THREE DIMENSIONAL CONFORMAL
RADIOThERAPY TREATMENT PLANNING FOR
NON-SMALL CELL LUNG CANCER

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ABSTRACT

The purpose was to determine whether new technological developments could improve radical radiotherapy for NSCLC. Patients treated with CHARTWEL to 60Gy were investigated.

3D Conformal Radiotherapy Treatment Planning

2D and 3D planning were compared in 24 patients. Dose volume histograms were constructed for planning target volumes (PTV), lung and spinal cord. 3D planning achieved a higher dose to the PTV due to a significant dosimetric advantage. Geometric coverage with 2D was adequate at the expense of higher doses to lung and spinal cord.

External Immobilisation Frame

An external metal immobilisation frame was validated with CT scanning. Alignment of internal and external anatomy occurred in all patients with the frame.

Active Breathing Control (ABC)

Intra- and inter-fraction variation with ABC and effect of ABC were assessed with CT scanning and the 3D radiotherapy treatment planning software. PTVs, doses to lung, spinal cord and oesophagus were compared for free breathing and ABC in 10 patients. ABC enabled better delineation of disease and normal structures and allowed reproducible breath holds over several weeks. Reduction in V20 occurred in all plans and maximum spinal cord dose in 80%. The reductions would give an extra margin of safety or could allow dose escalation.
Assessment of Lung and Oesophageal Morbidity

Acute and late lung (14 patients) and oesophageal (21 patients) morbidity were assessed. Although most developed radiological pneumonitis and spirometry generally decreased after treatment, dyspnoea did not necessarily develop. There was correlation between mean lung dose (MLD) and V20 and between PTV and the following: radiological pneumonitis score, MLD, V20.

Acute dysphagia occurred in most patients with full recovery by week 8. Maximum dysphagia score correlated with maximum dose to oesophagus but not length of oesophagus treated.

The results indicate that the dose limitations currently employed in the radiotherapy planning are safe and possibly conservative.
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DEDICATION

This thesis is dedicated to my parents, Mary and Howard, my daughters, Sophie and Corinne and my husband, Richard.
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Finally, and most importantly, I wish to thank Dr Ethan Lyn who first stimulated my interest in technical radiotherapy and to whom I am extremely grateful for training me to treat lung cancer patients with radical radiotherapy and for his support, help and advice.
SUMMARY OF ACHIEVEMENTS AND PUBLICATIONS

See personal bibliography overleaf for listing of papers published in/accepted for publication in peer reviewed journals, and proffered papers/posters presented at national and international scientific meetings.

Recipient of ESTRO Travelling Grant 2001
The following publications and presentations relate to work incorporated in this thesis:

3D Conformal Treatment Planning for Non-Small Cell Lung Cancer

Wilson E

Invited lecture presented at the Royal College of Radiologists’ CHART Study Day
Royal Marsden Hospital, London, 15th June 2000

The Application of Breathing Control for the Treatment of Lung Cancer with CHARTWEL


Presented to the American Association of Physics in Medicine, July 2000

Radical Radiotherapy for Non-Small Cell Lung Cancer: Current and Future Approaches

Wilson E

Invited lecture presented at St Thomas’ Hospital, London, 31st October 2000

Can the Radical Treatment of Inoperable Non-Small Cell Lung Cancer be Improved?

Wilson E

Invited Lecture to the William Beaumont Hospital, Royal Oak, Michigan, USA, 3rd July 2001
Active Breathing Control (ABC) in the treatment of non-small cell lung cancer (NSCLC) with CHART Week End Less (CHARTWEL)

**Wilson E, Williams J, Lyn E, Aird E**

Oral presentation to the 6th Biennial ESTRO Meeting “Physics for Clinical Radiotherapy” and “Radiation Technology for Clinical Radiotherapy” 19th September 2001, Seville, Spain

Radiotherapy & Oncology 2001;61:S63

Feasibility study of a custom-made immobilisation frame for treatment of patients with locally advanced non-small cell lung cancer (NSCLC) with CHART Week End Less (CHARTWEL)

**Williams J, Wilson E, Lyn E, Aird E**

Poster with Oral Presentation to the 6th Biennial ESTRO Meeting “Physics for Clinical radiotherapy” and “Radiation Technology for Clinical Radiotherapy” 17-20 September 2001, Seville, Spain

Radiotherapy & Oncology 2001;61:S66

Comparison of 2D and 3D radiotherapy in locally advanced non-small cell lung cancer (NSCLC) treated with CHART Week End Less (CHARTWEL)

**Wilson E, Williams J, Lyn E, Aird E**

Poster Presentation to the 6th Biennial ESTRO Meeting “Physics for Clinical radiotherapy” and “Radiation Technology for Clinical Radiotherapy” 17-20 September 2001, Seville, Spain

Radiotherapy & Oncology 2001;61:S99
CHART to CHARTWEL with neo-adjuvant chemotherapy

**Wilson E**, Lyn E, Williams J, Saunders MI


Book Chapter, Editors: Muers MF, Macbeth F, Wells FC, Miles A (In press)

Dose-escalation with CHARTWEL (Continuous Hyperfractionated Accelerated Radiotherapy Week-End Less) combined with neo-adjuvant chemotherapy in the treatment of locally advanced non-small cell lung cancer.

Saunders MI, Rojas A, Lyn BE, **Wilson E**, Phillips H

Clinical Oncology 2002;14:352-360

The Treatment of Lung Cancer

Invited lecture to the Lung Cancer Study Day, The Pasque Hospice, Luton, UK

29th January 2003

Three Dimensional Conformal Radiotherapy in the Radical Treatment of Non-Small Cell Lung Cancer.

**Wilson EM**

Clinical Oncology 2003 (In press)
2D vs 3D Conformal Planning in the Thorax

Wilson E

Invited lecture presented at the UK Radiation Oncology Teaching Course on Radiotherapy Planning in the Thorax, University of Bath, 10th April 2003

Clinical Oncology 2003 (In press)

Validation of Active Breathing Control in Patients with non-small cell lung cancer to be treated with CHARTWEL.

Wilson EM, Williams FJ, Lyn BE, Wong JW and Aird EGA


Comparison of 2 dimensional and 3 dimensional radiotherapy treatment planning in locally advanced non-small cell lung cancer treated with CHARTWEL.

Wilson EM, Williams FJ, Lyn BE and Aird EGA

Manuscript submitted to Radiotherapy and Oncology

CHART to CHARTWEL to chemotherapy and CHARTWEL in non-small cell lung cancer

Lyn BE, Wilson EM, Williams FJ, Saunders MI, Phillips H

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**Wilson E, Lyn E, Williams J**

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Radiotherapy & Oncology 2003 (In press)
STATEMENT OF ORIGINALITY

This thesis is based solely on original work carried out by the author between 1999 and 2002 whilst employed as a clinical research registrar in the Mount Vernon Centre for Cancer Treatment.

Design of the studies was by the author in liaison with the hospital departments of Medical Physics and Bioengineering. Patient selection and initial assessment were performed by the author, who was also responsible for the administrative aspects including organisation of the necessary pre-treatment investigations, hospital admission for neo-adjuvant chemotherapy, organisation of pre- and post-chemotherapy CT scans, volume drawing on the planning scans, follow-up assessments and toxicity gradings.

The author carried out data retrieval from case notes and investigations and performed the data analysis. The author prepared the manuscript and accompanying figures and performed the statistical analysis.
ETHICAL STATEMENT

The clinical studies described in this thesis received ethical approval by the Chairman of the Local Ethics Committee at Mount Vernon Hospital. All patients entered received full information and gave informed consent.
CHAPTER I.

INTRODUCTION: THE NATURAL HISTORY AND TREATMENT OF NON-SMALL CELL LUNG CANCER.

1.1 Natural history of Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the commonest malignancy in the Western world. In the United Kingdom there are about 42,000 new cases per year [1] and lung cancer causes approximately 40,000 deaths per year, 25% of all cancer deaths (Table 1.1).

Table 1.1. Incidence of lung cancer in a UK district according to age group [2]

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Incidence per 100,000 population per year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>All ages</td>
<td>100</td>
</tr>
<tr>
<td>75+</td>
<td>751</td>
</tr>
<tr>
<td>65-75</td>
<td>388</td>
</tr>
<tr>
<td>55-64</td>
<td>NC</td>
</tr>
<tr>
<td>45-54</td>
<td>NC</td>
</tr>
</tbody>
</table>

NC = not calculated (numbers too few)

Aetiology

90% of lung cancers are attributed to smoking and there is a direct relation to the cumulative number of cigarettes smoked in a lifetime (duration and number) [3]. Up to 2% of cases are related to passive smoking. Asbestos exposure increases the risk of lung cancer by a factor of 5 in the non-smoker and a factor of 50 in the smoker. There
is a similar synergistic relationship between smoking and exposure to radiation and arsenic. Other associations include radon; air pollution; occupational exposure to chromium, nickel or PVC; working in the coal and gas industry and previous lung disorders (tuberculosis and fibrosing alveolitis predispose to adenocarcinoma).

Pathology

NSCLC comprises 75% of all cases of lung cancer (Table 1.2). It is well known that NSCLC has an aggressive behaviour and 83% of patients die in the first year. Overall prognosis for NSCLC tends to be dismal whatever the therapeutic approach and long-term survival ranges from 8 to 15% [4]. There is scope for improvement in the results of radical treatment.

Table 1.2. WHO classification of lung cancer (1981)

<table>
<thead>
<tr>
<th>WHO</th>
<th>HISTOLOGY</th>
<th>%Worldwide</th>
<th>%UK</th>
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<tbody>
<tr>
<td>I</td>
<td>Squamous cell carcinoma</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>II</td>
<td>Adenocarcinoma</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>III</td>
<td>Large cell carcinoma</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>IV</td>
<td>Small cell carcinoma</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>(carcinoid, adenosquamous,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>adenoid cystic, mucoepidermoid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TX</strong></td>
<td>Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T0</strong></td>
<td>No evidence of primary tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tis</strong></td>
<td>Carcinoma in situ</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td>Tumour ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)</td>
<td></td>
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<tr>
<td><strong>T2</strong></td>
<td>Tumour with any of the following features of size or extent: &lt;br&gt; - &gt; 3 cm in greatest dimension &lt;br&gt; - Involves main bronchus ≥ 2 cm distal to the carina &lt;br&gt; - Invades visceral pleura &lt;br&gt; - Associated with atelectasis or obstructive pneumonitis which extends to the hilar region but does not involve the entire lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>Tumour of any size which directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus &lt; 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung</td>
<td></td>
<td></td>
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<tr>
<td><strong>T4</strong></td>
<td>Tumour of any size which invades any of the following: mediastinum, heart, great vessels, carina, trachea, oesophagus, vertebral body; or separate tumour nodule(s) in same lobe; or tumour with malignant pleural effusion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NX</strong></td>
<td>Regional lymph nodes cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N0</strong></td>
<td>No regional lymph node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>Metastasis in Ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and/or intrapulmonary nodes including involvement by direct extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N2</strong></td>
<td>Metastasis in Ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
<td></td>
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</tr>
<tr>
<td><strong>N3</strong></td>
<td>Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MX</strong></td>
<td>Distant metastasis cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>M0</strong></td>
<td>No distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>M1</strong></td>
<td>Distant metastasis, includes separate tumour nodule(s) in different lobe (ipsilateral or contralateral)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Primary tumour (T), regional lymph node metastasis (N), tumour node (lymph) metastasis (M) subsets.*
Table 1.4. International staging system, groupings of TNM subsets and survival (1997 version) [6].

<table>
<thead>
<tr>
<th>Stage groupings</th>
<th>TNM subset</th>
<th>Percentage of cases</th>
<th>% Survival after treatment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Stage I A</td>
<td>T1 N0 M0</td>
<td>13</td>
<td>91</td>
</tr>
<tr>
<td>Stage I B</td>
<td>T2 N0 M0</td>
<td>23</td>
<td>72</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T1 N1 M0</td>
<td>0.5</td>
<td>79</td>
</tr>
<tr>
<td>Stage II B</td>
<td>T2 N1 M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 N0 M0</td>
<td>7</td>
<td>59</td>
</tr>
<tr>
<td>Stage III A</td>
<td>T1-3 N2 M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 N1 M0</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Stage III B</td>
<td>T4 Any N M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any T N3 M0</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T Any N M1</td>
<td>27</td>
<td>19</td>
</tr>
</tbody>
</table>
1.2 Surgery

Surgical resection is recommended for patients with Stage I (T1-2N0M0) or II (T1-2N1M0) disease (Table 1.3, 1.4). Some patients with stage IIIA disease (T3N0), due to chest wall involvement and without nodal involvement, may be effectively treated by surgery and 5 year survival rates close to 50% may be achieved following en-bloc resection [7]. Other patients with stage III disease and positive nodes have a poor prognosis, resulting in overall 5-year survival rates lower than 15% following surgery (Table 1.4).

Surgery is appropriate for patients who are relatively fit, have adequate respiratory reserve as assessed with FEV1 and FVC measurements (usually FEV1 > 1.5 litres and FEV1/FVC predicted values of > 40% after resection), no evidence of metastases and no co-morbidity that might prejudice survival.

The surgical procedure of choice depends on the site and stage of disease:

- **Wedge or segmental resection** for small peripheral Stage I tumours (< 2 cm)
- **Lobectomy** for central tumours lying completely within one lobe. If the lobar bronchus is involved, an adequate clearance margin is required. Nodal involvement limited to the intrapulmonary or immediate hilar region can be removed en bloc for Stage II disease
- **Pneumonectomy** for fit patients with more extensive disease, including tumours within the orifice of a lobar or main stem bronchus or involving more than one lobe. Extended pneumonectomy is indicated in the presence of mediastinal node involvement (N2 or Stage III) if limited to ipsilateral tracheobronchial or subcarinal nodes
• Where disease extends proximally to major vessels radical pneumonectomy with intrapericardial ligation of vessels is technically possible
• Bronchoplastic or sleeve resection for carinal tumours

Prognostic factors in resectable NSCLC include:

• Performance status
• Weight loss (survival 74% if absent, 41% if present)
• Size of primary (survival of 70% for T1 and 50% for T2)
• Differentiation and lymphatic or vascular invasion

Unfortunately, most patients present with locally advanced or advanced disease and a therapeutic resection is achieved in only a minority of patients (Figure 1.1).

Figure 1.1 Outcome of patients referred for surgery (n=100)

100

25
operable

15
N2 at mediastinoscopy

60
inoperable

5
cure

15
local or distant recurrence

5
inoperable at thoracotomy

Surgery for NSCLC carries a 5% overall operative mortality risk and causes significant morbidity. 10% of patients have major life threatening complications and 50% have persistent pain at the thoracotomy site for 1-4 years. Quality of life is temporarily impaired, returning to pre-operative baseline after 6 months.
Stage IIIB disease is currently considered unresectable in the United Kingdom, although some locally advanced initially unresectable IIIB tumours may become operable after induction chemotherapy. Transternal bilateral lymphadenectomy, extended to the supraclavicular areas if necessary, is technically feasible [8]. Superior vena caval invasion can be resected, with or without a prosthetic graft [9]. A sleeve resection is possible in patients having tumours situated on the tracheal carina, or the lower wall of the trachea, if not too extensive [10]. Some tumours invading the vertebral bodies can be resected via an en-bloc procedure, including partial or total vertebrectomy [11]. Pancoast's tumours are now operated on through a transmanubrial osteomuscular sparing approach, avoiding cosmetic and functional disadvantages of the former transclavicular approaches [12]. Tumours invading the implantation of pulmonary veins in the left atrium are resectable by lateral clamping and direct suture of the atrial wall. These extended resections are associated with an increased risk of postoperative complications compared to operations on early stage disease. Moreover, locally advanced disease carries a high chance of metastatic spread and careful selection of cases is thus essential.

**Neo-adjuvant and Adjuvant Radiotherapy**

Pre-operative radiotherapy for tumours considered initially operable was tested in randomised trials conducted 20 years ago and failed to show any benefit, but did show a clear increase in postoperative complications [13, 14]. The role of pre-operative radiation for locally advanced tumours (Stage III disease) has never been evaluated in a large-scale randomised trial. Some are proposing this approach for tumours of the superior sulcus due to the risk of mediastinal node involvement. In a phase II study, the Lung Cancer Study Group (LCSG) observed a response rate of 50% among 32 patients with Stage III disease treated with 44 Gy in 22 fractions. However, only 11 had a
resection and only one complete response was seen [15]. The available data is conflicting and thus pre-operative radiation is not currently recommended in routine practice.

Advantages of postoperative radiation include avoidance of delay in definitive treatment (surgery), avoidance of morbidity associated with pre-operative radiotherapy and precise knowledge of the tumour extent from operative and pathological findings to guide the radiotherapy. A review of the data from several randomised trials allows the following general conclusions to be made:

(i) There is no place for routine postoperative thoracic radiotherapy after a complete resection of a Stage I or II tumour as all randomised trials have failed to show any benefit in survival; the data are in good agreement on the pattern of failure (less than 10% local failure) [16, 17].

(ii) In contrast, for N2 disease the results of the LCSG and the Medical Research Council (MRC) trials suggested that postoperative radiotherapy decreased the risk of local relapse, but this did not translate into a survival benefit. This may reflect the small sample size of most trials with consequently weak statistical power; there were only 106 cases in the last published MRC trial.

(iii) The Post Operative Radiotherapy (PORT) meta-analysis of data on 2128 patients in nine randomised controlled trials showed that postoperative radiotherapy had an adverse effect overall survival being reduced from 55% to 48% [18]. Subgroup analysis showed that the adverse effect was greatest in patients with Stage I/II, N0-1 disease. In those patients with stage III, N2 disease there was no clear adverse effect. It appeared that postoperative radiotherapy should not be routinely used although the role of postoperative radiotherapy in the treatment of completely resected N2 tumours was not clear. However, the trials included many patients with Stage I disease who were
known to have a low risk of failure, details of type of surgery were not known, Co60 machines (sub-optimal for lung irradiation) were used in all trials except one, radiation dose and fractionation was not standardised, computerised planning was used in only one trial and in only two trials was inhomogeneity correction used. It is possible that post-operative radiotherapy using modern machines, treatment planning and fractionation would not be detrimental and therefore further research is warranted.

**Neo-adjuvant and Adjuvant Chemotherapy**

Chemotherapy may be added to surgery in an attempt to improve local control and eradicate latent metastatic disease. The benefits of pre-operative chemotherapy for patients with Stage I and II NSCLC are unknown because there have been no randomised trials. A current trial, LU22, in the UK is addressing the question and results are awaited. Almost all trials of pre-operative chemotherapy have investigated patients with Stage IIIA/B disease. They have been largely non-randomised trials, usually with cisplatin based regimens. Two randomised trials have compared neo-adjuvant chemotherapy followed by surgery with surgery alone in Stage IIIA NSCLC and both were closed early as there was a highly significant improvement in survival for patients in the neo-adjuvant chemotherapy arms [19, 20]. There has been criticism of the trials because of the early closure, small sample size, definitive diagnosis of Stage IIIA disease prior to treatment and imbalances of prognostic factors.

Meta-analysis of data from 14 randomised controlled trials involving a total of 4357 patients with NSCLC suggests that adjuvant chemotherapy after surgical resection does not improve survival. The hazard ratios for earlier trials using alkylating agents favoured surgery alone. For later trials using regimens containing cisplatin there was a small, but non-significant, absolute survival benefit of 5% at five years. [21].
In 2000 Keller reported a trial where 488 patients with completely resected Stage I or IIIA NSCLC were randomised to receive postoperative chemotherapy with cisplatin and etoposide administered concurrently with radiotherapy, or radiotherapy alone. There was no improvement in local control or survival with the concurrent chemoradiotherapy compared with radiotherapy alone [22]. NSCLC thus appears responsive to chemotherapy but the value of adjuvant chemotherapy to surgical resection remains unanswered and trials are ongoing.

1.3 Radiotherapy

Patients with localised NSCLC who are inoperable, either because of extent of disease or co-morbidity, or who decline surgery, may be suitable for treatment with radical radiotherapy. The role of radical radiotherapy in these cases has not always been universally accepted [23], although extended survival was reported as early as 1968 [24]. A review of more recent literature indicates that radical radiotherapy may offer the chance of long-term survival [25]. A multi-centre randomised trial compared a novel fractionation regime, Continuous Hyperfractionated Accelerated RadioTherapy (CHART), with conventional daily radiotherapy in patients with locally advanced NSCLC. Patients treated with CHART showed a significant improvement in survival [26]. This led the Department of Health, in its guidance for the treatment of NSCLC, to recommend CHART as the treatment of choice for early inoperable disease. [27].

CHART

Laboratory and clinical research showed that human lung cancers have a capacity for rapid cellular proliferation. Growth of cancers was previously estimated using the Volume Doubling Time (VDT), the time taken by the tumour to double in volume,
which was usually weeks or months. The potential doubling time (Tpot) is the time taken by a tumour cell population to double in number, correction being made for the age distribution of the cell population. It may be measured in vivo in human tumours from a single biopsy using incorporation of bromodeoxyuridine (BrUdR) and flow cytometry and Tpot is considered to be a better reflection of the biological activity of the cancer than VDT. The median Tpot was 7 days in 28 human lung cancers and in some specimens it was as low as 1.6 days [28]. The implication in clinical practice of such short potential doubling times is that cancers may repopulate during a course of conventional daily radiotherapy where 2 Gy daily fractions are given Monday to Friday with weekend breaks to a total dose of about 60 Gy in 6 weeks. Acceleration of radiotherapy with earlier completion of treatment could improve results. However, experience showed that acceleration was associated with increased acute toxicity. The severity of reactions required breaks in treatment, to allow reactions to subside before treatment could be continued, and such interruptions defeated the principle of acceleration. For CHART, hyperfractionation (the use of smaller-than-conventional fractions) was utilised to reduce the acute reactions with the additional benefit of reduced late normal tissue toxicity. In CHART 1.5 Gy fractions are administered 3 times per day at 0800, 1400 and 2000 hrs, to a total dose of 54 Gy. Treatment is given 7 days per week without breaks for weekends and is completed in only 12 days compared to 40-42 days for a conventional 6-week course of treatment.

At Mount Vernon Hospital in a pilot study of 76 patients with NSCLC, the CHART regime showed improved local tumour control and survival compared to historical controls. A multi-centre randomised trial was performed between 1990 and 1995 comparing CHART with conventional radiotherapy (60 Gy in 30 fractions over 40 days) in patients with locally advanced inoperable NSCLC. Five hundred and sixty three patients were randomised. All patients were planned with computed tomograms
(CT) and lung correction was used and all participating centres were subject to quality assurance. In those patients treated with CHART there was an absolute improvement in two-year survival of 9% (29% compared with 20%, \( p=0.008 \)) and a 21% reduction in the relative risk of local progression \( (p=0.033) \). Subgroup analysis (predefined) showed that in those patients with squamous carcinoma (81% of cases), there was an absolute improvement in survival of 13% (from 20 to 33 %, \( p=0.0007 \)) at two years and a 27% reduction in the risk of local progression \( (p=0.012) \). Furthermore, in squamous carcinoma there was a 25% reduction in the relative risk of local and/or distant progression \( (p=0.025) \) and a 24% reduction in the relative risk of metastasis \( (p=0.043) \).

There were no important differences in acute or late morbidity. However, since the primary tumour was the cause of death in 61% of the cases treated with CHART [26], there was a need to improve local control: possible methods include dose escalation, addition of cytotoxic chemotherapy and improvement in the accuracy of planning and administration of treatment.

**CHART Week-End-Less (CHARTWEL)**

As centres found treatment at weekends difficult to implement, the CHARTWEL regime was designed and the dose escalated. It was desirable to maintain the interfraction interval to allow repair of normal tissue damage, and the low dose per fraction, to reduce acute and late toxicity. Dose escalation was therefore achieved by increasing the total number of fractions. As CHART was administered in only 12 days, there was scope to increase the number of fractions and overall treatment time without endangering the advantage of acceleration. In CHARTWEL treatment was given three times daily at 0800, 1400 and 2000 hrs, as in CHART, but Monday to Friday without treatment at weekends. Dose was escalated from 54 Gy in 16 days to 57 Gy, then to 58.5 Gy and then 60 Gy in an overall time of 18 days. Sixty four patients with locally
advanced NSCLC were treated. Analysis of toxicity data showed that dysphagia due to acute oesophageal mucositis was more severe in those patients treated with higher doses to 60 Gy but this was not clinically apparent and there was no late damage. After 6 months there was a higher incidence of Grade I pulmonary toxicity. No cases of radiation myelitis, oesophageal strictures or Grade II or III lung morbidity were seen. Retrospective comparison of tumour response with the previous CHART trials indicated that the increase in overall time from 12 to 18 days did not compromise tumour control or survival [29].

By contrast, the Radiation Therapy Oncology Group (RTOG) randomised phase I/II trial of dose escalation from 60 Gy to 79.2 Gy with hyperfractionation showed no increase in acute or late morbidity, possibly because the overall treatment time was sufficiently long to allow for full compensatory proliferation in the mucosa. There was an improvement in 2 year survival with hyperfractionated radiotherapy (treating twice daily at 1.2 Gy per fraction, ten fractions per week) at a total dose of 69.6 Gy compared to standard radiotherapy giving a 2 year survival of 29% and 13% respectively ($p=0.02$). There was no survival advantage at doses higher than 69.6 Gy [30].

**Chemotherapy**

Chemotherapy may be combined with radiotherapy, as with surgery, in an attempt to improve local tumour control, eradicate latent metastatic disease and improve survival. The chemotherapy may be neo-adjuvant, concomitant, adjuvant, or a combination.

(i) **Neo-adjuvant chemotherapy**

Several randomised trials, initiated in the mid 1980s, have tested the use of induction chemotherapy followed by definitive radiation compared with radiation alone as a curative approach in patients with previously untreated stage III NSCLC [31-36]. All were modest in size but three trials reported a survival benefit for sequential
chemoradiation. These were the French CEBI trial [32,35,36], the Cancer and Leukaemia Group B (CALGB) 8433 trial [31, 33] and the intergroup trial within the RTOG 8808/Eastern Cooperative Oncology Group (ECOG) 4588/Southwest Oncology Group (SWOG) trial [34]; survival was poor, as shown in Table 1.5.

Table 1.5: Neo-adjuvant chemotherapy and radiotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>No.</th>
<th>RT</th>
<th>Chemo.</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEBI Le Chevalier 1994 [36]</td>
<td>177</td>
<td>65Gy</td>
<td>None</td>
<td>14% (2yr)</td>
</tr>
<tr>
<td>(RCT)</td>
<td>176</td>
<td>65Gy</td>
<td>Induction Vindesine, cyclophosphamide, cisplatin, CCNU x3, + x3 post RT</td>
<td>21% (2yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.02</td>
</tr>
<tr>
<td>CALGB 8433 Dillman 1996 [33]</td>
<td>77</td>
<td>60Gy in 30Fo.d.</td>
<td>None</td>
<td>7% (5yr)/6% (7yr)</td>
</tr>
<tr>
<td></td>
<td>78</td>
<td>60Gy in 30Fo.d.</td>
<td>Weekly vinblastine for 5 wks and cisplatin wk 1 and 5</td>
<td>19% (5yr)/13% (7yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.007</td>
</tr>
<tr>
<td>RTOG 8808/ECOG 4588/SWOG Sause 2000 [34] Ph III</td>
<td>458</td>
<td>60Gy in 30F o.d.</td>
<td>Weekly vinblastine for 5 wks and cisplatin wk 1 and 5</td>
<td>5% (5yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.04</td>
</tr>
<tr>
<td></td>
<td>69.6Gy at 1.2Gy b.i.d.</td>
<td>Weekly vinblastine for 5 wks and cisplatin wk 1 and 5</td>
<td>6% (5yr)</td>
<td></td>
</tr>
</tbody>
</table>

Three meta-analyses of phase III randomised trials evaluating chemotherapy and radiation versus radiation alone were performed in the mid 1990s [21,37,38]. These analyses provided substantial additional statistical evidence in support of the utilisation of induction cisplatin-containing chemotherapy followed by radiation compared to radiation alone. It was also observed in these studies that the incidence of distant metastases was significantly lower in the chemoradiation-treated group, suggesting that chemotherapy was affecting distant micrometastatic disease sufficiently to improve
overall survival. Local control, however, remained a major problem requiring better systemic therapy or more effective radiotherapy.

(ii) Concurrent chemotherapy and radiotherapy

Three trials, reported in the 1990s, showed improvement in survival in patients treated with concurrent chemo-radiotherapy detailed in the Table 1.6 [39, 40, 41].

Table 1.6: Concurrent chemotherapy and radiotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Patients</th>
<th>RT</th>
<th>Chemo.</th>
<th>Survival (3 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schaae-Koning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1992 [39]</td>
<td>114</td>
<td>55Gy split course</td>
<td>None</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>55Gy split course</td>
<td>Weekly cisplatin</td>
<td>13% p=NS</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>55Gy split course</td>
<td>Daily cisplatin</td>
<td>16% p=0.009</td>
</tr>
<tr>
<td>Jeremic 1995 [40]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>64.8Gy,1.2Gy bid</td>
<td>None</td>
<td>6.6%</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>64.8Gy,1.2Gy bid</td>
<td>Carboplatin d1+2 and etoposide d1-3 of each week</td>
<td>23% p=0.0027</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>64.8Gy,1.2Gy bid</td>
<td>Carboplatin d1+2 and etoposide d1-5 of weeks 1, 3 and 5</td>
<td>16% p=NS</td>
</tr>
<tr>
<td>Jeremic 1996 [41]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>69.6Gy,1.2Gy bid</td>
<td>None</td>
<td>9% (4y)</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>69.6Gy,1.2Gy bid</td>
<td>Daily carboplatin and etoposide</td>
<td>23% (4y) p=0.021</td>
</tr>
</tbody>
</table>

Concurrent use of chemotherapy and radiotherapy was feasible. These randomised trials and a myriad of phase II studies have supported, but have not proven, the principle of concurrent chemo-radiotherapy and trials continue.

(iii) Sequential versus concurrent chemo-radiotherapy

In 1999, Furuse et al [42] reported the Japanese experience with a phase III trial evaluating sequential chemotherapy followed by radiation versus immediate concurrent treatment as shown in Table 1.7.
Table 1.7: Sequential versus concurrent chemo-radiotherapy

| Trial            | No. Patients | RT          | Chemo.           | Survival % 5 yr | p-
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Furuse 1999 [42]</td>
<td>156</td>
<td>56Gy split course</td>
<td>Concurrent MVP x 2</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>158</td>
<td>56Gy standard</td>
<td>Induction MVP x 2</td>
<td>8.9</td>
<td>0.04</td>
</tr>
<tr>
<td>RTOG 92-04</td>
<td>81</td>
<td>63Gy standard</td>
<td>Induction VP Concurrent P</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Komaki 2002 [43]</td>
<td>82</td>
<td>69.6Gy bid</td>
<td>Concurrent PE</td>
<td>16</td>
<td>0.39</td>
</tr>
<tr>
<td>Randomised Phase II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These, and other, phase II and III trials, some reported in abstract form only, continued to give conflicting results. Concurrent chemo-radiotherapy may be superior to sequential treatment, but in those trials with positive findings, the results were specific to the chemotherapy and radiotherapy regimes used and did not necessarily prove the principle. Toxicity was markedly increased with concurrent treatment, with about 30% of patients suffering grade 3 or 4 toxicity, and long term survival was only similar to or less than that for accelerated radiotherapy alone. Acute toxicity was already increased with accelerated radiotherapy. If concurrent chemotherapy was to be given with CHARTWEL there was the possibility of additive or synergistic effects on normal tissues precipitating more severe early and/or late morbidity [44]. Reduction of dose or interruption of radiotherapy, the definitive treatment, due to such toxicity could endanger potential cure.

Accelerated radiotherapy is completed quickly, within 2 weeks for CHART and 3 weeks for CHARTWEL to 60 Gy. Should concurrent chemotherapy be given at the beginning of each week of treatment the total dose of chemotherapy given would be low.
and although there might be enhancement of the radiotherapy with improved local control, systemic effects would not be expected.

Administration of the chemotherapy in the neo-adjuvant setting would allow full doses of chemotherapy and radiotherapy to be given.

Following the successful CHART trial described above, the CHARTWEL regime was developed and in a Phase I trial the total dose of radiotherapy was increased from 54 Gy in 16 days to 60 Gy in 18 days without undue increase in toxicity. It was then postulated that the addition of chemotherapy might improve results and another Phase I/II study was started where 3 courses of neo-adjuvant chemotherapy using the MIC regime containing Mitomycin C, Ifosphamide and Cisplatinum, were administered at 21 day intervals followed by CHARTWEL to 60 Gy. Later, the chemotherapy was changed to a regime using the newer agents; Paclitaxel and Carboplatin (PC). Again, 3 courses were given at 21 day intervals followed by CHARTWEL. Patients who were referred from distant centres received neo-adjuvant chemotherapy at their local centres using regimes with which their physicians were familiar, usually MVP -Mitomycin C, Vinblastine and Cisplatinum or NP -Navelbine and Cisplatinum. If it was thought that the patient would not tolerate chemotherapy (or he or she declined chemotherapy) they were treated with CHARTWEL to 60 Gy to accrue Phase II data for accelerated radiotherapy without chemotherapy.

Overall survival at three years was 47% for the 33 patients who had been treated with neo-adjuvant chemotherapy and CHARTWEL compared with 30% for the 55 patients treated with CHARTWEL alone as shown in Table 1.8 and Figure 1.2. There was no significant increase in dysphagia [45].
Table 1.8: Overall survival for patients with NSCLC treated with CHARTWEL ± neo-adjuvant chemotherapy.

<table>
<thead>
<tr>
<th>Treatment given</th>
<th>Number at risk</th>
<th>1-year survival (%)</th>
<th>2-year survival (%)</th>
<th>3-year survival (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60Gy</td>
<td>21</td>
<td>75</td>
<td>40</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>60Gy alone</td>
<td>55</td>
<td>78</td>
<td>47</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>60Gy+chemotherapy</td>
<td>33</td>
<td>59</td>
<td>47</td>
<td>47</td>
<td>awaited</td>
</tr>
</tbody>
</table>

Figure 1.2: Overall survival for patients with NSCLC treated with CHARTWEL ± neo-adjuvant chemotherapy.
(iv) Neo-adjuvant chemotherapy followed by concurrent chemo-radiotherapy

There are hypothetical reasons to combine neo-adjuvant chemotherapy with concurrent chemo-radiotherapy. By using 2 cycles of induction chemotherapy and then 2 additional cycles concurrent with conventional daily radiotherapy, the total exposure to chemotherapy is essentially doubled without prolonging the overall duration of treatment beyond that for sequential chemotherapy followed by radiotherapy. The additional chemotherapy may enhance the systemic effect.

Table 1.9: Neo-adjuvant chemotherapy followed by concurrent chemo-radiotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Patients</th>
<th>RT</th>
<th>Chemo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9431</td>
<td>60</td>
<td>66Gy standard</td>
<td>Paclitaxel/Cisplatin</td>
</tr>
<tr>
<td>Randomised phase II</td>
<td>58</td>
<td>66Gy standard</td>
<td>Vinorelbine/Cisplatin</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>66Gy standard</td>
<td>Gemcitabine/Cisplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Induction (x2), full dose + concurrent,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>reduced dose for all above</td>
</tr>
<tr>
<td>CALGB 39801</td>
<td>Accruing</td>
<td>66Gy standard</td>
<td>Paclitaxel 50mg/m2/Carboplatin AUC2-</td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
<td></td>
<td>weekly x7 during RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66Gy standard</td>
<td>Induction full dose PC x2 followed by</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>concurrent PC as above</td>
</tr>
</tbody>
</table>

The trials shown in Table 1.9 and other Phase III studies are in progress trying to determine whether the use of induction chemotherapy followed by concurrent chemo-radiotherapy will result in improved survival compared with immediate chemo-radiotherapy alone. Results are awaited.

(v) Adjuvant chemotherapy

The “bulk” of latent metastatic disease, locally or systemically, is likely to be least for post-operative patients where disease has been completely resected. That post-operative chemotherapy has not improved survival suggests that chemotherapy is unlikely to be
curative in NSCLC. Any viable disease remaining after radical radiotherapy is unlikely to be eradicated by chemotherapy. In addition, the tumour blood flow may be impaired by the radiotherapy, reducing drug access to the primary tumour. Perturbation of the tumour cell population by the radiotherapy may also lead to resistance to the chemotherapy. For these reasons adjuvant chemotherapy after CHARTWEL was not planned.

The optimal chemotherapy or radiotherapy regime has not yet been found. It is hoped that definitive information on optimal scheduling of chemotherapy and radiation and the integration of newer agents into non-surgical treatment of patients with locally advanced NSCLC will become available soon.

1.4 Three-Dimensional Conformal Radiotherapy to Treat Non-Small Cell Lung Cancer

There is scope for improvement in the results of radical radiotherapy to treat NSCLC. Arriagada et al found that local control at follow up bronchoscopy was less than 20% one year after radical radiotherapy [46]. Three-dimensional conformal radiotherapy (3D CRT) allows shaping of treatment fields and dose distribution to the target volume with the aim of delivering a high dose to disease and minimal dose to adjacent normal tissues: lung, spinal cord, heart and oesophagus.

Saunders et al have shown that the use of the novel fractionation method, CHART, has led to improved local tumour control and survival for inoperable NSCLC [26]. The CHARTWEL dose escalation study demonstrated that escalating the dose from 54 to 60 Gy did not cause significant increase in acute or late morbidity and suggested that omission of the weekend treatment did not compromise results [29]. Two-dimensional (2D) radiotherapy treatment planning was used in those studies. In 2D planning a composite volume, allowing a margin for microscopic extension, organ motion and set-up errors, was drawn around disease on a central or near central slice of the planning CT
scan. The 2D volumes were usually only drawn on a few slices and there was no
interaction between the information on the different slices to account for electron scatter
making the dosimetric information less complete in 2D compared with 3D planning.
It has been suggested that improving local control by optimisation of the radiotherapy,
with better localisation and delivery of dose to tumour and further sparing of normal
tissues, could have a greater effect on survival than trying to improve the treatment of
microscopic metastases with chemotherapy [47].
In 3D CRT regions of interest are marked on every slice of the planning CT scan. The
planning system then creates a complete picture of the disease that may be viewed in
three dimensions.
Conformal shielding may be provided by divergent customised blocks or multi-leaf
collimators (MLCs). The treatment planning to ensure optimum positioning of
shielding is performed using beam’s eye view (BEV) apertures and suitable field
positioning to provide adequate dosimetric coverage of the PTV and optimal sparing of
normal tissues. 3D CRT planning systems make it possible to view the relationship
between normal structures and target volumes throughout the entire region being treated
by using the CT-based anatomical data to reconstruct organs within the computer
system. The BEV is able to rotate the reconstructed patient within the computer and
enable the planner to view the patient in the same orientation as a radiation beam
pointed in that direction [48]. Thus, by rotating the patient and examining the
corresponding graphic displays, beam orientations and shapes can be selected to ensure
that the target volume is covered by the beams and the normal tissues excluded as much
as possible. It can be shown that maximally separated beams give the best conformal
distributions but only if the directions of the beams are chosen to account for the shape
of the PTV and the surrounding normal structures.
The potential advantages of 3D technology, in addition to more accurate assessment of the tumour volume, include better coverage by external beams, improved assessment of doses to critical normal structures and disease from dose-volume histograms (DVHs) and tools to compare and assess rival plans [49, 50]. It is hoped that the use of 3D CRT with accelerated radiotherapy may further improve cure rate and reduce normal tissue morbidity by more accurate dose delivery to disease which may then facilitate dose escalation.

The process of 3D CRT for NSCLC includes data acquisition, delineation of regions of interest (macroscopic disease, tissues thought to contain microscopic disease and critical normal tissues), techniques to minimise errors due to set-up and organ motion, treatment planning, verification and implementation.

1.5 3D CRT Procedures

**Data acquisition: Tumour and patient data for planning**

Patients with inoperable NSCLC considered suitable for treatment with radical radiotherapy will usually have been diagnosed by bronchoscopy or guided needle biopsy and other investigations such as pulmonary function tests, CT scan of the chest and abdomen, and sometimes mediastinoscopy and/or positron emission tomography (PET) scans will have been performed. Information from all of these investigations is incorporated into the gross tumour volume (GTV) definition and the treatment planning.

**Imaging**

All forms of radiotherapy suffer from inherent inaccuracy of the diagnostic images. The resolution of the CT scans is a source of inaccuracy in the process of defining the GTV and normal structures. The transverse resolution (typically 1 mm) and slice thickness determine the size of the voxels. Keeping the slice thickness to a minimum
through the thorax is therefore important. However, the thinness of the slices used is limited by artefact caused by breathing and there is no advantage to use slices thinner than 5mm in a breathing patient. Respiratory movement during scanning leads to “step” irregularities and inaccuracy in the positions of the tumour and normal tissues. Blurring which occurs on slower sequential scans may cause the tumour to appear bigger but the blurring itself provides a margin of safety [51]. Modern spiral and multi-slice CT scanners are so fast that when a planning scan is done on a breathing patient the whole chest may be scanned in a limited part of the respiratory excursion. There may again be “step” irregularities. The rapidity of the scan may also be such that the cancer was not imaged near its mean position. Delivery of treatment planned on that position could then result in geometric miss. CT window display settings may be varied to improve delineation of the GTV [52]. Optimal settings have not been defined: central structures in the mediastinum are usually seen better by using soft tissue window settings, whereas peripheral tumours may be seen better using lung density settings. Whilst intravenous contrast injections may be helpful to define abnormal lymph nodes in the diagnostic CT scan, the use of contrast is not possible with some planning systems as it can alter the tissue density and interfere with dose calculation algorithms.

Direct use of magnetic resonance imaging (MRI) for radiotherapy planning purposes suffers from the following disadvantages:

- Geometric distortion of the image
- Absence of tissue density information
- Poor definition of bone
- Digitally reconstructed radiographs (DRRs) cannot be created
- Disease imaging is strongly dependent upon the scan settings

In the diagnostic setting MRI has the advantage of increased accuracy over CT in detecting chest wall invasion and nodal enlargement at the aorto-pulmonary window
and hilar regions [53]. However, there is image degradation due to motion artefact from
the beating heart and breathing. In radiotherapy treatment planning electron densities
are obtained from CT numbers which are not available from MRI scans. However, the
diagnostic value of MRI scans may be incorporated into the planning CT scans using
image fusion or image registration improving definition of disease from normal tissues,
and the CT data may be used for dose calculation and treatment verification.

PET is believed to have accuracy rates of 80-100% in the detection of nodal metastases
compared with approximately 65% for CT and MRI and as a result has been shown to
increase the GTV by revealing previously unknown positive mediastinal nodes
necessitating treatment with larger fields [53]. However, PET may also reduce
treatment fields [54] by allowing distinction of atelectatic lung from tumour [55]. There
are problems again with motion artefact using PET as it can take up to 45 minutes to
take the PET scan and during this time the patient may move and is breathing freely.
Resolution on PET scans is poor but PET and CT image registration and fusion studies
are currently under investigation and may help to define the GTV more accurately [56-
61].

Target volume and normal tissue definition

When defining volumes for 3D conformal radiotherapy planning the volumes used are
as defined by ICRU report 50, 1993 [62] given in appendix 1 and its supplement ICRU

Definition of the GTV

The GTV is the original or visible extent of the disease. Previously, in 2D planning, a
composite volume (i.e. a planning target volume, PTV) was drawn around disease on
the planning CT scan, usually on a central or near central slice, with a margin to allow
for microscopic spread, organ motion and set-up error (Figure 1.3). It was possible to
check on other slices that disease had been encompassed in the composite PTV
although in 2D planning it was usual to draw the PTV and plan on a few slices only. In
3D planning the GTV is marked on every slice on which it is visible (Figure 1.4).
There is potential for error due to faulty definition of disease and intra- and inter-
observer variation. A study by Van de Steene et al [64] showed an unexpectedly large
inter-clinician variation with delineation of tumours varying by several centimetres.
Factors that are felt to hinder an unambiguous definition of GTV are:

- Difficulties in discriminating between tumour and atelectasis
- Difficulties in differentiating between normal structures, pathological structures
  and tumour
- The use of different CT window settings and partial volume effects
- Poor anatomical knowledge

A study by Giraud et al comparing GTV delineation by radiologists and radiation
oncologists revealed significant differences between the two groups with radiologists
tending to delineate smaller and more homogeneous volumes, especially for ‘difficult’
cases [65]. Delineation of target volumes and high-risk organs is a critical step during
the conformal radiotherapy procedure [66-70] and subsequent steps are dependent on
the GTV being correct. Shaping of fields and dosimetric decisions are exclusively
based on the delineated volumes of tumour and critical normal tissue and it has been
suggested by Giraud et al that radiation oncologists need better training in thoracic
imaging [65]. Collaboration between radiologists and oncologists would lead to
improved scanning protocols, optimal reporting of scans for oncologists, better
identification of disease, possibly using integration of different imaging modalities and
treatment planning. No clear data on clinical effects of inter-observer variation are
found in the literature. In lung cancer radiotherapy, increasingly high doses are given in
an attempt to improve tumour control in an environment where the cancer is in close
proximity to extremely sensitive normal tissues (lung) or dose limiting organs (spinal
cord and oesophagus). Clinical effects of variation in GTV definition as a result of systematic error through consistent misinterpretation of disease and normal tissues by a clinician or random fluctuation due to observer variation could lead to severe effects in lack of local control and acute and late morbidity. It may be inferred that site specialisation for radiologists and oncologists could lead to improved results.

Figure 1.3: 2D PTV outlined on a planning CT scan
Normal Tissue Constraints

Lung cancers are usually centrally located in the chest and are surrounded by normal tissues, lung, oesophagus, spinal cord and heart, with different tolerances to radiation.

(i) Spinal Cord Tolerance

The tolerance of the spinal cord for conventional radiotherapy with 2 Gy fractions delivered once daily is accepted to be 48 Gy which was the maximum dose allowed in the conventional arm of the CHART trial. For patients receiving accelerated regimens of treatment the spinal cord dose is lower. In the original CHART pilot study there were four cases of radiation myelopathy after CHART was given to treat head and neck cancer when the maximum spinal cord doses given were 45.2, 46.0, 46.6 and 48.3 Gy [71], although no such problems were seen in the lung cancer patients. Shortening the inter-fraction interval from 24 to 6-8 hours reduces the spinal cord tolerance by 10-15% [72]. Repair kinetics are slower for the spinal cord and use of interfraction intervals of less than 6 hours would not be recommended. Consequently in the randomised CHART
trial the absolute maximum dose to the spinal cord was 44 Gy for those patients receiving the CHART arm [26].

(ii) Oesophageal Tolerance

Acute oesophagitis is a common, although in most cases a manageable, side effect of radiotherapy to treat NSCLC. It is difficult to exclude the oesophagus from the treatment fields as disease is often centrally located. Estimates of oesophageal toxicity (TD 5/5) based on surveys of experienced clinicians have been reported as follows: 55 Gy for the entire organ, 58 Gy for two-thirds, and 60 Gy for one-third of the oesophagus irradiated [73]. Only a few reports [74-78] are available that focus on dosimetric or volumetric parameters as predictors of radiation oesophagitis. Maguire et al suggested that dosimetric models evaluating radiation-induced oesophagitis should consider the longitudinal and circumferential factors. However, they concluded that none of the parameters analysed was a significant predictor of radiation oesophagitis and the fact that their patient groups were heterogeneous in terms of treatment may have been a reason for this [74]. Langer et al [75] proposed that significantly higher rates of radiation oesophagitis would be seen in cases exceeding 16 cm of oesophageal irradiation compared with cases in which the treatment field is smaller. Choy et al [76] and Byhardt et al [77] could not demonstrate that length of oesophagus irradiated was predictive of radiation oesophagitis. Hirota et al carried out a study to establish dosimetric predictors of radiation oesophagitis in patients with NSCLC treated with a combination of carboplatin, paclitaxel, and radiotherapy and found that the length of oesophagus (total circumference) treated with > 45 Gy (LETT 45) and the percentage of oesophageal volume receiving >45 Gy (V45) were useful dosimetric predictors of radiation oesophagitis but the maximum dose in the oesophagus (Dmax) did not predict radiation oesophagitis [78]. Predictors of radiation oesophagitis require further investigation.
(iii) Lung Tolerance

Radiation-induced lung injury occurs in two phases: an early phase, radiation pneumonitis, developing 1-8 months after irradiation, which can be followed by a late phase, radiation fibrosis, which takes 6-24 months to develop and usually stabilises after two years [79, 80]. Mild radiation-induced pneumonitis may revert to normal, but the inflammatory response may also progress to distortion of the lung architecture and result in the late and irreversible phase of fibrosis [81]. The characteristic histological changes of pulmonary radiation fibrosis are progressive vascular sclerosis and interstitial changes.

The clinical consequence of radiation damage to the lung may vary from mild signs of dyspnoea and cough to lethal respiratory failure [79]. The late fibrotic phase may be asymptomatic, but sometimes chronic respiratory failure develops and the symptoms may persist for the life of the patient [80]. Radiation-induced lung injury is usually accompanied by a decrease of lung volumes: total lung capacity, vital capacity, residual volume, inspiratory capacity, tidal volume, and FEV1 [80, 82]. These decreases are first seen at 4-8 weeks after radiotherapy, and are maximal after 6-9 months [83, 84]. Graham et al found that a simple parameter, the percentage of lung volume that received greater than 20 Gy (V20), was related to the incidence of radiation pneumonitis [85]. In a dose volume histogram analysis a V20 of 32-40% resulted in 21-30% of patients developing Grade ≥ 2 pneumonitis (where steroids were needed for medical treatment) and at a V20 of greater than 40% over 30% of patients would develop Grade ≥ 2 pneumonitis [86]. Another parameter, the mean lung dose (MLD), also appears to correlate with the incidence of pneumonitis [87-89]. In a large 5-centre study of 540 patients, a dose-effect relationship was present between the MLD (NTDmean) and the incidence of radiation pneumonitis [90]. However, in that study the MLD was not
compared or evaluated with the V20 or the severity of pneumonitis; thus it is not known which of these parameters is more reliable and the issue remains under investigation.

Definition of the CTV

The clinical target volume (CTV) is a volume that contains the GTV and/or tissue with a significant probability of containing microscopic tumour extensions (subclinical disease), which has to be treated adequately to eliminate disease [91]. There are few proposed precise values for GTV to CTV margins for NSCLC in the literature. Graham et al estimated CTV margins to be 5 to 7mm [85, 88] whilst usually a value of 5mm is reported [66]. Giraud et al, from examination of 70 surgically resected NSCLC specimens, found that the mean value of the microscopic extension for squamous cell cancers and adenocarcinomas was 1.48mm and 2.69mm respectively. They have suggested that the usual margin of 5mm from GTV to CTV would only cover 80% of the microscopic extension for adenocarcinoma and 91% for squamous cell cancers and that margins of 8mm and 6mm, assuming a risk of error of 5%, are required to cover 95% of the microscopic extension for these cancers respectively [92]. Nodal areas having the potential to contain metastatic disease are outlined to form a subset of the CTV called elective nodal irradiation (ENI).

Definition of the PTV

Margins for Geometric Variations and Uncertainties

The definitions of GTV and CTV are as with ICRU Report 50 [62-appendix 1]. A further margin is then given, to allow for set-up error and organ motion, to create the planning target volume (PTV). Margins are also added to the CTV(s) to account for variations in tissue position, size and shape, as well as for variations in patient and beam
position, both intra-fractionally and inter-fractionally, to ensure uniform dose throughout the CTV (s).

The PTV has been specified with greater precision in the supplement to ICRU 50, ICRU 62 [63-appendix 2], to differentiate between internal movements and set-up inaccuracy. The internal margin (IM) definition has been added, to take account of physiological uncertainties such as those due to organ movements during breathing along with variation in the size, shape and position of the CTV during treatment, and the set-up margin (SM) has been added to take account of all uncertainties in patient positioning and alignment of the therapeutic beams during treatment planning and treatment sessions. Segregating the IM and SM within the PTV reflects the differences in the source of uncertainties. Underdosage of the CTV may result if inadequate margins are used (geometric miss). Set-up error and organ motion has necessitated the use of greater margins at the expense of normal tissues.

Rabinowitz et al reviewed, retrospectively or prospectively, simulator or portal films of 71 patients, of whom 16 had intrathoracic neoplasms. None of the patients had been immobilised during treatment. In the thoracic cancer category, the average inter-fraction variation on field margins and blocks was about 4-5 mm, and the average discrepancy between simulation and portal films was 6 mm. The worst discrepancy exceeded 10 mm in 32% of patients and 15 mm in 15% of patients [93]. Rudat et al measured positioning errors in 43 patients, of which 26 had intrathoracic neoplasms, by comparing simulator films with corresponding portal films. All underwent 3D conformal radiotherapy without the use of an immobilisation device. The mean positioning error in 2 dimensions (i.e. cranio-caudal and antero-posterior or medio-lateral depending on the orientation of the film) was 5.5 mm, and the mean positioning error in all 3 dimensions varied between 4 and 5 mm. As a consequence, changes in the respective dose-volume histograms (DVH) resulted in a loss of tumour control
probability (TCP) of 5% [94]. From these results it would appear that immobilisation may be of value and data on the improvement that can be achieved by the use of an immobilisation device is needed.

Lung tumours move significantly during quiet respiration, causing potential inaccuracies in treatment delivery [69, 95]. Stevens et al did not find tumour motion to be predictable by size or location of the tumour, or pulmonary function test results [96]. However, Ross et al [95], in an analysis of movement of intrathoracic neoplasms using ultrafast CT, found that tumour motion heavily depended on tumour location: whilst upper lobe tumours were almost always fixed, hilar and lower lobe tumours showed significant lateral motion (average 9.2 mm) for the former and cranio-caudal motion for the latter. All major geographic misses occurred in patients whose tumours moved 15 to 22 mm due to cardiac or respiratory motion [95]. Seppenwoolde et al [97] also investigated 3D motion of lung tumours during radiotherapy in real time with fiducial markers implanted in or near the tumour, and also found that tumour motion was greatest (12mm ± 2mm [SD]) in the cranial-caudal direction for tumours situated in the lower lobes and not attached to rigid structures such as the chest wall or vertebrae. For the lateral and anterior-posterior directions, tumour motion was small (2 ± 1mm) both for upper- and lower-lobe tumours. For tumours near the heart or attached to the aortic arch a measurable motion in the range of 1 – 4 mm was caused by the cardiac beat.

Chest wall movement also causes reference points to move which may lead to set-up errors.

The most accurate way of defining the PTV from the GTV is to “grow” a margin in three dimensions around the GTV. In planning, the margins for expansion of the GTV in millimetres in all dimensions to define the CTV and then the PTV are set and the 3D planning system performs the required expansions.
Another margin of specific interest in 3D conformal planning is the margin between the PTV and treated volume (TV) margin, which is effectively the margin between the PTV and the edge of the conformal shielding.

**PTV coverage**

The isodose level chosen as adequate to cover the PTV can vary from centre to centre. A value of 93% (relative to the prescription dose) as the isodose surface completely containing the PTV was suggested as the level of adequacy in the RTOG 93-11 study. When the 93% isodose completely contained the PTV there was “no variation” and “major variation” was scored when the 93% isodose contained less than 95% of the PTV.

**Conformal block/MLC penumbra**

Penumbra is dependent on beam energy, field size and depth. For a single beam produced by a modern linear accelerator the penumbra is dominated primarily by the range of secondary electrons generated in the tissue, which increases with increasing beam energy, and decreasing tissue density [98-103]. Consequently, the beam aperture margin should be increased for higher energy beams, and in the vicinity of low density regions, such as lung tissue and air cavities. It therefore becomes important to know the position of the 50% isodose curve with respect to the edge of the shielding device in order to determine accurate margins. For 6 MV photons in a lung phantom the open field penumbra is 11mm [104].

**PTV to TV margins**

When conformal blocks are used the PTV-TV margin (i.e. block margin) comprises the distance between the 50% isodose and the conformation isodose line (usually 95%).
There are no analogous displacement errors with MLC’s. A simple geometric method of positioning shielding is usually employed and a fixed margin is determined and added to the PTV on a BEV projection. The isodose that covers the PTV is made up from the contributions of several beams, so the optimal margin necessary depends on the dose contribution from each of the other beams.

**Dose calculations**

The calculations performed by 3D CRT planning systems are more accurate than 2D systems. The calculation algorithms are able to use pixel by pixel lung, bone and tissue density correction. The impact of wedges in both the x- and y-axis of a field can be displayed enabling tissue compensation in both of the principal planes. A full description of the planning software and dose calculations for 3D and 2D systems is described in Chapter 2, Methods: section 2.6.

**Evaluation of 3D plans**

3D systems utilize dose-volume histograms (DVHs), which may be cumulative or differential displayed in tabulated or graphical form (Figure 1.5a and b), and visual displays in the axial, sagittal, and coronal planes (Figure 1.6). Plans may be compared and the best selected for the individual case. The DVH is an innovation that provides accurate information concerning the percentage of an organ or target receiving a particular dose level making it possible to determine whether a target volume is being underdosed or a critical tissue overdosed. It is possible to use the data from DVHs to derive normal tissue complication probabilities [73, 105].
Figure 1.5a: Cumulative dose volume histogram

![Cumulative Dose Volume Histogram](image)

Figure 1.5b: Differential dose volume histogram

![Differential Dose Volume Histogram](image)
Figure 1.6: 3D PTV display viewed in axial, sagittal and coronal planes

Phase 1

Phase 2
Verification of 3D treatment plans

Day to day reproducibility is never perfect. Deviations from the ideal position, as defined on the treatment plan, are either systematic, due to discrepancies that occur during the preparation of the treatment plan, or random, resulting from day-to-day variations in patient position and organ motion. Port films, X-ray films taken on the treatment machine, are the usual technique available to assess field placement, block shape and position. However, they are inconvenient, time consuming and available for retrospective review only. The electronic portal imaging device (EPID) is now available for immediate evaluation of on-line portal images. EPID images are generated in digital form and image processing is possible. The quality of the image may be enhanced to make interpretation easier and comparison may be made with digital reference images such as digitally reconstructed radiographs (DRRs). Field placement may be audited providing feedback to the target volume definition process giving indication of the required margins that must be added to account for variability of set-up.

Quality Assurance (QA)

Conformal radiotherapy demands a high precision throughout the entire process, in the acquisition of data, definition of the treatment volumes, planning, verification and treatment delivery. Unless standards for all of these components are defined, the evaluation of outcomes and comparisons with standard techniques will remain difficult. Standards for QA in conformal radiotherapy have been proposed by the RTOG through phantom measurements.
1.6 Techniques to improve set-up and organ motion errors

**Immobilisation**

Patients with NSCLC are usually treated in the supine position as this gives greater stability. Immobilisation is essential to minimise set-up error (RTOG 9410) but at present no standard has been stipulated. Immobilisation devices have been designed to reduce major positioning errors and non-rigid body rotation whilst stabilising the relation between external skin marks and internal structures, to provide more comfort to the patient and to reduce the time for daily set-up. Commercially available devices include the Alpha-Cradle®, VacFix®, thermoplast and evacuated bags filled with beads or granular materials. There is no published data comparing immobilisation devices in the treatment of lung or any other intrathoracic cancers with radiotherapy.

At Mount Vernon Hospital an immobilisation frame, which was designed and built in-house, is in routine use [106].

**Organ Motion**

Methods of minimising error due to respiratory movement include gating, tracking, Deep Inspiration Breath Hold (DIBH) and Active Breathing Control (ABC).

Gating, or synchronising radiotherapy with a patient’s breathing, may be done either by controlling the patient’s breathing or through activation of the treatment beam during a specified range in the patient’s breathing cycle [107-109]. Kubo and Hill [110] reviewed the technical aspects of gated radiotherapy and concluded that sensors, verification systems, and beam delivery systems currently in use can be adapted for gated radiotherapy. Synchronising delivery of radiation with the respiratory cycle while the patient breathes freely can be used to deliver treatment at the same phase of each cycle. A variety of respiration sensors have been examined including a thermistor,
strain gauge, pneumotachograph, mask and airbag, and laser displacement [107, 109, 110]. Researchers at the University of California Davis Cancer Centre and Varian Associates have developed a breathing synchronised radiotherapy (BSRT) system, consisting of a breathing monitoring system (BMOS) and linear accelerator gating hardware and software [111]. The ideal treatment point where organ motion is stationary is defined from the BMOS signals and fluoroscopy. The authors have proposed that the BSRT system can be used to gate radiotherapy at breath hold (BH) or free breathing (FB). However, there will still be some movement of tumour while gating with free breathing which would need to be taken into account.

A group from the Memorial Sloan Kettering Cancer Centre has compared treatment plans generated from BH and FB scans for 5 patients with NSCLC [112]. Deep inspiration breath hold (DIBH) was performed utilising a slow vital capacity manoeuvre, using a spirometer. Compared to the FB plans, the DIBH technique, which incorporated reduced PTV margins in the treatment plans, showed that the volume of lung receiving more than 25 Gy was reduced by 30%, and that tumour immobilisation (reduced margins) alone reduced the volume by 18%. The same group subsequently published results on 7 patients receiving a total of 164 treatment sessions where DIBH alone without alteration of margins, potentially allowed dose escalation from 69.4 to 87.9 Gy [113].

Barnes et al. [114], in a dosimetric evaluation of lung tumour immobilisation using breath hold at deep inspiration, found that compared to FB conditions, at DIBH there was a mean reduction in V20 of 14.3% with the increase in lung volume alone, 22.1% with tumour immobilisation alone, the combined effect was 32.5%. This appeared to be patient dependent, and due to both the increased lung volume with DI and the PTV margin reduction with tumour immobilisation. However, DIBH could be uncomfortable for patients to maintain.
With the intention of addressing errors due to set-up and organ motion it was decided in this study to use the ABC technique developed at the William Beaumont Hospital by John Wong and colleagues [115] in conjunction with the immobilisation frame made at Mount Vernon Hospital which was designed to incorporate ABC. The principle of ABC is to arrest respiration, and hence tumour movement, temporarily at a chosen point in the respiratory cycle. Usually 75-80% of the vital capacity is chosen as this has been found to be comfortable for patients to maintain during breath-hold periods of up to 20 seconds [116]. Treatment planning and delivery may then be delivered in identical breathing conditions with minimal margins to account for breathing motion. By reducing motion artefact the size and shape of the GTV also has the potential to be reduced.

The aim of this thesis was to evaluate areas for improvement in the treatment of NSCLC with radical radiotherapy:

- 3D radiotherapy treatment planning aiming to give accurate and reproducible PTV coverage and lower doses to normal tissues compared to 2D radiotherapy treatment planning
- Accurate and reproducible immobilisation to improve set-up
- Gating with active breathing control (ABC) to prevent error due to organ motion

The 3D conformal radiotherapy planning system used was Pinnacle® version 4.2f (Pinnacle®, ADAC Laboratories, 540 Alder Drive, Milpitas, CA 95035, USA).

Normal lung and oesophageal morbidity for patients treated with 3D CRT were assessed to determine whether dose limitations for CHARTWEL were safe.
CHAPTER 2.

METHODS

2.1 Patient Eligibility

Patients with locally advanced, inoperable non-small cell lung cancer (NSCLC) were eligible for treatment with radical conformal 3D radiotherapy using the CHARTWEL regime if the following criteria were met:

- Inoperable NSCLC, confined to the thorax, which had been histologically or cytologically proven
- No evidence of pleural effusion
- No evidence of distant metastases including supraclavicular lymphadenopathy
- The site and volume of tumour within the chest were such that a radical course of radiotherapy could be given without exceeding normal tissue (lung and spinal cord) tolerances
- WHO performance status 0 or 1 (detailed in appendix 4)
- Adequate follow up was possible

The CHARTWEL protocol does not specify minimum requirements for respiratory function. An FEV1 of ≥ 1.50 litres is preferred but treatment may be given to patients with an FEV1 of 1.00 – 1.49 litres depending upon the site of disease.
2.2 Pre-treatment Investigations

Prior to treatment the following investigations were performed:

- Chest X Ray
- Bronchoscopy and/or guided needle biopsy or open biopsy of pulmonary masses.
- CT scan of the chest and also the upper abdomen to assess the liver and adrenal glands for metastatic disease
- Full blood count, serum urea and electrolytes, calcium and liver function tests
- Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) as determined by spirometry or formal pulmonary function tests

2.3 Treatment with chemotherapy before radiotherapy

Patients were treated in a Phase I/II study where 3 courses of neo-adjuvant chemotherapy using initially, the MIC regime containing Mitomycin C, Ifosphamide and Cisplatinum, or later, PC (Paclitaxel and Carboplatin), were administered at 21 day intervals followed by CHARTWEL to 60 Gy. Patients who were referred from distant centres received neo-adjuvant chemotherapy at their local centres using regimes with which their physicians were familiar, usually MVP (Mitomycin C, Vinblastine and Cisplatinum) or NP (Navelbine and Cisplatinum). If it was thought that the patient would not tolerate (or declined) chemotherapy they were treated with CHARTWEL to 60 Gy to accrue Phase II data for accelerated radiotherapy without chemotherapy.
2.4 Positioning of the Patient

The first five patients were positioned supine, without an immobilisation device, with arms and hands crossed above the head for the planning scans, verification in simulator and treatment. An external immobilisation frame was used for subsequent patients. The frame was designed and built in-house to improve set-up reproducibility, and thus avoid geometric miss and reduce dose to normal tissues. A knee roll was used for comfort and to enhance reproducibility.

**Immovilisation Frame**

The metal immobilisation frame was designed to improve set-up reproducibility and built in the Bioengineering department at Mount Vernon Hospital. The frame was made to be attached to the CT, simulator and treatment machine couches and to be accommodated within the CT aperture. Arms were supported and held in shoulder and elbow flexion by forearm rests adjustable for forearm length and in horizontal separation for shoulder width. Rotation of the forearm rests for comfort was possible. Vertically adjustable handgrips were attached separately to the main frame. All movements were continuously adjustable, and once optimal positions were achieved, settings from attached scales were recorded. Support for mouthpieces and tubing used for ABC and abort switches were incorporated into the frame. Figure 2.1a shows an annotated diagram of the frame and Figure 2.1b a model demonstrating the treatment position using the frame. Reproducibility of the frame was assessed using CT scans as described below.
Figure 2.1a – The Mount Vernon Immobilisation Frame

Figure 2.1b – Model demonstrating the treatment position using the frame attached to the couch in the CT scanner
2.5 Assessment of the immobilisation frame

Diagnostic and planning CT scans were performed before and after neo-adjuvant chemotherapy. Comparison of the pre- and post-chemotherapy scans of the 5 patients positioned without the frame and the first 5 patients positioned with the frame gave an indication of the ability of the frame to enhance reproducibility. The scans were compared by fusion achieved by manually aligning the vertebral bodies for each patient using Pinnacle®. An example of the fused pre-and post-chemotherapy scans without and with the frame is shown in Figures 2.2a and 2.2b respectively.

Figure 2.2a – Post-chemotherapy CT scan (greyscale) fused with pre-chemotherapy CT scan (blue) without the frame

![Figure 2.2a](image1)

Figure 2.2b – Post-chemotherapy CT scan (greyscale) fused with pre-chemotherapy CT scan (purple) taken with the frame

![Figure 2.2b](image2)
2.6 Planning Software

Multidata DSS® 2D planning system

(i) Calculation Theory – External Beams

The calculation module is based on the Memorial Sloan-Kettering Dose Distribution Calculation program and computes dose rate distributions of external x-ray and electron beams using tables of Tissue Phantom Ratios (TPR), Off Centre Ratios (OCR), and other relevant factors. The emphasis of the dose computation model is on the direct use of measured data rather than analytical functions.

The accuracy of the results may be limited by the fact that it is assumed that:

- All fields are square and rectangular fields are converted to equivalent square fields by use of a table.

- Both collimators lie at the same distance from the source with the result that the transverse and radial profiles are identical. In reality one pair of collimators will, out of necessity, be closer to the source than the other and the transverse and radial beam profiles will not be the same. Calculated off-axis doses would depend on the number and orientation of beam profiles entered into the beam database.

(ii) Inhomogeneities and Patient Curvature

Given that the human body is curved and has inhomogeneities the “exact” calculation of dose rate is impractical and therefore approximate empirical methods are used to estimate dose rates.

The Equivalent Path Length Method is the method of curvature and inhomogeneity used in RTP/2. The depth to a point is calculated by multiplying the physical depth (t) times the relative electron density of the material (r) and summing these products over the path and beam through the tissue. The effective depth is used in the tables of the TPR’s and OCR’s. The method of dose rate calculation, assumes that the dose rate at a given
point is affected by variations in density along the ray joining that point with the radiation source only and does not take into account any changes resulting from varying scatter conditions elsewhere in the body.

It is also possible to use the CT-image data to and perform the inhomogeneity correction on a pixel-by-pixel basis using a user-defined Hounsfield unit to density conversion table.

(iii) **Standard Beam Modifiers**

The presence of a beam modifier, such as a wedge, causes an attenuation in the dose rate while shifting the main energy of the beam. In the calculation of dose rate to a point, modifiers are accounted for through the use of a modifier transmission factor.

The profiles of modifiers are stored for the maximum field size. These profiles contain the Modifier Transmission factors and beam hardening correction factors. During the calculations, the system will take these profiles from the beam library and divide them by the set of open field profiles for the same field size at the same depths to yield the transmission profiles. If the transmission of the modifier varies with field width, then the Modifier Transmission Factor (MF) is adjusted by the Modifier Output Factor which represents the change in transmission width field size.

**3D Pinnacle® version 4.2 f planning system**

The Pinnacle® 3D planning system supports both the adaptive convolution and the Collapsed Cone Convolution Superposition (CC) dose algorithm [117] to calculate the dose distributions within the patient based on the work of Mackie et al [118-121]. In this work only the CC algorithm is used for the calculations of the dose distribution. Rather than correcting measured dose distributions, the CC algorithm computes dose
distributions from first principles and, therefore, can account for the effects of beam modifiers, the surface of the patient, and tissue heterogeneities on the dose distribution.

The CC dose model consists of three parts:

- Modeling the incident energy fluence as it exits the accelerator head.
- Projection of this incident energy fluence through the density representation of a patient to compute a TERMA (Total Energy Released per unit Mass) volume.
- A three-dimensional superposition of the TERMA with an energy deposition kernel to compute dose. A ray-tracing technique is used during the superposition to incorporate the effects of heterogeneities on lateral scatter.

The starting point for photon modeling is a uniform plane of energy fluence describing the intensity of radiation exiting the accelerator head. Pinnacle® then adjusts the fluence model to account for the flattening filter, the accelerator head, and beam modifiers such as blocks, wedges, and compensators.

- The “horns” in the beam produced by the flattening filter are modeled by removing an inverted cone from the distribution.
- Off-focus scatter produced in the accelerator head is modeled by defining a 2D Gaussian function as a scatter source and adjusting the incident energy fluence based on the portion of the scatter source visible from each point in the incident energy fluence plane.
- The geometric penumbra is modeled by convolving the fluence array with a focal spot blurring function.
- During planning, the shape of the field produced by blocks or multi-leaf collimators is cut out of the fluence array leaving behind the corresponding transmission through the shape-defining entity.
- Beam modifiers such as wedges and compensators are included in the fluence array by attenuating the energy fluence by the corresponding thickness of the
modifier. For static wedges and compensators, a radiological depth array is also stored which allows for proper modeling of the beam hardening due to the presence of the beam modifiers during the projection of the incident fluence array.

Pinnacle® manages each of these aspects of the model using a parameter or set of parameters which it iteratively adjusts during the modeling process so that the dose computed by the model matches the dose generated from the machine. During the modeling process, different regions of the measured depth doses and dose profiles are used to adjust the parameters which characterise the beam.

In summary, the primary incident energy fluence is ray-traced through the patient volume to calculate the TERMA volume while accounting for beam hardening and off-axis softening. This TERMA is then convolved with the polyenergetic kernel that accounts for the transport of charged particles as well as scattered photons generated in the patient.

Pinnacle P3®, v 4.2 f was the 3D planning system used to derive the treatment plan and prescription. The CC algorithm which gives a good compromise between speed and accuracy in dose calculation [102] is used as an alternative to the Monte Carlo calculation method that accurately predicts dose distributions in complex geometries within 1% [122]. Pinnacle® has been validated and dose volume histogram analysis has indicated that there is no consistent difference between the Monte Carlo and the convolution calculation used by Pinnacle® and it was concluded that the collapsed cone convolution algorithm was capable of giving results absolutely comparable to those of a Monte Carlo calculation [123]. In order to make a true comparison between the 2D and 3D systems the data from the 2D plan was fed into the 3D planning system to calculate
the dose that would have been given by the 3D system to deliver the same number of monitor units to the isocentre.

For this patient group a 3D conformal protocol has been applied to the department's current radical radiotherapy protocol, CHARTWEL, and evaluated to determine the doses given to the PTV and to critical normal tissues with 2D compared to 3D, the difference between the volumes treated with 2D and 3D and whether 3D offers a true dosimetric advantage over 2D by optimizing the dose to the PTV and sparing critical normal structures.

2.7 CT scanning for 2D/3D comparison

Patients were scanned with a Siemens Somatom Plus Four CT scanner, a single slice spiral CT scanner. A diagnostic spiral CT scan and a free-breathing (FB) sequential planning CT scan were performed. Intravenous contrast was given with the diagnostic scan at the radiologists' discretion: contrast enhancement was especially useful when there was associated pulmonary collapse/consolidation. The diagnostic spiral CT scan consisted of contiguous 10mm slices from the apices of the lungs to the lower limit of the kidneys, to allow assessment of the liver and adrenal glands for metastatic disease. This scan was used for staging and to aid interpretation of the planning scans. The patient was then set-up in the treatment position and skin markers were applied. An FB sequential planning CT scan of the thorax was performed with contiguous 5mm slices from the apices of the lungs to the lower limit of the diaphragms, to encompass the whole of both lungs. 5mm contiguous slices were required in order to produce digitally reconstructed radiographs (DRRs) of the beam’s eye views (BEVs) of sufficient quality for interpretation. The CT scanning procedure is documented in appendix 5.
2.8 2D Planning

With 2D planning systems the volumes can be drawn on as many or as few slices as required and a composite PTV created on the 2D planning system. Usually volumes are drawn on a few slices only and although the data available on each slice may be very accurate there is no interaction between the data on different slices and no account is taken of scatter between slices. Patients were also planned on Multidata DSS®, the 2 dimensional treatment planning system previously used for planning radical lung cancer treatments and for the CHART trial, with composite volumes as per ICRU 29 [124]. Composite volumes were drawn on a central or near central CT slice for phases 1 and 2. Treatment was usually planned on 3 – 5 CT slices for each phase without lead shielding. The isodose distributions created for the PTV on Multidata DSS® were checked on other CT slices to ensure that the volume had been adequately covered. Similar field arrangements were used as for the 3D plans to allow geometric and dosimetric comparisons.

2.9 3D Planning

The FB planning CT scan was transferred to the ADAC Pinnacle®, version 4.2f, planning system via a Dicom link.

A specialist thoracic radiologist reported the scans and was available for review of radiological investigations. Treatment was planned using full information from scans, bronchoscopy reports, thoracotomy findings (if performed) and pulmonary function tests.

The regions of interest were marked using mediastinal density settings but were checked using lung density settings. For the patients who received neo-adjuvant chemotherapy volumes were outlined on the post-chemotherapy CT scans and the
treatment planned. The plans and scans were fused with the pre-chemotherapy planning scans and, if necessary, the CTVs edited to encompass the original GTVs as chemotherapy was not curative and there could be residual microscopic disease.

Target volumes were defined as per ICRU 50 (Appendix 1) [62]:

**Gross Tumour Volume** (GTV) The primary tumour and visible nodal disease (nodes with ≥1.0cm short axis dimension on CT).

**Clinical Target Volume** (CTV) Generated to account for microscopic invasion by expansion of the GTV. The nodal stations in the mediastinum to be electively treated were included in the CTV as a subset called elective nodal irradiation (ENI) (Table 2.1, adapted from the American Thoracic Society lymph node map, 1993 [125]).

**Planning Target Volume** (PTV) Generated to account for set-up inaccuracy and organ motion by automatic expansion of the CTV to ensure that the prescribed dose is actually absorbed in the CTV.

\[
\begin{align*}
CTV & = \text{GTV+5mm} \\
\text{PTV 1 (Phase 1)} & = (\text{CTV+ENI})+5\text{mm} \\
\text{PTV 2 (Phase 2)} & = \text{CTV+5mm}
\end{align*}
\]

The recommended expansion of 10mm from CTV to PTV could give intolerably great volumes with excessive lung and spinal cord doses. Patients who would have been treatable with 2D planning would now be excluded from treatment. Reduction in the margin for the CTV to PTV expansion to 5mm gave acceptable V20 and spinal cord doses. Although the 10mm margin would not have always resulted in excessive V20 and spinal cord doses the reduced 5mm margin was used in all cases for consistency.
Table 2.1. Mediastinal nodal areas outlined as ENI

<table>
<thead>
<tr>
<th>Nodal Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper right paratracheal nodes</td>
</tr>
<tr>
<td>Lower right paratracheal nodes</td>
</tr>
<tr>
<td>Right tracheobronchial nodes</td>
</tr>
<tr>
<td>Lower left paratracheal nodes</td>
</tr>
<tr>
<td>Left tracheobronchial nodes</td>
</tr>
<tr>
<td>Aortopulmonary nodes</td>
</tr>
<tr>
<td>Subcarinal, including paraoesophageal, nodes</td>
</tr>
</tbody>
</table>

Adapted from the American Thoracic Society lymph node map, 1993 [125].

ENI = elective nodal irradiation

The usual protocol was for treatment to be delivered in two phases. In certain circumstances, treatment in 2 phases would have led to prohibitive lung and spinal cord doses but treatment with a single phase was possible. If, therefore, there was relatively poor respiratory function or an inoperable peripheral tumour without radiological evidence of mediastinal disease, treatment was given in a single phase (PTV 2) to known disease alone.

"Bulk" lung correction was used. PTV 1 was treated usually with four, sometimes three, fields and PTV 2 was always treated with three fields. Similar field arrangements were always used to allow geometric and dosimetric comparisons. 6 MV photons were used for all patients.
Prescribed dose and dose limits:

Phase 1  37.5 Gy was prescribed to the ICRU reference point in 25 fractions, treating three times daily at 0800, 1400 and 2000 hours, Monday to Friday.

Phase 2  22.5 Gy was prescribed to the ICRU reference point in 15 fractions, again treating three times daily at 0800, 1400 and 2000 hours, Monday to Friday.

The primary tumour and involved nodes therefore received a total dose of 60 Gy in 40 fractions over 18 days. Seven of the 24 patients were treated in a single phase 2.

2D dose limits

Dose to spinal cord: ≤ 40Gy optimally, ≤ 44Gy maximum.

Dose to contralateral lung: ≤ 20Gy to ≥ 50% of the lung, within the length of the treatment fields.

3D dose limits

Maximum permitted dose to spinal cord was 40Gy.

Maximum permitted V20 for whole lung was optimally ≤ 35%.

2.10 Radiotherapy 2D/3D Planning comparison

2D and 3D plans were generated as described above. Similar field arrangements were used as for the 2D and 3D plans to allow geometric and dosimetric comparisons.

The monitor units (MU) needed to give 1.5 Gy to the isocentre, including the lead tray factor if lead shielding would have been added in the simulator, were then calculated using the Units program, version 4.0.

The field sizes, position of isocentre and wedge modification for the 2D plan were recreated on the Pinnacle® 3D system. Straight edged lead blocks were drawn onto the DRRs, to shield lung and spinal cord, as would have been used in the CHART trial.
The MUs calculated with Multidata® and Units to give 1.5 Gy at the isocentre were applied and dose recalculated to determine the dose that would have been received according to the 3D CC algorithm. Estimate of dosimetric miss due to algorithm could then be made. Using the field sizes and beam directions, wedge factors, allowance being made for Pb shielding, the MUs to give 1.5Gy at the isocentre were calculated with Pinnacle®. Adequacy of coverage of the 3D PTV gave indication of geographic miss for the 2D system. Doses to PTV 1, PTV 2, spinal cord, whole lung were obtained from tabulated, cumulative DVHs to enable comparison of the planning systems and the plans.

2D and 3D plans were compared to identify:

- Difference in absolute dose to PTV
- Difference in isodose distribution around PTV
- Comparison of dose to critical structures

Examples of the 2D and 3D plans to demonstrate the isodose distributions are shown in Figure 2.3 and an example of the 2D and 3D field arrangements and position of lead shielding on DRRs in Figure 2.4.
Figure 2.3: 2D and 3D plans to display isodose distributions

Figure 2.4: 2D (a) and 3D (b) field arrangements and positioning of lead shielding
2.11 ABC procedure and CT scanning

CT scan procedure (appendix 5)

ABC procedure (appendix 6)

The ABC apparatus (Figure 2.5) consisted of a mouthpiece connected via a millipore filter and flexible tubing to a turbine equipped with a transducer electrically connected to a laptop control unit. The turbine and transducer converted airflow caused by breathing into a digital signal that produced a real time respiratory trace on a laptop monitor. Software allowed a variable gate volume to be set. When the machine was armed and the respiratory trace reached the gate a compressor would inflate a balloon valve, located between the filter and the turbine, to occlude the airway for an adjustable set time to achieve assisted breath hold (BH) at a set lung volume. Flow direction could be specified allowing the gate to be activated in either inspiration or expiration. During the ABC procedure breathing through the nose was prevented by a nose clip. Should the patient develop distress during breath hold an abort button incorporated into the hand rest could be activated causing the balloon valve to open or the patient could remove the mouthpiece. The controller could also abort the procedure from the laptop control unit.

During an initial ABC training session, which lasted approximately 20 minutes, the patient was positioned supine, in the ABC frame, the nose clip was applied and the mouthpiece was inserted. Verbal communication was maintained with the patient throughout the ABC procedure. The patient's respiratory trace was displayed continuously on the laptop monitor (Figure 2.6). After the patient's breathing settled, indicated by a regular trace, the patient was instructed to take a deep full inspiration followed by full expiration to measure the vital capacity. The gate volume was originally set at 80% of the vital capacity but patients found repeatedly achieving this
level tiring. 75% of the vital capacity was found to be more comfortable. Once breathing had settled again the gate time was set at 5 seconds (s) and the ABC machine was armed. The patient was instructed to take a deep breath and when the gate volume was reached the valve closed, preventing breathing, for the set time. If BH was successful the procedure was repeated with gate times of 10s, 15s and a maximum of 20s. Although patients were able to maintain BHs of over 20s it was decided to use a maximum time of 20s to prevent exhaustion. The gate volume and maximum gate time the patient was able to tolerate was recorded.

Several BHs would be required to perform a planning CT scan and administer a fraction of radiotherapy. It was therefore necessary to assess the reproducibility of ABC and this was done with planning CT scans and Pinnacle® to assess whether ABC could achieve BH at the same lung volume repeatedly on the same day (intra-fraction variation) and on different days (inter-fraction variation).

Patients were scanned with the Siemens Somatom Plus Four CT scanner as mentioned above. After the diagnostic spiral CT scan (used for staging and to aid interpretation of the planning scans) and FB sequential planning CT scan, three spiral CT scans using ABC were performed. ABC scans 1 and 2 were performed immediately after the FB planning scan. ABC scan 3 was done some weeks later during radiotherapy just prior to starting the second phase of treatment. Comparison of ABC 1 and 2 scans gave intra-fraction variation and comparison of ABC 1 and 3 scans, inter-fraction variation.

Following the FB planning scan the ABC equipment was activated and the gate time and volume determined from the practice session were set. The first ABC spiral CT scan (ABC 1) was performed with contiguous 5mm slices, and 15mm pitch, from the apices of the lungs to the lower limit of the diaphragms. Usually 3 breath holds were required to scan the whole chest and the scans were “stitched” together to give a
complete scan. ABC 2 was performed immediately afterwards. ABC 3 was performed some weeks later during treatment.

Figure 2.5: ABC apparatus
2.12 3D Planning for the FB and ABC comparison

The three ABC planning CT scans were also transferred to the ADAC Pinnacle®, v 4.2f, planning system via a Dicom link. The regions of interest were marked on the ABC 1 planning scan using mediastinal density settings but were checked to ensure disease was covered using lung density settings. Target volumes were defined in the same way as for the FB planning scan.

“Bulk” lung correction was again used. Separate plans were created to treat the PTV 1 and 2 for the FB and the ABC 1 scans. Similar field arrangements (usually four, sometimes three, fields for PTV 1 and three fields for PTV 2) were used to allow
geometric and dosimetric comparisons. Three of the ten ABC patients were treated in a single phase to cover disease alone.

Prescribed dose and dose limits were the same as those mentioned earlier in the 2D/3D comparison. Cumulative, tabulated dose volume histograms (DVH) were obtained from the Pinnacle® planning system for PTV 1 and 2, whole lung, spinal cord and oesophagus and comparisons were made between FB and ABC 1 plans comparing:

- Volumes of PTV1 and 2
- Percentage volume of PTV receiving 95% of the prescribed dose (V95) for PTV1 and 2
- V20 to whole lung
- Maximum dose to spinal cord
- Maximum and mean dose to oesophagus

The lungs were also marked on the ABC 2 and 3 planning scans. Lung volumes were calculated and compared for ABC land 2 and 1 and 3 to assess reproducibility of ABC.

2.13 Morbidity Assessment

Lung and oesophageal morbidity was recorded. Details of the morbidity scores used are given in Appendix 7. For patients who were in CR at 6 months post treatment the change in FEV1 and FVC measurement, the dyspnoea and pneumonitis scores, MLD, V20 and PTV were correlated. All patients were assessed for oesophageal morbidity and the dysphagia scores were assessed together with the volume and length of oesophagus treated, the maximum and mean dose received by the oesophagus to assess correlation.
2.14 Statistical Analysis

Statistical analysis was performed using the SPSS for Windows software package, version 10.0. Where the results were normally distributed, as they were for the V95 results in the 2D versus (vs) 3D comparison, the paired t-test was used.

For the results which did not have a normal distribution, 2D vs 3D comparison of lung and spinal cord doses as well as all of the free breathing vs ABC comparisons, non parametric tests were used. As all of the comparisons were of two different measurements on the same patient the Wilcoxon signed-rank test was used.

The morbidity assessment correlations were performed using the Pearson correlation coefficient and the Spearman rank correlation coefficient.
CHAPTER 3

COMPARISON OF 2 DIMENSIONAL AND 3 DIMENSIONAL RADIOTHERAPY TREATMENT PLANNING IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH RADICAL RADIOTHERAPY

3.1 Introduction

The CHART trial showed improvements in local tumour control and survival in those patients with locally advanced NSCLC treated with CHART to 54 Gy compared to those treated with conventional daily radiotherapy to 60 Gy [26]. 2D planning was used in that trial.

Results may be improved by dose escalation, as has been done with the CHARTWEL protocol to 60 Gy [29], and the addition of neo-adjuvant chemotherapy.

The use of 3D conformal radiotherapy could lead to further improvement. Although 3D treatment planning has been reported to be superior to 2D planning, previous comparisons have often compared 2D parallel opposed fields with 3D multi-field plans and 3D was therefore given an advantage [50, 126].

The processes of 2D and 3D planning differ. 2D planning was performed according to ICRU 29 [124]. A target volume was drawn around disease and tissues thought to contain disease with allowance (margins) for local invasive capacity, expected movements e.g. due to breathing, change in shape of the target, and inaccuracies in set-up. Planning was done on a central or near central slice and a few other slices. The
planning system gave accurate information within each slice but there was no allowance for margins extending between adjacent slices or electron scatter between slices.

In 3D planning ICRU 50 [62] is used. Disease or tissues thought to contain disease (GTV) are marked on all relevant slices on the planning CT scan. Expansions are then performed electronically to allow for microscopic invasion (CTV), organ motion and set-up error to define the PTV. The software allows expansions to be performed between adjacent slices in the superio-inferior direction in addition to antero-posterior and medio-lateral as in 2D planning. Calculation also allows for electron scatter between slices.

The differences in ICRU convention and planning processes in 2D and 3D radiotherapy treatment planning could lead to discrepancies in target volumes. The planning process, delineation of regions of interest, tumour and normal tissues on every relevant slice of the CT scan, and the algorithm give more complete dosimetric information in 3D planning compared with 2D planning.

The Pinnacle® 3D planning system has been validated and has been shown to correspond to the Monte Carlo calculation [122, 123].

Although QA tests could ensure that each system was accurate within itself the inherent differences in the planning processes and algorithms meant that in order to achieve a safe transition from 2D to 3D planning it was necessary to determine the relationship between the 2D and 3D target volumes and dosimetry. In addition it was also necessary to translate the dose limits for normal tissues, lung and spinal cord, from 2D into 3D criteria. This was achieved by planning the patients twice, in 2D using ICRU 29 recommendations and then again in 3D using ICRU 50 conventions. The 2D plans were then inserted into the 3D system and the doses received by the PTV, whole lung and spinal cord could be determined as if the patients had been planned in 3D and
compared with the 3D plans using DVHs. As patients would be treated with the 3D system Pinnacle® was the ‘gold’ standard.

3.2 Subjects

Twenty four patients with inoperable locally advanced stage I-IIIB NSCLC considered suitable for treatment with radical radiotherapy were treated between October 1999 and January 2002. All of the patients had histologically or cytologically proven NSCLC, confined to the primary site with or without direct or nodal involvement of the mediastinum. The volume to be irradiated had to be such that radical radiotherapy could be achieved without exceeding normal tissue tolerance, in particular for lung and spinal cord. Patient details are summarized in Table 3.1. There were 4 females and 20 males. The median age was 69 years, with a range of 49-79. All had WHO performance status 0 or 1. Eighteen of the 24 patients (75%) had squamous cell carcinoma, 3 NSCLC not otherwise specified, 2 adenocarcinoma and 1 large cell carcinoma. 14 patients (58%) had stage III disease, 6 patients (25%) had stage II disease and 4 patients (17%) had stage I disease and were inoperable due to co-existing disease. Seventeen of the 24 patients received neo-adjuvant chemotherapy as shown below:

- MIC (mitomycin C, ifosfamide and cisplatinum) 5 patients
- PC (paclitaxel and carboplatin) 7 patients
- MVP (mitomycin C, vinblastine and cisplatinum) 4 patients
- NP (navelbine and cisplatinum) 1 patient
<table>
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<tr>
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<th>Age</th>
<th>Tumour site</th>
<th>Histology</th>
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<td>62</td>
<td>L hilum-nil endobronchially</td>
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<td>69</td>
<td>LingB</td>
<td>SCC-3</td>
<td>T4N2M0</td>
</tr>
<tr>
<td>21.</td>
<td>F</td>
<td>69</td>
<td>RU,Mid,LLB</td>
<td>SCC-2</td>
<td>T3N2M0</td>
</tr>
<tr>
<td>22.</td>
<td>M</td>
<td>74</td>
<td>RULB</td>
<td>SCC-3</td>
<td>T4N1M0</td>
</tr>
<tr>
<td>23.</td>
<td>M</td>
<td>65</td>
<td>LLLB</td>
<td>SCC-2</td>
<td>T3N2M0</td>
</tr>
<tr>
<td>24.</td>
<td>M</td>
<td>76</td>
<td>RULB</td>
<td>SCC-2</td>
<td>T3N1M0</td>
</tr>
</tbody>
</table>

M = male; F = female; L = left; R = right; UL = upper lobe; Mid = middle; LL = lower lobe; Ling = lingular; B = bronchus; M = main; Z = zone; SCC = squamous cell carcinoma; 1 = well differentiated; 2 = moderately differentiated; 3 = poorly differentiated; NSCLC-nos = non-small cell lung cancer not otherwise specified; N/A = not applicable.
3.3 Methods

Patients were positioned, scanned and planned using the methods described in Chapter 2: 2.4, 2.7, 2.8 and 2.9. Seventeen patients were treated with a two-phase technique and 7 patients were treated with a single phase 2.

Bulk lung correction was used in the planning. Usually four (sometimes three) fields, were used to treat the PTV 1 and three fields to treat PTV 2. Three fields were used where possible as doses to normal lung were lower. Similar field arrangements were used for the 3D and 2D plans to allow geometric and dosimetric comparisons.

Patients were also planned on Multidata®, the 2 dimensional treatment planning system previously used for planning radical lung cancer treatments and for the CHART trial, with composite volumes as per ICRU 29 [124]. Composite volumes were drawn on a central or near central CT slice for phases 1 and 2. Treatment was planned on 3–5 CT slices for each phase without lead shielding.

- The phase I and phase II were planned on Multidata® with no lead shielding (Pb).
- Units v 4.0 was used to calculate the monitor units (MU) needed to give 1.5Gy to the isocentre, including the Pb tray factor if Pb would have been added in the simulator.
- The plan was recreated on the Pinnacle® 3D system. Straight edged Pb blocks were drawn onto the DRRs, to shield lung and spinal cord.
- The MUs were set as calculated from the Multidata® 2D plan and Units and the dose was recalculated.

The adequacy of the 2D planning was assessed by the percentage coverage of the 3D PTV. Differences could be due to geometric causes (differences in definition of
volumes in ICRU 29 and ICRU 50), dosimetric causes (differences in the 2D and 3D planning systems) or a combination of the two.

The field sizes and monitor units from the 2D plan were inserted into the 3D planning system and allowance made for lead shielding. The doses received by the ICRU Reference Points corresponding to those monitor units were then calculated according to the 3D system. The volumes of the PTV 1 and 2 receiving 95% of the prescribed doses ($V_{95 \text{ prescribed-2D}}$) were then derived from the DVHs, giving an indication of dosimetric and geometric miss due to the algorithm employed.

Another 3D plan was then generated as if the prescribed dose, i.e. 37.5Gy for PTV 1 and 22.5Gy for PTV 2, was given to the ICRU reference point and the volumes of the PTV 1 and 2 receiving 95% of those calculated doses ($V_{95 \text{ calculated-2D}}$) estimated from the DVHs, allowing assessment of geometric miss due to the difference in volume definition between ICRU 29 and ICRU 50.

$$V_{95 \text{ prescribed-2D}} \text{ compared with the } V_{95.3D} = \text{ dosimetric and geometric miss}$$

$$V_{95 \text{ calculated-2D}} \text{ compared with the } V_{95.3D} = \text{ geometric miss alone (assuming 3D is the definitive gold standard).}$$

Similar comparisons were made for whole lung and spinal cord.
3.4 Results

The assessment of the immobilisation frame showed that for those patients scanned without the frame, although skin and surface markers (tattoos) aligned, the internal anatomy of mediastinum and tumour were concordant in only 2 of 5 cases. When the frame was used external and internal anatomy agreed in 5 of 5 cases to within 2mm.

**Difference in absolute dose for 2D (2D -3D %)**

Phase I mean calculated dose to the isocentre = 36.0 Gy (−3.9%)  
(37.5Gy prescribed)

Phase II mean calculated dose to the isocentre = 21.5 Gy (−4.4%)  
(22.5Gy prescribed)

Single phase mean calculated dose to the isocentre = 57.2 Gy (−4.7%)  
(60.0Gy prescribed)

The underdosage seen with 2D could be due to dosimetric or geometric miss.

**Table 3.2:** Median dose to PTV ($V_{95}$) for 2D and 3D plans

<table>
<thead>
<tr>
<th>PTV</th>
<th>Median $V_{95,3D}$ % (range)</th>
<th>Median $V_{95}$ prescribed-2D % (range)</th>
<th>Median $V_{95}$ calculated-2D % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV 1:</td>
<td>91.8 (40.2-95.7)</td>
<td>60.5 (19.6-73.9)</td>
<td>87.2 (46.8-95.9)</td>
</tr>
<tr>
<td>N=17</td>
<td>$p=0.0003$</td>
<td>$p=NS$</td>
<td></td>
</tr>
<tr>
<td>PTV 2:</td>
<td>86.7 (38.6-96)</td>
<td>28.8 (2-73.9)</td>
<td>74.8 (34.8-96.2)</td>
</tr>
<tr>
<td>N=24</td>
<td>$p=0.0001$</td>
<td>$p=0.012$</td>
<td></td>
</tr>
</tbody>
</table>
Underdosage with 2D planning was seen for both PTV 1 and 2 but was more marked in PTV 2.

Table 3.2 shows the median dose to the PTV with the $V_{95\text{ prescribed-2D}}$ dose reduction effect in the 2D planning due to dosimetric and geometric miss and the $V_{95\text{ calculated-2D}}$ dose reduction due to geometric miss alone.

Figure 3.1 displays the $V_{95\text{ prescribed-2D}}$ dose reduction effect in the 2D planning due to dosimetric as well as geometric miss, whilst Figure 3.2 demonstrates the $V_{95\text{ calculated-2D}}$ dose reduction due to geometric miss alone.

Figure 3.1: Median $V_{95\text{ prescribed-2D}}$ and $V_{95\text{ 3D}}$

Displaying dosimetric and geometric differences between 2D and 3D (%)

![Bar chart showing dose comparison between 2D and 3D for PTV 1 and PTV 2.](figure3_1.png)
Therefore, geometric coverage of the PTV was similar in 2D and 3D planning for PTV 1 whilst there was a significant improvement with 3D planning for PTV 2 but there was a pronounced dosimetric miss with a lower dose being delivered in 2D compared to 3D.
Difference in dose to organs at risk

The 2D planning system was incapable of generating V20 for lung and maximum spinal cord doses due to the algorithm and the fact that planning was performed on a limited number of slices and data was limited to lung within the length of the treatment fields. The 3D planning system was therefore used to calculate V20 and maximum spinal cord doses using indices from the 2D plans.

The maximum dose to spinal cord was greater in 17 of the 2D plans, despite similar field arrangements for 2D and 3D plans, with a median dose reduction of 0.82 Gy (range -7.64 to 20.43) for 3D (p=0.04) (Figure 3.3 and Table 3.3).

Figure 3.3: Median maximum dose to spinal cord 2D and 3D

(Gy)
Table 3.3: Maximum dose to spinal cord 2D and 3D and the saving with 3D

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Maximum cord dose 2D (Gy)</th>
<th>Maximum cord dose 3D (Gy)</th>
<th>Difference in maximum cord dose 2D-3D (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42.7</td>
<td>39.2</td>
<td>3.54</td>
</tr>
<tr>
<td>2</td>
<td>35.8</td>
<td>38.4</td>
<td>-2.62</td>
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<tr>
<td>3</td>
<td>38.9</td>
<td>39.5</td>
<td>-5.2</td>
</tr>
<tr>
<td>4</td>
<td>37.5</td>
<td>39.1</td>
<td>-1.67</td>
</tr>
<tr>
<td>5</td>
<td>40.4</td>
<td>40.2</td>
<td>0.19</td>
</tr>
<tr>
<td>6</td>
<td>14.7</td>
<td>16.0</td>
<td>-1.25</td>
</tr>
<tr>
<td>7</td>
<td>39.4</td>
<td>38.6</td>
<td>0.82</td>
</tr>
<tr>
<td>8</td>
<td>46.4</td>
<td>35.4</td>
<td>10.98</td>
</tr>
<tr>
<td>9</td>
<td>36.4</td>
<td>35.6</td>
<td>0.82</td>
</tr>
<tr>
<td>10</td>
<td>12.3</td>
<td>11.7</td>
<td>0.60</td>
</tr>
<tr>
<td>11</td>
<td>31.1</td>
<td>38.8</td>
<td>-7.64</td>
</tr>
<tr>
<td>12</td>
<td>39.8</td>
<td>35.0</td>
<td>4.79</td>
</tr>
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<td>41.8</td>
<td>21.4</td>
<td>20.43</td>
</tr>
<tr>
<td>14</td>
<td>39.6</td>
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<td>40.9</td>
<td>40.3</td>
<td>0.63</td>
</tr>
<tr>
<td>16</td>
<td>40.0</td>
<td>35.5</td>
<td>4.50</td>
</tr>
<tr>
<td>17</td>
<td>39.0</td>
<td>35.8</td>
<td>3.16</td>
</tr>
<tr>
<td>18</td>
<td>39.0</td>
<td>36.9</td>
<td>2.02</td>
</tr>
<tr>
<td>19</td>
<td>39.3</td>
<td>43.4</td>
<td>-4.15</td>
</tr>
<tr>
<td>20</td>
<td>36.5</td>
<td>37.1</td>
<td>-0.59</td>
</tr>
<tr>
<td>21</td>
<td>37.3</td>
<td>36.9</td>
<td>0.39</td>
</tr>
<tr>
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</tr>
<tr>
<td>23</td>
<td>41.8</td>
<td>31.9</td>
<td>9.96</td>
</tr>
<tr>
<td>24</td>
<td>36.7</td>
<td>33.9</td>
<td>2.76</td>
</tr>
</tbody>
</table>
The V20 for whole lung was greater in 16 of the 2D plans with a median reduction of 2.4% (range -5.4 to 13.1) for 3D ($p=0.03$) (Figure 3.4 and Table 3.4).

Figure 3.4: Median whole lung V20 for 2D and 3D plans
Table 3.4: Whole lung V20 for 2D and 3D plans and the saving with 3D

<table>
<thead>
<tr>
<th>Patient number</th>
<th>V20 2D (%)</th>
<th>V20 3D (%)</th>
<th>Difference in V20 2D-3D (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29.6</td>
<td>26.2</td>
<td>3.40</td>
</tr>
<tr>
<td>2</td>
<td>19.0</td>
<td>24.4</td>
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<tr>
<td>3</td>
<td>32.4</td>
<td>32.0</td>
<td>0.40</td>
</tr>
<tr>
<td>4</td>
<td>24.9</td>
<td>26.9</td>
<td>-2.00</td>
</tr>
<tr>
<td>5</td>
<td>29.4</td>
<td>27.1</td>
<td>2.30</td>
</tr>
<tr>
<td>6</td>
<td>17.7</td>
<td>22.5</td>
<td>-4.80</td>
</tr>
<tr>
<td>7</td>
<td>40.0</td>
<td>36.2</td>
<td>3.80</td>
</tr>
<tr>
<td>8</td>
<td>36.0</td>
<td>33.5</td>
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<tr>
<td>9</td>
<td>21.3</td>
<td>19.6</td>
<td>1.70</td>
</tr>
<tr>
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<td>14.0</td>
<td>15.6</td>
<td>-1.60</td>
</tr>
<tr>
<td>11</td>
<td>27.3</td>
<td>20.2</td>
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<td>44.2</td>
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</tr>
<tr>
<td>13</td>
<td>28.1</td>
<td>32.8</td>
<td>-4.70</td>
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<tr>
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<td>30.8</td>
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<td>30.7</td>
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<tr>
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<td>12.1</td>
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<td>2.60</td>
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<td>7.00</td>
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<tr>
<td>21</td>
<td>38.6</td>
<td>39.1</td>
<td>-0.50</td>
</tr>
<tr>
<td>22</td>
<td>33.2</td>
<td>28.9</td>
<td>4.30</td>
</tr>
<tr>
<td>23</td>
<td>38.6</td>
<td>32.5</td>
<td>6.10</td>
</tr>
<tr>
<td>24</td>
<td>24.4</td>
<td>25.2</td>
<td>-0.80</td>
</tr>
</tbody>
</table>
Examples of cumulative DVHs to demonstrate 2D and 3D doses to PTV, Spinal cord and lung are displayed in Figure 3.5.

Figure 3.5: Cumulative DVHs to display the difference between 2D and 3D doses to the PTV and critical normal tissues.
Difference in isodose distribution

The $V_{95}^{3D}$ was poor due to inhomogeneity correction and penumbra. Fall-off in dose at the edge of the PTV (penumbra) was not seen in the 2D plans as there was no scatter component in the 2D algorithm. The effect was most marked for peripheral tumours which were completely surrounded by lung.

3.5 Conclusions

Coverage and delivery of dose to the PTV with the 2D planning system was significantly inferior to the 3D planning system. Previously, it was thought that the inadequate dose delivery and isodose coverage of the PTV was due to geographic miss with 2D planning, resulting from less accurate definition of the PTV compared to 3D planning (where a complete picture of disease is available which can be viewed from all directions). In this study it has been shown that the difference between 2D and 3D planning is more a dosimetric difference with a higher dose being delivered with 3D planning. This may, in part, be due to the difference in algorithm between the 2D and 3D systems as explained in Chapter 2-Methods section 2.6. Limitations of the Multidata® DSS 2D planning system include the assumption that all fields are square with rectangular fields being converted to equivalent square fields by the use of a table. It is also assumed that both collimators lie at the same level and are at the same distance from the source resulting in identical transverse and radial profiles, whereas in reality one pair of collimators will be closer to the source than the other and transverse and radial beam profiles will not be the same. Another difference between the two systems is that the 2D system does not take into account any changes resulting from varying scatter conditions elsewhere in the body. The CC algorithm used by the Pinnacle® 4.2f
planning system has been validated and no consistent difference was seen between the Monte Carlo and the convolution calculation used by Pinnacle® [123]. The reduction in mean dose to the isocentre for Phase 1 was 1.5 Gy, a whole fraction of radiotherapy, and 1.0 Gy for Phase 2, over a whole course of treatment. Such reductions could adversely affect the success of treatment.

Doses to normal tissues, lung and spinal cord were higher with the 2D planning system. The dose to spinal cord was lower in 17 of the 24 cases with 3D-CRT (71%). The dose to whole lung was lower in 16 of the 24 cases with 3D-CRT (67%). The use of straight edged lead shielding gave less protection to normal tissues than conformally shaped fields and may have contributed to the higher spinal cord doses on 2D planning. Although geometric coverage of the PTV in 2D planning was close to that in 3D planning this was at the expense of the normal tissues.

3D planning has been shown to be better than 2D through improved dosimetric accuracy for the PTV and reduced dose to normal tissues. The dose reductions to normal tissues would give an extra margin of safety or enable further dose escalation with CHARTWEL.
CHAPTER 4.

GATED THERAPY WITH ACTIVE BREATHING CONTROL TO REDUCE ERROR DUE TO RESPIRATORY EXCURSION IN RADICAL RADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER

4.1 Introduction

Three-dimensional conformal radiotherapy (3D-CRT) generates detailed dose distributions which enables planning to give a high dose of radiation to disease with minimal dose to adjacent normal tissues. However, accuracy of delivery of the radiation to disease then becomes very important and attention needs be paid to avoid dosimetric miss and geometric miss due to errors of set-up and organ motion. Errors caused by dosimetry have been described in Chapter 3 and errors due to set-up and organ motion and ways to correct them have been described in the Introduction, Chapter 1: 1.6.

Lung cancers move with respiration [69, 95]. The technique of ABC allows arrest of respiration, and hence tumour movement, at a chosen point in the respiratory cycle [115]. The ABC device may be used to arrest breathing at any point in the respiratory cycle, in inspiration or expiration. ABC has been investigated for use in patients with lymphoma and breast carcinoma [127, 128]. The patients with breast cancer, who had no respiratory problems, were easily able to maintain a BH of 20 seconds at 80% of vital capacity. In this study lung cancer patients had difficulty repeatedly achieving BHs at 80% of vital capacity. The gate volume was reduced to 75% of the vital
capacity without further problems. Twenty seconds was considered an adequate BH as a planning CT scan of the chest could be performed in 3 BHs and a whole segment of a fraction of radiotherapy could be given in one BH. As both scanners and treatment machines have become faster shorter BHs will become practical. Reproducibility (intra- and inter-fraction variation), PTV definition, dose to PTV, spinal cord, lung and oesophagus have been examined and comparisons made between FB and ABC plans.

4.2 Subjects and Methods

Patients with inoperable localised NSCLC who were to be treated radically using the CHARTWEL regime were studied. Eleven patients with inoperable locally advanced Stage III NSCLC, of WHO performance status 0 or 1, considered suitable for treatment with radical radiotherapy, were studied. Patients had to be able to comprehend instructions about the ABC procedure and to press the abort button or expectorate the mouthpiece if unable to maintain BH.

The immobilisation frame, ABC procedure and CT scanning and planning are described in Methods, Chapter 2: 2.4, 2.5, 2.11, 2.12. The statistical analysis is described in 2.14. Cumulative, tabulated dose volume histograms (DVH) were obtained using the Pinnacle® planning system to derive values for PTV 1 and 2, V95 for PTV 1 and 2, V20 for whole lung (which included lung within the PTV), maximum dose to spinal cord and maximum and mean dose and length and volume of oesophagus treated and comparisons made between FB and ABC plans.

Three of the ten patients, due to relatively poor respiratory reserve or peripheral site of the cancer, were treated in a single phase to cover known disease alone.
Lung volumes were calculated and compared for ABC 1 and 2 and ABC 1 and 3 (using the ABC 1 volume as the denominator in calculation of the percentage difference) to give the intra-and inter-fraction reproducibility respectively of ABC.

4.3 Results

One patient who developed a chest infection prior to the planning CT scan was not able to BH and data is therefore available for 10 patients. The characteristics of the patients and their cancers are shown in Table 4.1. Nine patients were male and one was female. Ages ranged from 53 to 79 years. Nine patients were WHO performance status 0 and one was performance status 1. Six cancers affected the right lung and 4 the left lung. Seven of the cancers were squamous, 1 was adenocarcinoma, 1 was NSCLC-nos and 1 was a large cell carcinoma. All patients had stage III cancers.

The ABC procedure was straightforward and all patients easily breath held for 15-20 seconds. An example of the FB and ABC phase 1 and 2 plans is shown in Figure 4.1. The differences between the FB and ABC scans reflect the effect of ABC. Figure 4.2 displays anterior movement of the chest wall and inferior movement of the diaphragms with ABC for another patient. The tumour, and hence the isocentre, also moved anteriorly away from the spinal cord.
Table 4.1: Patient and tumour characteristics for the ABC study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Tumour site</th>
<th>Histology</th>
<th>TNM stage</th>
<th>WHO Performance status</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>62</td>
<td>L hilum</td>
<td>Adenocarcinoma</td>
<td>T4N0M0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>59</td>
<td>RULB</td>
<td>SCC-2</td>
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<td>0</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>77</td>
<td>RUL+RMB</td>
<td>SCC-2</td>
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<td>0</td>
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<tr>
<td>4</td>
<td>M</td>
<td>79</td>
<td>LMB</td>
<td>SCC-2</td>
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<td>0</td>
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<td>M</td>
<td>65</td>
<td>RULB</td>
<td>Large CC</td>
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<td>0</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>53</td>
<td>RULB</td>
<td>NSCLC-nos</td>
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</tr>
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<td>M</td>
<td>69</td>
<td>Lingular B</td>
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<td>F</td>
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</tr>
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<td>9</td>
<td>M</td>
<td>65</td>
<td>LLLL</td>
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<td>10</td>
<td>M</td>
<td>76</td>
<td>RULB</td>
<td>SCC-2</td>
<td>T3N1M0</td>
<td>0</td>
</tr>
</tbody>
</table>

M = male; F = female; L = left; R = right; UL = upper lobe; B = bronchus; M = main; Mid = middle; LL = lower lobe; Large CC = large cell carcinoma; SCC = squamous cell carcinoma; 1 = well differentiated; 2 = moderately differentiated; 3 = poorly differentiated; NSCLC-nos = non-small cell lung cancer not otherwise specified; T = tumour stage; N = nodal stage; M = metastatic stage; WHO = World Health Authority
Figure 4.1: An example of the FB and ABC phase 1 and 2 plans

<table>
<thead>
<tr>
<th>Free Breathing</th>
<th>Active Breathing Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Phase 1 FB" /></td>
<td><img src="image2" alt="Phase 1 ABC" /></td>
</tr>
<tr>
<td><img src="image3" alt="Phase 2 FB" /></td>
<td><img src="image4" alt="Phase 2 ABC" /></td>
</tr>
</tbody>
</table>
The differences between ABC 1 and 2 represented intra-fraction variation and the differences between ABC 1 and 3, inter-fraction variation. Lung volumes were reproducible and differences between ABC 1 and 2 ranged from 0.1 to 5.7% (4 to 144.5 cm³).

One patient did not have an ABC 3 scan as he had developed metastases and did not receive the planned radical radiotherapy. For the first 2 patients the gate volume was set at 80 % vital capacity for ABC 1 and 2 scans. However, patients had difficulty achieving 80 % vital capacity for ABC 3. The gate was reduced to 75 % vital capacity and there were no further problems. The differences between the ABC 1 and 3 lung volumes for the first 2 patients therefore could not be used to assess reproducibility of
ABC. For 6 of the remaining 7 patients difference in lung volumes between ABC 1 and 3 ranged from 0.2 to 8.7%. Patient 9 showed a difference in right lung volume between ABC 1 and 3 scans of only 0.2% (5.6 cm$^3$) but 13.2% (289.8 cm$^3$) for the left lung. As it is not possible to differentially breathe with one or other lung the scans were examined in detail. Tumour had significantly shrunk between the scans suggesting that the difference seen for the left lung volume was due to restitution of lung volume caused by tumour regression rather than failure of ABC.

The intra- (ABC 1 and 2) and inter- (ABC 1 and 3) fraction variation in lung volumes was not statistically significant (Table 4.2).

The interval between ABC 1 and 3 ranged from 23 to 57 days, indicating that ABC was able to assist breath hold reliably over several weeks, the duration of a course of radical conventional daily radiotherapy.
Table 4.2: Intra and inter fraction differences in lung volumes with ABC

<table>
<thead>
<tr>
<th>Patient number</th>
<th>ABC2- % diff.</th>
<th>ABC2- % diff.</th>
<th>ABC3- % diff.</th>
<th>ABC3- % diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>right lung</td>
<td>left lung</td>
<td>right lung</td>
<td>left lung</td>
</tr>
<tr>
<td>1</td>
<td>-10.9</td>
<td>-0.3</td>
<td>45.0</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>10.7</td>
<td>0.3</td>
<td>24.0</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>-70.2</td>
<td>-1.8</td>
<td>-28.6</td>
<td>-0.9</td>
</tr>
<tr>
<td>4</td>
<td>-74.0</td>
<td>-2.1</td>
<td>-28.8</td>
<td>-0.7</td>
</tr>
<tr>
<td>5</td>
<td>-78.0</td>
<td>-2.8</td>
<td>-3.7</td>
<td>-0.2</td>
</tr>
<tr>
<td>6</td>
<td>-19.5</td>
<td>-0.7</td>
<td>6.1</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>-4.0</td>
<td>-0.1</td>
<td>84.8</td>
<td>2.9</td>
</tr>
<tr>
<td>8</td>
<td>-12.2</td>
<td>-0.6</td>
<td>21.9</td>
<td>1.1</td>
</tr>
<tr>
<td>9</td>
<td>108.0</td>
<td>3.0</td>
<td>46.6</td>
<td>2.1</td>
</tr>
<tr>
<td>10</td>
<td>69.4</td>
<td>2.5</td>
<td>-144.5</td>
<td>-5.7</td>
</tr>
</tbody>
</table>

GTV and ENI were easier to delineate on the ABC scans. GTVs were smaller with ABC reflected by reduced PTVs. There was a median reduction of the PTV; 10.2% (32.9cm$^3$) for PTV 1 ($p=0.128$, NS) and 9.2% (45.3cm$^3$) for PTV 2 ($p=0.032$) (Table 4.3). Five of 7 PTV 1 and 7 of 10 PTV 2 volumes were smaller on the ABC scans. The greatest difference in PTV between ABC and FB scans occurred for smaller tumours in the lower lobes. The tumours that were larger and fixed to other structures and which therefore did not move with breathing showed a smaller difference in PTV. The better definition of GTV and ENI and reduction of GTV were thought to be due to prevention of image blurring caused by breathing. Lagerwaard et al [51] have described similar findings.
ABC did not lead to significant differences between the percentages of PTVs 1 and 2 enclosed by the 95% isodose (V95) compared to the FB scans. The median V95 for PTV 1 was 90.2% (range 40.2 to 95.7) 3D FB vs 89.5% (range 50.8 to 96.6) 3D plus ABC (Table 4.4). Graphical displays of results for the 7 patients treated with a two-phase technique are shown in Figure 4.3. The median V95 for PTV 2 receiving 95% was 88.8% (range 38.6 to 95.3) 3D FB vs 89.4% (range 45.8 to 95.2) 3D plus ABC. The PTV 2 results are shown in Figure 4.4 and Table 4.5. The low V95 values occurred in patients whose tumours extended laterally and were surrounded by more lung than soft tissue causing a lower dose in the penumbral region.

Table 4.3: Differences between FB and ABC PTVs

<table>
<thead>
<tr>
<th>Patient number</th>
<th>PTV 1 FB (cm³)</th>
<th>PTV 1 ABC (cm³)</th>
<th>PTV 2 FB (cm³)</th>
<th>PTV 2 ABC (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>633.4</td>
<td>568.6</td>
<td>594.0</td>
<td>535.0</td>
</tr>
<tr>
<td>2</td>
<td>397.2</td>
<td>338.8</td>
<td>379.6</td>
<td>308.7</td>
</tr>
<tr>
<td>3</td>
<td>251.1</td>
<td>271.3</td>
<td>125.4</td>
<td>147.5</td>
</tr>
<tr>
<td>4</td>
<td>457.5</td>
<td>374.8</td>
<td>354.7</td>
<td>248.8</td>
</tr>
<tr>
<td>5</td>
<td>308.3</td>
<td>305.3</td>
<td>249.2</td>
<td>220.7</td>
</tr>
<tr>
<td>6</td>
<td>321.8</td>
<td>288.9</td>
<td>276.5</td>
<td>254.4</td>
</tr>
<tr>
<td>7</td>
<td>516.0</td>
<td>524.3</td>
<td>426.1</td>
<td>428.8</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>375.7</td>
<td>344.2</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>440.7</td>
<td>372.1</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
<td>386.2</td>
<td>400.9</td>
</tr>
</tbody>
</table>
Table 4.4 Differences in V95 for PTV 1 between FB and ABC plans

<table>
<thead>
<tr>
<th>Patient number</th>
<th>V95 PTV 1 FB (%)</th>
<th>V95 PTV 1 ABC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>89.4</td>
<td>89.5</td>
</tr>
<tr>
<td>2</td>
<td>82.8</td>
<td>81.2</td>
</tr>
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<td>3</td>
<td>95.2</td>
<td>96.6</td>
</tr>
<tr>
<td>4</td>
<td>93.1</td>
<td>87.0</td>
</tr>
<tr>
<td>5</td>
<td>95.7</td>
<td>94.7</td>
</tr>
<tr>
<td>6</td>
<td>90.2</td>
<td>93.4</td>
</tr>
<tr>
<td>7</td>
<td>40.2</td>
<td>50.8</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 4.3: V95 for PTV 1 FB and ABC
Table 4.5: Differences in $V_{95}$ for PTV 2 between FB and ABC plans

<table>
<thead>
<tr>
<th>Patient number</th>
<th>$V_{95}$ PTV 2 FB (%)</th>
<th>$V_{95}$ PTV 2 ABC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95.1</td>
<td>93.3</td>
</tr>
<tr>
<td>2</td>
<td>84.1</td>
<td>63.8</td>
</tr>
<tr>
<td>3</td>
<td>88.5</td>
<td>90.2</td>
</tr>
<tr>
<td>4</td>
<td>38.6</td>
<td>72.2</td>
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<td>5</td>
<td>89.9</td>
<td>93.7</td>
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<td>89.1</td>
<td>94.5</td>
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<td>7</td>
<td>56.9</td>
<td>45.8</td>
</tr>
<tr>
<td>8</td>
<td>57.0</td>
<td>62.1</td>
</tr>
<tr>
<td>9</td>
<td>95.3</td>
<td>95.1</td>
</tr>
<tr>
<td>10</td>
<td>89.3</td>
<td>88.5</td>
</tr>
</tbody>
</table>

Figure 4.4: $V_{95}$ for PTV 2 FB and ABC
ABC led to reduced lung and spinal cord doses. As ABC was performed in moderate deep inspiration lung volumes were increased in all 10 patients (Figure 4.5) and in one patient the lung volume increased by 97%, from 2.64 litres on the FB scan to 5.19 litres with ABC. The expansion of the lungs led to reduction of the volume of lung in the treatment fields and hence V20. With ABC the median reduction in V20 was 6.4% (range 1.7 to 14.2) ($p=0.0051$) (Figure 4.6 and Table 4.6).

Figure 4.5: Lung volumes for FB and ABC scans
Table 4.6: V20 for FB and ABC plans and the saving with ABC

<table>
<thead>
<tr>
<th>Patient number</th>
<th>V20 whole lung (%) FB</th>
<th>V20 whole lung (%) ABC</th>
<th>V20 saving (%) FB - ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26.2</td>
<td>22.7</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>24.4</td>
<td>17.0</td>
<td>7.4</td>
</tr>
<tr>
<td>3</td>
<td>31.0</td>
<td>16.8</td>
<td>14.2</td>
</tr>
<tr>
<td>4</td>
<td>24.4</td>
<td>17.6</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>18.6</td>
<td>16.9</td>
<td>1.7</td>
</tr>
<tr>
<td>6</td>
<td>22.0</td>
<td>16.0</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>27.1</td>
<td>24.0</td>
<td>3.1</td>
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<tr>
<td>8</td>
<td>39.1</td>
<td>33.2</td>
<td>5.9</td>
</tr>
<tr>
<td>9</td>
<td>32.5</td>
<td>24.8</td>
<td>7.7</td>
</tr>
<tr>
<td>10</td>
<td>25.2</td>
<td>18.1</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Figure 4.6: V20 for FB and ABC plans.
Lung volumes were increased with anterior movement of the chest wall and inferior movement of the diaphragm. As shown in Table 4.7, in 7 of the 10 patients the tumour also moved anteriorly and there was necessary shift of the isocentre anteriorly, by a median of 13, range 3 to 28, mm.

Table 4.7: Isocentre shift with ABC

<table>
<thead>
<tr>
<th>Patient number</th>
<th>ABC iso v FB iso (phase 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 mm posteriorly</td>
</tr>
<tr>
<td>2</td>
<td>13 mm anteriorly</td>
</tr>
<tr>
<td>3</td>
<td>3 mm anteriorly</td>
</tr>
<tr>
<td>4</td>
<td>13 mm anteriorly</td>
</tr>
<tr>
<td>5</td>
<td>10 mm anteriorly</td>
</tr>
<tr>
<td>6</td>
<td>0 mm</td>
</tr>
<tr>
<td>7</td>
<td>28 mm anteriorly</td>
</tr>
<tr>
<td>8</td>
<td>10 mm anteriorly</td>
</tr>
<tr>
<td>9</td>
<td>17 mm anteriorly</td>
</tr>
<tr>
<td>10</td>
<td>0 mm</td>
</tr>
</tbody>
</table>

ABC = active breathing control; Iso = isocentre; FB = free breathing

Movement of tumour and isocentre away from spinal cord with ABC led to a significant decrease in dose to spinal cord. The maximum dose to spinal cord was significantly reduced in 8 of the 10 ABC plans, Table 4.8 and Figure 4.7, with a median dose reduction of 1.03 Gy (range −0.26 to 7.97) (p=0.022).
Table 4.8: Maximum spinal cord dose for FB and ABC plans and the saving with ABC

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Maximum cord dose (Gy)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FB</td>
<td>ABC</td>
<td>FB-ABC</td>
</tr>
<tr>
<td>1</td>
<td>39.17</td>
<td>38.98</td>
<td>0.19</td>
</tr>
<tr>
<td>2</td>
<td>38.36</td>
<td>35.44</td>
<td>2.92</td>
</tr>
<tr>
<td>3</td>
<td>40.26</td>
<td>39.21</td>
<td>1.05</td>
</tr>
<tr>
<td>4</td>
<td>35.82</td>
<td>36.08</td>
<td>-0.26</td>
</tr>
<tr>
<td>5</td>
<td>36.94</td>
<td>36.07</td>
<td>0.87</td>
</tr>
<tr>
<td>6</td>
<td>43.47</td>
<td>38.63</td>
<td>4.84</td>
</tr>
<tr>
<td>7</td>
<td>37.10</td>
<td>36.09</td>
<td>1.01</td>
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<td>8</td>
<td>36.92</td>
<td>30.61</td>
<td>6.31</td>
</tr>
<tr>
<td>9</td>
<td>31.86</td>
<td>23.89</td>
<td>7.97</td>
</tr>
<tr>
<td>10</td>
<td>33.90</td>
<td>34.20</td>
<td>-0.23</td>
</tr>
</tbody>
</table>

Figure 4.7: Maximum spinal cord dose for FB and ABC plans
Occasionally tumours infiltrated the mediastinum and therefore did not move with breathing as shown in Figure 4.8.

Figure 4.8: Fused FB (greyscale) and ABC (purple) CT scans demonstrating minimal shift with ABC due to tumour infiltration of the mediastinum.

The FB and ABC oesophageal length and volume treated, maximum and mean doses are displayed in Table 4.9. There were no significant differences of lengths and volumes of oesophagus or maximum doses received by the oesophagus between FB and ABC scans. However, the mean dose received by the oesophagus was significantly less for the ABC plans ($p=0.04$).
Table 4.9: FB and ABC oesophageal lengths and volumes treated and the maximum and mean doses received by the oesophagus

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Oesophageal Length</th>
<th>Oesophageal Volume</th>
<th>Max. dose (Gy)</th>
<th>Mean dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>ABC (cm)</td>
<td>FB (cm³)</td>
<td>ABC (cm³)</td>
</tr>
<tr>
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<td>14.5</td>
<td>14.5</td>
<td>27.8</td>
<td>26.1</td>
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<td>2</td>
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<td>15.2</td>
<td>21.1</td>
<td>19.5</td>
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<tr>
<td>3</td>
<td>13.5</td>
<td>14.0</td>
<td>21.9</td>
<td>22.0</td>
</tr>
<tr>
<td>4</td>
<td>15.0</td>
<td>16.5</td>
<td>29.2</td>
<td>23.0</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
<td>13.1</td>
<td>15.7</td>
<td>13.2</td>
</tr>
<tr>
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<td>13.5</td>
<td>13.3</td>
<td>25.5</td>
<td>20.1</td>
</tr>
<tr>
<td>7</td>
<td>16.5</td>
<td>16.5</td>
<td>26.2</td>
<td>24.3</td>
</tr>
<tr>
<td>8</td>
<td>18.0</td>
<td>18.1</td>
<td>20.6</td>
<td>24.6</td>
</tr>
<tr>
<td>9</td>
<td>14.0</td>
<td>13.9</td>
<td>18.0</td>
<td>19.6</td>
</tr>
<tr>
<td>10</td>
<td>12.5</td>
<td>12.9</td>
<td>21.8</td>
<td>23.9</td>
</tr>
</tbody>
</table>
4.4 Conclusions

ABC allowed breath hold at reproducible lung volumes with minimal intra-fraction and inter-fraction variation. Fusion of the ABC 1 and 2 scans and the ABC 1 and 3 scans displayed minimal intra- and inter-fraction variation respectively as shown in Figures 4.9a and 4.9b.

GTV and ENI were more clearly defined. GTV and PTV were reduced on ABC compared with FB scans. As ABC was performed in moderate deep inspiration lung volumes were increased and V20 was reduced. Usually the tumours moved anteriorly with ABC and the spinal cord doses were reduced.

No notable problems were encountered in use of the frame and ABC by patients, radiographers and physicists.
Figure 4.9: Fused ABC 1 and 2 scans giving intrafraction variation (4.9a) and ABC 1 and scans giving interfraction variation (4.9b).

Figure 4.9a - ABC1 (greyscale) fused with ABC2 (blue)

Figure 4.9b - ABC1 (greyscale) fused with ABC3 (purple)
4.5 Discussion

The development of 3D conformal radiotherapy and intensity modulated radiotherapy (IMRT) enable very accurate planning and delivery of radiotherapy with the aim of giving a high dose of radiotherapy to disease and minimal dose to adjacent normal tissues. However, it is then very important to ensure the improved accuracy of 3D CRT is not defeated by geometric miss, due to set-up and organ motion errors. The immobilisation frame, validated with CT scans as discussed previously in Chapter 3, improved alignment of external and internal anatomy.

In DIBH a patient maintains BH at deep inspiration without special equipment [111, 112]. However, reproducibility was based on the position of the diaphragm and this may not relate to the position of the lung cancer. Reproducibility of lung volumes and tumour position and therefore the accuracy of the technique, for the tumour, are not known. Patients found repeated DIBH difficult to perform.

Gating may be performed while free breathing or in breath hold. If done while free breathing, although treatment is restricted to a particular range within the respiratory cycle, there may still be some movement of normal structures and tumour. Such movement would be avoided by gating in arrested respiration such as with ABC in moderate deep inspiration. During gating while free breathing treatment is activated by surrogate markers such as the position of the diaphragm or a sensor mounted on the abdominal wall. It is assumed that the position of the tumour correlates with the marker, which has not been proven.

As CT was used to validate ABC in this study reproducibility of position of tumour, chest wall and diaphragm were directly assessed.

ABC was originally to be used to improve accuracy of dose delivery to tumours. However, there were added benefits. Arrest of respiration prevented blurring of the
tumour resulting in better definition of GTV with subsequent reductions in PTV and doses to normal tissues. It was felt that the PTV 2 was significantly smaller on the ABC scan because the PTV 2, which contained the tumour alone, may be more prone to blurring during respiration than the more stable mediastinum. In agreement with this finding slow CT scans have been shown by others to generate larger target volumes due to better capture of tumour movement for peripheral lung tumours [51].

Coverage of the PTV, as assessed by the V95, was sometimes less than desirable which was believed to be a function of penumbra and choice of field sizes due to normal tissue constraints. Improving the coverage by using wider fields would have led to prohibitively high lung and spinal cord doses in those cases. Penumbra enhancement could be useful in these patients enabling the same size of fields to be used whilst improving dose to the PTV in lung [104].

In addition it has been found that there were added benefits with sparing of normal tissues, lung and spinal cord. In two patients the spinal cord doses on the FB plan were above 40 Gy making the patients unsuitable for radical treatment. The use of ABC for these patients reduced the maximum spinal dose from 40.26 to 39.21 Gy for one and from 43.47 to 38.63 Gy for the other patient and would have allowed them both to receive radical radiotherapy. In a further 6 patients the spinal cord dose was also reduced thereby giving an extra safety margin for the same prescribed dose or which could be used to allow dose escalation. With ABC the saving in spinal cord dose could enable a median dose escalation of 9.8% (range 2 - 40.3) equivalent to 4 Gy (range 0.8 – 16.1) based upon a maximum spinal cord dose of 40 Gy.

Similarly, with ABC, the V20 was reduced in all 10 patients. For one patient the V20 was 39.1 % whilst FB which would have been too high to allow radical radiotherapy. With ABC the V20 was reduced to 33.2 % making radical radiotherapy possible. For the other 9 patients ABC gave a further safety margin reducing the V20 by a median of
17.4% (range 10.2-19) based upon a maximum V20 of 35%. As with the spinal cord the gain with ABC in V20 could be used to facilitate dose escalation.

The ABC apparatus may be integrated with a linear accelerator to enable automated gating at breath hold during treatment.
CHAPTER 5.

EVALUATION OF LUNG AND OESOPHAGEAL MORBIDITY FOLLOWING RADICAL 3D CONFORMAL RADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER

5.1 Introduction

The treatment of tumours in the thoracic region to a high dose with radiotherapy is complicated by the tolerance of the lungs, spinal cord, oesophagus and heart to radiation [73], particularly in the case of NSCLC where local failure remains a problem [46]. Several studies suggest that improved local tumour control increases survival [129-132]. It has already been proposed in Chapters 3 and 4 that local tumour control may be improved by ensuring that the prescribed dose is accurately delivered to the cancer. Once this has been achieved, dose escalation (increasing the prescribed dose of radiation), might improve survival in locally advanced NSCLC. However, dose escalation requires knowledge of normal tissue tolerances and the clinical consequences of exceeding them. The risk of pneumonitis and pulmonary fibrosis increases with the dose received by the lungs and they are inevitable in close proximity to the tumour where lung tolerance will be exceeded. Irradiation of a partial volume of lung beyond tolerance may not have severe effects on function but the same may not be the case for spinal cord or oesophagus.

Normal tissue tolerance has been discussed in Chapter 1, Introduction: 1.5. The currently accepted normal tissue tolerance doses have been derived from clinical experience where different dose fractionation regimes have been used to treat a variety of cancers [73]. These tolerance doses are risk estimates and individual patients may
display wide variations in normal tissue reactions. Physical factors which influence normal tissue injury by radiotherapy include volume of normal tissue irradiated, total dose, dose per fraction, and elapsed time of treatment [133, 134]. Smaller doses per fraction (hyperfractionation) are better tolerated than larger doses per fraction.

During planning, indices such as V20 and MLD are calculated and used to estimate damage to the lungs which is compatible with function and survival. It would be expected that the V20 and MLD would increase with the extent of disease as treated volumes would necessarily increase, as found in the study by Allen et al [135]. Correlation has been found in different studies between MLD [90] or V20 [85, 86] and lung morbidity. In a dose volume histogram analysis Graham et al found that a V20 of 32-40% resulted in 21-30% of patients developing Grade≥ 2 pneumonitis (requiring treatment with steroids) and at when V20 exceeded 40% over 30% of patients would develop Grade≥ 2 pneumonitis [86]. MLD also appeared to correlate with the incidence of pneumonitis [87, 89, 90]. Although V20 and MLD were correlated with radiation pneumonitis they were not compared with changes in lung function. In the study by Allen et al 43 patients were treated once daily to a median dose of 76.9 Gy (range 63-102.9) and no correlation was found between V20, Veff, MLD and pulmonary function tests (PFTs) [135]. Absolute maximum values of V20 and MLD are not known for conventional daily radiotherapy with 2 Gy fractions and there is little clinical data for CHART type radiotherapy and at present decisions are made on knowledge of acceptable risk and experience.

Acute oesophagitis is a common and, in most cases, a manageable side effect of radiotherapy in NSCLC. It is difficult to exclude the oesophagus from the treatment fields as lung cancers are often centrally located and the oesophagus will be in close proximity to the disease or the areas for ENI. It is not clear whether dose-limiting
oesophagitis is a function of volume of oesophagus irradiated beyond a particular dose or a maximum point dose.

Concurrent chemotherapy and radiotherapy, given twice daily, has been shown to be associated with the highest grade and duration of acute oesophagitis in patients with lung cancer [134]. In that study the length of oesophagus in the radiation field did not predict the severity of acute oesophagitis. However, in another study where patients with NSCLC were treated with carboplatin, paclitaxel and radiotherapy Hirota found that the length of oesophagus treated, but not the maximum dose to the oesophagus (Dmax), was a predictor of oesophagitis [78].

Few reports [74-78] focus on dosimetric or volumetric parameters as predictors of radiation oesophagitis. Maguire et al suggested that dosimetric models evaluating radiation-induced oesophagitis should consider longitudinal and circumferential factors. However, none of the parameters analysed was a significant predictor of radiation oesophagitis. This may have been due to heterogeneity of treatment as patients treated with different fractionation regimes, with and without differing chemotherapy regimens, were grouped together [74]. Langer et al [75] proposed that significantly higher rates of radiation oesophagitis would be seen in cases where greater than 16 cm of oesophagus were irradiated compared with cases treated with smaller fields. Choy et al [76], Byhardt et al [77] and Werner-Wasik et al [136] could not demonstrate that length of oesophagus irradiated was predictive of radiation oesophagitis. Hirota et al carried out a study to establish predictors of radiation oesophagitis in patients with NSCLC treated with a combination of carboplatin, paclitaxel, and radiotherapy and found that the length of oesophagus (total circumference) treated with > 45 Gy (LET 45) and the percentage of oesophageal volume receiving >45 Gy (V45) were useful dosimetric predictors of radiation oesophagitis. However, the Dmax did not predict radiation oesophagitis [78]. They suggested that for NSCLC patients, when planning
radiotherapy concomitant with carboplatin/paclitaxel chemotherapy, it was preferable to have an LETT 45 less than 9.5 cm and a V45 less than 40% to avoid severe radiation oesophagitis.

Estimates of oesophageal toxicity (TD 5/5) based on surveys of experienced clinicians have been reported as 55 Gy for the entire organ, 58 Gy for two-thirds, and 60 Gy for one-third of the oesophagus irradiated [132].

A retrospective study by Singh et al has shown that concurrent chemotherapy and maximum oesophageal point dose were significantly associated with the risk of Grade 3-5 oesophageal toxicity in patients with NSCLC treated with high-dose 3D-CRT. For patients who received concurrent chemotherapy, the threshold maximum oesophageal point dose for Grade 3-5 oesophageal toxicity was 58 Gy. In those who did not receive chemotherapy, only 2 patients developed Grade 3-5 oesophageal toxicity. Both had a maximum oesophageal point dose of >69 Gy. The authors concluded that prospective trials would be needed to confirm this relationship [137].

The disparity of results would suggest that predictors of radiation oesophagitis require further investigation.

**Dose Volume and Dose Function Histograms**

Dose volume histograms (DVH) have been used as a tool to condense and display 3D dose data in a 2D format [133, 134]. The two types of histogram used are differential and cumulative. For the differential histogram, the y axis represents the percent of the organ irradiated to a dose range shown on the x axis. For the cumulative histograms, the y axis value represents the percent of target receiving any dose ≥ Dx. It is important to realise that the dose volume histograms do not give spatial information. Damage to particular regions of the lungs may be more critical than others and it has been found in practice that fibrosis of the lower lobes is less well tolerated than fibrosis of an
equivalent volume of the upper lobes [86, 87]. It is well known that there are perfusion and ventilation differences in the lung and it has been demonstrated that changes in regional perfusion occur after radiation and dose function histograms (DFHs) have been created to relate perfusion changes to the DVH [138]. The concept of the dose function histogram (DFH) was developed to incorporate spatial information, calculating the dose distribution within the perfused (functioning) portion of the lung [139, 140]. Damage to a partial volume of lung may not cause symptoms but, in cases of spinal cord and oesophagus exceeding a maximum dose in only a small section of the organ could have severe effects on function.

**DVH Simplification Strategies**

Investigators have tried to relate several parameters that can be extracted from the DVH to patient outcome. A DVH can be represented by the percentage of a volume receiving (at least) a given dose considering only a single point on the cumulative DVH (e.g. $V_{20}$ is the percentage of lung receiving $\geq 20$ Gy). Such a value implies no effect in areas receiving $< 20$ Gy and uniform damage to areas receiving $\geq 20$ Gy. Whilst it may be unlikely that such a simplistic dose-volume relationship exists Graham et al [85] found that the $V_{20}$ for lung was related to the incidence of radiation pneumonitis.

Another popular DVH simplification that incorporates the entire DVH into a single average is the mean lung dose (MLD). The MLD has been correlated with the incidence of pneumonitis [87, 89, 90]. In a large 5-centre study of 540 patients, a dose-effect relationship was present between the MLD and the incidence of radiation pneumonitis [90].

As it is not known which parameter is the better predictor $V_{20}$ and MLD have both been correlated with lung function, dyspnoea, pneumonitis scores, PTV, and each other in this study. It was decided to study only patients who achieved CR as recurrent or
residual tumour could confound the dyspnoea scores. Patients who had previously undergone surgical resection of a lung cancer were excluded from the lung morbidity analysis as their lung volumes were reduced before radiotherapy was given. FEV1 and FVC were measured in all patients prior to treatment to ensure that they had sufficient pulmonary reserve to withstand treatment. As pneumonitis develops 2 months after treatment and resolves or evolves to fibrosis over the ensuing months, radiological pneumonitis scores, corresponding dyspnoea scores, FEV1 and FVC were recorded at least 6 months after treatment for patients who achieved complete remission (CR). Oesophageal dose (maximum and mean), length and volume of oesophagus treated were correlated with post treatment dysphagia scores.

5.2 Subjects and Methods

Lung Morbidity
Tumour control following radiotherapy was assessed radiologically at each clinic visit according to the protocol detailed in appendix 7.3. Only patients who had achieved an apparent CR on CT scan of the thorax were included in the assessment of lung morbidity.

The pre- and post-treatment FEV1, FVC results and dyspnoea scores were recorded (as outlined in appendix 7.1). The PTV, V20 and MLD from the tabulated, cumulative DVHs generated on the 3D Pinnacle® plans and the changes in FEV1, FVC, dyspnoea and radiological pneumonitis scores were recorded for those patients in CR at a minimum of six months post radiotherapy. These results were analysed for correlation using the Spearman rank and the Pearson correlation coefficients.
Oesophageal Morbidity

The external surface of the oesophagus was outlined on every slice of the planning CT scan extending 2 cm proximal and distal to the most superior and inferior slices containing PTV for all patients who were treated according to the 3D conformal protocol. The 2 cm superior and inferior expansion included oesophagus that might have received some dose due to scatter and penumbra. The dose received by oesophagus > 2 cm from the PTV margin would have been negligible and its inclusion would result in the mean dose being unrealistically reduced. The maximum dose would remain the same irrespective of the length of oesophagus measured.

Dysphagia scores (appendix 7.2) were recorded pre-treatment and at follow up (Follow up protocol, appendix 3). Dysphagia scores during weeks 1-6 and at week 8 were used to assess acute radiation induced oesophagitis and those at 3 and 6 months after radiotherapy to reflect late oesophagitis.

Mean and maximum doses to the oesophagus were recorded from the cumulative, tabulated DVHs. The length and volume of oesophagus treated in each case for PTV 1 (PTV 2 if treated in a single phase) were also recorded. The mean dose to oesophagus was mean dose to length of oesophagus in PTV plus 4 cm as described above. The maximum and mean oesophageal doses and maximum dysphagia scores were correlated with the volume and length of oesophagus treated as described above. Scores of those patients who had received neo-adjuvant chemotherapy were compared with those who received radiotherapy alone to determine whether chemotherapy affected the oesophageal morbidity.
5.3 Results

**Lung Morbidity**

When the analysis was performed, 16 of the 22 treated patients (73%) were alive and in CR on CT scan of the thorax and upper abdomen. Of the original 24 patients, two did not receive radiotherapy because they developed metastatic disease following neoadjuvant chemotherapy, two died within 6 months of treatment (one from a pulmonary embolus and one from a myocardial infarction), three had developed brain metastases and one had residual disease in the chest. Two of the patients in CR were not suitable for assessment of lung morbidity as they had received CHARTWEL for recurrent disease following primary surgery, which would have affected their pulmonary function and radiological results.

The characteristics of the 14 patients, who were in CR and suitable for assessment, are shown in Table 5.1. Ten of the patients were male and 4 were female. The median age was 70 (range 49-79) years. Twelve patients (86%) had squamous cell cancers and two patients (14%) had NSCLC-nos. In 7 patients the cancer was located in the right lung and in 7 the left lung. Four patients had stage I, one had stage II and 9 had stage III disease. Ten patients had received neo-adjuvant chemotherapy.

The percentage change in pre- and six month post-treatment FEV1 and FVC measurements, the change in dyspnoea scores at 6 months and the 6 month post treatment CT radiation pneumonitis scores, V20, MLD, PTV 1 and 2 are given in Table 5.2.
Table 5.1: Patient characteristics for those in CR suitable for lung morbidity assessment.

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>SEX</th>
<th>AGE</th>
<th>SITE</th>
<th>TUMOUR</th>
<th>HISTOLOGY</th>
<th>TNM</th>
<th>INT. STAGING</th>
<th>CHEMO</th>
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<tbody>
<tr>
<td>2</td>
<td>M</td>
<td>59</td>
<td>RULB</td>
<td>SCC-2</td>
<td>T4N2M0</td>
<td>IIIB</td>
<td>MVPx4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>49</td>
<td>LUL+LMB</td>
<td>SCC-3</td>
<td>T4N1M0</td>
<td>IIIB</td>
<td>MVPx3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>51</td>
<td>RMB</td>
<td>SCC-2</td>
<td>T4N0M0</td>
<td>IIIB</td>
<td>MICx3</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>70</td>
<td>Ling,LLLB</td>
<td>NSCLC-nos</td>
<td>T2N0M0</td>
<td>IB</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>75</td>
<td>RULB</td>
<td>SCC-2</td>
<td>T4N0M0</td>
<td>IIIIB</td>
<td>MICx3</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>71</td>
<td>Nil endobr, LMZ</td>
<td>SCC-2</td>
<td>T1N0M0</td>
<td>IA</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>68</td>
<td>LLLB</td>
<td>SCC-2</td>
<td>T1N0M0</td>
<td>IA</td>
<td>MICx3</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>73</td>
<td>Nil endobr, RMZ</td>
<td>NSCLC-nos</td>
<td>T2N0M0</td>
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<td>NONE</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>77</td>
<td>RUL+RMB</td>
<td>SCC-2</td>
<td>T3N1M0</td>
<td>IIIA</td>
<td>PCx3</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>79</td>
<td>LMB</td>
<td>SCC-2</td>
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<td>IIIB</td>
<td>PCx3</td>
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<tr>
<td>20</td>
<td>M</td>
<td>69</td>
<td>LingB</td>
<td>SCC-3</td>
<td>T4N2M0</td>
<td>IIIB</td>
<td>PCx3</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>69</td>
<td>RU,Mid,LLB</td>
<td>SCC-2</td>
<td>T3N2M0</td>
<td>IIIA</td>
<td>PCx3</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>M</td>
<td>65</td>
<td>LLLB</td>
<td>SCC-2</td>
<td>T3N2M0</td>
<td>IIIA</td>
<td>NPx3</td>
<td></td>
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<tr>
<td>24</td>
<td>M</td>
<td>76</td>
<td>RULB</td>
<td>SCC-2</td>
<td>T3N1M0</td>
<td>IIIA</td>
<td>NONE</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.2: Lung morbidity data

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Change in FEV1</th>
<th>Change in FVC</th>
<th>Change in dyspnoea score</th>
<th>CT pneum. score</th>
<th>MLD (Gy)</th>
<th>V20 (%)</th>
<th>PTV1 (cm³)</th>
<th>PTV2 (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>post RT (%)</td>
<td>post RT (%)</td>
<td>(post-pre) (%)</td>
<td>(post-pre) score at 6 months (post-pre) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-2.90</td>
<td>-10.2</td>
<td>+1</td>
<td>1</td>
<td>13.41</td>
<td>24.4</td>
<td>397.2</td>
<td>379.5</td>
</tr>
<tr>
<td>3</td>
<td>-15.2</td>
<td>-40.5</td>
<td>0</td>
<td>1</td>
<td>15.99</td>
<td>32.0</td>
<td>451.5</td>
<td>417.2</td>
</tr>
<tr>
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<td>+56.9</td>
<td>+60.6</td>
<td>-1</td>
<td>1</td>
<td>15.27</td>
<td>26.9</td>
<td>446.8</td>
<td>395.9</td>
</tr>
<tr>
<td>6</td>
<td>-4.40</td>
<td>-6.50</td>
<td>0</td>
<td>1</td>
<td>12.99</td>
<td>22.5</td>
<td>-</td>
<td>280.3</td>
</tr>
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<td>7</td>
<td>-35.2</td>
<td>-35.6</td>
<td>+3</td>
<td>2</td>
<td>20.61</td>
<td>36.2</td>
<td>489.3</td>
<td>394.9</td>
</tr>
<tr>
<td>10</td>
<td>-12.7</td>
<td>-3.70</td>
<td>+1</td>
<td>1</td>
<td>9.21</td>
<td>15.6</td>
<td>-</td>
<td>187.4</td>
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<td>+42.9</td>
<td>0</td>
<td>1</td>
<td>13.44</td>
<td>20.2</td>
<td>247.3</td>
<td>188.4</td>
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<td>-7.70</td>
<td>+10.0</td>
<td>-2</td>
<td>1</td>
<td>16.41</td>
<td>32.8</td>
<td>-</td>
<td>316.1</td>
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<td>16</td>
<td>-15.7</td>
<td>+7.90</td>
<td>+2</td>
<td>2</td>
<td>14.25</td>
<td>24.4</td>
<td>457.5</td>
<td>354.7</td>
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<td>-15.6</td>
<td>0</td>
<td>0</td>
<td>10.31</td>
<td>18.6</td>
<td>251.1</td>
<td>125.4</td>
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<td>20</td>
<td>-31.7</td>
<td>-26.5</td>
<td>0</td>
<td>2</td>
<td>15.88</td>
<td>27.1</td>
<td>516.0</td>
<td>426.1</td>
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<td>21</td>
<td>-24.8</td>
<td>-14.7</td>
<td>0</td>
<td>1</td>
<td>21.16</td>
<td>39.1</td>
<td>-</td>
<td>375.7</td>
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<td>-0.53</td>
<td>+7.30</td>
<td>0</td>
<td>2</td>
<td>18.43</td>
<td>32.5</td>
<td>-</td>
<td>440.7</td>
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<td>ISQ</td>
<td>ISQ</td>
<td>0</td>
<td>2</td>
<td>15.26</td>
<td>25.2</td>
<td>386.2</td>
<td></td>
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</table>

ISQ = “in status quo” i.e. unchanged.
The FEV1 was reduced following radiotherapy in 10 of the 14 patients by a median of 12.7% but dyspnoea scores increased in only 4 of those 10.

There were significant positive correlations between the changes in FEV1 and FVC scores at 6 months post radiotherapy ($p<0.001$) Fig 5.1, the MLD and V20 ($p<0.0001$) Fig 5.2 and between the PTV and the following: the radiological pneumonitis score ($p=0.013$) Fig 5.3, the V20 ($p=0.016$) Fig 5.4 and the MLD ($p=0.013$) Fig 5.5.

Figure 5.1: Scatter plot of change in FEV1 and FVC post radiotherapy (RT)

![Figure 5.1: Scatter plot of change in FEV1 and FVC post radiotherapy (RT)](image)

Fig 5.1 shows that FEV1 and FVC usually decrease after radiotherapy but could increase. The smaller percentage increases could have been effort related or due to learning and the greater increases due to response of tumour to treatment.
Both MLD and V20 increased together.

Virtually all patients developed pneumonitis after radiotherapy and the pneumonitis score increased with the PTV.
As expected, increase in PTV led to more lung being treated and higher lung doses as represented by V20 and MLD.
There was no significant correlation between the reduction in FEV 1 or FVC and the
dyspnoea or radiological pneumonitis scores at 6 months post treatment, the MLD, V20
or PTV as displayed in Figures 5.6-5.15. There was also no significant correlation
between the change in dyspnoea score and the radiological pneumonitis scores, MLD,
V20 or PTV shown in Figures 5.16-5.19. The radiological pneumonitis scores did not
correlate with the MLD or V20 as shown in Figures 5.20 and 5.21.

All of the results are shown in Table 5.3.

Figure 5.6: Scatter plot of change in FEV 1 and dyspnoea scores post treatment

FEV 1 generally reduced after radiotherapy but patients did not necessarily develop
dyspnoea. Those who did develop dyspnoea had similar FEV 1 reductions to others
who did not become dyspnoeic.
Figure 5.7: Scatter plot of change in FEV 1 and radiological pneumonitis scores post treatment

Fig 5.7 shows that after radiotherapy FEV 1 decreased and radiological pneumonitis developed but there was no correlation between the reduction in FEV 1 and the radiological pneumonitis score.

Figure 5.8: Scatter plot of change in FEV 1 post treatment and the MLD
Figures 5.8 and 5.9 demonstrate no correlation with reduction in FEV1 post radiotherapy and MLD or V20, although there was a trend for greater reductions in FEV1 and FVC in those with higher lung doses.

Although FEV1 reduced after radiotherapy and there was a trend towards greater reduction with increased PTV there was no significant correlation.
Trends for changes in FVC were similar to FEV_1 for change in dyspnoea score, radiological pneumonitis score, MLD, V20 and PTV.
Figure 5.13: Scatter plot of change in FVC post treatment and the MLD

Figure 5.14: Scatter plot of change in FVC post treatment and the V20
Figure 5.15: Scatter plot of change in FVC post treatment and the PTV

![Figure 5.15](image)

Figure 5.16: Scatter plot of changes in dyspnoea and radiological pneumonitis scores post treatment

![Figure 5.16](image)

There was no correlation between radiation pneumonitis and change in dyspnoea scores, although with higher radiation pneumonitis scores there were greater changes in dyspnoea scores.
Despite increasing MLD and V20 patients did not suffer dyspnoea and those who did develop dyspnoea had similar MLDs and V20s to others who did not develop dyspnoea.

In most cases although V20 increased there was no increase in dyspnoea.
Figure 5.19: Scatter plot of changes in dyspnoea scores post treatment and the PTV

Again, patients did not necessarily develop dyspnoea despite increases in PTVs and volumes of lung treated.

Figure 5.20: Scatter plot of radiological pneumonitis scores post treatment and MLD

Radiological pneumonitis developed in all but one patient but there was no correlation with MLD and V20.
Figure 5.21: Scatter plot of radiological pneumonitis scores post treatment and the V20
Table 5.3: Lung Morbidity Correlations

<table>
<thead>
<tr>
<th>Change in FEV 1 post treatment</th>
<th>Change in FVC post treatment</th>
<th>Change in dyspnoea score post treatment</th>
<th>Radiological pneumonitis score post treatment</th>
<th>MLD (Gy)</th>
<th>V20 (%)</th>
<th>Max. PTV (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Correlation Sig(2-tailed) N</td>
<td>1.000</td>
<td>0.838**</td>
<td>0.000</td>
<td>-0.489</td>
<td>0.076</td>
<td>-0.357</td>
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<td>Pearson Correlation Sig(2-tailed) N</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
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<tr>
<td>Change in FVC post treatment</td>
<td>0.838**</td>
<td>1.000</td>
<td>0.000</td>
<td>0.143</td>
<td>0.142</td>
<td>-0.111</td>
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<tr>
<td>Pearson Correlation Sig(2-tailed) N</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Change in dyspnoea score post treatment</td>
<td>-0.489</td>
<td>0.076</td>
<td>0.000</td>
<td>-0.413</td>
<td>0.142</td>
<td>1.000</td>
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<tr>
<td>Pearson Correlation Sig(2-tailed) N</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Radiological pneumonitis score post treatment</td>
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<td>0.211</td>
<td>0.000</td>
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<td>0.707</td>
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<td>14</td>
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<tr>
<td>MLD (Gy)</td>
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<td>0.792</td>
<td>0.497</td>
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<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>V20 (%)</td>
<td>-0.328</td>
<td>0.252</td>
<td>0.000</td>
<td>-0.028</td>
<td>0.925</td>
<td>0.350</td>
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<td>Pearson Correlation Sig(2-tailed) N</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Maximum PTV (cm³)</td>
<td>-0.211</td>
<td>0.470</td>
<td>0.000</td>
<td>-0.285</td>
<td>0.322</td>
<td>0.240</td>
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<tr>
<td>Pearson Correlation Sig(2-tailed) N</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
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<td>14</td>
</tr>
</tbody>
</table>

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)
**Oesophageal Morbidity**

Twenty one of the 24 patients received treatment as planned and were available for follow-up and assessment of oesophageal morbidity. The patient and tumour characteristics are given in Table 5.4. There were 4 females and 17 males. The median age was 70 years, with a range of 49-79. Seventeen of the 21 patients (81%) had squamous cell carcinoma, 2 had NSCLC-nos and 2 had adenocarcinoma. Fourteen patients (67%) had stage III disease, 2 patients (10 %) had stage II disease, 4 patients (19%) had stage I disease and were medically inoperable and one patient had developed a nodal recurrence following surgery. Fourteen of the 21 patients (67%) had received neo-adjuvant chemotherapy.

The pre- and post-radiotherapy dysphagia scores are documented in Table 5.5. Almost all of the patients suffered acute dysphagia related to the radiotherapy but in all cases recovery occurred by week 8. There was no evidence of dysphagia in any of the patients at 3 and 6 months post treatment. There was no significant difference between the dysphagia scores of those patients who received chemotherapy and those who had radiotherapy alone.

The volume, length, maximum and mean dose of the oesophagus were correlated with the dysphagia scores and showed a significant positive correlation between the maximum dysphagia score and the maximum oesophageal dose received using the Spearman rank correlation coefficient ($p=0.033$) displayed in Figure 5.22. There was also a significant positive correlation between the oesophageal volume and the length of oesophagus treated ($p=0.012$) shown in Figure 5.23 and between the maximum and mean doses received by the oesophagus ($p=0.008$) shown in Figure 5.24.
Table 5.4: Patient and tumour characteristics for patients suitable for oesophageal morbidty study

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Sex</th>
<th>Age</th>
<th>Tumour site</th>
<th>Histology</th>
<th>TNM stage</th>
<th>Chemotherapy</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>62</td>
<td>L hilum,nil endobronch</td>
<td>Adeno</td>
<td>T4N0M0/IIIB</td>
<td>PCx3</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>59</td>
<td>RULB</td>
<td>SCC-2</td>
<td>T4N2M0/IIIB</td>
<td>MVPx4</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>49</td>
<td>LUL+LMB</td>
<td>SCC-3</td>
<td>T4N1M0/IIIB</td>
<td>MVPx3</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>51</td>
<td>RMB</td>
<td>SCC-2</td>
<td>T4N0M0/IIIB</td>
<td>MICx3</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>71</td>
<td>LULB</td>
<td>SCC-3</td>
<td>T4N2M0/IIIB</td>
<td>MICx3</td>
</tr>
<tr>
<td>6 *</td>
<td>F</td>
<td>70</td>
<td>Ling,LLLB</td>
<td>NSCLC-nos</td>
<td>T2N0M0/IB</td>
<td>NONE</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>75</td>
<td>RULB</td>
<td>SCC-2</td>
<td>T4N0M0/IIIB</td>
<td>MICx3</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>57</td>
<td>RULB</td>
<td>SCC-3</td>
<td>T4N2M0/IIIB</td>
<td>MICx3</td>
</tr>
<tr>
<td>9 *</td>
<td>M</td>
<td>72</td>
<td>LM+LLLB Post op</td>
<td>SCC-2</td>
<td>T3N0M0/IIIB</td>
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</tr>
<tr>
<td>10*</td>
<td>F</td>
<td>71</td>
<td>Nil endobr, LMZ</td>
<td>SCC-2</td>
<td>T1N0M0/IA</td>
<td>NONE</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>68</td>
<td>LLLB</td>
<td>SCC-2</td>
<td>T1N0M0/IA</td>
<td>MICx3</td>
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<tr>
<td>12</td>
<td>M</td>
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<td>RmidLB</td>
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<td>Adeno</td>
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<td>16</td>
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<td>T3N1M0/IIIA</td>
<td>PCx3</td>
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<td>17</td>
<td>M</td>
<td>79</td>
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<td>SCC-2</td>
<td>T3N0M0/IIIB</td>
<td>PCx3</td>
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<td>SCC-3</td>
<td>T4N2M0/IIIB</td>
<td>PCx3</td>
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<td>21*</td>
<td>F</td>
<td>69</td>
<td>RU,Mid,LLB</td>
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<td>PCx3</td>
</tr>
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<td>22</td>
<td>M</td>
<td>74</td>
<td>RULB</td>
<td>SCC</td>
<td>T4N1M0/IIIB</td>
<td>MICx3</td>
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<tr>
<td>23*</td>
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<td>65</td>
<td>LLLB</td>
<td>SCC-2</td>
<td>T3N2M0/IIIA</td>
<td>NPx3</td>
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<tr>
<td>24*</td>
<td>M</td>
<td>76</td>
<td>RULB</td>
<td>SCC-2</td>
<td>T3N1M0/IIIA</td>
<td>NONE</td>
</tr>
</tbody>
</table>

* = Patients treated with a single phase 2 to cover disease alone omitting elective nodal regions
Table 5.5: Pre-and post-treatment dysphagia scores

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Pre-treatment Dysphagia score</th>
<th>Maximum Dysphagia score due to RT wks 1-6</th>
<th>Dysphagia score due to RT at week 8</th>
<th>Dysphagia score at 3 months post RT</th>
<th>Dysphagia score at 6 months post RT</th>
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<tbody>
<tr>
<td>1</td>
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<td>0</td>
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<td>0</td>
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<tr>
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<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

N/A=Not Available
Significant correlation was seen for the maximum dysphagia score and the maximum dose received by the oesophagus. The patient who developed a dysphagia score of 4, as shown on Fig. 5.22 above had received 4 instead of 3 courses of neo-adjuvant chemotherapy which may have contributed to the increased severity of dysphagia.

Figure 5.23 below demonstrates a significant correlation between oesophageal length and volume as would be expected if the radius does not change much throughout the normal oesophagus. It may therefore be possible to use length as a surrogate for volume and vice versa although both indices can be easily obtained from the 3D planning system once the oesophagus has been outlined.
Figure 5.23: Scatter plot of oesophageal volume and oesophageal length treated

![ Scatter plot of oesophageal volume and oesophageal length treated ]

Figure 5.24: Scatter plot of maximum and mean oesophageal dose received

![ Scatter plot of maximum and mean oesophageal dose received ]
There was no significant correlation between the maximum dysphagia score and the oesophageal volume (Figure 5.25), length (Figure 5.26) or mean dose received (Figure 5.27). There was also no significant correlation between the oesophageal length or volume treated and maximum (Figure 5.28 and Figure 5.29) and mean doses received (Figure 5.30 and Figure 5.31) using the Spearman rank correlation coefficient however, using the Pearson correlation coefficient there was a significant correlation between the oesophageal volume treated and the mean oesophageal dose received ($p=0.04$). These results are given in Table 5.6.

Figure 5.25: Scatter plot of maximum dysphagia scores post treatment and the oesophageal volume treated
Most patients developed Grade 2 oesophagitis irrespective of the volume or length of oesophagus treated or mean oesophageal dose.
Although the length of oesophagus treated increased the maximum dose received did not necessarily increase. Most of the points in Figure 5.28 are clustered between 55 and 62.5 Gy i.e. the tumour dose, irrespective of the length treated, implying that restricting the length treated would not reduce the dose received. There was also no correlation between the volume and maximum dose received as shown in Figure 5.29, nor length and mean dose received by the oesophagus.
Figure 5.29: Scatter plot of oesophageal volume treated and the maximum oesophageal dose received

Figure 5.30: Scatter plot of oesophageal length treated and the mean oesophageal dose received
There was a significant correlation; all patients developed dysphagia and all subsequently healed.
### Table 5.6: Oesophageal Morbidity Correlations

<table>
<thead>
<tr>
<th>Correlations</th>
<th>Max Dysphagia score</th>
<th>oesophageal volume</th>
<th>oesophageal length</th>
<th>max oesophageal dose</th>
<th>mean oesophageal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman’s r</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max Dysphagia score Correlation Coeff</td>
<td>1.000</td>
<td>.113</td>
<td>-.025</td>
<td>.466*</td>
<td>.335</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>oesophageal volume Correlation Coeff</td>
<td>.113</td>
<td>1.000</td>
<td>.537*</td>
<td>.037</td>
<td>.202</td>
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<td>Sig. (2-tailed)</td>
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<td>.012</td>
<td>.872</td>
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<td>21</td>
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<td>21</td>
</tr>
<tr>
<td>oesophageal length Correlation Coeff</td>
<td>-.025</td>
<td>.537*</td>
<td>1.000</td>
<td>-.210</td>
<td>-.048</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
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<td>.361</td>
<td>.835</td>
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<tr>
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<td>21</td>
</tr>
<tr>
<td>max oesophageal dose Correlation Coeff</td>
<td>.466*</td>
<td>.037</td>
<td>-.210</td>
<td>1.000</td>
<td>.561*</td>
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<td>Sig. (2-tailed)</td>
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<td>21</td>
</tr>
<tr>
<td>mean oesophageal dose Correlation Coeff</td>
<td>.335</td>
<td>.202</td>
<td>-.048</td>
<td>.561*</td>
<td>1.000</td>
</tr>
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<td>Sig. (2-tailed)</td>
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<td>.835</td>
<td>.008</td>
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</table>

*Correlation is significant at the .05 level (2-tailed).

### Table 5.6: Oesophageal Morbidity Correlations

<table>
<thead>
<tr>
<th>Correlations</th>
<th>Max Dysphagia score</th>
<th>oesophageal volume</th>
<th>oesophageal length</th>
<th>max oesophageal dose</th>
<th>mean oesophageal dose</th>
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</thead>
<tbody>
<tr>
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<td>-.065</td>
<td>.319</td>
<td>.422</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>oesophageal volume Pearson Correlation Coeff</td>
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<td>1.000</td>
<td>.446*</td>
<td>.382</td>
<td>.452*</td>
</tr>
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<td>.043</td>
<td>.088</td>
<td>.040</td>
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<td>21</td>
<td>21</td>
</tr>
<tr>
<td>oesophageal length Pearson Correlation Coeff</td>
<td>-.065</td>
<td>.446*</td>
<td>1.000</td>
<td>.268</td>
<td>.133</td>
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<td>.239</td>
<td>.565</td>
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<td>max oesophageal dose Pearson Correlation Coeff</td>
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<td>.382</td>
<td>.268</td>
<td>1.000</td>
<td>.842*</td>
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<td>Sig. (2-tailed)</td>
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<td>.088</td>
<td>.239</td>
<td>.000</td>
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</tr>
<tr>
<td>mean oesophageal dose Pearson Correlation Coeff</td>
<td>.422</td>
<td>.452*</td>
<td>.133</td>
<td>.842*</td>
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<td>.040</td>
<td>.565</td>
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</table>

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).
The maximum dysphagia scores available for the 14 patients who received neo-adjuvant chemotherapy and the 7 patients who did not receive chemotherapy are given in Table 5.7. The mean dysphagia score for the group who received chemotherapy was 1.71 and the median was 2 (range 0-4). For the group that received radiotherapy alone the mean dysphagia score was 1.57 and the median was 2 (range 0-2). Patient 2, who developed a maximum dysphagia score of 4, had received an extra course of neo-adjuvant chemotherapy and this may have contributed to the more severe reaction. The number of cases was too small to allow a valid statistical comparison to be made.

Table 5.7: Maximum dysphagia scores for patients who did and did not receive chemotherapy

<table>
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<th>Patient number</th>
<th>Maximum dysphagia score Chemotherapy given</th>
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5.4 Conclusions

It was expected that there would be a positive correlation between PTV, V20, MLD and radiological pneumonitis as the greater the PTV the greater the volume of lung treated and dose to the PTV exceeds lung tolerance. Examination of the cases revealed that only one patient did not develop radiological evidence of pneumonitis. However, in that case there was small volume right paratracheal disease which was treated with relatively small and narrow fields. Paramediastinal pneumonitis and fibrosis may have occurred. The fibrosed lung may then have contracted medially and become indistinguishable from the mediastinum and the space of that lung filled by expansion of normal lung (Figure 5.3). Lung volume would decrease with development of pneumonitis and fibrosis. Radiological pneumonitis developed in 93% of cases and FEV1 and FVC were reduced in 71% after radiotherapy. However, patients did not necessarily become dyspnoeic and dyspnoea scores worsened in only 4 of 10 cases where there was a reduction in FEV1 and FVC after radiotherapy.

Almost all patients experienced acute dysphagia but the reaction resolved by week 8 and there was no evidence of dysphagia at 3 and 6 months after treatment. One patient who received 4 instead of 3 courses of chemotherapy suffered Grade 4 dysphagia otherwise the maximum dysphagia score was 2 whether or not the patients received chemotherapy. There was no significant difference in dysphagia scores between those patients who received neo-adjuvant chemotherapy and those who received radiotherapy alone. There was a significant positive correlation between the maximum oesophageal dose and the dysphagia score and between the mean oesophageal dose and the oesophageal volume. However, it should be noted that mean oesophageal dose applied to the oesophagus from 2cm proximal to 2cm distal to the PTV. Others who defined the oesophagus with greater lengths included oesophagus which did not receive significant
dose, these mean doses would consequently be lower and of uncertain clinical meaning [74, 78].

5.5 Discussion

Graham et al found a positive correlation between V20 and MLD and V20 was found to be a significant predictor of radiation pneumonitis but surprisingly V20 was not related to tumour size [86]. Kwa et al found that MLD was a useful predictor of risk of pneumonitis [90] but MLD was not compared or evaluated against V20 in the severity of pneumonitis. In this study there was a significant positive correlation between V20 and MLD and between PTV and both the V20 and MLD. However, V20 and MLD did not correlate with radiation pneumonitis which could be explained by radiation pneumonitis being almost inevitable close to disease and a dose response effect would not be expected. Dyspnoea did not correlate with reductions in FEV1 and FVC but it is well known that dyspnoea does not correlate with lung function [135]. Also, the dyspnoea scoring system was subjective relying on patients' perception of their dyspnoea and may not have been sensitive. An objective test may have yielded results which correlated with spirometry results. As reductions in FEV1 and FVC reflect pulmonary fibrosis, which is detected by radiological radiation pneumonitis, the lack of correlation of breathlessness with radiation pneumonitis was consistent. The lack of correlation between dyspnoea and radiation pneumonitis may also be explained by the improvement in pulmonary function which may occur as tumours regress after treatment, in addition to compensatory changes in the unirradiated lung as suggested by Choi et al [141]. FEV1, which is partly effort-related, can improve with learning (which occurs with repeat testing). Both may explain the smaller improvements seen after treatment when reductions would have been expected. The lack of correlation
between dyspnoea and PTV, V20, MLD, radiation pneumontis and reductions in FEV 1, FVC could also be explained by the dose limitations, V20 ≤ 35% and spinal cord dose ≤ 40 Gy, being safe. The constraints may have prevented a dose response from being detected and prevented occurrence of a critical degree of damage. Treatment with hyperfractionated radiotherapy may have protected against pneumonitis. In the studies by Graham [86] and Kwa [90] treatment was given once daily with 1.8 or more often 2 Gy fractions, compared to this study where treatment was given with 1.5 Gy fractions three times daily. Although critical lung damage was not reached reduction in PTV and hence pneumonitis by reduction of set-up error with improved immobilisation and elimination of the margin for organ motion could increase safety. The lack of severe acute and late reactions suggest the potential for relaxation of normal tissue dose constraints and dose escalation.

Others have found a correlation between the length of oesophagus treated and development of oesophagitis and have suggested restriction of the length of oesophagus treated to avoid morbidity. In this study there was correlation between dysphagia and maximum dose received by the oesophagus but not mean dose or length treated. Singh et al found that when concurrent chemotherapy was given there was a significant association between the maximum oesophageal point dose and the risk of grade 3-5 oesophageal toxicity [137], which was not seen in previous studies [74, 78]. In Figure 5.28 it is seen that maximum oesophageal doses clustered around 60 Gy, the tumour dose, irrespective of the length treated so that reduction in the length of oesophagus treated would not reduce the maximum dose received by the oesophagus. Figure 5.22 showed that patients developed Grade 1 or 2 dysphagia irrespective of the maximum oesophageal dose apart from the patient who received 4 instead of 3 courses of chemotherapy and who suffered Grade 4 dysphagia. The level of dysphagia was mild and resolved in all cases. These results, compatible with references 74, 76, 77 and 136,
confirm that restriction of length would not reduce maximum dose received by the oesophagus and decrease morbidity. Also, the level of dysphagia suffered was mild and transient and application of a restriction of length of oesophagus treated may compromise tumour dose and endanger cure.
CHAPTER 6.

CONCLUSIONS AND FUTURE WORK

6.1 Summary

The aim of this thesis was to determine whether the results of radical radiotherapy for inoperable NSCLC could be improved by new technological developments. The use of 3D CRT, an immobilisation device to reduce set-up error and ABC to overcome error due to respiratory movement were examined in patients treated with CHARTWEL to a total dose of 60 Gy. In addition, lung and oesophageal morbidity were assessed and correlated with doses received and volumes treated to see whether dose escalation would be possible.

In the transition from 2D to 3D radiotherapy there was potential for geometric and dosimetric errors due to differences in ICRU convention and treatment planning algorithms that could endanger cure and safety. Twenty four patients were planned using 3D (Pinnacle®) and 2D (Multidata®) systems. 2D and 3D plans could be compared using DVHs but the 2D planning system was not capable of calculating DVHs. The 2D plans were therefore transferred onto the 3D system and recalculated. DVHs could then be constructed of PTVs, lung and spinal cord for 2D plans and compared with the 3D plans to see whether 3D CRT gave better coverage of the PTV, with a lower dose to adjacent normal tissues, and whether the differences were geometric or dosimetric. The median $V_{95\text{ prescribed}}$ for PTV 1 was 91.8 % (range 40.2-95.7) 3D vs 60.5 % (range 19.6-73.9) 2D ($p=0.0003$) and for PTV 2 was 86.7 % (range 38.6-96) 3D vs 28.8 % (range 2-73.9) 2D ($p=0.0001$). These differences could be due to geometry or dosimetry. The 2D median $V_{95\text{ calculated}}$ for PTV 1 was 87.2 % (range 46.8-95.9) and for PTV 2 was 74.8 % (range 34.8-96.2) $p=0.012$, indicating miss was
due to dosimetry. The dosimetric information with 3D planning was more complete. Doses to spinal cord and lung were significantly lower with 3D compared to 2D planning. The maximum dose to spinal cord was greater in 17 of the 24 2D plans with a median dose reduction of 0.82 Gy (range -7.64 to 20.43) for 3D (p=0.04). The V20 for whole lung was greater in 16 of the 24 2D plans with a median reduction of 2.4 % (range -5.4 to 13.1) for 3D (p=0.03). The results showed that a higher dose was given to the PTV with 3D compared to 2D planning, due to a significant dosimetric advantage of the 3D planning system. Geometric coverage with 2D was adequate at the expense of higher doses to lung and spinal cord.

The accuracy with which patients may be planned with 3D systems mandated that an external immobilisation device was used to minimise set-up error. A metal immobilisation frame was designed and built in house and validated by CT scanning. Planning scans done before and after neo-adjuvant chemotherapy were fused in 10 patients (5 without and 5 with the frame). Although skin, surface markers and vertebral bodies (external anatomy) generally aligned, tumour and mediastinum (internal anatomy) aligned in only 2 of 5 patients without the frame. With the frame there was alignment of internal anatomy in 5 of 5 patients.

ABC is a technique of assisted breath hold which may minimise geometric miss caused by movement of lung cancers with breathing. The technique was validated with CT scans. ABC was performed in moderate deep inspiration, 75 % of vital capacity. Eleven patients underwent free breathing (FB) planning scans. Immediately afterwards two further scans were done in breath hold, ABC 1 and 2. Some weeks later during treatment a third ABC scan, ABC 3, was performed. Reproducibility was assessed using CT lung volumes. PTVs, doses to lung and spinal cord for FB and ABC 1 scans were compared. Comparison of ABC 1 and 2 scans gave intra-fraction reproducibility and ABC 1 and 3 scans inter-fraction reproducibility.
Disease and nodal areas for elective nodal irradiation were easier to define on ABC scans and PTVs were smaller. ABC was reproducible, lung volumes showed minimal variation over intervals of up to 8 weeks indicating that ABC could assist breath hold reliably over the duration of a course of conventional daily radiotherapy. The small variation in lung volume using moderate DIBH with ABC meant that a margin of 3mm could be used with ABC BH. Apart from increased accuracy there were additional benefits with ABC: doses to lung and spinal cord were significantly reduced. As ABC was performed in moderate deep inspiration the increase in lung volume resulted in a reduction in V20 in all of the plans by a median of 6.4 % (range 1.7 to 14.2), \( p=0.005 \). Generally tumours moved anteriorly away from the spinal cord with inspiration, resulting in reduction in the maximum dose to spinal cord in 80 % of the plans by a median of 1.03 Gy (range -0.26 to 7.97), \( p=0.02 \). This reduction in dose to critical structures could give an extra margin of safety, or could allow dose escalation. Some patients whose lung and spinal cord doses would be excessive and prohibitive to treatment if planned whilst free breathing could be rendered treatable with ABC.

The prospect for dose escalation with 3D CRT and ABC had been demonstrated but there was concern over toxicity. Lung and oesophageal morbidity were therefore assessed, to see whether there would be room for dose escalation, by correlation of the morbidity scores (dyspnoea and dysphagia) with lung function test results, MLD and V20 for lung and with the length and volume of oesophagus treated and the dose received by the oesophagus. The lung morbidity assessment was confined to patients who had achieved a complete response at least six months after treatment, as the presence of tumour might have confounded the dyspnoea scores. Thirteen of 14 patients (93 %) developed radiological pneumonitis and in 10 of 14 lung function, as measured by spirometry, was reduced after treatment but only 4 of these developed dyspnoea. There was significant correlation between the MLD and V20 (\( p<0.0001 \)) and
between the PTV and the following: radiological pneumonitis score ($p=0.013$), MLD ($p=0.013$), V20 ($p=0.016$). However, the reduction in FEV 1 or FVC did not correlate with dyspnoea. The results confirm that methods to reduce the PTV, with sharper definition and reduced tumour movement achieved with ABC, can be used to reduce V20 and MLD and consequently pneumonitis.

Almost all (90%) of the patients experienced dysphagia in the acute phase; 5 patients developed Grade 1 dysphagia, 13 patients developed Grade 2 dysphagia and one patient developed Grade 4 dysphagia. All recovered and were on a normal diet by week 8. There was a significant positive correlation between the maximum dysphagia score and the maximum dose to the oesophagus ($p=0.033$), but not the length of oesophagus treated. Restriction of length would not reduce maximum dose to oesophagus and acute morbidity.

3D CRT led to reduction in dose to normal tissues, lung and spinal cord, and use of ABC would lead to further reductions. These savings would give extra margins of safety or could allow escalation of dose. Morbidity assessments on the clinical group in this study showed that lung and oesophageal morbidity was mild even when chemotherapy was added to radiotherapy suggesting that dose limitations used in the treatment planning may be conservative and therefore attempt at dose escalation would be safe. The reduction in spinal cord dose in 80% of the patients studied with ABC could enable escalation of dose to tumour by a median of 9.8% (range 2 to 40.3), equivalent to a median increase in dose of 4 Gy (range 1.2 to 24) with ABC and CHARTWEL.
6.2 Prospects for future research

3D conformal radiotherapy planning with reproducible immobilisation and ABC has improved dose administered to the PTV and reduction of dose received by normal tissues. Potential for future work includes:

- Further dose escalation of CHARTWEL
- Incorporation of chemotherapy neo-adjuvantly and concomitantly
- Improvement in the accuracy of planning and delivery of radiotherapy
  - The external immobilisation frame is now in routine clinical practice
  - Clinical implementation of ABC
  - Measurement and correction of systematic and random error
  - Image guided radiotherapy incorporating PET and CT image fusion to ensure that active disease is included in the GTV
  - Adaptive radiotherapy
  - Penumbra enhancement to improve dose delivery to the PTV

Intensity modulated radiotherapy (IMRT) takes conformal radiotherapy a step further through improved dose deposition, delivering complex dose distributions derived from inverse or forward treatment planning. These techniques produce high dose conformation to the target with normal tissue avoidance and the potential benefit of both reduced normal tissue toxicity and dose escalation to the tumour to increase local control. Conformal radiotherapy and IMRT may offer an advantage at tumour sites where:

- Existing local control is poor or modest
- The dose-response curve is steep for specific tumours
- Dose is compromised by proximity of sensitive tissues (organs at risk)
• A volume effect exists for sensitive tissues

IMRT may have limited application in the chest apart from penumbra enhancement and the situation where disease is in the paravertebral area when the ability of IMRT to produce a concave dose distribution could reduce dose to the spinal cord. The benefit of accelerated fractionation, CHART and CHART-type radiotherapy could be defeated if the treatment is not delivered accurately. Technical developments should aim to release the potential of accelerated fractionation, through optimisation of the delivery of radiotherapy to the cancer.
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APPENDICES

Appendix 1:

Volumes as defined by ICRU Report 50

Gross Tumour Volume: GTV
The GTV is the original or visible extent of the disease. This is the first link in the chain and its accurate determination influences all the subsequent steps taken to conform an isodose curve to this volume.

Clinical Target Volume: CTV
The CTV is a volume of tissue that contains a GTV and/or subclinical microscopic malignant disease, which has to be treated adequately to eliminate disease.

Planning Target Volume: PTV
The PTV consists of the CTV and a margin to account for the variations in size, shape and position relative to the treatment fields. The PTV is therefore a geometrical concept, used to ensure that the CTV receives the prescribed dose. (The margin around the CTV can be of different widths in different directions according to the site of disease.)

Treated Volume: TV
The TV is the volume enclosed by an isodose surface, selected as being appropriate to achieve the purpose of treatment.

Irradiated Volume: IV
The IV is the volume of tissue that receives a dose that is considered significant in relation to normal tissue tolerance.
Appendix 2:

Volumes as defined by ICRU report 62

The definitions of GTV and CTV are as with ICRU 50 and constitute part of the basic prescription of treatment; they are essential to the medical record. Their definition must precede the selection of the treatment modality and the subsequent treatment planning procedures.

PTV

Margins for Geometric Variations and Uncertainties

Computation of dose distribution can currently be done only for a static representation. There are variations and uncertainties in the positions, sizes, shapes and orientations of the tissues, patient and the beams in relation to the common coordinate system. These will be seen both during a single session (intrafractionally) and from one session to another (interfractionally). Errors can be introduced between the imaging procedure and the treatment planning and between the treatment planning and the first treatment session. Margins must be added to take account of tissue movement in or out of the therapeutic beam.

To avoid significant deviation from the prescribed dose in any part of the CTV(s), one must add margins to the CTV(s) for variations in tissue position, size and shape, as well as for variations in patient and beam position, both intrafractionally and interfractionally. These variations are difficult to quantify.

In order to determine margins, it is useful to think of the two types of uncertainties, internal and set-up margins.
Internal Margin (IM) and Internal Target Volume (ITV)

The internal margin (IM) is to account for expected physiological movements and variation in size, shape, and position of the CTV during therapy in relation to an internal reference point and its corresponding coordinate system. The IM is commonly asymmetric around the CTV.

The term internal target volume (ITV) has been proposed as representing and encompassing the CTV and the IM.

Set-up Margin (SM)

To account for uncertainties (inaccuracies and lack of reproducibility) in patient positioning and alignment of the therapeutic beams during treatment planning and through all treatment sessions, a set-up margin (SM) for each beam is needed and is referenced in the external coordinate system. The uncertainties depend on different types of factors, such as:

- variations in patient positioning
- mechanical uncertainties of the equipment (e.g. sagging of gantry, collimators, and couch)
- dosimetric uncertainties
- transfer of set-up errors from CT and simulator to the treatment unit
- human factors

These may vary from centre to centre and, within a given centre from machine to machine. The use of patient immobilisation devices, the application of quality assurance programs, and human factors such as skill and experience of the radiographers/radiotherapists are important and must be taken into account. The use of different record and verification systems (in real time or not) may also be important and may significantly alter the size of the needed SM.
Appendix 3:

Follow up protocol for patients treated with CHARTWEL

Weeks 1-6 from start of treatment

Clinical assessment of acute side effects of treatment

CXR at week 4

Week 8

CXR

CT scan of the thorax and upper abdomen

FBC, urea and electrolytes, calcium, liver function tests

Patients are only seen if unwell

Three months

CXR

CT scan of the thorax and upper abdomen

FBC, urea and electrolytes, calcium, liver function tests

Clinical assessment

Six months

CXR

CT scan of the thorax and upper abdomen

FBC, urea and electrolytes, calcium, liver function tests

Clinical assessment

Nine months

CXR

CT scan of the thorax and upper abdomen

FBC, urea and electrolytes, calcium, liver function tests

Clinical assessment
Twelve months
CXR
CT scan of the thorax and upper abdomen
FBC, urea and electrolytes, calcium, liver function tests
Clinical assessment

Fifteen months
CXR
FBC, urea and electrolytes, calcium, liver function tests
Clinical assessment

Eighteen months
CXR
CT scan of the thorax and upper abdomen
FBC, urea and electrolytes, calcium, liver function tests
Clinical assessment

Twenty one months
CXR
FBC, urea and electrolytes, calcium, liver function tests
Clinical assessment

Twenty four months
CXR
CT scan of the thorax and upper abdomen
FBC, urea and electrolytes, calcium, liver function tests
Clinical assessment

Patients are then seen six monthly for a further three years up to year five and the following investigations are performed at each visit:

CXR
CT scan of the thorax and upper abdomen

FBC, urea and electrolytes, calcium, liver function tests

Clinical assessment

Patients are seen annually thereafter with investigations as above.

If at any time symptoms to suggest recurrent or metastatic disease occur patients are seen, appropriate investigations performed and further treatment given at the physician’s discretion.
Appendix 4:

WHO PERFORMANCE SCALE

Grade: 0 - Normal activity

1 - Symptoms are present but activities are almost normal

2 - Confined to bed < 50% of each day

3 - Confined to bed > 50% but < 100% of each day

4 - Incapable of rising
Appendix 5: Conformal Bronchus Planning CT Scanning Protocol

Pre-chemotherapy scan

1. Scans should be performed before chemotherapy starts. The scan may be booked by presenting a CT request form, filled in by the relevant doctor, to the diagnostic radiographers. All CT appointments should be booked on either a Tuesday after 1pm or anytime on a Thursday.

2. A Conformal Bronchus Planning form will be provided before the scan date. This should clearly denote that the patient is a conformal CHARTWEL lung patient having a pre-chemo scan. Relevant bleep numbers for therapy radiographers should also be provided.

3. Diagnostic radiographers working in CT will bleep either the CHART radiographer or the floor superintendent when the patient arrives.

4. The diagnostic radiographers will perform the diagnostic (spiral) CT scan with contiguous 10mm slices from the apices of the lungs to the lower limit of the kidneys to visualise the liver and the adrenal glands.

5. For the planning CT scan the patient will be positioned on the flat table top in the following way: supine, on Bronchus pad, arms up using the ABC Frame, with Large Knee Roll. The frame measurements will be recorded on the Conformal Bronchus planning form. Ensure patient is straight and flat.

6. Marker wires will be placed on the patient’s skin to indicate tattoo levels, one anterior (midline) and one on each side.

7. The diagnostic radiographers will perform the planning (sequential) CT scan with contiguous 5mm slices from the apices of the lungs to the lower limit of the diaphragms. (To encompass whole of both lungs).
8. The diagnostic radiographers will indicate a SUP/INF level at which to tattoo the patient – based on the centre of the mass visualised on the CT scans. The therapy radiographer will assess this for suitability with regards to reproducibility of set-up (e.g. too sup is an unstable point at which to tattoo) and liaise with diagnostic radiographers as to any adjustments required.

9. The patient will then be given 3 tattoos – 1 AP and 2 laterally. The Lt/Rt and Ant/Post positions of these are predetermined by the positions of the CT markers placed on the patient before scanning (see 6). The TTH, the distance between couch top and Hz tattoo, will also be recorded on the Conformal Bronchus planning form.

10. The scans are reported and kept in the Scanner Centre until the patient returns for the post-chemo CT scan.

Post-chemotherapy scan

1. Scan should be performed at least two days after the last course of chemotherapy. (E.g. if last course of chemotherapy on Tuesday book CT scan for Thursday). Book with the CT scanner as before. All CT appointments should be booked on either a Tuesday after 1pm or anytime on a Thursday.

2. Diagnostic radiographers working in CT will bleep either the CHART radiographer or the floor superintendent when the patient arrives. If patient is for ABC CT scan:
ABC Scan - practice

- Practice with the ABC equipment needs to be carried out with the patient prior to entering the CT scanner.
- Set up ABC equipment (protocol - Use of Active Breathing Control equipment) in Sim II.
- With patient lying on the couch, in ABC frame, insert mouthpiece and attach nose clip. Watch breathing trace on screen.
- When trace has settled, ask patient to take a series of deep breaths in and out. Assess maximum lung volume.
- Set gate volume at 75% of maximum lung volume.
- Set gate time at 5 seconds and arm ABC. If breath hold procedure is successful, repeat with gate times of 10s, 15s and a maximum of 20s.
- Record gate volume and maximum gate time patient is able to tolerate on ABC Log form (ref-ABC CT).
- Patient can now be transferred to the CT scanner.

3. The diagnostic radiographers will perform the diagnostic (spiral) CT scan with contiguous 10mm slices from the apices of the lungs to the lower limit of the kidneys to visualise the liver and the adrenal glands.

4. For the planning CT scan the patient will be positioned in the same way as they were for the pre-chemo scan. Frame measurements can be obtained from the Conformal Bronchus planning form.

5. The therapy radiographers will line up the three tattoos given to the patient during the pre-chemo scan with the recorded TTH. The position of two additional anterior tattoos will then be marked onto the patient's skin, one 5cm sup to the existing tattoo
and one 5cm inf. (This procedure does not need to be duplicated on the lateral tattoos).

6. Ball bearings, provided by the therapy radiographers, will then be placed onto the patients skin at the five tattoo points. (E.g. 3 anteriorly and 2 laterally). Any alignment difficulties/differences will be recorded on the Conformal Bronchus planning form for future reference. (NB if the alignment is different to the original tattoos, still put the ball bearings onto the tattoos – not the alignment marks).

7. The diagnostic radiographers will perform the planning (sequential) CT scan with contiguous 5mm slices from the apices of the lungs to the lower limit of the diaphragms. If the patient is for ABC CT scan:

**ABC Scanning Protocol**

- Set up ABC equipment in CT scanner. (protocol)
- Set gate volume and gate time found from practice session.
- The diagnostic radiographers will perform the first ABC spiral CT scan (ABC1) with 5mm slices from the apices of the lungs to the lower limit of the diaphragm. The scan will usually need to be split into three matched spirals with the time/spiral set to fit within the gate time. (A 15s scan time fits within a gate time of 20s.)
- Record scan parameters on ABC Log form.
- Repeat ABC CT scan (ABC2) using the same parameters.
- Check patient has an appointment for ABC3 CT scan, to be performed while on treatment. (Usually 2-3 days before the start of Phase 2).

8. The patient will then be given the additional two anterior tattoos. The Lt/Rt position of these is determined by the previous anterior tattoo.
9. Before the patient leaves ensure that they have an appointment to return to the Simulator.

10. The scans are reported and ready for Physics collection two working days after the CT scan is performed.
Appendix 6: Protocol for use of Active Breathing Control equipment

ABC equipment set (I) is kept on a trolley in the control room of Sim II (Scanner Centre).

Laptop computer (I) is kept in Clinical Physics Dept. (JW office)

A second set (II) is kept in a box in the control room of Sim II.

Second laptop computer (II) is kept in Clinical Physics Dept. (GL office)

USE
1. connect up all equipment (see diagram) and switch on ABC device.
2. switch on computer. (ABC equipment MUST be connected before computer is switched on)
3. select ABC icon. (if trace does not appear, exit from ABC and restart the computer)
4. set gate volume and gate time.
Appendix 7: Lung and Oesophageal Morbidity Scoring System

7.1. LUNG MORBIDITY

7.11. DYSPNOEA

<table>
<thead>
<tr>
<th>DYSPNOEA SCORE</th>
<th>SYMPTOMS</th>
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<tbody>
<tr>
<td>0</td>
<td>Climbs hills and stairs at normal speed without dyspnoea</td>
</tr>
<tr>
<td>1</td>
<td>Walks any distance on the flat at normal speed without dyspnoea</td>
</tr>
<tr>
<td>2</td>
<td>Walks &gt; 100 yards at any speed without dyspnoea</td>
</tr>
<tr>
<td>3</td>
<td>Dyspnoea at walking &lt; 100 yards</td>
</tr>
<tr>
<td>4</td>
<td>Dyspnoea on mild exertion e.g. undressing</td>
</tr>
<tr>
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7.12. X-RAY OR CT EVIDENCE OF PNEUMONITIS

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</tr>
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<td>Moderate</td>
</tr>
<tr>
<td>3</td>
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### 7.2. OESOPHAGEAL MORBIDITY

#### 7.21 ACUTE DYSPHAGIA REACTIONS DUE TO RADIOTHERAPY

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</tr>
<tr>
<td>1</td>
<td>Some discomfort, no diet disturbance</td>
</tr>
<tr>
<td>2</td>
<td>Difficulty with diet, soft diet needed</td>
</tr>
<tr>
<td>3</td>
<td>Considerable difficulty, fluids only</td>
</tr>
<tr>
<td>4</td>
<td>Severe difficulty with fluids</td>
</tr>
<tr>
<td>9</td>
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</tbody>
</table>

#### 7.22 DYSPHAGIA AFTER RADIOTHERAPY REACTIONS HAVE SETTLED

<table>
<thead>
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<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Present due to tumour</td>
</tr>
<tr>
<td>2</td>
<td>Present due to radiotherapy</td>
</tr>
<tr>
<td>3</td>
<td>Present, cause unknown</td>
</tr>
<tr>
<td>9</td>
<td>Not known</td>
</tr>
</tbody>
</table>
### TUMOUR CONTROL

<table>
<thead>
<tr>
<th>SCORE</th>
<th>ASSESSMENT OF RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not done</td>
</tr>
<tr>
<td>1</td>
<td>Complete Response (CR)</td>
</tr>
<tr>
<td>2</td>
<td>Partial Response ≥ 50% (PR)</td>
</tr>
<tr>
<td>3</td>
<td>Static &lt; 50%</td>
</tr>
<tr>
<td>4</td>
<td>Regrowth</td>
</tr>
<tr>
<td>5</td>
<td>Not known</td>
</tr>
</tbody>
</table>