1589-97

Vinorelbine

For:

Second or third line therapy of NSCLC

Dosages:

Vinorelbine 30mg/m^2 IV day 1 and day 8

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day 1	1	Sodium Chloride Vinorelbine	0.9% 30mg/m²	50ml	IV bolus
Day 8	1	Sodium Chloride Vinorelbine	0.9% 30mg/m²	50ml	IV bolus

Associated medication:

Metoclopramide 10-20mg qds prn

Expected toxicity:

Myelosuppression, fatigue, neuropathy, constipation, myalgia, mucositis, pain at injection site
Vesicant drug – risk of tissue damage with extravasation

Required investigations pre-treatment:

- CXR or CT staging

On-treatment assessments:

- CXR

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
<2.9	>1.5	<99	Defer one week, then proceed with 75% dose on both drugs. If further delay then reduce dose to 50%

Infective

Febrile neutropaenia (1st episode)	Defer one week, then proceed with 75% dose on all drugs
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with 50% dose on all drugs

Gastrointestinal:
Any grade 3/4 toxicity – defer until settled and reduce dose by 75%

Cost:

4 cycles around £1500

Notes:

- Vinorelbine is superior to best supportive care in stage IIIB and IV NSCLC when used as a first line treatment
- Oral vinorelbine is as effective as intravenous but excess of deaths due to febrile neutropaenia observed with 80mg/m2 dose.
- If giving oral vinorelbine start 60mg/m^2 on day 1 only. Escalate to 80mg/m^2 after 3 cycles if tolerated and no grade IV neutropaenia

References:

Elderly Lung Cancer Vinorelbine Italian Study Group.(1999) J Natl Cancer Inst 91:66-72
Jassem et al. A multicenter randomized phase II study of oral vs. intravenous vinorelbine in advanced non-small-cell lung cancer patients (2001) Ann Oncol 12: 1677-81

PE – Sequential Chemoradiotherapy or Alone

For:

Limited/extensive stage SCLC, extrapulmonary small cell carcinoma or adjuvant therapy of resected small cell carcinoma

Dosages:

Cisplatin 80 mg/m^2 on day 1, etoposide 120mg/m^2 on days 1-3.

*Carboplatin AUC 6 on day 1 if cisplatin not suitable: eGFR/EDTA clearance <50ml/min, serum creatinine >ULN, severe emesis despite appropriate prophylaxis or co-morbidity precluding cisplatin.

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route/ Duration
Day 1	1	Sodium chloride	0.9%	1000ml	IV 1 hour
		Potassium chloride	20 mmol		
		Magnesium sulphate	10 mmol		
	2	Mannitol	20%	200ml	IV 20 minutes
	3	Sodium chloride	0.9%	1000ml	IV 1 hour
		Cisplatin	80 mg/m^2		
	4	Sodium chloride	0.9%	1000ml	IV 90 minutes
		Etoposide	120mg/m^2		
	5	Sodium chloride	0.9%	1000ml	IV 1 hour
		Potassium chloride	20 mmol		
		Magnesium sulphate	10 mmol		
	6	Sodium chloride	0.9%	500ml	IV 1 hour
Day 2	1	Sodium chloride	0.9%	500ml	IV 45 minutes
		Etoposide	120mg/m^2		
Day 3	1	Sodium chloride	0.9%	500ml	IV 45 minutes
		Etoposide	120mg/m^2		
Alternative Day 1 if using carboplatin:					
Day 1	1	Dextrose	5%	500ml	IV 1 hour
		Carboplatin	AUC 6		
	2	Sodium chloride	0.9%	500ml	IV 45 minutes
		Etoposide	120mg/m^2		

Number of Cycles and Scheduling:

4-6, q3/52

Associated medication:

- Pre-chemotherapy: ondansetron 8 mg + dexamethasone 8 mg iv
- Post-chemotherapy (TTO): ondansetron 8 mg bd + dexamethasone 4 mg od po for 2 days (also metoclopramide 10 mg qds prn)
- Consider antibiotic prophylaxis if poor PS and/or co-morbidity, or if airway obstruction/consolidation: levofloxacin 500mg po od from day 8 for 10 days

Expected toxicity:

Emesis (severe), alopecia (total), myelotoxicity (moderate-severe), nephrotoxicity, ototoxicity, peripheral neuropathy, infertility

Required investigations pre-treatment:

- CXR
- Staging CT – chest and abdomen, consider CT brain depending on symptoms
- GFR (calculated) ≥50 ml/min – see above comments

On-treatment assessments:

- Protocol led assessment on day 1
- Toxicity assessment – on day 15 every cycle.
- CXR to assess response
- eGFR with each cycle. If uncertain check EDTA clearance.
- CT thorax/abdomen after 3 cycles and 6 cycles and refer for PCI. Include brain if limited stage and considering PCI

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
2.0-2.9	0.5-0.9	50-99	Defer one week, the continue full dose
<1.0	<0.5	<49	Defer one week then proceed with 25% dose reduction (consider GCSF)

Infective

Febrile neutropaenia (1st episode)	Defer one week, then full dose with GCSF (days 4-10)
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with 75% dose + GCSF

Renal: use eGFR/EDTA clearance:

>60	Full dose
50-59	Give cisplatin at 75% dose or consider carboplatin. Etoposide full dose
40-49	Use carboplatin AUC 5. Give etoposide at 75% dose.
>40	Omit

Biochemical:
Bilirubin >1.5xULN – omit cisplatin/etoposide, can give carboplatin single agent
AST/ALT >2.5xULN (>5XULN if due to liver metastases) – omit cisplatin/etoposide, can give carboplatin single agent

Neuropathy: grade 2 – reduce cisplatin by 50%, Grade 3/4 – discontinue until grade 1 or less

Ototoxicity: substitute carboplatin

Cost:

4 cycles typically costs around £400 (cisplatin) or £1300 (carboplatin)

Notes:

- Regimen can be administered as outpatient but admit if poor PS, SVCO, respiratory distress or patient preference
- Treatment given on a Monday
- Give via leg vein if SVCO present
- Prophylactic cranial irradiation is performed 4-6 weeks after final cycle of chemotherapy. PCI is never given concurrently with chemotherapy

Reference:

Skarlos DV *et al.* (1994) Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. *Ann Oncol* **5**: 601-7

Lo Re *et al.* (1994) Extrapulmonary small cell carcinoma: a single-institution experience and review of the literature. *Ann Oncol* **5**: 909-13

The Role of Thoracic Radiotherapy as an Adjunct to Standard Chemotherapy in Limited-Stage Small Cell Lung Cancer. Cancer Care Ontario Practice Guidelines Initiative. Guideline #7-13-3

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Concurrent Chemoradiotherapy (SCLC) off trial

For:

Limited stage SCLC

Dosages:

Cisplatin 60 mg/m^2 on day 1, etoposide 120mg/m^2 on days 1-3. Radiotherapy starts on cycle 2 day 1 and is given daily for 20 fractions
*Carboplatin AUC 5 on day 1 if cisplatin not suitable: eGFR/EDTA clearance <50ml/min, serum creatinine >ULN, severe emesis despite appropriate prophylaxis or co-morbidity precluding cisplatin.

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route/ Duration
Day 1	1	Sodium chloride	0.9%	1000ml	IV 1 hour
		Potassium chloride	20 mmol		
	2	Sodium chloride	0.9%	1000ml	IV 90 minutes
		Magnesium sulphate	1g		
		Cisplatin	60 mg/m^2		
	3	Sodium chloride	0.9%	1000ml	IV 1 hour
		Etoposide	120mg/m^2		
Day 2	1	Sodium chloride	0.9%	500ml	IV 45 minutes
		Etoposide	120mg/m^2		
Day 3	1	Sodium chloride	0.9%	500ml	IV 45 minutes
		Etoposide	120mg/m^2		
Alternative Day 1 if using carboplatin:					
Day 1	1	Dextrose	5%	500ml	IV 1 hour
		Carboplatin	AUC 5		
	2	Sodium chloride	0.9%	500ml	IV 45 minutes
		Etoposide	120mg/m^2		

Number of Cycles and Scheduling:

4, q3/52

Associated medication:

- Pre-chemotherapy: ondansetron 8 mg + dexamethasone 8 mg iv
- Post-chemotherapy (TTO): ondansetron 8 mg bd + dexamethasone 4 mg od po for 2 days (also metoclopramide 10 mg qds prn)
- Consider antibiotic prophylaxis if poor PS and/or co-morbidity, or if airway obstruction/consolidation: levofloxacin 500mg po od from day 8 for 10 days
- Lansoprazole 30mg od
- Consider mis-paracetamol, sucralfate, gaviscon, oramorph for relief of oesophagitis

Expected toxicity:

Emesis (severe), alopecia (total), myelotoxicity (moderate-severe), nephrotoxicity, pneumonitis, oesophagitis, ototoxicity, peripheral neuropathy, infertility

Required investigations pre-treatment:

- Full lung function including transfer factor
- CXR
- Staging CT – brain, chest and abdomen
- WHO PS 0-1
- eGFR/EDTA clearance ≥50 ml/min – see above comments

On-treatment assessments:

- Toxicity assessment – weekly whilst undergoing radiotherapy - Monday am OPD
- CXR to assess response
- eGFR with each cycle. If uncertain check EDTA clearance.
- CT brain(if not done pre-treatment)/thorax abdomen after 4 cycles and refer for PCI.

Dose modifications:

Haematological: Use FBC on day 1 of treatment cycle:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
2.0-2.9	0.5-0.9	50-99	Defer one week, then continue full dose
<1.0	<0.5	<49	Defer one week then proceed with 75% dose (consider GCSF)

Infective

Febrile neutropaenia (1st episode)	Defer one week, then full dose with GCSF (days 4-10)
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with 75% dose + GCSF

Renal: use calculated GFR:

>60	Full dose
50-59	Give cisplatin at 75% dose or consider carboplatin. Etoposide full dose
40-49	Use carboplatin AUC 5. Give etoposide at 75% dose.
<40	Omit

Biochemical:
Bilirubin >1.5xULN – omit cisplatin/etoposide, can give carboplatin single agent
AST/ALT >2.5xULN – omit cisplatin/etoposide, can give carboplatin single agent

Neuropathy: grade 2 – reduce cisplatin by 50%, Grade 3/4 – discontinue until grade 1 or less

Ototoxicity: substitute carboplatin

Cost:

4 cycles typically costs around £400 (cisplatin) or £1300 (carboplatin)

Notes:

- Regimen can be administered as outpatient but admit if poor PS, SVCO, respiratory distress or patient preference. Usually patients with poor PS, SVCO or respiratory distress are not suitable for concurrent treatment. Give via leg vein if SVCO present.
- Treatment given on a Monday
- Prophylactic cranial irradiation is performed 4-6 weeks after cycle 4. PCI is never given concurrently with chemotherapy
- Complete CTRT toxicity sheet

Reference:

JP Pignon et al., (1992) A meta-analysis of thoracic radiotherapy for small-cell lung cancer, N Engl J Med 327: 1618–1624
Takada M et al., (2002) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104 J Clin Oncol 20: 3054–3060.
The Role of Thoracic Radiotherapy as an Adjunct to Standard Chemotherapy in Limited-Stage Small Cell Lung Cancer. Cancer Care Ontario Practice Guidelines Initiative. Guideline #7-13-3
Turissi reference NEJM

Carboplatin Monotherapy

For:

Poor prognosis SCLC with renal and/or hepatic impairment, poor performance status/high Manchester score/co-morbidity

Dosages:

Carboplatin AUC 6 on day 1

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route/ Duration
Day 1	1	Dextrose	5%	500ml	IV 1 hour
		Carboplatin	AUC 6		

Number of Cycles and Scheduling:

4, q3/52

Associated medication:

- Pre-chemotherapy: ondansetron 8 mg + dexamethasone 8 mg iv
- Post-chemotherapy (TTO): ondansetron 8 mg bd + dexamethasone 4 mg od po for 2 days (metoclopramide 10 mg qds prn)
- Levofloxacin 500mg od to commence on day 8 for 10 days

Expected toxicity:

Emesis (mild-moderate), myelotoxicity (platelets), nephrotoxicity, peripheral neuropathy, alopecia (mild)

Required investigations pre-treatment:

- CXR
- Staging CT – chest and abdomen
- GFR (calculated)

On-treatment assessments:

- Protocol led assessment on day 1
- Toxicity assessment – on day 15 every cycle.
- CXR to assess response
- Check eGFR with each cycle. If uncertain check EDTA clearance.

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
2.0-2.9	0.5-0.9	50-99	Defer one week, the continue full dose
<1.0	<0.5	<49	Defer one week then proceed with 25% dose reduction (consider GCSF)

Infective

Febrile neutropaenia (1st episode)	Defer one week, then full dose with GCSF (days 4-10)
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with 75% dose + GCSF

Renal: use eGFR/EDTA clearance:

<40	Omit

Neuropathy: grade 2 – use AUC 5, Grade 3/4 – discontinue

Cost:

4 cycles typically costs £1000

Reference:

White et al. (2001) Randomized phase II study of cyclophosphamide, doxorubicin, and vincristine compared with single-agent carboplatin in patients with poor prognosis small cell lung carcinoma. Cancer 92(3): 601-8

VAC

For:

SCLC, poor prognosis or in relapse

Dosages:

Vincristine 1.3mg/m² IV (max 2mg), Doxorubicin 40mg/m² IV, Cyclophosphamide 750mg/m²

Regimen:

Order		Fluid/Drugs	Dose	Volume	Route & Duration
Day 1	1	Sodium Chloride	0.9%	20ml	IV bolus
		Vincristine	1.3mg/m² (max 2mg)		
	2	Doxorubicin	40mg/m²		IV bolus
	3	Cyclophosphamide	750mg/m²		IV bolus

Number of Cycles and Scheduling:

4 – 6, q21 days

Associated medication:

- Pre-chemotherapy: ondansetron 8 mg + dexamethasone 8 mg iv
- Post-chemotherapy (TTO): ondansetron 8 mg bd + dexamethasone 4 mg od po for 2 days (also metoclopramide 10 mg qds prn)
- Levofloxacin 500mg od to commence on day 8 for 10 days

Expected toxicity:

Emesis (moderate), alopecia (total), myelotoxicity (moderate-severe), mucositis, peripheral neuropathy, infertility myelosuppression, constipation, cardiotoxicity
Vesicant drugs – risk of extravasation injury

Required investigations pre-treatment:

- CT staging – thorax/abdomen
- CXR

On-treatment assessments:

- Protocol led assessment on day 1
- Toxicity assessment – on day 15 every cycle.
- CXR to assess response

Dose modifications:

Haematological: Use FBC on day of treatment:

WBC	Neut	Plt	Dose adjustment
>3.0	>1.5	>100	None
2.0-2.9	0.5-0.9	50-99	Defer one week, the continue full dose
<1.0	<0.5	<49	Defer one week then proceed with 75% dose

Infective

Febrile neutropaenia (1st episode)	Defer one week, then proceed with 75% dose
Febrile neutropaenia (2nd episode)	Defer one week, then proceed with 50% dose

Biochemistry:

Bilirubin >1.5x ULN	Omit
AST/ALT >2.5xULN	Omit
(5xULN if due to liver mets)	

Neuropathy: Give 1mg of vincristine to those age >70 or with grade 1 neuropathy. Omit if vinca bowel or grade 2 neuropathy or above.

Notes:

- VAC (or CAV) is usually given for relapsed SCLC where relapse has occurred within three months of a platinum containing regimen or following two platinum containing regimens

References:

Thatcher N. (1996) Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. Lancet 348: 563–6.

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Stereotactic Body Radiation Therapy (SBRT) for Patients with Early Stage Non-small Cell Lung Cancer: A Resource

UK SBRT Consortium

September 2009

These guidelines provide:

- Literature Review of key lung SBRT publications
- An overview of patient selection criteria
- An Introduction to Quality Assurance for Lung SBRT
- Some examples from the literature of radiotherapy dose/fractionation schedules and associated planning guidelines

Lung SBRT is a team effort and requires a clear clinical process to be defined. It is essential that these suggestions be read in conjunction with published guidelines and other scholarly texts, including:

1. American College of Radiology (ACR) and American Society for Therapeutic Radiology and Oncology (ASTRO): Practice guideline for the performance of stereotactic body radiation therapy http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=9433&nbr=5054

2. Timmerman, Robert, Galvin, James, Michalski, Jeff, Straube, William, Ibbott, Geoffrey, Martin, Elizabeth, Abdulrahman, Ramzi, Swann, Suzanne, Fowler, Jack and Choy, Hak(2006)'Accreditation and quality assurance for Radiation Therapy Oncology Group: Multicenter clinical trials using Stereotactic Body Radiation Therapy in lung cancer',Acta Oncologica,45:7,779 — 786 http://pdfserve.informaworld.com/885920__757968552.pdf

3. Volume 71, Issue 1, Supplement 1, Pages S1-S214 (1 May 2008). Quality Assurance for Radiation Therapy, Quality Assurance of Radiation Therapy: The Challenges of Advanced Technologies Symposium
Dallas, TX 20-22 February 2007
Edited by Jeffrey F. Williamson and Bruce R. Thomadsen
American Society for Therapeutic Radiology and Oncology, American Association of Physicists in Medicine and National Cancer Institute

Disclaimer: This document is an information resource only. It does not constitute an instructional document for the carrying out of lung SBRT, nor does it represent a legal standard of care. It is the responsibility of each treating team to ensure that they have received adequate and appropriate training and that their equipment is fit for purpose. Due to the varying technical equipment and systems available at radiotherapy centres it is advisable that each centre must determine the appropriate treatment selection and conduct of treatment for each of their patients and gain approval of their own institution's clinical governance body.

UK SBRT Consortium Guidelines

June 2009

Contents

Early Lung Cancer: Introduction

Lung cancer is responsible for 1 in 7 new cases of cancer and is responsible for 22% of all cancer deaths [1, 2]. Approximately 80% of patients have non-small cell lung cancer (NSCLC), of whom about 20% have early-stage disease (AJCC Stage I, TNM Stage T1-2N0M0) which is associated with the best chance of cure. Lung cancer is more common in elderly patients and smokers, who have a higher incidence of medical co-morbidity. This means that in a proportion of patients with early stage NSCLC, surgery is too risky. Such patients are termed 'medically inoperable'. Some other patients may be inoperable for technical reasons, or decline surgery of their own volition. An effective, non-surgical treatment is needed for all of these scenarios.

1.1 Conventional Therapy and Outcome

The time-honoured gold standard for the treatment of Stage I lung cancer is surgical resection. This is associated with five-year overall survival rates in the range of 60-70% [3]. For those patients who are not operable or who decline surgery, external beam radiation therapy (RT) is an alternative treatment approach. It is difficult to accurately compare survival rates in patients treated with surgery (resulting in accurate pathological staging) or radiation therapy (when patients may be under-staged by clinical investigations). However, long-term survival rates with radiation therapy alone (5 year survival 10-30%), seem to be about half (or less) of those seen in surgical series[4]. The 2001 Cochrane review suggested that local recurrence rates in medically inoperable patients treated with external beam radiation therapy ranged from 6-70% [4]. Even with a dose of 84 Gy administered in 1.8-2.0 Gy fractions over 8 weeks a third of patients may recur locally [5]. Furthermore, attempts to escalate the radiation dose beyond this, to 90 Gy or more, in standard fractionation, have been associated with unacceptable toxicity in some series [6].

1.2 Stereotactic Body Radiotherapy (SBRT)

With improvements in radiation technology, a number of groups began to investigate the use of hypofractionated stereotactic body radiotherapy (SBRT) for lung tumours, both primary NSCLC and metastatic carcinomas. The treatment technique utilized is similar to that used for intracranial lesions, and employs multiple radiation beams to target a tumour with high precision, delivering an ablative dose of radiation, made possible by limiting the treatment volume, and the parallel nature of lung tissue.

Radiotherapy doses are prescribed to an isodose line covering the planning target volume (PTV), which means that within the PTV or to the isocentre, the dose may be much greater. Various dose and fractionation schedules have been used, ranging from a single to ten or more fractions [7, 8]. In some of these studies a body frame with stereotactic coordinates to aid set up and some form of respiratory management/compensation (e.g. to identify and take into account tumour motion in treatment planning and to limit motion and thereby reduce the amount of normal tissue irradiated) were used. A large retrospective analysis of Japanese patients supported dose and fractionation regimens that delivered a BED of > 100Gy [9]. These were associated with a 5 –year overall survival of approximately 70% in medically operable patients. In 2003 Timmerman published a phase I dose escalation study which confirmed 3 x 20 Gy as a safe dose for T1-2 peripheral lung tumours. Local failures were seen below a median dose of 3 x 12 Gy [10]. The subsequent phase II study by Timmerman investigated a dose of 3 x 20 Gy and 3 x 22 Gy for T1-2 tumours, excessive toxicity was seen at a dose of 3 x 22 Gy and at 3 x 20 Gy for central tumours [11]. RTOG 0236 was a multicentre phase II study following on from the dose escalation study and has now closed. Initial reports from this study suggest that rates of acute toxicity are acceptable. There was one (2%) grade 4 and 7 (13%) grade 3 pulmonary/upper respiratory adverse events reported as related to protocol treatment [12].

There is now considerable non-randomised evidence supporting SBRT as superior to conventional RT with respect to local control and survival. This is biologically plausible. Lung SBRT also appears to have an acceptable therapeutic index. Table 1.1 lists the RT regimen, control rates and toxicity seen in studies in which more than 40 patients were treated. The toxicity of this technique is relatively low when treating T1-2 tumours in the periphery of the lung. It is important to bear in mind that a number of these studies were done prior to the era of on-line kilovoltage (kV) cone beam CT (CBCT) image guidance. The introduction of onboard imaging with kV CBCT has the potential to enhance target localisation and the safety of SBRT treatments.

Following various discussions within the UK clinical oncology lung community over the last two successive British Thoracic Oncology Group (BTOG) meetings there was considerable support and interest in providing (SBRT for patients with early NSCLC. This has resulted in the formation of a consortium of interested parties for Lung SBRT. Many of the following comments in sections 2, 3 and 5 are consistent with, or

drawn from the RTOG 0236 trial (http://www.rtog.org/members/protocols/0236/0236.pdf) and the ROSEL trial protocol [13, 14].

Table 1-1 Summary of outcome and toxicity of SBRT in studies (n >40)

Study	Patient Numbers	Schedule	BED (α/β = 10)	Median FU (months)	Actuarial local control	Complications
Baumann et al, 2006 [15]	138	30-48 Gy in 2-4 #	60-120 Gy	33	85% (3 yr)	Atelectasis >Grade 2 (2%) Pneumonitis >Grade 2 (1%) Rib fractures (4%)
Lagerwaard et al, 2007 [16]	197	3 x 20Gy 5 x 12 Gy	180 Gy 132 Gy	12	94% (2 yr)	Pneumonitis >Grade 2 (3%) Rib fractures (2%)
Nagata et al, 2005 [17]	45	4 x 12 Gy	106 Gy	30	98% (2 yr)	Pneumonitis >Grade 2 (0%)
Nyman et al, 2006 [18]	45	3 x 15 Gy	113 Gy	43	80% (crude)	Pneumonitis >Grade 2 (0%) Rib fractures (4%)
Onishi et al, 2007 [9]	257	18-75 Gy in 1-22 #	Miscellaneous	38	84% (5 yr BED > 100) 37% (5 yr BED <100)	Pneumonitis >Grade 2 (5%)
Timmerman et al, 2006 [11]	70	3 x 20 Gy 3 x 22 Gy	180 Gy 211 Gy	18	96% (2 yr)	Pericardial effusion Grade 5 (1%) Bleeding Grade 5 (1%) Bacterial pneumonia Grade 5 (6%)
Wulf et al, 2001 [19]	50	50-60 Gy in 5-10 #	Miscellaneous	36	94% (crude)	Pneumonitis >Grade 2 (0%) Rib fractures (4%)
Xia et al, 2006 [20]	43	5 x 10 Gy	100 Gy	27	95% (3 yr)	Pneumonitis >Grade 2 (2%)

Patient selection for SBRT

2.1 Inclusion Criteria

- MDT confirmed diagnosis of NSCLC based on findings of positive histology, positive PET scan or growth on serial CT scan.
- Clinical stages of: T1 N0 M0

  T2 (≤5cm) N0 M0

  T3 (≤5cm) N0 M0

If radiologically N2 (CT or PET), patients may still be eligible if possible nodal disease is subsequently confirmed as histologically negative with mediastinoscopy or endoscopic bronchial or oesophageal ultra-sound biopsy.

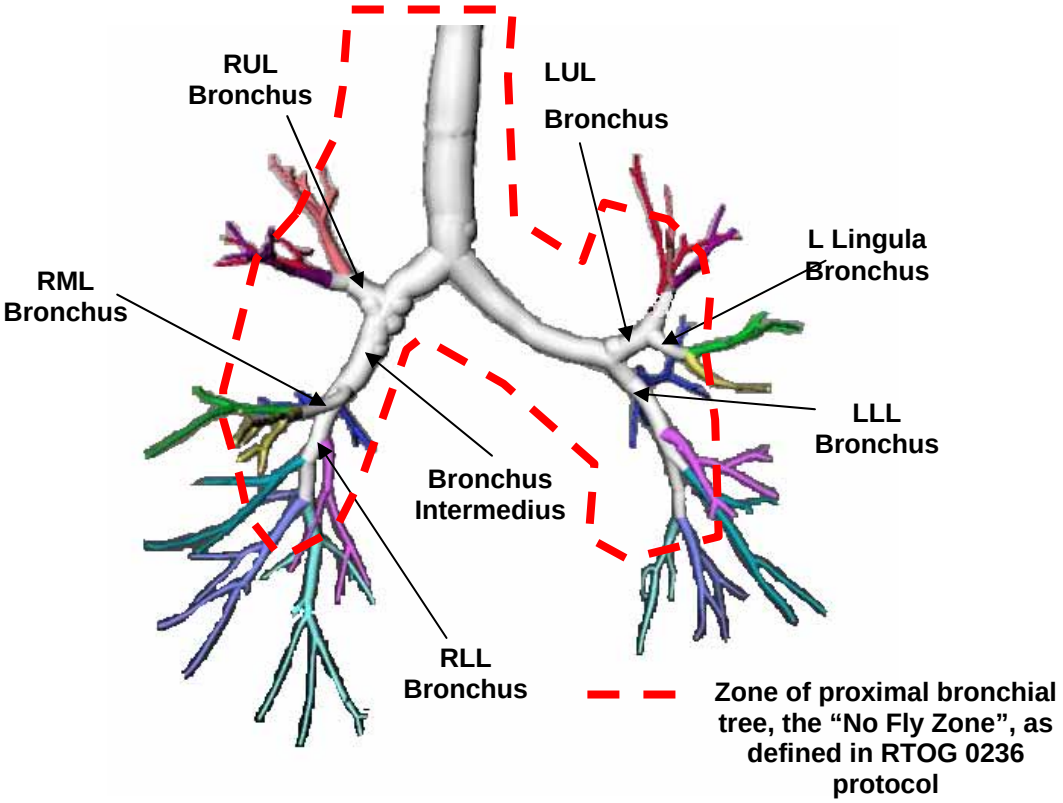
- Not suitable for surgery because of medical co-morbidity, lesion is technically inoperable or patient declines surgery after surgical assessment.
- WHO performance status 0-2.
- Peripheral lesions outside a 2cm radius of main airways and proximal bronchial tree. This is defined as 2cm from the bifurcation of the second order bronchus e.g. where the right upper lobe bronchus splits (figure 2.1)
- Age ≥ 18 years

2.2 Exclusion Criteria

- NSCLC patients with T2 or T3 primary tumours > 5cm.
- T3 primary NSCLC tumours involving the mediastinal structures or central T3 primary tumours.
- Metastatic lung tumours
- Any tumour that is not clinically definable on the treatment planning CT scan e.g. surrounded by consolidation or atelectasis.
- Tumours with respiratory motion ≥ 1cm despite using techniques to reduce tumour motion. If it is possible to achieve the suggested normal tissue and tumour planning constraints then only can mobile tumours be treated with this technique.

- Tumours within 2cm radius of main airways and proximal bronchial tree (figure 2.1).
- Primary NSCLC tumours with clinical evidence of regional or distant metastasis after appropriate staging studies.
- Previous radiotherapy within the planned treatment volume
- Chemotherapy administered within 6 weeks prior to study entry or planned for < 6 weeks following SBRT.
- Pregnant or lactating females
- Inability to obtain informed consent or comply with treatment requirements

Figure 2-2-1 Proximal bronchial tree as defined by RTOG 0236 protocol



Radiotherapy

3.1 Radiotherapy Planning

3.1.1 Patient positioning

Given the additional length of each treatment fraction more consideration needs to be given to patient comfort as well as their positional stability and the reproducibility of their set-up.

We would suggest that patients should be placed supine in a comfortable and reproducible position, with their arms above their heads, although alternative positions may be required for individual patients.

Devices such as customized vacuum bags can be used to achieve patient comfort and stability.

Custom immobilisation devices can also be used for immobilisation and to facilitate abdominal compression. The immobilization device should allow for patient and tumour imaging as necessary using CT, CBCT and/or fluoroscopy, and not interfere with dose calculation or treatment delivery.

In addition, analgesics +/- mild sedatives and oxygen can be considered to help the patient maintain the treatment position during each fraction.

Minimum standard: Centres should assess the accuracy of immobilisation device/s used for positioning patients for SBRT. Systematic setup errors should be within 3-5mm.

3.1.2 Tumour motion

Once the patient has been appropriately positioned, we recommend that ideally 4DCT is used to assess tumour motion but if this is unavailable then other methods must be used such as fluoroscopy or slow CT.

Over time all centres should aim to eventually use 4DCT scan for assessing and incorporating tumour motion for planning patients.

In some published series special consideration was given to tumours that moved more than 1cm in any direction. There are two main strategies to deal with mobile (>1cm) tumours.

(a) Motion Restriction to reduce tumour motion (to <1cm), e.g. by using one of the following methods:

1. Abdominal compression.

2. Respiratory gating.

3. Coached respiration

4. Active Breathing Control (ABC) device for patients with sufficient respiratory reserve to be able to breath hold for >20 seconds.

(b) Accounting for motion in RT planning:

1. Provided that the dose conformity, dose spillage and OAR constraints can be met the whole motion envelope may be included in the ITV and the patient treated whilst breathing normally (usually applies to small mobile tumours).

2. Planning using the mid-ventilation or time-weighted average image from 4DCT and accept that the ITV and PTV may not always include all tumour motion.

A patient may be deemed ineligible for SBRT if:

- ✓ tumour motion is felt to be unacceptable or non-correctable with currently available respiratory immobilization techniques

  AND

- ✓ dose conformity, dose spillage and OAR constraints can not be met

It is the responsibility of each radiotherapy department to assess the reproducibility of their chosen method of managing tumour motion prior to commencing SBRT treatments.

3.1.3 CT simulation

Patients will undergo a treatment planning CT scan in the treatment position within the chosen immobilization device. The extent of the scan must be sufficient to include all potential organs at risk, especially when non-coplanar beams are used. As a guide contiguous axial slices of ≤3mm 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.

More than one planning CT scan (e.g. slow-CT/4DCT), may be required for target definition/motion assessment.

The planning CT scan(s) must allow for simultaneous viewing of internal organ anatomy as well as any fiducial systems if a stereotactic frame is used for immobilisation, which will be identical for the treatment-planning phase and for each radiation fraction.

3.1.4 Tumour Delineation

Gross Tumour Volume (GTV) = The GTV is defined as the radiologically visible tumour in the lung, contoured using lung settings. Mediastinal windows may be suitable for defining tumours proximal to the chest wall. Where available information from PET/CT will be incorporated into delineating the GTV.

Clinical Target Volume (CTV) = The CTV is the GTV with no margin for microscopic disease extension. This is the accepted standard in the majority of SBRT trials.

The margins from CTV to PTV will depend on the method of immobilisation, the assessment of tumour motion and methods for on treatment set-up verification/repositioning (e.g. CBCT).

Internal Target Volume (ITV) = tumour volume obtained using a 4DCT scan. This is defined as tumour contoured using either the (i) maximum intensity projection scan, (ii) maximum inspiratory and expiratory scans or (iii) as contoured on all 10 phases of a 4DCT scan.

Each Centre will need to confirm the adequacy of the PTV margins with their immobilisation techniques. Example margins are:

Helical CT Planning:	From CTV to PTV	(RTOG 0236)
	Cranio/Caudal = 10mm	
	Ant/Post = 5mm	
	Lateral =5m	

4DCT Planning: From ITV to PTV

(1) Universal (isotropic) 5mm margins (PMH)

(2) Universal 3mm margin (VU)

All tumour and critical organ contours must be reviewed by 2 consultant oncologists with an additional review by a consultant radiologist highly recommended.

3.1.5 Organs at Risks (OAR)

It is recommended that the following organs at risk are delineated on the CT planning dataset. Please refer to the presentation provided by Dr Brendan Carey for reference.

Spinal cord

The spinal cord should be contoured on all slices based on the bony limits of the spinal canal.

Oesophagus

The oesophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia

Brachial Plexus

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neural foramina on the involved side from around C5 to T2. However, for the purposes of this protocol 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. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries), and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the 2nd rib.

Heart

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring is defined as the superior aspect of pulmonary artery (as seen in a coronal reconstruction of the CT scan) and extended inferiorly to the apex of the heart.

Trachea and proximal bronchial tree

The trachea and bronchial tree will be contoured as two separate structures using lung windows. For this purpose, the trachea will be divided into two sections: the

proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree. Differentiating these structures in this fashion will facilitate the eligibility requirement for excluding patients with tumours within 2 cm of the proximal bronchial tree (figure 2.1)

Proximal trachea

Contours should begin 10cm superior to superior extent of PTV or 5cm superior to the carina (whichever is the more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

Proximal bronchial tree

This will include the most inferior distal 2cm of trachea and the proximal airways on both sides as indicated in diagram 1. The following airways will be included: distal 2cm trachea, carina, right and left mainstem bronchi, right and left upper lobe bronchi, the bronchus intermedius, right middle lobe bronchus, lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

Whole lung

Both lungs should be contoured as one structure using pulmonary windows. All inflated and collapsed lung should be included. However, GTV and trachea/ipsilateral bronchus as defined above should not be included. The Lungs-GTV should be kept at V20< 10%, and V12.5<15%.

Proximal bronchial tree plus 2cm

As part of adhering to the ineligibility requirements for not enrolling patients with tumours in the zone of the proximal bronchial tree listed in 3.2.2 above, it is convenient to define an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this artificial structure, the patient should not be treated with the SBRT outside the context of a clinical trial.

The OARs should be inspected to ensure that wherever a treatment beam traverses the OAR, it has been contoured. The body contour should also be contoured wherever the beams traverse it. The skin should be inspected to ensure that beams do not overlap, producing excessive skin dose, especially where there is a skin fold.

3.1.6 Treatment Planning

The V.U. group in Amsterdam have recently published their SBRT experience in >200 patients, 43% of patients receiving 60Gy in three fractions and 45% of patients receiving 60Gy in five fractions [30]. Their experience has formed the basis for the ROSEL study, a randomised trial comparing Lung SBRT vs. Surgery in medically operable patients with Stage IA NSCLC.

http://clinicaltrials.gov/ct2/show?term=stereotactic&rank=11

The constraints recommended in this protocol are based on those that have been safely used to treat >500 patients at the VU centre in Amsterdam and subsequently implemented for the ROSEL study.

Beam selection

To achieve adequate target coverage using SBRT whilst sparing critical structures, including the skin surface, at least seven beams are typically required. The beam configuration may be coplanar or non-coplanar, depending on the size and location of the lesion. The paradigm dictates that the high-dose region should be conformal to the PTV, the medium-dose region surrounding the PTV should be compact and the low-dose region is permitted to be relatively large by comparison to the other regions. All dose calculations should be performed using heterogeneity correction.

Due to uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, individual centres should satisfy themselves of the veracity of their small-field dosimetry. Lower energy such as 6MV beams should be used, due to the wide penumbra of high-energy beams, the small beam apertures used in SBRT and the problems associated with build up. Analysis of the dose-volume histogram (DVH) for the PTV and critical normal structures forms the basis for selecting a particular treatment plan. It is therefore recommended that plans be calculated on a fine dose grid, with a separation no greater than 2.5mm, to ensure the accuracy of the DHV calculations.

Treatment Planning System

Inhomogeneity corrections have a large influence on the dose delivered to the PTV and OARs for SBRT of lung tumours. Type A algorithms, which use an extended path length (EPL) calculation to account for heterogeneity, result in a wide range of errors relative to the actual dose distribution. This includes overestimation of the isocentric prescription dose and target coverage. The target coverage errors vary significantly depending on the location of the lesion. This means that a simple rescaling of the prescription dose, as used in the RTOG and ROSEL studies, does not provide a reliable correction. In view of this, it is strongly recommended that Type B algorithms that consider changes in lateral electron transport should be used. (ref: Shuring & Hurkmans, Radiation Oncology, 2008 Jul.28(3)p21) Examples include Pinnacle/CC, Eclipse/AAA, OMP/CC, I-Plan dose with Monte-Carlo algorithm and XIO/Superposition.

Tumour Location/OAR doses

As defined above the GTV must be outside the defined 2cm margin around the proximal airways (Figure 3.1). Table 3.1 lists the dose constraints used in the ROSEL study. These dose limits are based on the highest dose/fractionation regimes reported in lung SBRT and therefore should be safe for lower biological equivalent dose regimes used in lung SBRT.

Note: when non-coplanar treatment beams are used additional organs may be irradiated (e.g. liver, bowel) – allowances must be made for this. It is recommended the entire liver be scanned, especially for lower lobe lesions and where non-coplanar beams are to be used. The tolerances for these organs are detailed in the OAR section of the guidelines. **In addition, the dose to skin should be limited to minimise cutaneous and subcutaneous toxicity [21].** This is assisted by ensuring that beam entry points do not overlap on the skin.

Table 3-2 Dose constraints as used in the ROSEL study

Organ	Volume	Three Fraction Regime		Five Fraction Regime	
		Tolerance	Minor Deviation	Tolarance	Minor Deviation
Spinal cord	Any point	18 Gy	> 18 to 22 Gy	25 Gy	> 25 to 28 Gy
Oesophagus	1 cm^3	24 Gy	> 24 to 27 Gy	27 Gy	>27 to 28.5Gy
Ipsilateral Brachial Plexus	1 cm^3	24 Gy	> 24 to 26 Gy	27 Gy	> 27 tp 29 Gy
Heart	1 cm^3	24 Gy	> 24 to 26 Gy	27 Gy	> 27 to 29 Gy
Trachea, Ipsilateral Bronchus	1 cm^3	30 Gy	> 30 to 32 Gy	32 Gy	> 32 to 35 Gy
Lungs - GTV	V20			<10%	N/A

Fractionation

Acceptable dose fractionation regimes are suggested below. Individual centres may choose to prescribe dose fractionation regimes other than those suggested, however they must ensure that the BED is less than the highest dose in these guidelines, and the appropriate OAR tolerances are meet.

Standard Dose Fractionation:

18Gy x 3 fractions (NB 20Gyx3 is not allowed)

Conservative Dose Fraction:

12Gy x 5 fractions or 11Gy x 5 fractions

The Conservative dose fractionation is recommended when any a part of the PTV is in contact with the chest wall. It is recommended that the inter-fraction interval be at least 40 hours, with a maximum interval of ideally 4 days between treatment fractions (Hurkmans, C. W., et al., *Recommendations for implementing Stereotactic radiotherapy in peripheral stage 1A non-small cell lung cancer: report for the Quality*

Assurance Working Party Party of the randomised phase III ROSEL study, Radiation Oncology, 2009. **4**:1).

Dose distribution requirements (assuming 54Gy in 3 fractions)

Successful treatment planning will require accomplishment of all of the following criteria:

1. The dose prescription will be chosen such that 95% of the target volume (PTV) receives at least the nominal fraction dose (e.g., 18 Gy per fraction = 54 Gy total), and 99% of the target volume (PTV) receives a minimum of 90% of the fraction dose (i.e., 16.2 Gy per fraction = 48.6 Gy total)

2. The dosemax within the PTV should preferably not be less than 59.4Gy or exceed 75.6Gy. A minor deviation will be scored in cases where the dosemax lies between either 56.7- 59.4Gy or between 75.6--78.3Gy.

3. Conformity of PTV coverage will be judged as given in the tables below below, incorporating constraints used in the ROSEL study.

Table-2 Dose conformity requirements for type B models
54Gy in 3 fractions

Vol(PTV) (cc)	**Vol(100%)/ Vol(PTV)**		**Vol(50%) / Vol(PTV)**		**Max dose >2cm**		**V20 (%)**	
	tolerance	minor dev	tolerance	minor dev	tolerance	minor dev	tolerance	minor dev
<20	<1.25	1.25-1.40	<12	12-14	<35.1Gy	35.1-40.5Gy	<5	5-8
20-40	<1.15	1.15-1.25	<9	9-11	<37.8Gy	37.8-43.2Gy	<6	6-10
>40	<1.10	1.10-1.20	<6	6-8	<37.8Gy	37.8-43.2Gy	<10	10-15

55Gy in 5 fractions

Vol(PTV) (cc)	Vol(100%)/ Vol(PTV)		Vol(50%) / Vol(PTV)		Max dose >2cm		V20 (%)	
	tolerance	minor dev	tolerance	minor dev	tolerance	minor dev	tolerance	minor dev
<20	<1.25	1.25-1.40	<12	12-14	<35.8Gy	35.8-41.3Gy	<5	5-8
20-40	<1.15	1.15-1.25	<9	9-11	<38.5Gy	38.5-44.0Gy	<6	6-10
>40	<1.10	1.10-1.20	<6	6-8	<38.5Gy	38.5-44.0Gy	<10	10-15

Vol(100%)/Vol(PTV): ratio of prescription isodose (54Gy) volume to the PTV

Vol(50%)/Vol(PTV): ratio of 50% prescription isodose (27Gy) volume to the PTV

Max dose >2cm: maximum dose (% of nominal prescription dose) at least 2cm from the PTV in any direction

V20: percentage of total lung volume – GTV receiving >20Gy

Departments are urged to complete the plan evaluation forms included in these guidelines, to allow for the collection of dosimetric data that will be useful in the development of future guidelines.

3.2 Treatment Verification

Once the treatment plan has been generated, it is recommended that centres conduct a 'trial set up' session, prior to starting treatment, in order to confirm that all the beams are deliverable, that the patient can maintain the treatment position, to verify patient setup, acquire a CBCT scan and perform a match to the planning CT scan, and once the technology is available, use respiratory-correlated CBCT to assess margin adequacy.

It is suggested that centres verify patient setup before +/- during treatment, with volumetric imaging (e.g. CBCT) for online image matching and correction. See Appendix A for an example of a verification process for an Elekta-based treatment platform (based on the process developed at Princess Margaret Hospital, Toronto).

We suggest that individual centres develop experience in online CBCT lung imaging/registration prior to commencing SBRT. The patient should have an initial CBCT, followed by image registration and patient shifts if required. A verification CBCT is suggested to ascertain that the shift was made in the correct direction.

Further CBCT imaging should be performed if there are concerns that the patient has moved during the treatment.

Centres using other treatment systems such as CyberKnife® or TomoTherapy® will need to design their own verification techniques.

Treatment assessments & Follow Up

Table 4.1 and 4.2 detail the suggested assessments to be undertaken if performing SBRT in your centre. Patients should be reviewed prior to delivery of each fraction to review any symptoms and toxicity. We recommend using the CTC v3.0 (appendix B) for assessing toxicity during and after RT.

Post SBRT we suggest that the first follow up should be at 4-6 weeks post radiotherapy to assess acute toxicity. Patients should have a repeat chest x-ray at each follow up visit. Subsequent follow up visits should be of the order of 3 monthly for the 1st year, and 6 monthly for subsequent years. Consideration should be given to collecting quality of life data if possible. First post treatment CT scan should usually be done at 3 months and then repeated at least every 3-12 months depending on circumstances. Due attention must be given to the difficulty that can arise in differentiating local recurrence from tumour progression in certain scenarios [22]. In addition a greater awareness of the potential for certain toxicities (e.g. chest wall/rib) is required [23-25]. If feasible full lung function tests should be considered annually. Response may be documented using the RECIST criteria (Appendix C). If possible patients should be followed for a minimum of five years.

Table 4-3 Assessments at baseline and during radiotherapy.

Procedure	Base-line	During RT	4-6 weeks post RT
Medical History	X	X	X
Physical Examination	X	X	X
Weight	X		X
WHO PS score	X	X	X
FBC	X		
Biochemistry profile1	X		
Lung function test	X		
Pregnancy test2	X		
CT scan thorax and abdomen	X		
Chest Xray	X		X
CT/ MRI head	optional		
PET/CT	X		
Informed Consent	X		
Adverse event monitoring CTCAE v3.0	X	X	X
QOL (QLQ C30)	X		

Table 4-4 Suggested Assessments during follow up post-SBRT

Procedure	Months post RT											
	3	6	9	12	18	24	30	36	42	48	54	60
Medical History	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
ECOG score	X	X	X	X	X	X	X	X	X	X	X	X
Lung function test		X		X		X		X		X		X
CT scan thorax and abdomen	X			X		X		X		X		X
Chest Xray		X	X		X		X		X		X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X
QOL		X	X	X	X	X	X	X	X	X	X	X

Quality Assurance

Centres carrying out this treatment should adhere to the recommendations detailed in the NPSA report 'Towards Safety in Radiotherapy' [26]. In particular the staff involved need to appropriately trained, competent and have the experience required. Local procedures need to be documented and there should be good multidisciplinary communication and team working. All procedures should be part of the departments QART procedures in accordance with ISO9001:2000. The linear accelerators used should be commissioned in line with IPEM report 94 'Acceptance Testing and Commissioning of Linear Accelerators' [27]. To ensure that the planning and treatment process is safe the appropriate recommendations in IPEM report 81 'Physics Aspects of Quality Control in Radiotherapy' should be adhered to [28]. Additional guidance may be found in AAPM report TG66 'Quality Assurance for computed-tomography simulators and the computed-simulation process [29].

Standards for delivering SBRT have been developed and are listed under Appendix D along with a list of publications specifically dealing with quality assurance related to CBCT and other issues relevant to lung SBRT.

All centres should:

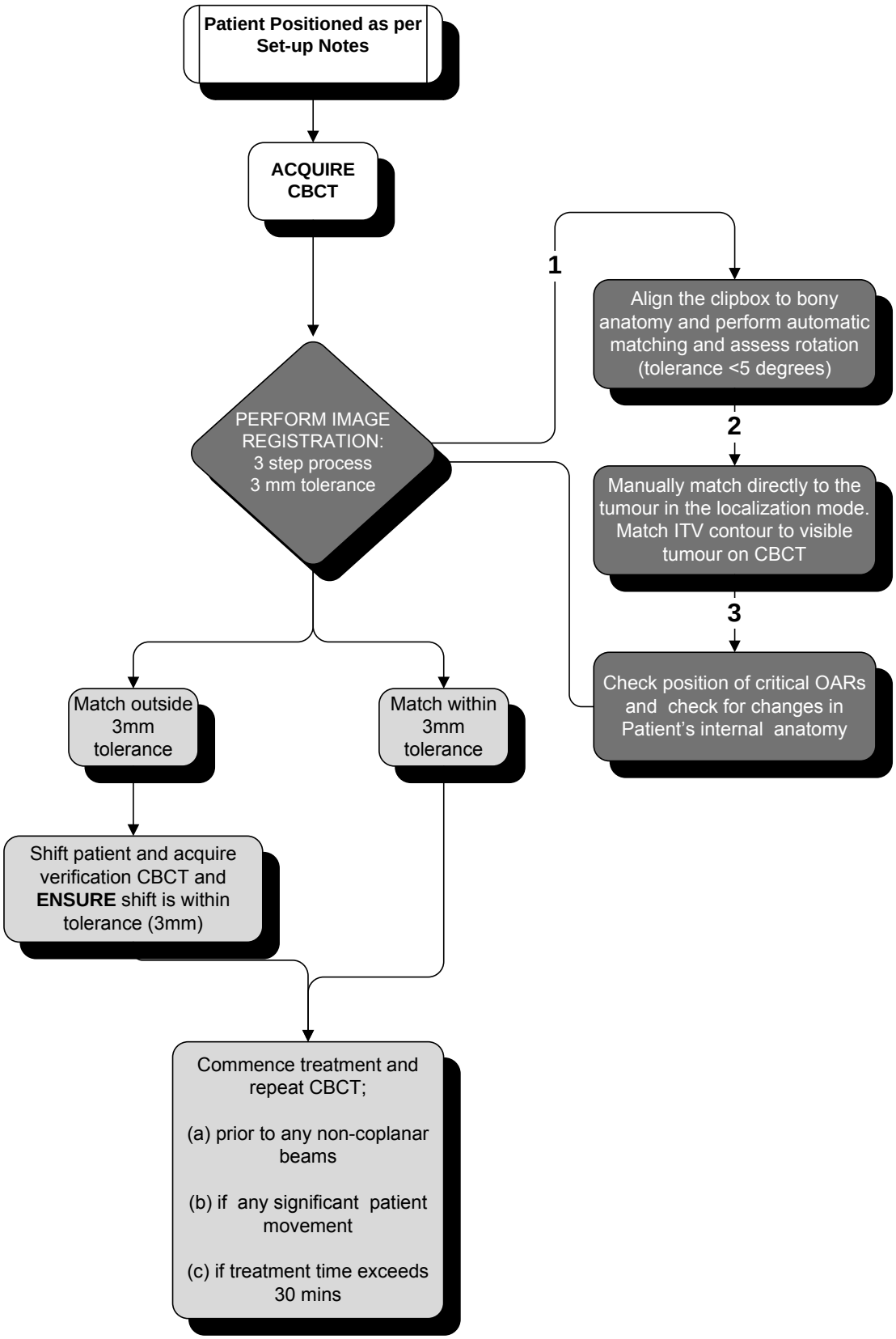
- have a method to identify tumour motion (e.g. kV fluoroscopy, 4DCT, slow CT, maximum inspiration/expiration breath hold CT etc). If 4DCT is being used then should be already be a routine procedure for some patients and must there must have been appropriate checks completed to ensure its validity.
- be using CT based 3D planning routinely for delivery of radical radiotherapy to lung cancers and performing dose calculations with one of the algorithms listed in the appendix (see section on ROSEL study Appendix A).
- have a suitable immobilisation device which maintains patient comfort yet limits patient motion. The reproducibility and stability of patient set up must be assessed
- have a strategy (e.g. abdominal compression, breath hold or gating) to reduce tumour motion to < 1cm
- have on-line imaging for tumor localisation and positional verification, e.g. an integrated kV conebeam CT or CT on rails. The co-incidence of the KV isocentre and MV isocentre must be checked at suitable intervals.

- be routinely using kV CBCT for radical lung cancer patients and be familiar with on line correction techniques
- have had appropriately trained physicians, radiographers and physicists to plan and deliver lung SBRT.

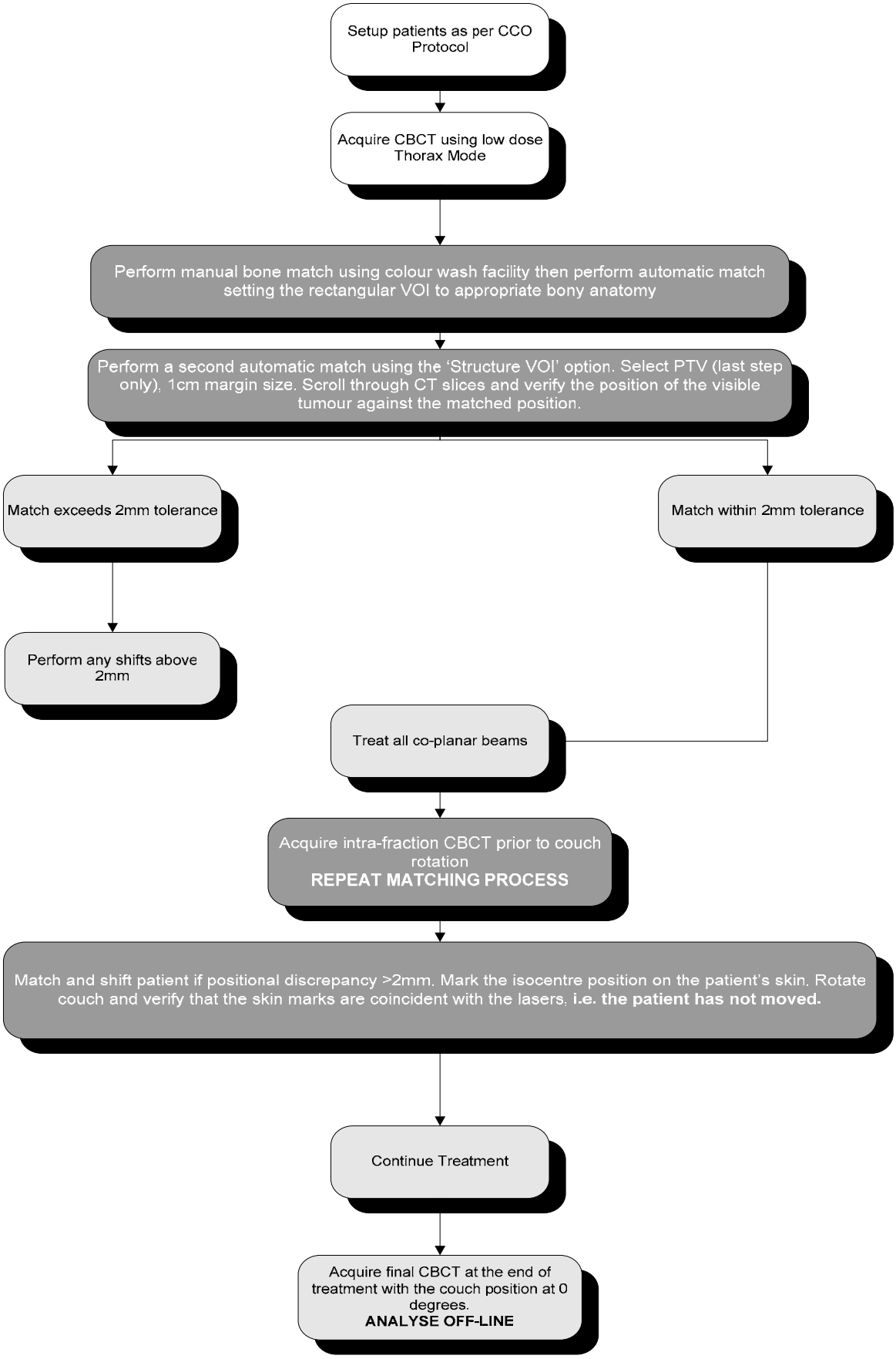
QA should also be undertaken to ensure that appropriate patients for this particular lung SBRT indication (e.g. meeting inclusion/exclusion criteria) are being selected by meeting of the clinical oncology team. Contours and RT plans should be reviewed by two clinicians to ensure that planning constraints are met as detailed in this protocol.

It is the responsibility of the clinicians who agree to treat patients with such a regimen to follow these patients in order to document local control and toxicity.

Appendix A: Suggested Elekta Synergy CBCT matching schedule



CCO Varian OBI Protocol



Appendix B: CTCAE v3.0 scoring system.

Symptom	Grade				
	1	2	3	4	5
Atelectasis	Asymptomatic	Symptomatic (e.g. dyspnea, cough) Medical intervention indicated (e.g. bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g. stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
Anorexia	Loss of appetite w/o alteration in eating habits	Altered oral intake with significant weight loss or malnutrition; Oral supplements indicated	Significant weight loss or malnutrition; iv fluids, tube feedings or TPN indicated	Life threatening consequences	Death
Bronchospasm/ wheezing	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	n/a	n/a
Dyspnoea	Dyspnoea on exertion, but can walk 1 flight of stairs without stopping	Dyspnoea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnoea with ADL	Dyspnoea at rest; Intubation/ventilator indicated	Death
Fatigue	Mild fatigue over baseline	Moderate/ causing difficult performing some ADL	Interfering with ADL	Disabling	N/A
FEV1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Hypoxia	n/a	Decreased O2 saturation with exercise (e.g. pulse oximeter <88%); Intermittent supplemental oxygen	Decreased O2 saturation at rest; Continuous oxygen indicated	Life-threatening; Intubation or ventilation indicated	Death
Nausea	Loss of appetite w/o alteration in eating habits	↓ oral intake w/o significant wt loss, dehydration or malnutrition; iv fluids < 24 hrs	Inadequate oral caloric or fluid intake; iv fluids, tube feeding or TPN indicated ≥ 24 hrs	Life threatening consequences	Death

Obstruction/ Stenosis of airway select: – Bronchus – Larynx – Pharynx – Trachea	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; Medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic, supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O2 indicated	Life-threatening; ventilatory support indicated	Death
Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Pulmonary fibrosis	Minimal radiographic findings (or patchy or bibasilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/ consoliation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
Pulmonary – Other	Mild	Moderate	Severe	Life-threatening; disabling	Death
Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Vomiting	1 episode in 24 hrs	2-5 episodes in 24 hrs; iv fluids indicated < 24 hrs	≥ 6 episodes in 24 hrs; iv fluids or TPN indicated ≥24 hrs	Life threatening consequences	Death

Appendix C: Data Collection form for patients undergoing SBRT (best converted into an excel sheet)

Demographics

Pt id

DoB

Sex

ECOG PS

Stage

Histology

Site

Size

Baseline lung func tests Fev1, FVC, DLCO, pO2

Reason against surgery: declined, unfit due to medical comorbidities

Follow up (at applicable times)

PS

Response

Toxicity CTC v3.0

FU lung function tests

Site of progression

Date of progression

Salvage treatment

Cause of death

Date of death

Lung SBRT Plan Assessment Form

Motion management (body frame, body fix, gating, not suitable)

Residual motion incorporated

Prescription dose (xGy/x#/xdays):

Prescription isodose line:

Dose Conformity

Minimum PTV dose	**Maximum PTV dose**	**Mean PTV dose**	**Vol(PTV) (cc)**	**Vol(100%) / Vol(PTV)**	**Vol(50%) / Vol(PTV)**	**Max dose >2cm**

Refer to the Lung SBRT guidelines for definitions of the above indices

Lung dose

MLD	**V30**	**V20**	**V15**	**V10**	**V5**

OAR dose

Organ	**Maximum point dose**	**Maximum dose to 1cc**
Spinal cord		
Oesophagus		
Ipsilateral Brachial Plexus		
Heart		
Trachea, Ipsilateral Bronchus		
Skin (5mm ring of tissue inside the patient contour)		
Small bowel (if applicable)		

Heart and Liver (if applicable) dose

Maximum Dose Received	**Portion of total organ volume**		
	1/3	**2/3**	**3/3**
Heart			
Liver			

Appendix D: Response Evaluation Criteria In Solid Tumours

(i) (RECIST) – Quick Reference Eligibility

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter >20 mm using conventional techniques or >10 mm with spiral CT scan.

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

METHODS OF MEASUREMENT

CT is the best currently available and reproducible method to measure target lesions selected for response assessment in lung cancers. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

BASELINE DOCUMENTATION OF "TARGET" LESIONS

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumour.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

RESPONSE CRITERIA

Evaluation of target lesions	
* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target lesions	Evaluation of non-target lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

(ii) ‘GREEN’ Criteria

The complete disappearance of all evidence of malignant disease or residual radiographic abnormalities assessed by chest CT-scan at 3 and 6 months after completion of RT, which then remains stable for an additional 6 months or more, qualifies as controlled local disease

Given that the RECIST criteria may be difficult to classify after SBRT the ‘Green’ criteria may be more appropriate and should be recorded in addition to RECIST.

Lung cancer, 2004; 11 (suppl 3) S11-13

Radiother Oncol, 2004. 71(2): p. 139-46 (EORTC guidelines)

Appendix E: Suggested Standards for SBRT & Published literature on QA for SBRT

Standard No.	Standard	Examples of evidence
A.1	Before the commencement of SBRT treatments the centre shall have carried out a number of planning studies and completed 'dummy-runs' of treatment planning and delivery. The results of these planning studies should be compared with those obtained by published data/ another department experienced in the use of the same equipment and techniques to ensure that adequate plan quality and accuracy is being achieved.	Records of test cases and results of inter-comparisons with other departments.
A.2	Within 6 months of commencing SBRT the centre should have undergone an independent external audit of its SBRT processes and in-house quality assurance. Such external audit would ideally take place within the context of a suitable clinical trial, but could also be arranged on an ad-hoc basis with another department which is delivering SBRT.	Records of an independent external audit.
A.3	Before commencing SBRT treatments the centre should have assessed their immobilisation device, online image guidance technology and proposed method of respiratory compensation to ensure they are adequate to maintain patients well mobilised in a comfortable position, reduce tumour motion to < 1cm and CBCT scans are of sufficient quality to allow soft tissue matching.	Staff training record for soft tissue matching, Record of tumour motion after using technique for respiratory motion compensation.
C.1	Tumour should be delineated on lung settings.	Protocol documentation
C.2	Normal tissue structures should be delineated as specified in the protocol. If needed radiology input may be beneficial.	Protocol documentation
C.3	Target volume and dose reporting procedures should comply with departmental protocol and the UK guidelines for SBRT.	Protocol documentation.
C.4	All patients receiving SBRT shall have clinical follow-up for a minimum of 2 years, and ideally for at least 5 years. Full records must be kept of all late toxicity using CTCAE v3.0. Any local recurrences should be documented and fully investigated to determine if they represent in-field or marginal failures.	Follow-up records for a sample of patients
C.5	There shall be an electronic patient record for each SBRT case consisting of planning images, structure sets, plan details and 3D dose-grids. Ideally these records should be stored in the form of DICOM-RT objects within an organisational PACS system.	Details of the electronic records system used.

M.1	Each department shall establish an SBRT core multi-disciplinary team consisting of, as a minimum, a clinical oncologist, a therapy radiographer and a radiotherapy physicist who will each act as professional lead for the relevant components of the service. The team will consist of named individuals agreed by the Head of Service. The lead clinical oncologist will act as overall clinical lead for SBRT and will be responsible for ensuring that the other standards are met.	Document agreed by the Head of Service with named individuals.
M.2	The implementation of SBRT shall form part of an agreed service development within the organisational business plan to ensure that adequate resources are made available.	Business plan agreed by Head of Service and senior management
M.3	There should be detailed documents defining the processes involved in selecting, outlining, planning, QA and delivering SBRT and follow up of patients.	Process documents agreed by the Head of Service
M.4	There shall be a regular multi-disciplinary review of all SBRT cases.	Minutes of review meetings
QA.1	Individual patient specific quality assurance measurements must be made for at least the first 10 patients.	Records of patient QA
QA.2	There should be a regular, documented, review of QA results.	Records of QA reviews
QA.3	There should be a documented procedure to be followed after software updates, upgrades or other significant changes to the SBRT system. The procedure will detail the additional QA required.	Procedure agreed by the HoS.
QA.4	There should be documentation supporting the choice of QA tolerance values e.g. data from an initial period of measurements with the local QA kit	Documentation
QA.5	There should be sufficient machine-based MLC QA to support the chosen level of patient specific QA, especially if per patient QA is an independent calculation, and vice versa	Details of machine specific SBRT QA procedures.
TE.1	Each member of the SBRT core team must be able to demonstrate appropriate specialist training in use of SBRT. Such training could take the form of attendance at an approved SBRT course or visit to a centre established in delivering SBRT to observe the various processes, in addition to significant clinical experience in the application of advanced 3D conformal radiotherapy.	Records of attendance at suitable courses/sites CVs of core team members
TE.2	In addition to a broad knowledge and experience of advanced radiotherapy members of the core team should have received detailed training relevant to the equipment that will be used within the centre.	Records of attendance at manufacturers approved training courses

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