Symptom documentation and tumor repopulation factors as a basis for treatment modifications in Non-Small Cell Lung Cancer radiotherapy.

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Patras, September 2009, Greece
Τοιχογραφία: Άμεση αποτελεσματική απόδοση και γενικά συνεπείες της θεραπείας είναι αναφέρεται σε συνεργασία με την επιλογή της υπολείπουσας δόσης και της συνεπικρατής της. Η επιλογή της υπολείπουσας δόσης και της συνεπικρατής της επιπηδίωσης αναφέρεται σε συνεργασία με την επιλογή της υπολείπουσας δόσης και της συνεπικρατής της επιπηδίωσης .

ΠΕΡΙΛΗΨΗ

Symptom documentation and tumor repopulation factors as a basis for treatment modifications in Non-Small Cell Lung Cancer radiotherapy.

Σκοπός:
Πρόσφατες μελέτες έχουν αναδείξει σημαντική ποικιλία στα ακτινοθεραπευτικά σχήματα που χρησιμοποιούνται στην ακτινοθεραπεία του μη μικροκυτταρικού καρκίνου του πνεύμονα προχωρημένου στάδιου. Στη συγκεκριμένη μελέτη θεραπευτικές μεθοδολογίες έχουν διερευνηθεί χρησιμοποιώντας τεχνικές που προτείνονται από ογκολόγους ακτινοθεραπευτές.

Υλικά και Μέθοδοι:
Η μελέτη αποτελείται από δύο μέρη. Στο πρώτο ένα ερωτηματολόγιο εστάλη σε είκοσι τέσσερα ακτινοθεραπευτικά κέντρα στην Ευρώπη . Το ερωτηματολόγιο αποτελούνταν από δύο τμήματα. Στο πρώτο ζητούνταν οι λόγοι για τους οποίους γίνεται έναρξη της ακτινοθεραπείας, οι παράμετροι που επηρεάζουν την επιλογή για τη συνολική δόση και τις συνεδρίες για την θεραπεία και τον εξοπλισμό που χρησιμοποιούν. Στο δεύτερο τμήμα παρουσιάστηκαν πέντε θεραπητικά κλινικά περιστατικά και ζητήθηκε η αντιμετώπιση αυτών των θεραπητικών ασθενών. Στο δεύτερο μέρος της μελέτης πραγματοποιήθηκε ανασκόπηση στη βιβλιογραφία και σύγκριση των αποτελεσμάτων κλινικών δοκιμών που έχουν πραγματοποιηθεί στο παρελθόν.

Αποτελέσματα:
Στο ερωτηματολόγιο απάντησαν το εβδομήντα τους εκατό των κέντρων στα όποια εστάλη. Στο πρώτο μέρος οι πιο σημαντικοί παρόντες που επηρεάζουν την επιλογή της τελικής δόσης και τις συνεδρίες οριστήκαν οι παρουσία απομακρυσμένων μεταστάσεων, η κλινική εικόνα του ασθενούς, η πνευμονική λειτουργία και το μέγεθος του πρωτογενούς όγκου. Οι σημαντικότεροι λόγοι για έναρξη θεραπείας είναι ανακούφιση από τα συμπτώματα καθώς και επιμήκυνση της ζωής. Στο δεύτερο μέρος ενενήντα πέντε τους εκατό των κέντρων απάντησαν ότι θα πραγματοποιούσαν ακτινοθεραπεία και στους πέντε αυτούς ασθενείς. Η επιλογή της συνολικής δόσης και συνεπών επηρεάζεται από την θεώρηση της θεραπείας ως παρηγορική ή θεραπευτική. Τα κέντρα που είχαν στόχο την επιμήκυνση της ζωής είδαν μεγαλύτερες δόσεις και περισσότερες συνεδρίες εν αντιθέσει με τα κέντρα που είχαν στόχο την υποχώρηση των συμπτωμάτων που είδαν μικρότερες δόσεις σε λιγότερες συνεδρίες.
Στο δεύτερο μέρος υπολογιστήκαν οι σχετικές βιολογικές δραστικότητες από τα δεδομένα της βιβλιογραφίας καθώς και ο παράγοντας πολλαπλασιασμού του όγκου και κατασκευάστηκαν καμπύλες δόσης απόκρισης.

Συμπεράσματα:
Η μελέτη αποδεικνύει την ύπαρξη ποικιλίας στις τεχνικές που χρησιμοποιούνται στη θεραπεία προχωρημένου και ανεγχείρητου μη μικροκυτταρικού καρκίνου του πνεύμονα. Αυτοί οι παράγοντες πρέπει να συνοπλογίζονται όταν εκτιμάται η αποτελεσματικότητα διαφορετικών ακτινοθεραπευτικών τεχνικών, κυρίως στο προσδιορισμό ακτινολογικών παραμέτρων και σχέσεων δόσης –απόκρισης.
ABSTRACT

Symptom documentation and tumor repopulation factors as a basis for treatment modifications in Non-Small Cell Lung Cancer radiotherapy.

Purpose
Recent studies have suggested significant variation in radiotherapy schedules used to treat advanced NSCLC, both between different centres as well as between countries. In this study, treatment methodologies have been explored using management plans proposed by radiation oncologists when given general questions and theoretical case histories for patients with advanced NSCLC.

Methods and Materials
The survey was conducted by sending a questionnaire to twenty four radiotherapy centres in Europe. The questionnaire was composed of two sections. The first section concerned reasons for starting radiotherapy, parameters that influence the choice of total dose and fractionation for radiotherapy and the kind of equipment that is used. The second section examines five case histories and asked the responders about the management of these five theoretical patients also regarding the radiotherapy techniques proposed and the aim of treatment (radical or palliative).

Furthermore, trials comparing different regimens of palliative radiotherapy in patients with NSCLC were compared. Nineteen trials were reviewed. There were important differences in the doses of radiotherapy investigated, the patient characteristics and the outcome measures.

Results
In the first part responders (70% of the centres) suggested as the most important factors that influence the choice of total dose and fractionation for radiotherapy, distant metastases, performance status of the patient, lung function and size of the primary tumour. The most common reasons for starting the treatment is not only symptom relief, but also cure and prolongation of life. In the second part, more than 95% of the responders replied that they would give radiotherapy in each of these cases. The median total doses proposed where 20Gy/5fractions/1week or 30Gy/10fractions/2weeks for cases A and D (equivalent dose for fractionation 2Gy per fraction=23 and 33Gy) and 60-68Gy/30fractions/6weeks or
68Gy/34fractions/7weeks for cases B, C and E. For case E, 20% of the responders suggested Stereotactic Body Radiotherapy with 63Gy in 3 Fractions. The total dose and number of fractions of radiotherapy could be related to the perceived aims and expectations of treatment e.g. those aiming to extent life would give significantly higher total doses in a larger number of fractions, whereas those aiming to relieve symptoms would give significantly lower total doses.

For the review to the literature there is no strong evidence that any regimen gives greater palliation. Higher dose regimens give more acute toxicity, especially oesophagitis. There is evidence for a modest increase in survival (5% at 1 year and 3% at 2 years) in patients with better performance status (PS) given higher dose radiotherapy. Some regimens are associated with an increased risk of radiation myelitis.

**Conclusions**

This survey demonstrates a range of treatment strategies for advanced and inoperable NSCLC within Europe. There are a number of factors that influence the perceived aims of treatment and treatment planning. These factors should be taken into account when evaluating the effectiveness of different irradiation techniques, especially in the determination of radiobiological parameters and dose-response relations.

The majority of patients should be treated with short courses of palliative radiotherapy, of 1 or 2 fractions. Care should be taken with the dose to the spinal cord. The use of high dose palliative regimens should be considered for and discussed with selected patients with good performance status. More research is needed into reducing the acute toxicity of large fraction regimens and into the role of radical compared to high dose palliative radiotherapy. In the future, large trials comparing different RT regimens may be difficult to set up because of the increasing use of systemic chemotherapy. Trials looking at how best to integrate these two modalities, particularly in good PS patients need to be carried out.

This thesis has been done in collaboration with:
Division of Medical radiation Physics, Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweeden.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BED</td>
<td>Biologically Effective Dose</td>
</tr>
<tr>
<td>CBCT</td>
<td>Cone-Beam Computed Tomography</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>Deq</td>
<td>Equivalent dose for fractionation 2Gy per fraction</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRRs</td>
<td>Digital Reconstructed Radiographs</td>
</tr>
<tr>
<td>DSB</td>
<td>Double-strand break</td>
</tr>
<tr>
<td>DVH</td>
<td>Dose –volume histogram</td>
</tr>
<tr>
<td>EUD</td>
<td>Equivalent uniform dose</td>
</tr>
<tr>
<td>FSU</td>
<td>Functional subunit</td>
</tr>
<tr>
<td>GT</td>
<td>Gross tumour</td>
</tr>
<tr>
<td>IGRT</td>
<td>Image-Guided Radiation Therapy</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity-modulated radiation therapy</td>
</tr>
<tr>
<td>ITV</td>
<td>Internal target volume</td>
</tr>
<tr>
<td>LQ</td>
<td>Linear-quadratic model</td>
</tr>
<tr>
<td>LN</td>
<td>Lymph nodes</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non-Small Cell Lung Cancer</td>
</tr>
<tr>
<td>NTCP</td>
<td>Normal tissue complication probability</td>
</tr>
<tr>
<td>PCI</td>
<td>Prophylactic Cranial Irradiation</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PET-CT</td>
<td>Positron emission tomography- Computed tomography</td>
</tr>
<tr>
<td>PS</td>
<td>Performance Status</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RT</td>
<td>Radiation Therapy</td>
</tr>
<tr>
<td>SBRT</td>
<td>Stereotactic Body Radiotherapy</td>
</tr>
<tr>
<td>SCLC</td>
<td>Small Cell Lung Cancer</td>
</tr>
<tr>
<td>SSB</td>
<td>Single-strand break</td>
</tr>
<tr>
<td>SBRT</td>
<td>Stereotactic Body Radiotherapy</td>
</tr>
</tbody>
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**Introduction**

The incidence of cancer continues to rise globally. Because the tumor will be extensive in many at the time diagnosis, treatment with curative intent will be possible in only one-half of these people. Therefore, the majority of patients with cancer will require relief of the symptoms and signs caused by their disease [1].

Objectives of palliative treatment are independent of prolongation of life, although this may be a secondary benefit. Relief of suffering and avoidance of doing harm are basic tenets of medicine. Indeed patients may fear suffering more than death.

Palliative management of the patient with cancer requires the coordinated team effort of a multidisciplinary group of dedicated health professionals, including physicians, nurses, physicists, therapists, social workers, psychologists, physiatrists, medical support workers, support organizations.

Assessment of the accomplishments of palliative treatment may be more difficult than it is for curative treatment where tumor free-survival can be measured. However, scales for pain assessment recently have been developed. Relief from problems such as cessation of bleeding or cough may be satisfying to both the patient and physician [8].
1.1 Background

1.1.1 Anatomy

The lungs are the essential organs of respiration; they are two in number, placed one on either side within the thorax, and separated from each other by the heart and other contents of the mediastinum. The substance of the lung is of a light, porous, spongy texture; it floats in water, and crepitates when handled, owing to the presence of air in the alveoli; it is also highly elastic; hence the retracted state of these organs when they are removed from the closed cavity of the thorax. The surface is smooth, shining, and marked out into numerous polyhedral areas, indicating the lobules of the organ: each of these areas is crossed by numerous lighter lines. The right lung is composed of three lobes: upper, middle and lower. The left lung is composed of two lobes. The trachea enters the superior mediastinum and bifurcates approximately at the level of the fifth thoracic vertebra. The hila of the lungs contain the bronchi, pulmonary arteries and veins, various branches from the pulmonary plexus, bronchial arteries and veins and lymphatics.

The lung has a rich network of lymphatic vessels throughout its loose interstitial connective tissue, ultimately draining into the various lymph node stations which may be divided into the following groups: intrapulmonary nodes, bronchopulmonary nodes, mediastinal nodes, and supraclavicular or scalene nodes [4].

Figure 1.1: The picture illustrates the position of the lungs in the human body, the lobes that the lung is divided, the trachea and the main bronchus.
1.2 Lung Cancer

Lung cancer is one of the commonest malignant tumours for both men and women in developed countries and an increasing problem in developing countries. Lung cancer develops from pulmonary parenchymal or bronchial supportive tissues. Although multiple cell types are often found within a single lung tumour, one type usually predominates. Based on the therapeutic approach, there are two major subdivisions of lung cancer: small-cell lung cancer (SCLC), for which chemotherapy is the primary treatment, and non–small-cell lung cancer (NSCLC), which in its early stages (I and II) is treated primarily with surgery.

The majority of patients (between 75% and 85%) have non-small cell lung cancer (squamous cell, adeno- and large cell undifferentiated carcinomas), of whom only 15 to 25% will have tumours that are potentially curable. The remainders are thought incurable, either because of the extent of local tumour or because of known metastases [4].

1.2.1 Classification

The vast majority of lung cancers are malignancies that arise from epithelial cells. There are two main types of lung carcinoma, categorized by the size and appearance of the malignant cells seen by histopathologist under a microscope: non-small cell (80.4%) and small-cell
lung carcinoma. This classification, based on histological criteria, has important implications for clinical management and prognosis of the disease [4].

### 1.2.1.1 Non-Small Cell Lung Cancer

The NSCLC are grouped together because their prognosis and management are similar. There are three main sub-types: squamous cell lung carcinoma, adenocarcinoma, and large cell lung carcinoma.

Accounting for 31.2% of lung cancers, squamous cell lung carcinoma usually starts near a central bronchus. A hollow cavity and associated necrosis are commonly found at the centre of the tumour. Well-differentiated squamous cell lung cancers often grow more slowly than other cancer types.

Adenocarcinoma accounts for 29.4% of lung cancers. It usually originates in peripheral lung tissue. Most cases of adenocarcinoma are associated with smoking; however, among people who have never smoked ("never-smokers"), adenocarcinoma is the most common form of lung cancer. A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may have different responses to treatment [2].

Large cell carcinoma is the uncontrolled growth of abnormal cells in the lungs. This non-small cell lung cancer that represents 10% to 20% of all tumours that start in the bronchi, which are the main branches of the windpipe (trachea) that lead to the lungs. This type of lung cancer is associated strongly with smoking.

### 1.2.1.2 Small Cell Lung Cancer

Small cell lung carcinoma (SCLC, also called "oat cell carcinoma") is less common. It tends to arise in the larger airways (primary and secondary bronchi) and grows rapidly, becoming quite large. The "oat" cell contains dense neurosecretory granules (vesicles containing neuroendocrine hormones), which give this an endocrine/paraneoplastic syndrome association. While initially more sensitive to chemotherapy, it ultimately carries a worse prognosis and is often metastatic at presentation. Small cell lung cancers are divided into limited stage and extensive stage disease. This type of lung cancer is strongly associated with smoking.
<table>
<thead>
<tr>
<th>WHO CLASSIFICATION</th>
<th>% DISTRIBUTION</th>
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<tbody>
<tr>
<td>HISTOLOGICAL TYPE</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>25-35</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>15-25</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>20-35</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>10-15</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Carcinomas with sarcomatous elements</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pulmonary blastoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Carcinois</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

*Varies from country to country

Table 1: Histological types of the major lung and pleural tumors

1.2.2 Staging

Clinical staging of lung cancer helps to determine the extent of disease and to stratify patients into similar prognostic and therapeutic categories. For lung cancer patients, an important goal is to separate patients with potentially respectable disease from those who are unrespectable. The staging of lung cancer must be conducted in a methodical and detailed manner. The TNM staging system, updated by Mountain, applies equally well to all histologies of NSCLC, but TNM for SCLC is less helpful. Most patients have advanced disease at the time of presentation.

TNM system is used to numerically describe the anatomical extent of cancer and is based on three components: T, extent of the primary tumour; N, absence or presence of the disease in the regional lymph nodes. M, absence or presence of distant metastasis. The numerical staging aids oncologists in planning treatment and evaluating treatment results. The TNM staging system considers the disease only at diagnosis and has been suggested to use the clinical state from diagnosis to death as a dynamic model of disease progression.
**Primary tumor(T)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx:</td>
<td>Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or broncoscopically or any tumor that cannot be assessed as in pretreatment staging.</td>
</tr>
<tr>
<td>To:</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis:</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1:</td>
<td>Tumor ≤3.0 cm in greatest dimension, surrounded by lung or vinceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.</td>
</tr>
<tr>
<td>T2:</td>
<td>Tumor ≥3.0 cm in greatest dimension or tumor of any size that either invades the vinceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region (but involving less than the entire lung). At bronchoscopy the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina.</td>
</tr>
<tr>
<td>T3:</td>
<td>Tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm or mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus or vertebral body or the tumor in the main bronchus within 2 cm of, but not involving, the carina.</td>
</tr>
<tr>
<td>T4:</td>
<td>Tumor of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, esophagus, vertebral body or carina or presence of exudative pleural effusion (whether cytology positive or negative).</td>
</tr>
</tbody>
</table>

**Regional lymph nodes(N)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx:</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0:</td>
<td>No demonstrable metastasis to regional lymph nodes</td>
</tr>
<tr>
<td>N1:</td>
<td>Metastases to lymph nodes in the peribronchial and/or ipsilateral hilar region including direct extension.</td>
</tr>
<tr>
<td>N2:</td>
<td>Metastases to ipsilateral mediastinal and subcarinal lymph nodes</td>
</tr>
<tr>
<td>N3:</td>
<td>Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes.</td>
</tr>
</tbody>
</table>

**Distant metastases(M)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx:</td>
<td>Distant metastases cannot be assessed</td>
</tr>
<tr>
<td>M0:</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M:</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

**Stage grouping**
Occult carcinoma  Tx N0 M0  
Stage 0  Tis N0 M0  
Stage IA  T1 N0 M0  
Stage IB  T2 N0 M0  
Stage IIA  T1 N1 M0  
Stage IIB  T2 N1 M0  
Stage IIIA  T3 N1 M0  
               T1-3 N2 M0  
Stage IIIB  Any T N3 M0  
               T4 Any N M0  
Stage IV  Any T Any N M1

Table 2: TNM staging of lung cancer

1.2.3 Clinical Presentation
Carcinoma of the lung is the most insidious of all neoplasms. Signs and symptoms may arise from local tumor growth, invasion of adjacent structures, regional growth or distant metastases (hematogenous dissemination) or from a secondary effect of the tumors (paraneoplastic syndromes).

Cough is a major symptom in 75% of patients and is severe in 40%. Hemoptysis has been described in 57% of patients and was the first symptom in 4%. Other symptoms found in approximately 40% of patients are dyspnea and chest pain resulting from involvement of the pleura, chest wall, or mediastinal structures. Nonspecific initial symptoms such as weight loss, weakness, anorexia and malaise may occur in 10% to 15% of patients. Less common are febrile respiratory episodes.

Tumors located in the apex of the lung usually grow by local extension and involve cervical and thoracic nerves, resulting in Pancoasts or superior sulcus tumor syndrome. Sympathetic nerve involvement results in Horner’s syndrome which consists of enophthalmos, ptosis, meiosis and ipsilateral loss of sweating. Involvement of the recurrent laryngeal lymph node may lead to paralysis of the nerve and hoarseness. Involvement of the phrenic nerve can result in paralysis of the hemidiaphragm with resulting dyspnea. Dysphagia may result from a mechanical compression of the tumor on the esophagus. Primary tumors located in the right lung or metastatic tumor in the right mediastinal lymph nodes may cause superior vena cava syndrome. Large tumors in the upper lobes with massive upper mediastinal lymph adenopathy may cause thoracic inlet obstruction with severe respiratory distress. Tumor involvement of
the pericardium and the heart may result in pericardial tamponade and congestive heart failure.

Common sites of metastasis include the brain, bone, adrenal glands, contralateral (opposite) lung, liver, pericardium, and kidneys. About 10% of people with lung cancer do not have symptoms at diagnosis; these cancers are incidentally found on routine chest radiograph.

<table>
<thead>
<tr>
<th>Site of metastasis</th>
<th>Squamous %</th>
<th>Small Cell %</th>
<th>Anaplastic %</th>
<th>Adenocarcinoma %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes</td>
<td>54</td>
<td>85</td>
<td>76</td>
<td>75</td>
</tr>
<tr>
<td>Liver</td>
<td>23</td>
<td>64</td>
<td>38</td>
<td>47</td>
</tr>
<tr>
<td>Adrenals</td>
<td>21</td>
<td>44</td>
<td>39</td>
<td>30</td>
</tr>
<tr>
<td>Bones</td>
<td>23</td>
<td>39</td>
<td>30</td>
<td>41</td>
</tr>
<tr>
<td>Brain</td>
<td>17</td>
<td>42</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>Kidney</td>
<td>15</td>
<td>14.5</td>
<td>13.5</td>
<td>20</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3.5</td>
<td>24</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Preura</td>
<td>7</td>
<td>11</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>


1.2.4 Causes

The main causes of lung cancer (and cancer in general) include carcinogens (such as those in tobacco smoke), ionizing radiation, and viral infection. This exposure causes cumulative changes to the DNA in the tissue lining the bronchi of the lungs (the bronchial epithelium). As more tissue becomes damaged, eventually a cancer develops.

1.2.5 Diagnosis

Diagnostic workup includes the following examinations:

- **Radiologic Examination**

Routine chest x-ray studies, posteroanterior and lateral, are the most commonly used radiologic examinations in patients with lung cancer. Computed Tomography (CT) is the most important and valuable radiologic tool in diagnostic evaluation and therapeutic planning of lung cancer. Staging of lung cancer by CT clearly is superior to conventional radiologic techniques.

Computed tomography also has proven to be extremely useful for radiation therapy treatment planning in bronchogenic carcinoma. One of the most important potential uses of CT scan is in three-dimensional treatment planning in radiation therapy.
Figure 1.3: Chest radiograph showing a cancerous tumour in the left lung.

Figure 1.4: CT scan showing a cancerous tumour in the left lung.

Other special diagnostic procedures are:
**Pulmonary Function Tests**
Pulmonary function tests are also important predictors of the patients ability to undergo surgical resection or withstand irradiation.

**Bone Marrow Biopsy and Aspiration**
Bone marrow involvement is present in 11% to 47% of patients with small cell carcinoma. In recent years, as patients with less-advanced disease have entered chemotherapy trials, the incidence of marrow involvement at diagnosis has declined to about 20%.

**Sputum Cytology**
In many cases it is possible to determine the presence of malignancy as well as the cell type. Sputum cytology has diagnosed malignancy in 65.2% to 75% of patients.

**Bronchoscopy**
Bronchoscopic examination provides important data even in the presence of preoperative cytologic proof of cancer.

**Thoracic Fine-Needle Aspiration Biopsy**
The differential diagnosis for patients who present with abnormalities on chest radiograph includes lung cancer as well as non-malignant diseases. These include infectious causes such as tuberculosis or pneumonia, or inflammatory conditions such as sarcoidosis. These diseases can result in mediastinal lymphadenopathy or lung nodules, and sometimes mimic lung cancers. Lung cancer can also be an incidental finding: a solitary pulmonary nodule (also called a coin lesion) on a chest radiograph or CT scan taken for an unrelated reason.

**1.2.6 Prognostic factors**
Numerous reports in the literature deal with the prognostic significance of anatomic extent of disease and non anatomic factors in carcinoma of the lung. The three most important prognostic factors affecting survival are stage, performance status of the patient and weight loss. Other factors such as tumor size and histologic type appeared to be important. A group of new genetic prognostic factors has been added to the list of well-known clinical prognostic factors. Among these are mutations in the K-ras oncogene, deletion of tumor
suppressor genes (e.g. *p53*), and the presence of NCAM (neural cell adhesion molecule) expression.

<table>
<thead>
<tr>
<th>Status</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to carry on normal activity and to work; no special care needed.</td>
<td>100</td>
<td>Normal no complaints; no evidence of disease.</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
<td></td>
</tr>
<tr>
<td>Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.</td>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or to do active work.</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most of his personal needs.</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care.</td>
<td></td>
</tr>
<tr>
<td>Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.</td>
<td>40</td>
<td>Disabled; requires special care and assistance.</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospital admission is indicated although death not imminent.</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospital admission necessary; active supportive treatment necessary.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>ECOG</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Karnofsky performance status scale definitions rate (%) criteria.

Table 5: ECOG index for Performance Status

1.3 Management options of lung tumours

Treatment for lung cancer depends on the cancer's specific cell type, how far it has spread, and the patient's performance status. Common treatments include surgery, chemotherapy, and radiation therapy.

In operable candidates, clinically staged IA, IB, IIA, and IIB NSCLC should undergo anatomic complete surgical resection. Primarily, patients with stages IIIB and IV disease are treated nonoperatively. Although multimodality therapy is routinely recommended for stage IIIA disease, it is recommended that it be performed within a clinical trial.
1.3.1 Surgery

The appropriate treatment of NSCLC is resection of the lobe containing the tumour. Occasionally, a bilobectomy or pneumonectomy is required. Mortality approximates 3% following lobectomy and 7% following pneumonectomy. A wedge or segmental resection has a three to five time’s higher incidence of local recurrence and a lower 5-year survival than a lobectomy. Therefore, if the patient can tolerate the procedure, the standard operation should be a lobectomy, rather than a wedge resection or segmentectomy. As a curative resection, segmentectomy, though, has not been sufficiently evaluated, and more recent investigation demonstrates that in selected tumours, when the bronchus and vascular supply are individually ligated with a regional node resection, survival appears to be comparable and it salvages lung parenchyma.

Video-assisted thoracoscopic surgery Traditionally, lung cancers have been resected through a posterolateral thoracotomy incision. Muscle-sparing incisions may reduce pain. The current trend is toward an even less invasive approach: lobectomy and lymph node dissection with VATS. This approach appears to offer the same cancer operation and survival with perhaps lower morbidity.

Two VATS methods have been described: the mass hilar ligation technique and individual ligation of the vasculature and airway. Patients with peripheral tumours up to 4 to 6 cm without clinical hilar or mediastinal adenopathy appear to be good candidates for a VATS procedure. Conversion rates to open thoracotomy are 10%, and hospital stays are usually 3 to 5 days.

The results of several VATS series show lower complication rates than reported series for thoracotomy; granted a selection bias may have occurred. One small randomized trial showed a significant benefit favoring VATS. Patients have better shoulder function, better performance on the 6-minute walk, and less impairment of vital capacity after VATS than after thoracotomy. A VATS approach may be better tolerated than other approaches for older patients.

Patients with pathologic stage IA disease have a 70% to 80% 5-year survival rate after resection, whereas 5-year survival rates are 60% in those with stage IB disease and 40% to 50% in those with stage IIA/IIB disease. Patients found to have N2 (stage IIIA) disease located at a single nodal level have a 25% to 30% 5-year survival rate. A radiological and PET evaluation has demonstrated that lesions less than 2 cm in size, peripheral ground-glass opacity with a PET max SUV of less than 2.5 and no evidence of metastatic disease may be considered for a more limited resection if the surgical margin is approximately the size of the lesion.
Mediastinal lymph node involvement The standard lung cancer operation should include sampling or dissection of mediastinal lymph nodes. The presence of metastases in any of the mediastinal lymph nodes (N2 and/or N3 disease) is indicative of advanced disease and is thought by some to represent a contraindication to surgery. Resection of mediastinal disease may have prognostic significance, implications for postoperative care, and potential therapeutic value. Some series of patients with N2 disease have shown a 5-year survival rate of 20% to 30%, but patients in these series are highly selected.

Patients with N2 disease may potentially benefit from neoadjuvant treatment. Patients with N3 disease are considered to be stage IIIB and less likely to benefit from surgical resection. There have been a few retrospective reports that have demonstrated survival from induction therapy in patients with microscopic N3 involvement. The American College of Surgeons has completed accrual to a randomized, prospective study comparing survival following mediastinal lymph node sampling versus dissection. Complications and operative mortality appear equivalent between the sampling and dissection groups. Long-term survival is under investigation. Also, clinical trials are currently testing preoperative chemotherapy and chemoradiation therapy in patients with mediastinal node involvement.

Preoperative histologic assessment of the mediastinal lymph nodes is essential if multilevel metastases are suspected, as there have been few long-term survivors among patients with metastatic disease at more than one level. Nonsurgical treatment appears preferable, or patients should be offered participation in a trial designed to assess the benefits of neoadjuvant therapy. Although patients with stage IIIB tumors are usually treated with irradiation and chemotherapy (see later discussions), the occasional patient with isolated involvement of the vena cava or atrium can undergo resection.

The majority of patients with SCLC present with advanced-stage disease. In the 5% to 10% of patients whose tumor is limited to the lung parenchyma, very often the diagnosis is established only after the lung mass has been removed. If, however, the histology has been determined by bronchoscopic biopsy or fine-needle aspiration and there is no evidence of metastatic disease following extensive scanning, examination of the bone marrow, and biopsy of the mediastinal lymph nodes, resection should be performed. Adjuvant chemotherapy is recommended because of the high likelihood of the development of distant metastases following surgery.

The surgical approach in SCLC is similar to that used in NSCLC: A lobectomy or pneumonectomy should be followed by a thorough mediastinal lymph node dissection. Tumor resection in SCLC should be limited to patients who have no evidence of mediastinal or supraclavicular lymph node metastases. Recent data suggest that patients with SCLC,
Presenting as a solitary pulmonary nodule and proven pathologically to be stage I, have a 5-year survival rate of ~70% when treated with resection and adjuvant chemotherapy. Approximately one-third of SCLC patients present with disease that is limited to the thorax and can be encompassed within a tolerable radiation portal. In early studies in which either radiation therapy or surgery alone was used to treat such patients, median survival was only 3 to 4 months, and the 5-year survival rate was in the range of 1% to 2%. The reason for the failure of these therapies was both rapid recurrence of intrathoracic tumor and development of distant metastasis [1, 8].

1.3.2 Chemotherapy

Small cell lung carcinoma is treated primarily with chemotherapy and radiation, as surgery has no demonstrable influence on survival. Primary chemotherapy is also given in metastatic non-small cell lung carcinoma.

The combination regimen depends on the tumour type. Non-small cell lung carcinoma is often treated with cisplatin or carboplatin, in combination with gemcitabine, paclitaxel, docetaxel, etoposide, or vinorelbine. In small cell lung carcinoma, cisplatin and etoposide are most commonly used. Combinations with carboplatin, gemcitabine, paclitaxel, vinorelbine, topotecan, and irinotecan are also used. In extensive-stage small-cell lung cancer celecoxib may safely be combined with etoposide, this combination showed improve outcomes.

Adjuvant chemotherapy for NSCLC: refers to the use of chemotherapy after surgery to improve the outcome. During surgery, samples are taken from the lymph nodes. If these samples contain cancer, the patient has stage II or III disease. In this situation, adjuvant chemotherapy may improve survival by up to 15%. Standard practice is to offer platinum-based chemotherapy (including either cisplatin or carboplatin).

Adjuvant chemotherapy for patients with stage IB cancer is controversial, as clinical trials have not clearly demonstrated a survival benefit. Trials of preoperative chemotherapy (neoadjuvant chemotherapy) in resectable non-small cell lung carcinoma have been inconclusive.

1.3.3 Targeted Therapy

In recent years, various molecular targeted therapies have been developed for the treatment of advanced lung cancer. Gefitinib (Iressa) is one such drug, which targets the tyrosine kinase domain of the epidermal growth factor receptor (EGF-R), expressed in many cases of non-small cell lung carcinoma. It was not shown to increase survival, although females, Asians,
nonsmokers, and those with bronchioloalveolar carcinoma appear to derive the most benefit from gefitinib[66]. Erlotinib (Tarceva), another tyrosine kinase inhibitor, has been shown to increase survival in lung cancer patients and has recently been approved for second-line treatment of advanced non-small cell lung carcinoma[68]. Similar to gefitinib, it also appeared to work best in females, Asians, nonsmokers, and those with bronchioloalveolar carcinoma[66].

The angiogenesis inhibitor bevacizumab, (in combination with paclitaxel and carboplatin), improves the survival of patients with advanced non-small cell lung carcinoma. However, this increases the risk of lung bleeding, particularly in patients with squamous cell carcinoma. Advances in cytotoxic drugs, pharmacogenetics and targeted drug design show promise. A number of targeted agents are at the early stages of clinical research, such as cyclooxygenase-2 inhibitors, the apoptosis promoter exisulind, proteasome inhibitors, bexarotene, and vaccines.

1.3.4 Radiation Therapy
For over a century, physicists and clinicians have been trying to develop ways and means of delivering doses, to tumours in different anatomical sites of patients. Various types of equipment and methods of treatment delivery have been developed to meet different clinical requirements. Metallic beam modifiers were first used in the 1960s to alter the spatial distribution of the intensity of the treatment beams. These have been an effective means of providing better coverage of dose to the tumours. Beam blocks, wedge filters, and beam compensators have been commonly used in 2-dimensional (2D) radiotherapy treatments. Practical means of delivering intensity modulated beams to achieve 3D dose conformity were not available until the mid 1990s. It was then that computer controlled linear accelerators with fully motorised multi-leaf collimators (MLC) were developed. In addition, 3D treatment planning computers with inverse planning algorithms for optimisation of dose were developed. Since then linear accelerator based IMRT treatment delivery systems that include the binary multi-leaf intensity-modulating collimator (MIMiC), step-and-shoot MLC, dynamic MLC (sliding window) and intensity modulated arc therapy (IMAT) have been developed. They are commercially available for clinical implementation. Two other types of IMRT equipment, with different designs, namely Cyberknife and helical tomotherapy tool have also been developed and are commercially available.
Radiotherapy is the most commonly used treatment modality for patients with lung cancer, with established, although frequently ignored, indications. It has a role in early, medically inoperable, and locally advanced unresectable NSCLC, where some patients are cured, in the palliation of advanced lung cancer of all types, and in the adjuvant treatment of limited stage SCLC where meta-analyses have shown it increases survival. Much variation in practice exists among various countries and even within different institutions in the same country.

Figure 1.5 : Linear Accelerator

Figure 1.6 : Multi-leaf collimator
1.3.5 Radiotherapy for Lung Cancer

1.3.5.1 Radical radiotherapy for in medically inoperable NSCLC

No randomized trials have compared radical radiotherapy with active supportive care. A Cochrane review identified only one acceptable phase III trial—the CHART study [37]—which showed an increase in 5 year survival for all patients (60% of whom had stage III disease) from 7% to 12% with 54Gy in 36 fractions over 12 days.

Attempts to improve these results focus on radiation dose escalation above the longstanding international standard dose of 60Gy. Dose escalation has been facilitated by advances in radiotherapy physics, particularly the techniques for beam shaping and treatment verification described below. In an ongoing phase I trial at Ann Arbor the radiotherapy dose has been increased using the estimated risk of radiation pneumonitis based on the lung volume irradiated. To date, the dose delivered to the largest volumes has been increased by less than 10%, but with the smallest volumes it has been possible to almost double the radiation dose to 102.9Gy. Other groups are exploring doses from 77.4 to 94.5Gy, having established that lower doses appear safe. Importantly for dose escalation, it is becoming apparent that elective nodal irradiation is unnecessary. Failure in unirradiated mediastinal nodes has not been a problem in the Ann Arbor series, while a Dutch series reported 2% isolated regional relapse. If the dose
escalation studies ultimately show improved local control, isolated nodal failure may become more important and the issue of elective nodal irradiation will need to be readdressed. Unfortunately, increasing the radiation dose in these studies has often required increased overall treatment time, and current estimates suggest that tumour repopulation during treatment necessitates an extra 0.2–0.4 Gy for each additional treatment day. CHART was designed to overcome this repopulation by shortening overall time to 12 days. In the North of Britain, fraction sizes of 2.75–3 Gy delivered to small volumes have been standard for radical treatments for over 50 years, allowing 3–4 week treatments rather than the 6–7 weeks used in the United States, Europe, and the South of Britain. Such fractionation schemes are now being explored in dose escalation trials to avoid the problems of increased time and in a current EORTC chemo radiotherapy trial[36].

1.3.5.2 Curative Radiotherapy in surgically unresectable NSCLC

- Chemoradiotherapy

There is little doubt that chemotherapy added to conventionally fractionated radical radiotherapy produces a small improvement in survival. Both a large meta-analysis and two subsequent randomised studies have shown a small survival benefit (2–3% at 5 years) for full dose cisplatin-based combination chemotherapy before radical radiotherapy. These studies included a wide range of chemotherapy and radiotherapy regimes, many of which would now be considered inadequate. It remains unclear whether chemotherapy should be given prior to or synchronously with radiotherapy and, if the later, whether at cytotoxic or radiosensitising doses. Chemotherapy after radical radiotherapy has never been formally assessed. An important EORTC study is currently comparing sequential chemoradiotherapy at cytotoxic doses and concurrent chemoradiotherapy at sensitising doses, delivering 66 Gy in 24 fractions over 4.5 weeks. The safety data accumulating with this regime suggest that, far from needing to reduce the radiotherapy dose to accommodate chemotherapy, it may be possible to dose escalate radiotherapy even when synchronous chemotherapy is given[36].

- Radiotherapy alone

In patients who are not fit for chemotherapy CHART is the treatment of choice. A dose of 60 Gy in 40thrice daily fractions over 18 days is safe and appears worth pursuing as an alternative to CHART, although this will require further randomised trials to prove equivalence. Trials of increased radiation dose without altered fractionation have not shown any benefit to date [36].
1.3.5.3 Postoperative Radiotherapy in NSCLC

A meta-analysis of 2128 patients treated in nine randomised trials of postoperative radiotherapy reported a 7% decrease in survival at 2 years in irradiated patients. This effect was apparent in patients with stages I and II disease but not stage III. These studies used a wide range of doses, volumes, and techniques over a 30 year period, and their applicability to contemporary practice has been debated. Radiotherapy does produce an improvement in local control, particularly in patients with stage III disease. The techniques which allow higher doses of radical radiotherapy are also pertinent to postoperative treatment. However, to allow high doses of radiotherapy to be focused on sites at high risk of recurrence, it will be necessary to collect much better data than are currently available about precise sites of relapse—whether local at the bronchial resection margin or regional at nodal sites and, if the latter, which nodal levels are involved for each primary site. Simply recording failure as loco regional (somewhere in the chest) is inadequate [35, 36].

1.3.5.4 Palliative Radiotherapy

Palliative care is defined by the World Health Organization as the active total care of patients whose disease is not responsive to curative treatment. The goals of the treatment in the palliative care phase are mainly to control the symptoms, to enhance the quality of life, and to optimize the patient’s limited remaining time. For palliative treatment of cancer patients, anti-cancer treatments such as radiotherapy, chemotherapy, molecular targeted therapy and hormonal therapy can help in achieving these goals.

About 34–50% of patients receiving radiotherapy are of palliative intent. Similar to other clinical domains, the practice of palliative radiotherapy is always guided by basic ethical principles and available clinical evidence. It requires sophisticated assessment to balance the potential benefits and burdens to the patients with respect to patient’s autonomy and expectations, and consideration of logistical factors. Palliative radiotherapy is mainly indicated to relieve various local symptoms in cancer patients; to prevent debilitation such as spinal cord compression and pathological fracture; and to achieve durable loco regional control. The effectiveness has been confirmed by cumulative clinical evidence. For metastatic bone pain, palliative radiotherapy can achieve an overall pain response rate of 59–62%, and a complete pain response rate of 32–34%. For multiple brain metastases, the overall response rate to external irradiation is around 60% with
30–40% achieving marked neurological improvement. On the other hand, palliative radiotherapy may sometimes cause significant burdens to the patient such as acute side effects, hospitalization, multiple visits to the treatment machine with associated discomfort in transport, and loss of opportunity cost.

Poor performance status, short predicted life expectancy, perception of slow onset of therapeutic effects and overly burdensome of palliative radiotherapy often preclude palliative radiotherapy as a tool for symptom relief in terminal cancer patients.

However, it is noted that physicians’ estimation of the life expectancy of the patients may not be accurate, the poor performance status may be related to the uncontrolled symptoms and the onset of the therapeutic effect of radiotherapy to some common symptoms such as metastatic bone pain and bleeding caused by cancer can be rapid. With appropriate patient selection, palliative radiotherapy can have a significant role in symptom control in end of life care of cancer patients. “One-shop approach” with the patient assessed, radiotherapy planned and delivered by a single fraction on the same day will be very useful in this group of patients.

In the past two decades, there has been increasing clinical evidence suggesting that shorter fractionation schedules and more protracted schedules have the same effectiveness in symptom control of incurable cancer patients, particularly, for metastatic bone pain and multiple brain metastases. In some clinical situations, protracted fractionated course of palliative radiotherapy will be more favourable than shorter hypofractionated schedule. Patients who have advanced loco regional cancers with good performance status and long life expectancy are preferably treated by protracted fractionated schedule with higher total dose and small dose per fraction to achieve durable local control [8].

<table>
<thead>
<tr>
<th>Pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic bone pain</td>
</tr>
<tr>
<td>Painful lymphadenopathy</td>
</tr>
<tr>
<td>Pain due to soft tissue infiltration by cancers</td>
</tr>
<tr>
<td>Neuropathic pain due to nerve compression and infiltration</td>
</tr>
<tr>
<td>Rescue of neurological deficit</td>
</tr>
<tr>
<td>Spinal cord compression</td>
</tr>
<tr>
<td>Brain metastases</td>
</tr>
<tr>
<td>Relief of pressure symptoms</td>
</tr>
<tr>
<td>Thoracic tumours:</td>
</tr>
</tbody>
</table>
SVCO
Upper airway obstruction
Dysphagia
Collapse of lung
Reduced the increased intracranial pressure secondary to
brain metastases
Retroperitoneal tumours
Relief of hydronephrosis
Pelvic tumours
Relief of hydronephrosis
Urinary retention
Intestinal obstruction
Control of fungation and ulceration of metastatic or primary
skin cancers
Haemostasis:
Bleeding rectal or gynaecological cancers
Bleeding skin cancers
Prophylaxis of impending symptoms
Prevention of spinal cord compression
Prevention of pathological fracture
Prevention of pending pressure symptoms
Durable control of advanced locoregional disease beyond cure.

Table 6: Indications for Palliative Radiotherapy

Palliative radiotherapy is commonly used in lung cancer to relief from symptoms that are
produced from the primary tumour such as haemoptysis, dyspnoea, cough, chest pain, malaise
or to reduce symptoms from metastasis such as pain from bone metastasis.
An MARC trial reported a 7 week increase in median survival with 39Gy in 13 fractions over
2.5 weeks compared with 17Gy in two fractions over 1 week in patients otherwise deemed
suitable for radical radiotherapy but whose tumours were considered too big, comparable to
the benefit seen with combination chemotherapy.
A trial in Edinburgh comparing 30Gy in 10 fractions with a 10Gy single fraction found better
physician reported palliation of cough, pain, and dyspnoea with the fractionated regime. A
Canadian study comparing 20Gy in five fractions over 1 week with a 10Gy single fraction reported a survival advantage with the former in patients with better performance status.

1.3.5.5 Radiotherapy in SCLC

In patients with SCLC, adjuvant thoracic and cranial irradiation prolong survival. The optimum dose and timing of these treatments is the subject of ongoing research. Patients with limited stage small cell lung carcinoma are usually given prophylactic cranial irradiation (PCI). This is a type of radiotherapy to the brain, used to reduce the risk of metastasis. More recently, PCI has also been shown to be beneficial in those with extensive small cell lung cancer. In patients whose cancer has improved following a course of chemotherapy, PCI has been shown to reduce the cumulative risk of brain metastases within one year from 40.4% to 14.6%.

1.3.5.6 Brachytherapy

Endobronchial radiotherapy may be given directly inside the airway when cancer affects a short section of bronchus. It is used when inoperable lung cancer causes blockage of a large airway. Endobronchial radiation was compared with palliative external beam radiotherapy in a randomised trial in Manchester. Survival was better and retreatment less frequent but toxicity greater with external beam therapy. The addition of endobronchial therapy to external beam treatment increased the re-expansion rate of collapsed lungs (57% v 35%), but there was no difference in the palliation of dyspnoea. With potentially curative radiotherapy the addition of endobronchial radiation had no effect on survival but improved local control in the subgroup with squamous carcinoma. Endobronchial therapy may have a role in patients with symptomatic local recurrence after external beam therapy. Hernandez and colleagues treated 29 patients with re-expansion in 28%, palliation of haemoptysis in 69%, and improved performance status in 24%.
1.3.5.7 Stereotactic Body Radiotherapy (SBRT)

SBRT delivers higher doses per radiation treatment for fewer treatments. It is thought to be more effective biologically as more tumour cells will be killed with higher radiation doses. Multiple individual fields are used to focus a few high doses of radiation on a single area. Each radiation dose is 5-10 times traditional daily dose of radiation. Diseases that this technique has been actively studied are early stage lung cancer and limited metastatic cancer to the lung and liver. For medically inoperable patients with early stage lung cancer the traditional radiotherapy controls tumours 30-40 %, on the other hand SBRT controls tumours 70-90%.

Immobilisation is an essential component when using SBRT for high accuracy and reproducibility of dose delivery. For extracranial targets internal motion must be considered. The four cornerstones of this method are: 1) Stereotactic methodology for target localization and treatment set-up, 2) CT verification in order to directly verify the position of the tumour in the stereotactic coordinate system, 3) Heterogeneous dose distribution in the target, in order to increase the probability to kill the most resistant tumour cells anticipated to be localised to the central parts of the tumour, 4) Hypofractionation, in order to prevent repopulation of the tumours as well as increasing cost effectiveness and improving the convenience for the patient. The method is furthermore based on the use of abdominal compression in order to reduce the tumour motion with breathing. By reducing the motion of the target and increasing the geometrical accuracy, SBRT allows smaller margins.

A survey was conducted at Karolinska University Hospital from Pia Baumann et al [55], where the factors that are important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer were examined. The results of SBRT treatment of 138 patients with medically inoperable stage I NSCLC treated during 1996-2003 at five different centers in Sweden and Denmark were reviewed. Mean age was 74 years. SBRT was delivered using a 3D conformal multifield technique and a stereotactic body frame. Doses delivered were 30-48Gy in 2-4 fractions. Equivalent dose in 2Gy fractions (EQD2) was in the range of 50-100Gy. Mean gross tumor volume (GTV) was 39 cm$^3$ and planning target volume was 101 cm$^3$. Overall response rate was 61%. Stable disease was noted in 36%. During a median follow-up period of 33 months local failures occurred, ten of which also included distant metastases. Local failure was associated with tumor size, target definition and central or pleura proximity. Distant metastases occurred in 25% of the patients. Three- and 5-year
overall survival was 52 and 26% respectively. Fifty nine percent of the patients had no side effects. Fourteen patients experienced grade 3-4 toxicity according to radiation therapy oncology group (RTOG). EQD2 showed a statistically significant benefit survival for the higher doses. As a result SBRT for stage I NSCLC results in favorable local control not inferior to fractionated RT and with acceptable toxicity.

Another survey was also conducted at Karolinska University Hospital from Baumann Pia et al [55] where the toxicity related with chronic obstructive pulmonary disease (COPD) and cardio vascular disease (CVD) were examined for patients with medically inoperable stage I NSCLC. Sixty patients were entered in the study between August 2003 and September 2005. Fifty seven patients (T1 65%, T2 35%) with a median age of 75 years (59–87 years) were evaluable. The baseline mean FEV1% was 64% and median Karnofsky index was 80. A total dose of 45Gy was delivered in three fractions at the 67% isodose of the PTV. Clinical, pulmonary and radiological evaluations were made at 6 weeks, 3, 6, 9, 12, 18, and 36 months post- SBRT. Toxicity was graded according to CTC v2.0 and performance status was graded according to the Karnofsky scale. At a median follow-up of 23 months, 2 patients had relapsed locally. No grade 4 or 5 toxicity was reported. Grade 3 toxicity was seen in 12 patients (21%). There was no significant decline of FEV1% during follow-up. Low grade pneumonitis developed to the same extent in the CVD 3/17 (18%) and COPD 7/40 (18%) groups. The incidence of fibrosis was 9/17 (53%) and pleural effusions was 8/17 (47%) in the CVD group compared with 13/40 (33%) and 5/40 (13%) in the COPD group. SBRT for stage I NSCLC patients who are medically inoperable because of COPD and CVD results in a favourable local control rate with a low incidence of grade 3 and no grade 4 or 5 toxicity.
Figure 1.8: Multiple individual fields focus high doses on a single area.
Figure 1.9: SBRT used for medically inoperable early stage lung cancer.

Figure 1.10: Stereotactic Body Frame.
1.3.5.8 Image Guided Radiotherapy

Image-guided radiation therapy (IGRT) is the process of frequent two and three-dimensional imaging, during a course of radiation treatment, used to direct radiation therapy utilizing the imaging coordinates of the actual radiation treatment plan [56]. The patient is localized in the treatment room in the same position as planned from the reference imaging dataset. An example of Three-dimensional (3D) IGRT would include localization of a cone-beam computed tomography (CBCT) dataset with the planning computed tomography (CT) dataset from planning. Similarly Two-dimensional (2D) IGRT would include matching planar kilovoltage (kV) radiographs fluoroscopy or megavoltage (MV) images with digital reconstructed radiographs (DRRs) from the planning CT.

This process is distinct from the use of imaging to delineate targets and organs in the planning process of radiation therapy. However, there is clearly a connection between the imaging processes as IGRT relies directly on the imaging modalities from planning as the reference coordinates for localizing the patient. The variety of image gathering hardware used in planning includes Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) among others. Through advancements in imaging technology, combined with a further understanding of human biology at the molecular level, the impact of IGRT on radiotherapy treatment continues to evolve.

The goal of the IGRT process is to improve the accuracy of the radiation field placement, and to reduce the exposure of healthy tissue during radiation treatments. In years past, larger planning target volume (PTV) margins were used to compensate for localization errors during treatment. (Jaffray et al. 1999) This resulted in healthy human tissues receiving unnecessary doses of radiation during treatment. PTV margins are the most widely used method to correct geometric uncertainties. By improving precision and accuracy through IGRT, radiation is decreased to surrounding healthy tissues, allowing for increased radiation to the tumour for control. (Jaffray et al. 1999).
Figure 1.11: Image guided Radiotherapy

Figure 1.12: Modern 3-D Radiotherapy Planning
1.3.5.9 Radiotherapy planning and treatment delivery

Multi-leaf collimation uses 0.5–1 cm tungsten leaves in the linear accelerator jaws which can be moved incrementally into set positions at the start of, or dynamically during, treatment to allow shaping of the radiation portal to spare normal tissues and deliver dose gradients across the radiotherapy volume.

Patient immobilisation and portal imaging during radiotherapy to monitor set up accuracy allow tolerances of 5mm or less in the day to day variation of field position [57, 58]. Unfortunately these tolerances are substantially less than the movements of tumour and normal structures due to breathing, and this has to be incorporated into the target volume around the tumour and tissues at risk of involvement with the cancer.

Studies measuring this movement have shown it to be maximal in the craniocaudal direction, with a mean of 12 (2) mm in one study [59] and of 8 (9) mm in another. More accurate delineation of the extremes of tumour movement is being developed as part of the planning process using slower CT scans with altered pitch and slice thickness [60].

Attempts have been made to limit tumour movement by breath holding or to make allowance for it by gating radiotherapy. Significant reductions in the lung volume receiving more than 20Gy and in the average lung dose [61, 62] delivered have been reported when patients held their breath in deep inspiration, but the mean breath holding time was only 23 seconds which may be too short for image acquisition for planning, and two out of 10 patients were unable to perform this manoeuvre. Gating techniques, such that the linear accelerator stops irradiation when a marker has moved more than a certain distance, have been described but no clinical data have been published[63,64].

PET scanning may also improve radiotherapy outcomes, both by identifying patients with occult metastatic disease and allowing more precise definition of the target volume, decreasing the risk of geographical miss of the tumour and, in a few patients, reducing the target volume with lower risk of complications. One study using PET reported target volume reduction in four patients but increases in seven to encompass occult nodal disease[65].
1.3.5.10 Radiation Morbidity

The dose limiting normal tissues are lung, spinal cord and oesophagus, with the first being most important with radiation alone and the third with combined modality treatment. The risk of acute radiation pneumonitis is related to performance status [69, 70] underlying lung function, the lung volume irradiated, and the radiotherapy dose. Data on the long term effects of radiotherapy on lung function are limited. Oesophageal toxicity is more severe when synchronous chemoradiotherapy or multiple daily fractions are given, but the importance of the length of oesophagus irradiated is the subject of debate.

Susan Tucker et al contacted a survey in order to identify clinical risk factors and dose–volume thresholds for treatment-related pneumonitis (TRP) NSCLC.

Data were retrospectively collected from patients with inoperable NSCLC treated with radiotherapy with or without chemotherapy. TRP was graded according to Common Terminology Criteria for Adverse Events, version 3.0, with time to grade P3 TRP calculated from start of radiotherapy. Clinical factors and dose–volume parameters were analyzed for their associations with risk of TRP. Data from 576 patients (75% with stage III NSCLC) were included in this study. The Kaplan–Meier estimate of the incidence of gradeP3 TRP at 12
months was 22%. An analysis of dose–volume parameters identified a threshold dose–volume histogram (DVH) curve defined by V20 625%, V25 620%, V35 615%, and V50 610%. Patients with lung DVHs satisfying these constraints had only 2% incidence of grade P3 TRP. Smoking status was the only clinical factor that affected the risk of TRP independent of dosimetric factors.

The risk of TRP varied significantly, depending on radiation dose–volume parameters and patient smoking status. Further studies are needed to identify biological basis of smoking effect and methods to reduce the incidence of TRP [71].

<table>
<thead>
<tr>
<th>Acute Radiation Morbidity Scoring Criteria</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>Mild symptoms of dry cough or dyspnoea on exertion</td>
<td>Persistent cough requiring narcotic, antitussive agents/ dyspnoea with minimal effort but not at rest</td>
<td>Severe cough unresponsive to narcotic antitussive agent or dyspnoea at rest/ clinical or radiologic evidence of acute pneumonitis/ intermittent oxygen or steroids may be required</td>
<td>Severe respiratory insufficiency/ continuous oxygen or assisted ventilation</td>
<td></td>
</tr>
</tbody>
</table>

| Late Radiation Morbidity Scoring Schema | None | Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances | Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy | Severe symptomatic fibrosis or pneumonitis Dense radiographic changes | Severe respiratory insufficiency/ Continuous O₂/ Assisted ventilation |
1.4 The significance of Radiobiology for Radiotherapy
Many developments in radiotherapy have resulted from new technologies or have been made empirically by clinicians; there are few examples of developments that have begun in the radiobiological laboratory and been carried through the point where patient survival has significantly improved.
Radiotherapy can be administered in short duration schemes up to extremely long schemes, lasting for several weeks. The justification for applications in small daily fractions is based on radiobiology “5 Rs”: reoxygenation, redistribution, recruitment, repopulation and regeneration. Most patients on radiotherapy receive a total dose of 50-70Gy as curative dose. These doses are fractioned during a period of 5-7 weeks, once a day, 5 days a week, with a daily dose of approximately 2Gy. On the concomitant treatment, 45Gy are used on the pre-operative stage and 55-60Gy on the post-operative [73].
In order to express the amount of absorbed radiation by the tissues, an international unit, rad (radiation absorbed dose) was initially proposed, that is to say, the difference between the applied radiation and that which went through the tissues. Recently, this unit was replaced by Gray, defined as 1 joule per kilogram. Gy is short for Gray, thus: 1Gy = 100cGy =100rad [78,79].

1.4.1. The growth rate of tumors
The speed of development of the disease process in patients with cancer depends to a large extent on the growth rate of primary and metastatic tumors. In patients in whom treatment is unsuccessful the speed of recurrence and the survival of the patient also depend on tumor growth rate.
Exponential growth is where tumour volume increases by a constant fraction in equal intervals of time. The equation of exponential growth is:
\[ V = \exp (0.693 \times \text{time}/T_d) \]

Where 0.693 is \(\ln 2\). The logarithm of tumour volume increases linearly with time. Non-exponential growth can thus arise by any combination of 3 factors: increasing cell cycle time, decreasing growth factor, increasing rate of cell loss.

Exponential growth of tumours in laboratory is uncommon, it is more usual to find that the doubling time increases progressively as the tumour gets bigger.

Growth curves have often been described by the Gompertzian equation:

\[ V = V_0 \exp \left[ \frac{A}{B} \{1-\exp (-B \cdot t)\} \right] \]

Where \(V_0\) is the volume at time zero and \(A\) are parameters that determine the growth [73].

After treatment, some tumors show a rapid volume response and others respond much more slowly. It is important to distinguish between speed of shrinkage and the probability of local tumor control. Thomlinson (1982) found that in tumors that were treated by radiotherapy as well as by chemotherapy the rate of regression was independent of the treatment: it was characteristic of the biology of the tumor [74].

The volume doubling time of a tumor is determined by three main factors: the cell cycle time, the growth fraction and the rate of cell loss. Tumors grow faster if: the cycle time is short, the growth fraction is high and the cell loss is low. The potential doubling time, or \(T_{pot}\), is defined as the time within which the cell population of the tumor would double if there were no cell loss (Steel, 1977). It depends on the cell cycle time and the growth fraction.

Potential doubling time (\(T_{pot}\)) = \(\lambda \times \frac{T_s}{L_i}\)

Where \(T_s\) is the duration of the S-phase and \(\lambda\) is a parameter that corrects for the non-rectangular age distribution of growing cell populations, usually between 0.7 and 1.0 and \(L_i\) is a thymidine labeling index. The volume doubling time (\(T_d\)) is found using calipers, from radiographs or from CT scans. The rate of cell loss from a tumor can be estimated from the cell loss factor:

\[
\text{Cell loss factor} = 1 - \frac{T_{pot}}{T_d}
\]

<table>
<thead>
<tr>
<th></th>
<th>Thymidine labeling index (%)</th>
<th>Volume doubling time (days)</th>
<th>(T_{pot}) (days)</th>
<th>Cell loss factor (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated</td>
<td>6.9(5-17)</td>
<td>45(33-150)</td>
<td>6.8</td>
<td>85</td>
</tr>
</tbody>
</table>
Tumor repopulation can be handled in the response models below by multiplying $N_0$ with a factor that amounts for the accelerated repopulation that is often seen in radiation therapy. The factor $f_{i, \text{acc}}$ can be defined according to

$$f_{i, \text{acc}} = e^{\frac{(n_i-1) \ln 2}{T_{\text{pot}}}}$$

if $t_i > T_k$ or $f_{i, \text{acc}} = 1$ if $t_i \leq T_k$

where $t_i$ is the time when fraction $i$ is delivered, $T_k$ is the time of onset of accelerated proliferation and $T_{\text{pot}}$ is the potential doubling time of the tumor.

$T_{\text{pot}}$ for prostate cancer is about 40 days and for non-inflammatory breast cancer about 14 days, in contrast with head and neck cancer, in which the mean $T_{\text{pot}}$ can be as short as 4 days and, as we have seen overall treatment time is an important factor governing tumor control.

### 1.5 Radiobiological Models

Models are necessary part of radiobiology research, to provide a framework in which to analyze and compare data and ultimately to assist in building up a consistent theory of radiation action both in vivo and in vitro. Models and mathematics are also sometimes necessary to relate experimental studies to clinical cancer treatment with the aim of improving therapy.

### 1.5.1 The linear-quadratic model

This model gives a better description of radiation response in the low dose region (0-3Gy).

$$S(dn) = e^{-\gamma nd^2}$$

Where $n$ is the number of fractions and $d$ is the dose per fraction. Since most clinical data gives $D_{50}$ the dose where 50% response is achieved and $\gamma$ the normalized dose response gradient, $\alpha$ and $\beta$ have to be calculated under the assumptions that the responses for the LQ-model are the same for the dose per fraction $d$ used in the clinical trial where the data comes from and that $\alpha/\beta$ is known.

$$\alpha = \frac{1}{D \ 0 \left(1 + \frac{d}{\alpha / \beta}\right)}$$

and
The dimensions of $\alpha/\beta$ are Gy. For acutely responding tissues which express their damage within a period of days to weeks after irradiation, the $\alpha/\beta$ ratio is in the range 7-20 Gy, while for late–responding tissues which express their damage months to years after irradiation, $\alpha/\beta$ generally ranges from 0.5-6 Gy. The $\alpha/\beta$ ratio is not constant and its value should be chosen carefully to match the specific tissue under consideration.

This model is in widespread use in radiobiology and generally works well in describing responses to radiation in vitro and also in vivo [73].

1.5.2 Dose Response models

1.5.2.1 The Probit Model

$$P(D) = \gamma_{50}/D_{50} \int_0^D e^{-\frac{x}{\gamma}} \left(\frac{D - D_{50}}{D_{50}}\right)^2 dx,$$

Where $D_{50}$ is the dose that gives 50% response probability and $\gamma_{50}$ is the normalized dose response gradient defined according to $\gamma_{50} = D_{50} P'(D_{50})$.

1.5.2.2 The Logit model

The Logit model is not based on any statistical distribution. It is an empirical sigmoid shaped curve commonly used in biology defined as:

$$P(D) = \frac{1}{1 + \left(\frac{D}{D_{50}}\right)^\gamma_{50}}$$

1.5.2.3 The Weibull model

The response is given by:

$$P(D) = 1 - e^{-\ln^2 \left(\frac{D}{D_{50}}\right)^\gamma_{50}}$$
1.6.3 *Cell survival based response models*

1.6.3.1. The Poisson model

Assuming \( N_0 \) clonogenic cells (or functional subunits for healthy tissue) and a probability of cell survival, \( S(D) \), at a dose \( D \), the probability for response using Poisson statistics is given by

\[
P(D) = e^{-N_0 S(D)}
\]

With the linear model for clonogenic cell survival

\[
S(d, n) = e^{-nd/D_0} = S(nd) = S(D)
\]

together with the Poisson model for response \( D_{50} \) and \( \gamma \) becomes:

\[
D_{50} = D_0 \left( \ln N_0 - \ln \ln 2 \right) \quad \text{and} \quad \gamma = \frac{\ln N_0}{e}
\]

The maximum slope of the response function is for the Poisson model at the dose where the response is 37%. In order to compare with response models where the use of \( \gamma_{50} \) is the natural choice the following transformation can be used:

\[
\gamma_{50} = \frac{\ln 2}{2} \left( e\gamma - \ln \ln 2 \right)
\]

1.6.3.2 The Binomial model

Assuming \( N_0 \) clonogenic cells (or functional subunits for healthy tissue) and a probability of cell survival, \( S(D) \), at a dose \( D \), the probability for response assuming Binomial statistics is given by

\[
P(D) = (1 - S(D))^{N_0}
\]

With the linear model for clonogenic cell survival together with the Binomial model for response \( D_{50} \) and \( \gamma \) becomes:

\[
D_{50} = -D_0 \ln \left( 1 - \frac{1}{2^{1/N_0}} \right)
\]

and
\[ \tilde{\gamma} = \ln N_0 \left( 1 - \frac{1}{N_0} \right)^{N_0-1} \]

Respectively, for large \( N_0 \) the expressions for \( D_{50} \) and \( \gamma \) for the Binomial model becomes identical to the expressions for the Poisson model.

### 1.7 Biologically Effective Dose (BED)

BED is a measure of the effect of a course of fractionated or continuous irradiation. It has the units of dose and is usually expressed in grays.

\[
BED = D \left[ 1 + \left( \frac{d}{\alpha / \beta} \right) \right]
\]

where \( D \) is the total dose received and \( d \) the dose per fraction.

As the dose per fraction (\( d \)) is reduced towards zero, BED becomes \( D \), i.e. the total radiation dose.

BED thus has a simple conceptual significance: it is the theoretical total dose that would be required to produce the isoeffect \( E \) using a large number of very small fractions. It is also the total dose required for a single exposure at a very low dose rate.

As it is defined at Lind et al 1999, Mavroidis et al 2000, the biologically effective uniform dose \( D \) is the uniform dose that causes exactly the same total tumour control or normal tissue complication probability as a given non-uniform dose distribution on a complex patient case.

The notation \( D \) indicates that the quantity has been averaged over both the dosimetric (dose distribution) and the biological (dose response relations) information of the complex patient.

The general expression of \( D \) is defined for a given tumour or tissue from its dose–response relation without dependence on the radiobiological model used and it is then given by

\[
P(D) = P(D) \equiv P(D(D)).
\]

The advantages of the \( D \) concept and its differences from other reporting means that have been used have to be specified. In clinical practice the mean dose of the dose distribution delivered to the tumour or the ITV and its standard deviation are mainly used to compare the effectiveness of different plans in terms of tumour control. However, these data neither take into account the biological characteristics of the targets nor do they provide a common dose-scaling basis for comparison of different plans. This is because different plans deliver
generally different mean dose to the ITV at the same control rate and the effect of the
treatment to the rest of the involved organs is harder to compare using this scale. [80]
The EQD2 with the dose 2 Gy per fraction can be described by:

\[
D \left( 1 + \frac{d_i}{\alpha} \right) = EQD \left( 1 + \frac{2}{\alpha} \right) = EQD = D \left( \frac{\alpha + d_i}{\beta} + 2 \right)
\]

1.8 Tumor control probability
The level of success with radiotherapy for cancer varies considerably from one disease and
tumor stage to another. It is common clinical experience that some tumors are highly curable,
others not. A quantitative description of this picture is provided by a comparison of tumor
control probability curves.
The steepness of each dose-response curve reflects a number of variables, which include:

- An underlying Poisson relationship. If the average number of clonogenic tumor cells
  that survive treatment is m, then the probability that no cells survive and that the
  tumor is cured is \(e^{-m}\). Tumor control probability therefore has a sigmoid dependence
  on m, with a finite maximum slope.

- Variability in curability among tumors of the same type, arising from differences in
  cellular radiosensitivity, repopulation, hypoxia etc.

- Inter-patient variation in the quality of radiation dose delivery.

The steepness of tumor control curves has been quantified in a variety of ways which have
been reviewed by Mijnheer et al (1987) and Brahme (1988). Widely used is the \(\gamma_{50}\) value,
this is the percentage change in tumor control probability for a 1% change in dose. For human
tumors values range from 1 to 5 with a mean of 2.6 [73, 75].
Materials and methods

2.1 Study Bases
This study is composed of two parts. In the first part a questionnaire was constructed in collaboration with Bengt Lind, Helena Lind and Panayiotis Mavroidis and was sent to radiotherapy centers in Europe. In the second part a review to the literature was done. Trials that referred to advanced NSCLC were selected and were compared.

2.2. Questionnaire
The survey was conducted by sending a questionnaire (Table 8) to twenty four radiotherapy centers in Europe (Sweden, Greece and United Kingdom) in December 2008. There were seventeen replies received by March 2009.

The questionnaire was composed of two sections. The first section concerned reasons for starting radiotherapy, parameters that influence the choice of total dose and fractionation for radiotherapy, the kind of equipment that is used and the main reasons for starting the therapy. The second section examines five case histories and asked the responders about the management of these five theoretical patients also regarding the radiotherapy techniques proposed and the aim of treatment (radical or palliative).

1. Do you treat patients with lung cancer?
If not, thank you very much. If you treat patients with lung cancer, please continue to the next question.

2. Which parameters influence your choice of total dose and fractionation for radiotherapy for NSCLC?
   Size of the primary tumor
   Location of the tumor
   Age of the patient
   Performance status of the patient
Distant Metastases
Metastases to loco regional lymph nodes
Symptoms
Lung function
Previous chemotherapy or other treatment
Histology
Sex
Other parameters

3. What kind of equipment would you normally use when treating lung cancer patients?

4. Which is the main reason for initiating the treatment?
Symptom relief
Prolongation of life
Better quality of life
Cure
Other reasons

5. Consider the following scenarios:

A. 80 year old man, smoker with ECOG performance status 3, hemoptysis, dyspnoea, weight loss, malaise and anorexia diagnosed with squamous NSCLC stage IV. CT scan reveals occlusion of the right bronchus. What would you recommend for this patient:
Total Dose
Number of fractions
Overall treatment time
Additional treatment
Number of fields
Energy
B. 50 year old man, smoker with ECOG performance status 2, dyspnöea and cough diagnosed with anaplastic NSCLC stage IIIB. CT scan shows a central mass of 3cm diameter. What would you recommend for this patient:

Total Dose
Number of fractions
Overall treatment time
Additional treatment
Number of fields
Energy
Fixation
Gating
Other recommendations

C. 57 year old woman with ECOG performance status 1 and productive and severe cough diagnosed with adenocarcinoma NSCLC stage IIIA. CT scan reveals occlusion of the left main bronchus by a mass of 5cm diameter. What would you recommend for this patient:

Total Dose
Number of fractions
Overall treatment time
Additional treatment
Number of fields
Energy
Fixation
Gating
Other recommendations

D. 70 year old woman with ECOG performance status 4, hemoptysis and superior vena cava syndrome diagnosed with NSCLC stadium IV. CT scan reveals occlusion of the left main bronchus. What would you recommend for this patient:

Total Dose
E.55 year old man with ECOG performance status 1, chest pain, dyspnoea and FEV1= 60% diagnosed with NSCLC stage IIB adenocarcinoma. CT scan reveals peripheral mass of 4cm diameter. No information on other diseases. What would you recommend for this patient:

Total Dose
Number of fractions
Overall treatment time
Additional treatment
Number of fields
Energy
Fixation
Gating
Other recommendations

Thank you very much for your participation in this study. If you wish to have information regarding the results of the study, please note your e-mail address here:-----------------------

Table 9: Questionnaire.
2.3 Review to the literature

Palliative radiotherapy to the chest is often used in patients with lung cancer, but radiotherapy regimens are more often based on tradition than research results. The object of this research is to discover the most effective and least toxic regimens of palliative radiotherapy for non-small cell lung cancer and weather higher doses increase survival. The electronic databases MEDLINE, EMBASE, Cancerlit and the Cochrane Central Register of Controlled Trials [10], reference lists, hand searching of journals (Journal of Clinical Oncology, Clinical Oncology, Lung Cancer, Radiotherapy and Oncology, International Journal of Radiation Oncology, Biology and Physics, Thorax, Chest, American Journal of Clinical Oncology) and conference proceedings and discussion with experts were used to identify potentially eligible trials, published and unpublished. The trials that were selected were controlled trials comparing different regimens of palliative radiotherapy in patients with non-small cell lung cancer. Nineteen trials were reviewed. There were important differences in the doses of radiotherapy investigated, the patient characteristics and the outcome measures. This review shows that in the majority of patients, a short course of radiotherapy with only one or two visits, improves symptoms as effectively as longer courses, without more side effects. For some fitter patients, a longer course of radiotherapy may give a slightly better chance of living for one or two years, but with more immediate side effects, especially sore swallowing. The dose regimens for palliative RT evolved empirically from clinical experience and surveys in Europe and the USA in the early 1990s showed widespread variation in clinical practice (Maher 1992). However the regimens were not subject to rigorous evaluation in clinical trials until the late 1980s and 1990s.

2.3.1 Objectives

The two objectives of this review are:

- To evaluate which is the most effective and least toxic palliative RT regimen to improve or control thoracic symptoms in patients with locally advanced or metastatic NSCLC who are not suitable for radical RT given with curative intent.
- To evaluate whether higher dose regimens are associated with increased survival in such patients.
2.3.2 Criteria for considering studies for this review

2.3.2.1 Types of studies

Controlled clinical trials (CTs) fully published in journals and those identified from other sources (abstracts and proceedings of relevant scientific meetings, and contact with investigators) for which full details were available from the investigators. A Randomised Controlled Trial is a study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control.

2.3.2.2 Types of participants

Patients with histologically confirmed (or a high clinical likelihood of) lung cancer of non-small cell type, locally advanced or metastatic and with thoracic symptoms.

2.3.2.3 Types of intervention

External beam, megavoltage RT to the chest given with palliative intent (i.e. with the intent of controlling symptoms, not cure) with a total tumour dose of less than 63Gy in 2Gy fractions, or its radiobiological equivalent. The doses given and their prescription points must be clearly defined. RT with endobronchial brachytherapy and combination treatment with RT and chemotherapy were not considered.

2.3.2.4 Types of outcome measures

- Improvement of major thoracic symptoms, both degree and duration.
- Short- and long-term toxicity
- Quality of life
- Survival from date of randomization of first treatment

2.3.3 Description of studies

The literature search identified a number of randomised trials comparing RT with chemotherapy alone or in combination, which were not included. Two studies, one randomised (Exposito 1994) and one non-randomised (Carroll 1986) compared palliative RT
with 'best supportive care' (Exposito 1994) or with delayed palliative RT (Carroll 1986). Neither were included.

A total of 19 trials which compared RT regimens and met the inclusion criteria were identified (Abratt 1995[81], Bezjak 2002[82], Erridge 2005[84], Kramer 2005[85], MRC 1991[87], MRC 1992[88], MRC 1996[86], Nestle 2000[83], Rees 1997[90], Reinfuss 1999[91], Senkus-Konefka 2005[92], Simpson 1985[93], Sundstrom 2004[89], Cross 2004[94], Koutaissof 1999[100], Nestle 1996[101], Lupatelli 2000[102], Teo 1988[103], Appold 1999[103]). A total of 4336 patients were randomised in these trials. There were five studies (Simpson 1985; Sundstrom 2004; Teo 1988; Kramer 2005; Erridge 2005) in which there was a discrepancy between the numbers of patients randomised and those evaluated for outcomes. Twelve studies had two-way comparisons (Abratt 1995; MRC 1991; MRC 1992; MRC 1996; Nestle 2000; Rees 1997; Teo 1988; Erridge 2005; Kramer 2005; Bezjak 2002; Senkus-Konefka 2005, Nestle 1996), four had three arms (Simpson 1985; Sundstrom 2004; Reinfuss 1999, Appold 1999) and three had one arm (Cross 2004, Koutaissof 1999, Lupatelli 2000). In one three-arm study (Reinfuss 1999) the third arm was 'delayed' RT, given when the patients became symptomatic.

The doses of RT investigated ranged from 10Gy in 1 fraction (10Gy/1F) to 60Gy/30F over six weeks, with a total of 22 different dose/fractionation regimens. The biologically equivalent doses for carcinoma cells (BED10) were calculated. In only one study (Nestle 2000) was one arm of the study a dose (60Gy in 30 fractions) that would be normally considered as 'radical' and potentially curative, with a BED10 in excess of 70Gy.

The studies included slightly different patient groups. The majority included only patients with histologically or cytologically proven NSCLC but one trial (Rees 1997) included 18% of patients in whom a clinical diagnosis had been made. Two studies (Rees 1997; Erridge 2005) included a few patients with small cell lung cancer (3% and 6% respectively). Another (Teo 1988) included 2 patients with bronchial carcinoid tumours. Inclusion of these patients is unlikely to influence the assessment of palliation or toxicity but might affect the survival results.

More important is the performance status (PS) of the patients. PS is a well known major determinant of prognosis in these patients. The Eastern Cooperative Oncology Group (ECOG) PS scale scores patients 0 to 4, with 0 being the best and 4 the worst score for living patients. Only two studies (MRC 1992, Cross 2004) specifically included patients with poor PS (ECOG2 or worse). Kramer 2005 included ECOG PS 3 to 4 patients, or PS 0 to 2 patients with metastatic disease. Five studies (Abratt 1995; MRC 1996; Nestle2000; Reinfuss 1999; Simpson 1985) only included patients with better PS (ECOG 0-2), while seven (MRC 1991;
Rees 1997; Teo 1988; Sundstrom 2004, Lupattelli 2000, Appold 1999, Koutaissof 1999) included patients with any PS. One study (Senkus-Konefka 2005) excluded patients with PS 0, and two studies excluded PS 4 patients (Bezjak 2002; Erridge 2005). Also one study (Nestle 1996) included patients with Karnofky PS 40% or worse.

Age data are reported differently in different studies. All but one (Simpson 1985) which excluded those over 75 years, included patients of any age. But the age ranges do seem to be different. Reinfuss 1999 did not exclude older patients, but only 43% of the population was over 60. In contrast, the five British studies (MRC 1991; MRC 1992; MRC 1996; Rees 1997; Erridge 2005) had between 59% and 77% of patients over 65 years. Although age has not been shown to be an independent prognostic factor, it may reflect co-morbidity and give information about case selection.

Finally, one study (Reinfuss 1999) included patients who were asymptomatic, because in one arm of the trial RT was only given when the patients were, or became symptomatic. Most of the trials examined symptoms such as coughing, haemoptysis, chest pain, dyspnoea, dysphagia, dysphonia, lack of energy and nausea and anorexia.

Different outcomes were measured and reported in these studies. All reported survival as an outcome, although in the context of a palliative treatment this may be less important than the measurement of symptom control and quality of life (QOL).

The assessment of symptoms, both tumour related and treatment toxicity, as part of a trial is difficult and the methodology for collecting and analysing the data have evolved and been validated during the time period of these trials (Aaronson 1993; Fayers 1991; Montazeri 1996; Hopwood 1994). There was no standard methodology for assessing symptoms and their change with time, nor for interpreting the data.

Ten studies (MRC 1991; MRC 1992; MRC 1996; Nestle 2000; Nestle 1996; Bezjak 2002; Sundstrom 2004; Senkus-Konefka 2005; Lupatelli 2000; Cross 2004) used the most thorough and systematic symptom assessment, with records of both the clinicians’ and patients’ assessment at each time point using validated instruments. The MRC studies also pioneered the use of daily diary cards (Fayers 1991) which gave particular insights into the time course of radiation oesophagitis and other acute symptoms following treatment. Two studies (Rees 1997; Kramer 2005) used only patient questionnaires. Four studies (Abratt 1995; Simpson 1985; Teo 1988; Erridge 2005) appear to have relied entirely on the clinicians’ assessment of symptoms, which has been shown to underestimate symptoms compared to the patients’ own assessment (Stephens 1997). Reinfuss 1999 did not specifically assess symptoms and only assessed tumour response radiologically.

Three studies reported QOL outcomes using validated tools (Sundstrom 2004; Bezjak 2002; Erridge 2005). Erridge 2005 used the patient-completed Spitzer QOL index at baseline and
after RT. Sundstrom 2004 used the European Organisation for Research and Treatment of Cancer (EORTC) QOL questionnaire (QLQC30) and EORTC QOL questionnaire -lung cancer-specific module (LC13) at baseline, 2 and 6 weeks after RT and 8-weekly thereafter up to 54 weeks. Bezjak 2002 used QLQ-C30 and the Lung Cancer Symptom Scale (LCSS) at baseline at 1 month after RT.

It is therefore clear that these 19 studies are heterogeneous in the dose regimens compared, in the age and PS of the patients recruited and in the way in which key outcomes were assessed and reported. Formal meta-analysis of the numerical data is therefore inappropriate and only narrative synthesis was attempted.

### 2.3.4 Methodological quality

The entry criteria and treatment options (including adequate technical details of the RT regimens) were clearly stated in all studies. Withdrawal and drop-outs were fully accounted for in all but one study (Reinfuss 1999). In none of the studies was it reported that the clinicians were blind to the allocation of treatment.

The methods of symptom assessment and toxicity varied between studies in detail and quality (see Description of Studies, above). Where tumour response was reported, standard criteria were used. The methods of statistical analysis were fully or partly described in all studies. Survival analysis was performed using the Kaplan- Meier method in all trials except Abratt 1995 and Nestle 2000 where the precise method was not stated. Groups were compared using the Logrank test in all trials except Abratt 1995 where again the method used was not stated. All trials contained adequate information on the statistical tests used for analysis of differences in symptom control, toxicity differences and risk factor analysis where appropriate.
Results

3.1 Questionnaire

3.1.1 First Part

Seventeen centres replied (seventy per cent). All of the responders replied that they treat patients with lung cancer and that these centres are available not only for radical but also for palliative treatment.

The responders suggested that the most important factors, which influence the choice of total dose and fractionation schedule, are distant metastases (100 %), patients’ performance status (100 %), lung function (75 %), size of the primary tumour (69 %) and metastases to locoregional lymph nodes (69%). Less important factors are location of the tumour (56%), age of the patient (56%), previous chemotherapy or other treatment, histology of the tumour and sex of the patient.

The equipment that is used when treating lung cancer patients are Linear Accelerators. Also EPI 3D conformal radiotherapy and multileaf collimators are used.

The most common reasons for starting the treatment is not only cure, but also symptom relief and better quality of life. Other reason for initiating the treatment is prophylactic radiotherapy for brain metastases, in order to reduce the possibility of brain metastases from the primary lung tumour.
Figure 3.1: Parameters that influence the choice of total dose and fractionation for NSCLC RT.
3.1.2 Second Part – Case Histories

3.1.2.1 Patient A

All of the responders from all the countries proposed to treat this patient with palliative radiotherapy and considered the patient incurable, although the majority in all groups thought that important aim of treatment was to relieve symptoms. There was a relationship between the total dose and number of fractions and the aim of treatment, that is, those who felt that life could not be extended by treatment chose a lower dose and fewer fractions than those who felt they could extend life.

There were differences in the total dose, the number of fractions proposed and the overall treatment time proposed which ranged from 8Gy in 1 fraction in 1 day (Equivalent Dose for fractionation 2Gy per fraction =12Gy) to 39Gy in 13 fractions in 13 days (Deq=42Gy). The most common total doses proposed from the majority of the responders were 20Gy in 5 fractions in 1 week (Deq=23Gy) and 30Gy in 10 fractions in 2 weeks (Deq=33Gy). One Swedish center answered that it would not give radiotherapy to this theoretical patient.

The majority of responders from all countries proposed to treat this patient with radiotherapy using simulated two opposed fields and only two responders from Sweden proposed three or four fields. The energy suggested was 6MV or 18MV and the fixation proposed was vacuum.
pillows and support for knees. None of the responders suggested gating for this patient. Other recommendations for this theoretical patient were palliative care and drugs in order to relieve from symptoms.

### 3.1.2.2 Patient B

All the responders considered the radiotherapy for this patient as curative. The range of dose and number of fractions proposed was wide and ranged from 55Gy in 20 fractions in 4 weeks (Deq= 58Gy) to 68Gy in 34 fractions in 7 weeks (Deq =68Gy). The most common dose proposed from the majority of the responders was 60Gy in 30 fractions in 6 weeks (Deq= 60Gy). Two Swedish centers suggested Stereotactic Body Radiotherapy with 40Gy in 4 fractions in 4 days (Deq = 67Gy).

Nearly all the responders proposed to treat this patient with simulated radiotherapy fields which ranged from 3 to 7 fields and the energies suggested were 6 to 15 MV. All of the radiotherapy centers recommended chemotherapy as additional treatment.

### 3.1.2.3 Patient C

All the responders considered this radiotherapy scheme as radical. All of them answered that they would give the same total dose an in case B. The number of fractions and the overall treatment time would also be the same. The centers that in the previous case suggested SBRT proposed for those 68Gy in 34 fractions in 7 weeks.

All of the centers suggested giving additional post-RT chemotherapy. Fifty percent of the responders also suggested surgery if that was possible.

The energy, number of fields, fixation and gating recommended were the same as in the previous cases.

### 3.1.2.4 Patient D

The majority of responders from all the countries proposed palliative radiotherapy with radiotherapy using simulated two opposed fields. Only one center proposed multiple fields. There were differences in the total doses and the number of fractions proposed which ranged from 16Gy in 2 fractions in 2 days (Deq= 24Gy) to 40Gy in 15 fractions in 3 weeks (Deq =
42Gy). The most common scheme proposed was 30Gy in 10 fractions in 2 weeks (Deq= 33Gy).

The energies for this scenario were 6 or 10 MV. Fifty per cent of the responders did not suggest additional treatment, while the others proposed steroids, drugs in order to reduce symptoms such as dispose, cough and pain, vena cava stent in order to relieve from vena cava syndrome and additional chemotherapy. Suggestions for fixation and gating did not differ from the previous cases.

### 3.1.2.5 Patient E

All responders viewed the aim of treatment as curative. The total doses proposed ranged from 55Gy in 20 fractions in 4 weeks (Deq= 58Gy) to 68Gy in 34 fractions in 7 weeks (Deq= 68Gy). The most common scheme proposed was 68Gy in 34 fractions in 7 weeks (60 % of the responders). Furthermore, three of the centers (two Swedish and one Greek) proposed SBRT with 45Gy in 3 fractions in 5 days or 21Gy in 3 fractions.

Other recommendations for the treatment of this patient were chemotherapy or surgery if that was possible. All of the centers would use multiple field technique for this theoretical patient.

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<tr>
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<th>A</th>
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<th>C</th>
<th>D</th>
<th>E</th>
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<td>24</td>
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<tr>
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</tr>
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<td>6</td>
<td>-</td>
<td>35</td>
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</tr>
</tbody>
</table>

Table 10: Other treatment recommended except RT.

<table>
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<td>55-68</td>
<td>16-40</td>
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<td>4-34</td>
<td>20-34</td>
<td>2-15</td>
<td>2-15</td>
</tr>
</tbody>
</table>

Table 11: Range of dose and number of fractions proposed for each case.
3.2 Review to the literature

3.2.1 Symptomatic response

All studies that investigated symptoms reported that major thoracic symptoms improved following RT. Only three studies (Teo 1988; Bezjak 2002; Erridge 2005) reported a difference in symptom control between regimens tested. In Teo 1988, the higher dose and more fractionated regimen (45 Gy/18F) appeared to give significantly better palliation. It is not entirely clear how symptoms were assessed in this trial but it appears to have been solely by doctors. The definition of partial response “reduced severity or frequency for one or more of the pre-treatment thoracic symptoms without concurrent emergence of new intrathoracic symptoms” is also imprecise. Of the 291 patients randomised, only 237 were included in the response assessment because of either defaulting (18) or dying (36) before the end of RT. The other two studies (Bezjak 2002; Erridge 2005) also reported better palliation with the higher dose, more fractionated regimen. In Bezjak 2002, changes on the Lung Cancer Symptom Scale (LCSS) showed that 20Gy/5F resulted in significant improvement in symptoms related to lung cancer. In Erridge 2005, the 30Gy/10F regimen was significantly better at reducing chest pain and dyspnoea compared to 10Gy/1F. In addition, a significant improvement in PS and less patient-scored anxiety was reported with the 30Gy/10F regimen, but it is not clear if this was compared to 10Gy/1F or to the pretreatment baseline readings.

In MRC 1996 the shorter (2 fraction) regimen appeared to have a more rapid onset of effect in palliating symptoms than the longer, higher dose, 13 fraction regimen, although the differences in the proportion of patients with various symptoms who were palliated were not significant.

The duration of symptom control is a difficult endpoint to define and record. Only one trial showed a significant difference between the regimens investigated (Kramer 2005). This trial showed both regimens were effective in controlling symptoms, but the duration of palliative effect was significantly longer with 30Gy/10F compared to 16Gy/2F.

In MRC 1991, MRC 1992 and Sundstrom 2004, palliation seemed to last at least 50% of the survival time. Rees 1997 noted that only one symptom, haemoptysis, was improved in more than 50% of patients at eight weeks but that relief of other symptoms was “disappointing in both degree and duration”.

65
In summary, all the studies showed a beneficial effect of RT on thoracic symptoms due to lung cancer, but there is no strong evidence to support the view that higher dose are associated with better or longer lasting palliation.

The data for the symptom of hemoptysis were selected for these trials. The total dose, number of fractions, the number of patients having the symptom as well as the number of patients that relieved from the symptom were used and the Poisson probability was calculated. Poisson model for these data shows that the possibility of relieving from hemoptysis reduces as the dose gets higher.

![Figure 3.3: Possibility of hemoptysis palliation in relation with the dose given.](image)

### 3.2.2 Quality of life

One study (Erridge 2005) reported no difference in QOL outcomes between the regimens tested. In Bezjak 2002, the LCSS scores reported significantly better global QOL with 20Gy/5F compared to 10Gy/1F. Using QLQ-C30 however, there was no difference in QOL between the two regimens tested except for a statistically significant improvement in pain scores with 20Gy/5F. Sundstrom 2004 reported reduced physical and social functioning with 17Gy/2F compared to 50Gy/25F, and more emesis and appetite loss with 42Gy/15F compared to 50Gy/25F, but otherwise no differences between the three RT schedules.
3.2.3 Toxicity

The acute side effects of RT to the chest, in particular radiation, oesophagitis, tiredness and acute pneumonitis, are well recognised. These were reported as generally mild (Grade 1 or 2) for the majority of patients in all of the trials. A consistent finding in all these studies is that higher equivalent doses of RT are associated with more acute side effects. The best documented toxicity is radiation oesophagitis, especially in the MRC trials (MRC 1991, MRC 1992, MRC 1996) and Nestle 2000 where the patient diary cards clearly record the time course and intensity of dysphagia. Sundstrom 2004 reported earlier dysphagia with the two shorter treatment regimens. MRC 1996 also showed that the higher dose (13 fractions) regimen caused more tiredness and anorexia than the 2 fraction regimen. Lupatelli 2000 reported WHO grade III dysphagia in only 4 (5%) of the patients and the treatment was generally well tolerated.

None of the trials formally monitored or reported the side effects of acute chest pain, rigors, sweating and fevers which have been reported to occur in the first 24 hours in over 50% of patients receiving hypo-fractionated RT (Devereux 1997).

In two studies (Abratt 1995, Teo 1988) the spinal cord was shielded at tolerance doses. Simpson et al (Simpson 1985) limited the spinal cord dose to 25 Gy in the split course regimen and adjusted the field arrangement in the conventionally fractionated regimen, as did Nestle et al (Nestle 2000), to ensure the dose to the spinal cord did not exceed their tolerance limits. While this is necessary, it does introduce a degree of uncertainty to the dosimetry and in some cases may shield tumour itself.

Radiation myelopathy was suspected (although not confirmed at autopsy) in one patient in MRC 1991 and confirmed in one patient in MRC 1992, both of whom received 17Gy/ 2 fractions.

In MRC 1996, three patients - one receiving 17Gy/ 2 fractions and two 39 Gy/ 13 fractions - had clinical evidence of radiation myelopathy. In none of these trials was spinal shielding added or specific guidance given on the use of wedged fields to compensate for changes in antero-posterior diameter of the chest, but clinicians had the option of giving 36 Gy/ 12 fractions rather than 39 Gy/ 13 fractions in MRC 1996. One patient in Sundstrom 2004 in the 50Gy/25F arm developed radiation myelopathy, but it is not stated whether this was a clinical or autopsy diagnosis. None of the other trials reported any cases of radiation myelopathy.

Reinfuss 1999 reported broncho-oesophageal fistulae in two patients who had significant comorbidity. This complication was not reported in any other trial.

In Simpson 1985, lung haemorrhage was seen in one patient (2%) given 30Gy/10F.
3.2.4 Radiological response

In the 7 studies (Abratt 1995; MRC 1991; Nestle 2000; Reinfuss 1999; Simpson 1985; Teo 1988; Senkus-Konefka 2005) in which radiological response was reported, there was no significant difference reported between any of the RT regimens studied. Reinfuss et al (Reinfuss 1999) did report a difference in response of 44% versus 34% between regimens of 50Gy/25F and 40Gy/10F, but did not carry out a statistical test of significance.

3.2.5 Survival

All studies reported survival as an important endpoint. Because of the heterogeneity of the studies with respect to RT doses and patient PS, combining these results would be inappropriate. The worst survival (median 3.6 months) is seen in the only study that specifically excluded better PS patients (MRC 1992). The 3 studies that specifically recruited patients with better PS (Abratt 1995; MRC 1996; Simpson 1985) had better survival (median 6.2 - 9 months). This is in keeping with the well known prognostic significance of PS.

Four studies (MRC 1996; Reinfuss 1999; Bezjak 2002; Kramer 2005) showed a significant survival benefit for those patients treated with the higher dose regimen. In MRC 1996 the improvement was modest with a two month increase in median survival (9 months vs. 7 months), and 5% and 3% increases in the 1- and 2-year survival respectively.

Reinfuss 1999 reported a statistically significant survival benefit at two years (18% vs 6%) for the 50 Gy/25 fraction regimen compared to 40Gy/10 fraction split course regimen. This must be interpreted with caution for a number of reasons. The entry criteria were different in that asymptomatic patients were included, and the numbers of patients in each arm of the study (79 and 81) are small. In addition, the confidence limits of 1-year and 2- year survival figures were not reported. The patients were relatively young compared to those in other studies and were of generally good PS. The difference may reflect the fact that the less effective 40Gy/10F regimen was a 'split’ course with a 4 week gap in the middle. Prolonged, interrupted and split course treatments have been shown to be less effective than equivalent continuous treatments in non-small cell lung cancer (Ching 2000; Cox 1993; Koukourakis 1996).
Kramer 2005 reported a significant improvement in 1-year survival with 30Gy/10F compared to 16Gy/2F (19.6% vs. 10.9%). On subgroup analysis, this was only significant in patients with PS 0-1, not in PS 2-4. Interestingly, all the PS 0-1 patients in this trial had stage 4 disease.

Bezjak 2002 reported a significant improvement in median survival with 20Gy/5F compared to 10Gy/1F (6 months vs. 4.2 months). On post subgroup analysis, the improvement only persisted for patients who were PS 0-1 and had localised disease.

Senkus-Konefka 2005 reported a significant improvement in median survival with 16Gy/2F compared to 20Gy/5F (8 months vs. 5.3 months). This result must be interpreted with caution, as only 100 patients were randomised, and the study was closed early due to poor accrual resulting in an imbalance in the number of patients in each arm.

Koutaissof 1999 reported that the 1-, 2-, and 3-year survival rates were 61% (6 10), 39% (6 10), and 19% (6 8), respectively, with a median survival of 16.8 months.

Nestle 1996 showed that survival of PAIR patients was overall significantly longer than survival of controls. The 1-year-survival rate was 45.6% and 21.2%, respectively. Median survival was 11.8 vs. 5.8 months.

Cross 2004 reported that the median survival was 4.3 months (range, 0.3–38). Of the 23 patients, 21 have died. Five patients lived past 1 year and 2 patients were alive 14 and 37 months after treatment completion. The cause of death was locoregional progression in 4 patients, metastatic progression in 14, pulmonary embolism in 1, cardiac disease in 1, and unknown in 1 patient. Of those patients who died of metastatic disease, 6 had brain metastases, 4 had progressive pleural effusions, and 1 had other lung parenchymal disease.

Lupatelli 2000 reported that median survival from the beginning of radiotherapy was 148 days. Stage of disease and previous chemotherapy did not influence survival, whereas there was a statistically significant increase in survival dependent on PS. Median survival of PS 1-2 and PS 3 patients was 200 days and 77 days, respectively.

Finally, Appold 1999 reported that median overall survival for all patients was 6 months. Survival of the patients treated with 60Gy was significantly better than survival in the other groups. Median survival was 11 months after 60Gy, 6 months after 40Gy and 5 months after 25Gy. The most important prognostic factor was the PS of the patients.

Data from these trails were selected. The equivalent dose for fractionation 2Gy per fraction was calculated. The number of patients and the number of responders was also used and the Poisson Possibility for one year survival was calculated and presented in the diagram below.
Figure 3.4: This diagram illustrates the probability of one year survival according with the dose. Dots represent the data for the trails selected and the line represents the Poisson possibility.

Figure 3.5: Relationship between overall treatment time, survival and dose.
From the diagram it is obvious that tumour repopulation has a significant impact in prolonged treatment schedules. Consequently, the accurate determination of the repopulation rate that is expressed by T1/2 and tumour repopulation lag time that is expressed by Tk are of primary importance for a close prediction of treatment outcome using radiobiological models.

<table>
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<th>RT REGIMEN</th>
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<tbody>
<tr>
<td>63Gy/42F/4,2W</td>
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</tr>
<tr>
<td>60Gy/39F/6W</td>
<td>Nestle 2000</td>
<td>69</td>
</tr>
<tr>
<td>60Gy/30F</td>
<td>Appold 1999</td>
<td>72</td>
</tr>
<tr>
<td>50Gy/25F/5W</td>
<td>Reinfuss 1999; Sundstrom 2004</td>
<td>60</td>
</tr>
<tr>
<td>45Gy/15/3.5W (4 days per week)</td>
<td>Abratt 1995</td>
<td>59</td>
</tr>
<tr>
<td>45Gy/18F/3.4W</td>
<td>Teo 1988</td>
<td>56</td>
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<tr>
<td>40GY/10F/4W(split)</td>
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<td>42Gy/15F/3W</td>
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Table 12: Radiotherapy regimens and biological effective doses (BED) for carcinoma cells
Discussion
For the first part this study illustrates the wide range of practices in the management of advanced and inoperable NSCLC among European radiotherapists and has attempted to explore some of the reasons behind such variations. Case histories may not reliably reflect the management that would be in all clinical settings. While this may undoubtedly be true in the case of individual patients, they may be a useful method to explore the type of policy used by clinicians. This criticism may be particularly applied to the care of NSCLC, where important prognostic indicators e.g. lung function was not supplied. It is notable, however, that a similar range of treatment strategies was found in the expert surrogate study of Palmer et al., in which a number of non-tumour, non-patient variables could be shown to influence proposed therapy e.g. specialty of doctor (surgeon, radiotherapist or medical oncologist) or country of origin. The study revealed a number of areas of uncertainty. Although the majority of the responders agreed that the treatment would be palliative for cases A, D and E and radical for cases B and C, there were differences in the perceived prognosis and aims of treatment. Variation in dose and fractionation could be related to some of these differences, for example those who aimed to prevent symptoms or extend life tended to give a higher dose than those who aimed simply to relieve symptoms and those who predicted a longer survival tended to give a higher dose and more treatments.
For the patient D there was a generally poor agreement as to the aims of treatment and a wide range in the total dose and number of fractions proposed. This confirms the variation seen in other studies [95, 96, and 97]. The perceived aim of radiotherapy was clearly influential with those proposing radical therapy giving higher doses and more fractions than those proposing palliative therapy.
Palliation doses were higher that 8Gy and less than 40Gy. On the other hand radical doses were higher than 55Gy. Furthermore, some responders viewed treatment as both radical and palliative and gave higher doses and more fractions than those who regarded the treatment as palliative only. There is some evidence that low doses of radiotherapy will relieve common symptoms of cancer, e.g. a single fraction of 8Gy can relieve pain from bone metastases and short fractionation regimens will relieve symptoms related to lung cancer.
This study suggests that radiation oncologists believe that a higher dose of radiotherapy is needed to prevent or maintain symptom response as opposed to relief of symptoms only in the treatment of metastatic disease and the longer the patients live, the higher the dose required to achieve this. More data are required to support this belief. The variation in predicted survival
times confirms other work suggesting that radiation oncologists are poor at predicting survival for patients with advanced and incurable disease [98, 99].

A main difference was the suggestion of SBRT from some Swedish centers and only one other center (Greek) proposed this therapy. This difference may be related to cultural differences in attitude to advanced disease and its treatment, but may also be related to different methods or organization of cancer care and training of radiation oncologists.

For the second part it is shown that patients with inoperable lung cancer that is too large for radical RT have a poor prognosis and the therapeutic options are limited. Controlling their symptoms and maintaining their quality of life should therefore be the main aim of treatment. This review has shown that palliative RT to the chest appears to be effective in controlling troublesome symptoms from intrathoracic tumour. There was a consistent finding in all the studies that symptoms improved to some extent and for some time after RT.

It has not been within its scope to investigate either the role of chemotherapy or of combination treatment in this situation. Nor have we reviewed the effectiveness of endobronchial brachytherapy.

The first objective was to evaluate which is the most effective and least toxic regimen of palliative RT to improve and control thoracic symptoms. Three studies reported better palliation from higher dose more fractionated regimens (Teo 1988; Erridge 2005; Bezjak 2002). However, Teo 1988 and Erridge 2005 both used physician assessed scores, which may not be as accurate as patient self-assessment and are subject to bias. In addition, the method of defining response in Teo 1988 was imprecise, and patient numbers in Erridge 2005 were small. Bezjak 2002 did show better symptom palliation at 1 month with the higher dose regimen and it is the only one of the three trials that collected outcome data using validated tools. Kramer 2005 reported the duration of palliative effect was significantly longer with the higher dose regimen, but there were a higher proportion of PS 3 patients in the lower dose arm (34% vs. 22%). It is possible that those patients with a poor PS have more thoracic and systemic symptoms, and therefore derive less durable palliative effect from RT, irrespective of dose. In addition, less than 40% of patients randomised were alive and assessable at 22 weeks when the difference between the regimens became statistically significant. There is good evidence that regimens with higher doses (or higher biological effective doses) give more toxicity, especially radiation oesophagitis. Overall, it would seem therefore that in most patients, short hypofractionated regimens such as 10Gy/1F or 17Gy/2F are probably as effective at providing palliation as more protracted schedules, and have the advantage of fewer patient visits to hospital and reduced workload for RT departments.

Several non-randomised studies have reported the use of hypofractionated regimens with 10Gy/1 fraction (Scolaro 1995[104]), 16Gy/2F (Lupattelli 2000), 17Gy/2F (Stevens
1995[105]; Vyas 1998[106]) and 24Gy/3F (Slotman 1993[107]). They give supporting evidence of the effectiveness and the patterns of toxicity of these regimens.

Toxicities not identified in the randomised trials but subsequently described (Lupattelli 2000; Scolaro 1995; Stevens 1995; Vyas 1998) include nausea, episodes of acute chest pain, or fever and rigors during the first 24 to 48 hours after treatment, experienced by up to 50% of patients receiving large fraction RT to the chest. These are transient, rarely severe and usually managed by appropriate medication and warning the patients. Hatton et al [108] documented changes in peak expiratory flow rate immediately after RT to the chest. This study included patients receiving fractions of 10 Gy, 8.5Gy and 3Gy. The numbers were small and they could not identify an increased risk with large fractions, but suggested caution and the use of corticosteroids in patients with severe airway obstruction.

More serious is the incidence of spinal cord damage (radiation myelitis) following the use of 17Gy/2F and 39Gy/13F reported in MRC 1991, MRC 1992 and MRC 1996. Cases of probable radiation myelopathy following 17Gy/2 fractions to the chest have also been reported by Dardoufas et al [109], Stevens et al and Vyas et al. A case was also reported in Sundstrom 2004 using 50Gy/25F. The data on myelopathy from the MRC studies was reviewed by Macbeth [110] and the annual risks, with associated 95% confidence intervals, were presented. This suggested that the distribution of radiation myelopathy between regimens could have been random, but supported the conclusion of Schultheiss et al [111] that the alpha/beta ratio for spinal cord should be about 2. If an alpha/beta ratio of 1.7 is taken for spinal cord as proposed by Singer et al [112], 17Gy/2F, 39 Gy/13F, and 50Gy/25F all give biological equivalent doses (BED1.7) of greater than 100Gy. No regimen with a BED1.7 of less than 100Gy has been reported as causing myelopathy. It should be recognised that above such level the risk of myelopathy increases and measures such as spinal cord shielding or oblique fields shielding should be introduced. The minimum time between treatment and the development of myelopathy in the cases reported was 6 weeks in Sundstrom 2004, which is much earlier than in other trials (earliest onset 8 months). However, it was not stated if the diagnosis was confirmed on autopsy.

QOL was assessed using validated tools in only three trials (Sundstrom 2004; Erridge 2005; Bezjak 2002). There were no consistent findings between the trials, and it is not possible to comment on whether QOL is better with a particular RT regimen.

In conclusion, patients with NSCLC and thoracic symptoms needing palliation can be treated safely and effectively with 1 or 2-fraction RT regimens. If 17Gy/2F is used, measures should be taken to reduce the dose to the spinal cord (Macbeth 1996). It may be more practical to reduce the dose to 16Gy/2F (BED1.7 = 91), which in a non randomised series of 91 patients (Lupattelli 2000) was shown to be effective, with no cases of myelopathy.
The second objective was to evaluate whether higher dose regimens are associated with increased survival. There is strong evidence for a modest increase in survival (5% at 1 year and 3% at 2 years) in patients with localised disease and better PS given higher dose RT from 1 large, high quality, CT (MRC 1996). Three other trials have also reported a survival advantage with higher dose regimens (Reinfuss 1999; Bezjak 2002; Kramer 2005). In Reinfuss 1999 a large difference in survival was reported, in a group of patients who seemed to have better PS. However the difference may reflect the fact that the less effective 40Gy/10F regimen was a 'split' course with a 4 week gap in the middle. The Bezjak 2002 trial supports the results from MRC 1996; Subgroup analysis showed the improvement in survival seen with the higher dose regimen only persisted for patients who were PS 0-1 and had localised disease. The Kramer 2005 trial also showed that the survival advantage seen with the higher dose regimen only applied to good PS patients.

None of the other studies demonstrated a significant difference in survival, although most were too small to reliably demonstrate changes in survival that might be clinically significant. Unfortunately because of the heterogeneity of the studies, formal metaanalysis was not feasible. It therefore seems likely that any survival benefit is modest and confined to good PS patients and those with localised disease. Although no evidence has been found to exclude the possibility that poor PS patients might get a small survival benefit from higher dose RT, it is unlikely. Most poor PS patients will have either overt or occult metastases which will be unaffected by local therapy.

Higher dose palliative RT is clearly associated with more visits to hospital and more toxicity, and so the balance of benefit and risk needs to be carefully assessed and discussed openly with each patient.

Finally it has not been within the scope of this review to consider chemotherapy and its increasing role in the palliation of patients with non-small cell lung cancer. But there clearly is a need for more research into the integration of chemotherapy with palliative RT.

There needs to be more research into the acute toxicities of large fraction palliative RT for lung cancer and into ways of reducing them. More research is needed into the role of radical compared to high dose palliative RT in good PS patients with bulky tumours and no obvious metastases. In particular there needs to be greater homogeneity of entry criteria and treatment regimens, so that metaanalysis is possible. In the future, however, large trials comparing different RT regimens may be difficult to establish due to the increasing use of systemic chemotherapy. Trials looking at how best to integrate these two modalities, particularly in good PS, patients need to be carried out.
Conclusions
This survey demonstrates a range of treatment strategies for advanced NSCLC within Europe. Influential factors in this study included the perceived aims of treatment and the estimated prognosis of the patient. Those aiming to extent life would give significantly higher total doses in a larger number of fractions, whereas those aiming to relieve symptoms would give significantly lower total doses. These factors should be taken into account when evaluating the effectiveness of different irradiation.

The majority of patients with locally advanced non-small cell lung cancer and thoracic symptoms, especially those with poor PS should be treated with short courses of palliative RT (such as 10Gy/1F or 16-17Gy/2F). Care should be taken to avoid irradiating, or to reduce the dose to, the spinal cord if 17Gy/2F is used. Selected patients with good PS should be considered for treatment with higher dose palliative regimens (such as 36Gy/12F), if the chance of a modest increase in survival is after informed discussion with the patient, considered to be worth the extra visits to hospital and the increased risk of toxicity (especially oesophagitis).
Acknowledgments

First of all I would like to thank Associate Professor (Docent) Panayiotis Mavroidis, my supervisor, for the opportunity he gave to me to participate in this research, his lively interest and friendly support and his help in the scientific part of this work.

I would like to thank especially adjunct Professor Bengt K.Lind, for the great supervision, his scientific advises and his friendly support.

Helena Lind, MD for her valuable help in this project and her great supervision.
My examination committee, Professor Georgios Nikiforidis, Assistant Professor Georgios Sakellaropoulos from the Department of Medical physics of Patras University.
The entire staff of medical radiation Physics Department and particularly Lil Engström for her valuable help with the administrative and bureaucratic part.
My colleagues from the master of Medical Radiation Physics, University of Patras for their warm friendship.

My colleagues Ioanna and Christiana from the master of Medical Radiation Physics, University of Patras for their friendship and the days we spent together in Stockholm.
My Family and friends who support me all these years.
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