Chapter 1

Introduction and outline of the thesis

Lung Cancer: The Scope of the Problem

Lung cancer is the leading cause of cancer death in both men and women worldwide.[1] In 2002, lung cancer was responsible for 223,000 deaths in the European Union, far exceeding the deaths caused by cancers of the colon/rectum (152,000), breast (90,000), or prostate (67,000).[2] Lung cancer death rates have risen dramatically since the early 1900's, when lung cancer was a relatively rare disease and caused fewer deaths than gastric, colorectal, prostate, breast, uterine and liver cancers.[3] In the United States, lung cancer became the leading cause of cancer death in men by 1960, whereas for women, lung cancer deaths surpassed other cancer types in 1985.[3]

The lifetime probability of developing lung cancer is 1 in 13 for men and 1 in 16 for women in the United States.[3] The majority of risk is attributed to environmental causes: the major risk factor for lung cancer is smoking (responsible for approximately 90% of cases). Other risk factors include occupational exposure (including asbestos, tar, and soot), radon and other radiation sources, and air pollution. Host factors, including genetic phenotype and lung disease, also play a role in susceptibility.[4]

Most lung cancers are classified histologically as non-small cell lung cancer (NSCLC). NSCLCs comprise 80% of all lung cancers, including adenocarcinomas, squamous cell carcinomas, and large cell carcinomas), 15% are small-cell lung cancers, and 5% are other histologies, such as carcinoid tumors.[5]

The majority of patients with NSCLC have disease that has spread to the regional lymph nodes (stages II and III) or is metastatic (stage IV) at diagnosis. In the previous internationally-accepted staging system (in effect before 2010), stage I disease included tumors of any size with no nodal involvement and limited local invasion (i.e. invasion of visceral pleura or within 2 cm of carina allowed, and partial lung atelectasis allowed). Further invasion was classified as a higher stage disease (for example, invasion within less than 2 cm of the carina, or invasion of chest wall, diaphragm, mediastinal pleura, or pericardium would be classfied as stage II disease or higher). With the newest staging system adopted in January 2010, tumors greater than 5 cm in size are reclassified as stage II, rather than stage I.[6] Patients with stage I disease comprise about 20% of NSCLC patients and have the best survival, approximately 50-70% at five years,[6] yet individual survival varies substantially depending on patient, tumor, and treatment characteristics.

Stage I Disease: Evolution of Treatment Approaches

Lobectomies for lung cancer were recorded as early as 1912, and the first successful one-stage pneumonectomy for lung cancer was completed in 1933.[7,8] At that time, only a pneumonectomy was considered to be a potentially curative treatment for lung cancer. In subsequent decades, existing surgical techniques were refined, staging was introduced, and new procedures were developed, including segmentectomy in the 1970's and video-assisted thoracoscopic surgery (VATS) in the 1990's.[8] Surgery came to be recognized as the gold-standard curative-intent treatment for lung cancer, yet with a more conservative treatment paradigm than existed in earlier decades: the extent of resection was chosen based on tumor stage and patient fitness. In the modern era, long-term results for patients treated surgically for stage I disease are excellent, with 5-year survival rates in the range of 60-95% and local control >90% in most studies.[9]

Despite the progress achieved in surgical treatment, a substantial proportion of patients with stage I NSCLC are unfit to undergo surgery. Prior to the advent of SBRT, the treatment for such patients was often conventional 3-dimensional conformal radiotherapy (3D-CRT) using typical radiation doses of approximately 55-70 Gy delivered over 4-7 weeks.[10] Local tumor control with such schemes was suboptimal, with reported local failure rates as high as 60-70% in some series.[10] In the absence of highly effective alternatives to surgery, patients were often untreated, either by personal choice or physician recommendation, a decision associated with poor overall survival.[11]

Dose escalation has been studied as a method of improving local control for stage I NSCLC. In one multicenter phase I/II trial of dose escalation for patients with early stage disease, doses were escalated from 70.9 Gy in 33 fractions up to 90.3 Gy in 42 fractions, depending on lung dose constraint targets.[12] Two-year locoregional control was approximately 75% for patients with stage I disease, and maximum tolerated doses ranged from 77.4-83.8 Gy. A dose of 90.3 Gy was found to be too toxic, with treatment-related deaths occurring in two patients. A relationship between higher doses and response rates was not observed, potentially because higher doses were associated with prolonged treatment time. As treatment time exceeds 28 days, accelerated tumor repopulation occurs, reducing the chances of tumor control.[13]

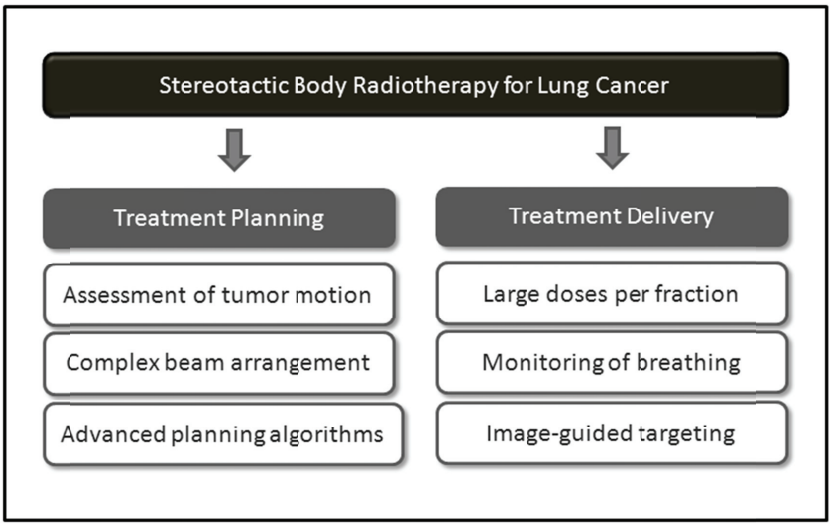
Several studies have attempted to elucidate the underlying radiation dose-response relationship, to predict the doses that would be required to achieve high rates of tumor control. A systematic review estimated that in order to achieve local control rates of >90%, a biologically effective dose of approximately 80 Gy or more would be required, and suggested that improvements in local control would be associated with improvements in overall survival.[14] More sophisticated calculations involving tumor control probability (TCP) that incorporate accelerated repopulation suggest that even doses of >80 Gy in 2 Gy daily fractions (which would take >8 weeks to deliver) would result in treatment failure in more than 50% of patients.[13] Clearly, better techniques were required.

Introduction of SBRT and Early Results

Stereotactic body radiation therapy (SBRT) for lung cancer was developed based on stereotactic radiosurgery (SRS) techniques used to treat brain metastases. SRS requires precise immobilization, often using a rigid metal head frame that is attached directly to the skull by a neurosurgeon and subsequently fixed to the treatment couch. SRS delivers very high, ablative hypofractionated doses, up 24 Gy in a single fraction, with excellent local control.[15] Delivery of such doses was considered prohibitive at other body sites, due to concerns about accuracy and toxicity.

The extension of stereotactic treatments to lung cancer was based on developments in imaging, planning, and treatment delivery (Figure 1).[16] Techniques were developed to account for tumor motion with breathing, such as four-dimensional CT scans (Figure 2). Advances in computer technology allowed for more sophisticated treatment plans, increasing the number of radiation beams from 2-3 with conventional techniques up to 7-10 with SBRT. The introduction of image-guidance has allowed for confirmation of tumor position immediately before treatment.

Figure 1. Features of stereotactic body radiation therapy.



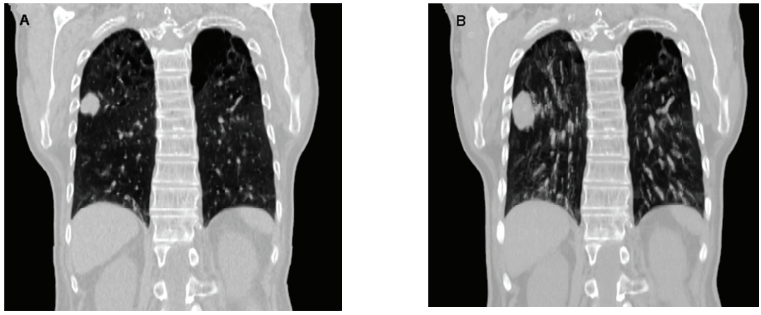
These advances have resulted in a major shift in the approach to radiotherapy for stage I NSCLC. SBRT delivers doses of 48-60 Gy in 3-8 fractions, completed within 2.5 weeks. This hypo-fractionation has several postulated biological advantages: shorter treatment times avoid the accelerated repopulation that occurs after 4 weeks of treatment; while large doses per fraction may enhance mechanisms of cell killing, overcome hypoxia, and more effectively eradicate cancer stem cells.[13]

A growing body of evidence now supports the excellent outcomes achievable with SBRT. Although local control depends on several factors, including dose, fractionation, and tumor size, local control with SBRT is >90% in most series using adequate doses, with a favourable toxicity profile, even in patients with multiple medical co-morbidities.[17-21]

However, several important questions remain to be addressed. The role of SBRT in the treatment of patients with stage I NSCLC is unclear: is SBRT equivalent to surgery for all patients, in patients at high-risk of surgical complications, or not at all? The benefits of SBRT are evident in individual institutional studies, but does implementing an SBRT program provide any benefits at the population level? The short- and long-term effects of SBRT on normal lung have not been well characterized, and the effects of treating large tumors with SBRT are not clear.

Addressing these important questions will help to define the role of SBRT in the general approach to treating stage I NSCLC, and to refine the treatment of individual patients.

Figure 2. Planning CT scans for radiotherapy. **A.** A standard three-dimensional CT scan showing the position of a stage I NSCLC tumor, not accounting for breathing motion. **B.** A four-dimensional CT scan shows the position of the tumor throughout the respiratory cycle, allowing for more precise tumor targeting. Reproduced from Spoelstra *et al* 2008.[22]



Outline of the thesis

The introduction and early success of SBRT has stimulated widespread research interest, to help refine delivery techniques, to understand its impact upon patient populations, to define its role in high-risk patients, and to define the long-term pulmonary changes that occur after SBRT. This thesis evaluates the role of SBRT, both at the population level and at the individual patient level.

The first two chapters of this thesis focus on patient outcomes in the pre-SBRT era. **Chapter 2** examines outcomes after conventional RT, palliative RT, or no treatment, in a population of Canadian patients with early NSCLC, in which two-thirds of patients did not receive curative therapy. **Chapter 3** explores the role of age in survival after curative treatment for stage I NSCLC, either surgery or conventional RT, to address the question of whether patients should be denied treatment based on elderly age alone.

The two subsequent chapters are population-based studies of outcomes for elderly patients after implementation of SBRT in the North Holland region. **Chapter 4** examines patterns of care and survival in three time periods, ranging from pre-SBRT to widespread SBRT availability. **Chapter 5** uses a matched-pair technique to facilitate a comparison of survival after SBRT or surgery in the North Holland region.

Chapter 6 focuses on another high-risk group, patients who have stage I NSCLC with severe COPD, reporting survival outcomes in these patients treated at the VUmc SBRT program, and also systematically reviewing the literature to assess evidence supporting treatment with surgery or SBRT.

The focus of the thesis then narrows from a population perspective to concentrate on the individual patient, examining issues of treatment delivery and side-effects. **Chapter 7** is a review of modern arc radiation therapy techniques, which have improved the delivery of SBRT. **Chapters 8 and 9** examine early and late radiological changes after SBRT, to characterize pattern, severity, and timing of lung injury, as scored by physician observers. **Chapter 10** outlines the development of a new technique to assess lung injury using computer-based CT density measurements and a deformable image registration technique. In **Chapter 11**, this technique is used to determine the dose-response relationship for lung injury, and to assess the relationship between baseline patient characteristics and CT density changes. **Chapter 12**

examines treatment planning considerations and outcomes after expanding the use of SBRT to a small group of patients with large stage I tumors and few other treatment options, who would not normally be candidates for SBRT. Chapter 13 examines the issues surrounding the use of implantable fiducial markers for tumor tracking in SBRT. Finally, **Chapter 14** is a review of many of the current controversies surrounding SBRT and the treatment of stage I NSCLC.

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