Image-guided stereotactic radiotherapy for early stage lung cancer

Haasbeek, C.J.A.

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Chapter 1

Introduction and outline of the thesis

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Introduction

Lung cancer is the most important cause of cancer-related death worldwide, with more than 1 million deaths every year[1]. The most common cause of lung cancer is tobacco smoking. Lung cancer is also linked to a combination of genetic factors, radon gas, asbestos and air pollution[2-5]. The two main types of lung cancer are non-small cell lung cancer and small cell lung cancer. Small cell lung cancer comprises about 20% of all lung tumors and has the tendency to metastasize early. It is usually treated with a combination of chemotherapy and radiation. Eighty percent of patients are diagnosed with non-small cell lung cancer (NSCLC). Treatment options for NSCLC include surgery, radiotherapy or chemotherapy, and frequently consist of a combination of two or three of these treatment modalities, depending on the stage of disease. The studies reported in this thesis focus on the treatment of early stage NSCLC treated by stereotactic radiation therapy, or SRT.

The incidence of stage I disease

Patients presenting with early stage NSCLC have the best prognosis, but only 20 percent of patients are diagnosed with stage I disease. Stage I includes lung tumors without evidence of lymph node or distant metastasis, and without invasion of the structures surrounding the lung. Unfortunately, the percentage of lung cancer patients diagnosed with stage I disease has decreased in the last 10 years[6], in contrast to the growing number of patients who present with metastasized disease. The latter is probably a reflection of stage migration due to improvements in the imaging techniques used for staging, including computed tomography (CT) and positron-emitting tomography (PET) scans.

Much effort is being put into screening studies of high risk populations to increase the number of patients that are detected with early stage disease. Preliminary studies suggest that 60% of lung cancer patients detected through screening have stage I disease[7,8]. A survival advantage to screening remains to be proven, but the first results of two large randomized screening trials, the

Dutch-Belgian Nelson trial and the U.S. National lung screening trial in high risk populations are expected in 2010[9].

A factor complicating the treatment of lung cancer is the ageing population in the Netherlands, which has resulted in an increase in the number of patients aged 75 years or older. Elderly patients generally have multiple important comorbidities, which may preclude or complicate curative treatment options, prolong recovery from treatments, and increase overall costs[10].

Treatment of stage I disease

Surgery

Surgery has traditionally been regarded as the treatment of choice for patients with early stage NSCLC, in line with the current ACCP guidelines[11]. Surgery ranges from an open pneumonectomy to more limited resections using less invasive techniques, such as video assisted thoracoscopic surgery (VATS). However, although local control is approximately 90% after 5 years[12], surgery is associated with significant morbidity and a decrease in quality of life[13], especially when extended resections are necessary in elderly patients. Surgical mortality rates in the Netherlands in selected, relatively fit patients, range from 1.7% for patients aged 60 years or younger, to up to 9.4% for octogenarians[14]. An additional problem in lung cancer is that many patients, even with stage I disease, are considered medically inoperable because of advanced age and a combination of multiple comorbidities[10].

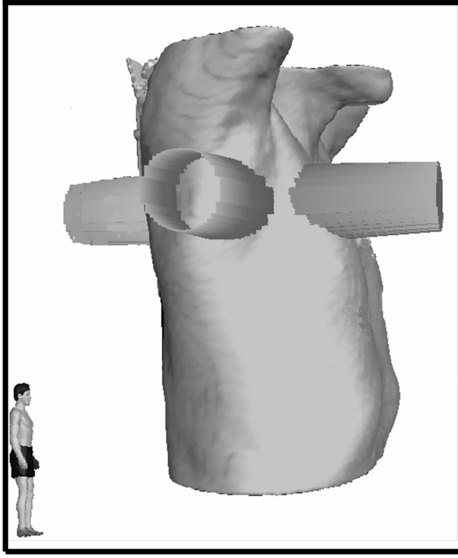
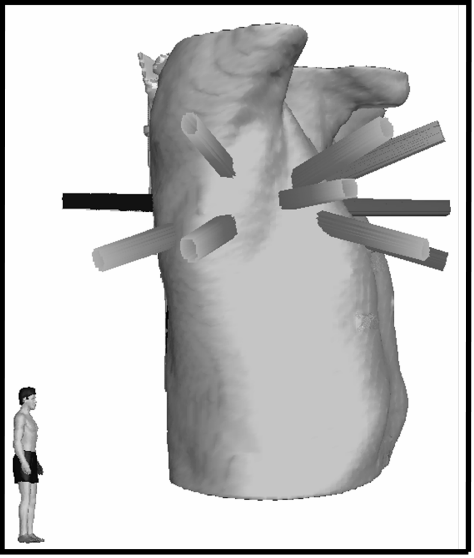
Conventional radiation treatment

Until recently, conventional radiation therapy was the only alternative curative treatment option available to patients who presented with an early stage NSCLC and who were unfit for, or refused surgery. However, local control rates of conventional radiation treatment are far inferior to surgery even after delivery of doses of 70 Gy[15]. In conventional treatment simulation, respiratory movement of tumors was evaluated using less optimal techniques such as fluoroscopy, if at all. In addition, patient setup during treatment was not always reproducible, and a fear of serious toxicity limited the total delivered dose. Conventional curative radiotherapy was generally delivered in 20-35 daily doses of 2-3 Gy over a period of 5-7 weeks. For many frail, elderly patients the long overall treatment time of conventional radiation treatment was a reason to decline curative treatment[16]. The median survival rate in untreated stage I NSCLC patients is in the range of 9-14 months, and the 5-year disease specific survival rate for T1 tumors is only 23%[17].

Stereotactic Radiation Therapy (SRT)

Due to the limited success of conventional radiotherapy, improved techniques were explored in order to deliver higher biologically effective doses in a shorter period of time. In recent years, technical advances have resulted in the development of stereotactic radiation therapy (SRT) as a novel alternative treatment for lung cancer [18-20]. SRT was first developed in the 1950's for the treatment of intracranial lesions. Technological developments in planning and treatment delivery of radiation therapy in the last decade have led to the application of this technique to extracranial sites including the thorax and abdomen.

SRT is a form of high-precision radiotherapy delivery characterized by reproducible immobilization to avoid patient movement during treatment sessions and advanced measures to account for tumor motion. SRT results in dose distributions which tightly cover the tumor, with rapid dose falloff in surrounding normal tissues to reduce toxicity. This allows extremely high biological doses of radiation to be delivered in only 3 to 8 treatment fractions with an overall treatment time of less than two weeks[21]. This technique was adopted at the VU University medical center in April 2003.

Conventional Radiotherapy ±3 beams High dose to large volume	Stereotactic Radiotherapy ±10 beams Extremely high dose to small volume
	

<u>Evolution of the technique for SRT at the VUmc</u>

Respiratory motion of lung tumors is a complex issue but it is important because it may cause the radiation beams to miss the tumor (‘geographical miss’) and increase the probability of tumor recurrence. Older approaches to radiotherapy simulation used a single free breathing CT scan or conventional simulation with plain X-ray imaging, and then compensated for the uncertainty in tumor position by using large population-based safety margins. This led in an increase in the volume of irradiated normal tissues and limited total doses. Since then, many attempts have been made to cope with the effect of respiratory movement of tumors. Two different strategies were followed. The first strategy aimed at limiting breathing motion using methods such as abdominal compression or the active breathing control (ABC) device. The second strategy aimed at incorporating all tumor movement into the treatment planning process, using imaging methods such as fluoroscopy or respiration correlated (4-dimensional) CT scanning. The main benefit of the second strategy is that it is more comfortable because it does not interfere with the patient’s own breathing pattern. The initial few SRT patients treated in the VUmc were simulated using multiple fast conventional CT scans, followed by a summation of the target volume from each scan[22]. Subsequently, the first commercial 4-dimensional CT scanner (4DCT) was installed in the VUmc in September 2003. A 4DCT scanner enables imaging of the tumor during the full respiratory cycle, resulting in movie loops of the tumor during respiratory movement. This enables the use of individualized safety margins to account for the respiratory motion of lung tumors, which are typically smaller than population based margins.

	Conventional radiation treatment	**Stereotactic radiation treatment (VUmc)**
Method of treatment simulation	Conventional simulator or CT	Respiration correlated 4DCT incorporating all tumor motion
Safety margins	Standard (generous) population-based margins for mobility	Smaller individualized margins
Patient positioning	External skin markings	Image guided, based on internal anatomy
Monitoring during treatment	None	Continuous patient position monitoring during treatment using infrared cameras and skin markers
Number of radiation beams	2-4 static beams	8-12 static beams or arc therapy
Biological effective dose (BED)*	60-84 Gy	100-180 Gy
Local control rates	±60%	≥90%
Number of treatments	20-35x	3-8x
Total treatment time	5-7 weeks	≤2 weeks
Severe side-effects	Fatigue (Long overall treatment time), pneumonitis	Rare (≤5%)

*BED = D (1+ d/ (α/β)), where D is total dose, d is dose per fraction, and the α/β ratio is assumed to be 10 for tumor tissue

When 4DCT scanning started in the VUmc, the technique was relatively new and there was still uncertainty about its accuracy. One of the weak points of 4DCT is that it captures tumor movement during a short period of time only. A change in breathing pattern or in patient anatomy in the weeks between the 4DCT and the end of treatment could cause a geographical miss. In the initial phase of using 4DCT scans at the VUmc, a comprehensive strategy was adopted in order to account for interfraction changes in tumor position and the 4DCT scans were always performed twice to provide two “snapshots” in time. However, work by Van der Geld et al.[23] in 2006 showed that the observed differences between a single and a double 4DCT scan were not clinically relevant. Following this, treatment plans were based on a single 4DCT scan for each fraction, reducing the time needed to scan patients, reducing the radiation dose needed for imaging, and reducing workload. Subsequent work in the VUmc by Underberg et al.[24] showed that workload could be further reduced by using Maximum Intensity Projection (MIP) scans for target delineation. Using MIP, tumors can be delineated using just one CT set, instead of using the full set of respiratory phase bins provided by a 4DCT scan, thus significantly reducing the time needed for contouring.

Another part of the initial protocol that gave rise to a high workload was the step of re-imaging and re-planning treatment for every fraction. Although little was known about the usefulness of this adaptive treatment planning strategy, this repeat step was kept in the protocol out of fear of possible interfraction changes during the weeks of treatment, and because the total overall treatment time was longer when the SRT lung program was started. A typical 5 fraction treatment would have a 5 week overall treatment time, and that time has now been reduced to within 2 weeks, reducing the likelihood of interfraction changes.

A common problem of 4DCT scanning is that variation in breathing patterns during a free breathing 4DCT scan can give rise to imaging artifacts. Imaging artifacts hinder the assessment of tumor motion and accurate target delineation. A potential approach to decrease the amount of 4DCT artifacts is the use of audio coaching, which should result in more regular breathing, and make 4DCT scanning more reproducible[25]. However, audio-coaching is often not feasible during the SRT treatment itself due to the long treatment time per fraction and the poor pulmonary condition of the average patient referred for this procedure. This would mean that audio-coaching might be used only during the 4DCT, but not during treatment itself, possibly giving rise to a systematic error in tumor position.

Evaluation of the clinical results of SRT in the VUmc

Surgery has traditionally been the standard of care for early stage lung cancer. However, it is important to realize that patient selection between surgical and SRT studies differs. SRT has mainly been used in medically inoperable patients: in patients with high rates of comorbidity, advanced age, or both. The first SRT studies reported series of generally less than 50 patients, and more extensive data was needed before recommending SRT as standard treatment for inoperable patients. The large single institution SRT database of the VUmc was used to evaluate two potential high risk patient groups: elderly patients above 75 years of age, and patients with a new tumor in the single remaining lung after previous contralateral pneumonectomy. Elderly patients are often excluded from surgical treatment because of multiple comorbidities, and those comorbidities might also pose a contraindication for SRT[26]. In contrast to selection criteria applied in surgical studies, all frail patients were accepted for SRT treatment in the VUmc without exclusion criteria for advanced age or comorbidities. The other high risk group was patients presenting with second lung tumors, as damage caused by previous treatments frequently complicates the treatment for second tumors. Patients with lung cancer are at higher risk of developing a second, non-synchronous lung cancer[27,28]. The treatment of a first lung cancer is frequently a lobectomy, but bilobectomies and even pneumonectomy are not uncommon for stage I lung cancer[29,30]. Surgical treatment options for second tumors in a remaining single lung are limited, and SRT was evaluated as treatment alternative as part of this thesis.

Aims and outline of the thesis:

Many patients with stage I lung cancer are considered inoperable because of major comorbidities, advanced age or both. Although performed with curative intent, surgery carries a risk of mortality, and post-surgical morbidity commonly results in a decline in quality of life. Stereotactic radiation therapy (SRT) is a novel treatment alternative for patients that are at high risk for mortality or morbidity from surgery. This thesis focuses on technical improvements in treatment simulation using 4DCT scanning, adaptive treatment planning, and on the clinical results of SRT. **Chapter 2** provides a general overview of newer radiation therapy techniques used in lung cancer, and expected future developments. Due to the extremely high biological doses of radiation used in SRT, optimal tumor imaging and motion management strategies are crucial. Repeating the 4DCT scan and treatment planning halfway through treatment could account for theoretical changes in tumor position or tumor shape during treatment, but this also increases departmental workload, and the necessity of such a repeat scanning procedure is evaluated in **Chapter 3**. An important technical issue is the problem of the reproducibility of target position during a course of treatment, which in turn is related to the influence of variations in breathing patterns during 4DCT scanning. One approach advocated to improve breathing regularity is the use of audio-coaching. However, introducing a difference in breathing patterns between 4DCT imaging and treatment delivery could give rise to systematic changes in tumor position, and the pros and cons of coaching are discussed in **Chapter 4**. As SRT is a new treatment option for early stage lung cancer, it is important to generate data on local control and toxicity outcomes during follow-up. **Chapter 5** discusses the clinical results of SRT in a large single-center series of 206 patients treated by SRT between 2003 and 2007. **Chapters 6 and 7** report on the results of SRT in two high-risk patient groups: elderly patients, and patients with a single remaining lung after previous surgery. **Chapter 8** provides a general overview of the available published evidence on the use of non-surgical techniques in the treatment of early stage lung cancer, and especially the use of SRT. Finally, **Chapter 9** addresses newer developments in technique which will further improve the accuracy and speed of SRT, and will help address the issue as to whether SRT can be an alternative to surgery in selected patients with early stage lung cancer.

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