Radiotherapy for lung cancer
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Introduction
Chapter 1

1. Lung Cancer
Lung cancer is the most common cause of cancer mortality for both men and women, causing approximately 1.2 million deaths per year worldwide [1]. More than 90 percent of all lung cancers is caused by cigarette smoking [2]. A decreasing prevalence of lung cancer is observed in men caused by a reduction of smoking [2]. Unfortunately, the incidence of lung cancer and lung related death is still increasing for women, and currently almost one half of all lung cancer related death occurs in women. About 80 % of the lung cancers are diagnosed as non-small cell lung cancer (NSCLC). The distinction between NSCLC and small cell lung cancer (SCLC) is important for the treatment of choice. The studies included in this thesis are focussed on the treatment of NSCLC.

Lung cancer is mostly diagnosed after presentation of clinical symptoms of the patient. Complaints of the patients are caused by the primary tumour or its spread (metastasis) and are presented by one or more symptoms like coughing, chest pain, haemoptysis and dyspnoea [3]. To date, no screening test (e.g. chest X-ray, CT thorax, sputum test) in smokers has been found to reduce the mortality in lung cancer patients, but randomized screening trials are ongoing to evaluate the beneficial effect of screening techniques [4,5].

Radiotherapy is the cornerstone of the treatment of the majority of NSCLC patients. The first reason is that lung cancer is an aggressive disease whereby most patients are diagnosed in an locally advanced stage of the disease. For these patients definitive (chemo)radiation (i.e. technically inoperable) or neoadjuvant chemoradiation (i.e. potentially technically operable) is indicated. Secondly, because lung cancer is so strongly related with smoking, patients are often suffering from smoking induced pulmonary and cardiovascular co-morbidities [6] resulting in a physical performance that is insufficient for a major surgical procedure and/or removal of lung tissue (i.e. medically inoperable) and also these patients are candidates for irradiation. Thirdly, sometimes (older) patients refuse surgery and prefer radiotherapy (RT). This third group of patients is increasing after the introduction of hypofractionated RT (see later) for early stage NSCLC. A fourth group of lung cancer patients who are often referred for RT are non-curable lung cancer patients (i.e. metastasized disease) whereby symptoms caused by the tumour spread or metastasis can often be (temporarily) relieved by irradiation.

2. Staging and Prognosis of NSCLC
The prognosis of lung cancer patients is dependent on tumour, patient and treatment related characteristics. Higher tumour stages and larger tumour volumes are related with worse outcome. Stage I patients have a five year survival of 73 percent. Five-year survival of stages II and III are 36 to 46 percent and 9 to 24 percent, respectively. For patients with clinical stage IV disease the five-year survival rate is 2 percent, with a
median survival of 6 months [7].

The histopathology of the tumour also is of prognostic value and important for the decision on treatment strategy [8]. Consequently, pathological verification (and specification) of the tumour is aimed for all lung cancer patients. Unfortunately, tumour material cannot always be obtained (biopsy failed or the biopsy is a too invasive procedure). For patients who are candidates for radiotherapy (whereby tumour material is not available in contrast to surgery), evaluation of the clinical setting is important before a decision for treatment is made (e.g. tumour growing on CT images and Positron Emission Tomography (PET) positive lesions) [9]. Patient related factors (e.g. age, performance status, weight loss and co-morbidity) are also influencing both the prognosis and treatment choice.

After appropriate tumour staging and assessment of the patient characteristics, a multidisciplinary team (i.e. pulmonologist, surgeon, radiation oncologist, nuclear medicine physician, pathologist, radiologist) should determine the most suitable individually adapted treatment strategy because good patient selection for the often multi-modality treatment is crucial to maximize the survival rate and minimize toxicity.

3. Indication for Irradiation of NSCLC

3.1 Stage I and II

For medically inoperable stage I patients with a centrally located tumour and stage II patients, conventional fractionated (2-3 Gy / fraction) radiotherapy is the treatment of choice. The addition of chemotherapy for stage II is depending on the physical performance of the patient (which is deprived since the surgery could not be performed for this reason). For small peripherally located stage I tumours hypofractionated RT (i.e. >2-3 Gy/fraction) is used in an increasing number of institutes. This is a technique whereby a high dose to the lung tumour is delivered with only a small number of fractions using high accuracy irradiation. This technique is first described by Blomgren et al. in 1995 [10] and is derived from stereotactic radiosurgery used for intracranial, orbital and base of skull malignancies or non-malignant anatomical malformations (e.g. arteriovenous malformations). Hypofractionated RT shows encouraging reports of good tumour control and little toxicity resulting in an increasing number of RT departments treating early stage lung cancer and lung metastases with hypofractionated RT [10-17]. Ongoing studies are evaluating the differences between operable stage I patients undergoing surgery or hypofractionated RT (ROSEL-study).

A meta-analysis evaluating postoperative radiotherapy (PORT) showed a detrimental effect for patients irradiated after surgery for stage I/II lung cancer patients [18].
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3.2 Stage III
The optimal treatment for stage III patients is a moving field subject to improvements in staging and therapy. For stage T3N1 and T4N0-N1 (stage IIIA in the IASLC proposals for the revision of the TNM staging [7]), surgery is recommended (with or without (neo)adjuvant chemotherapy). If pathology shows positive margins, nodal extra capsular extension or N2 disease, PORT can be considered [19-21]. Although surgery is also performed for N2 disease, concomitant chemoradiation is increasingly becoming the standard of care [22]. For operated N2 patients, PORT did not show an adverse effect as was observed in stage I and II patients but only a small reduction in local recurrence was observed [18]. This issue is currently prospectively studied in the LUNG-ART trial [23]. For stage IIIB a recent phase II study of Stupp et al. showed that chemoradiation followed by surgery is feasible with a favourable outcome compared to historical stage IIIA patients [24]. For inoperable stage IIIA or stage IIIB patients (who are physically capable to receive chemotherapy), concurrent radiation-chemotherapy (chemotherapy is given as a radio-sensitizer) followed or proceeded by (neo)adjuvant chemotherapy is the treatment of choice [25]. Patients for whom the physical performance is insufficient for adding chemotherapy are treated by conventional fractionated radiotherapy alone. (Marginally) operable stage I and II patients are treated similar to possibly technical operable stage IIIA patients.

3.3 Stage IV
A large group of lung cancer patients are ineligible for a (irradiation) treatment regimen with a curative intent. These are patients presenting with metastasized disease or with a locoregional recurrence. Although these patients can be referred for systemic treatment the survival remains very poor [7]. Especially these patients with advanced tumour stage are often suffering from tumour induced complaints. These patients should be optimally supported in the terminal phase of their life. Individually adapted treatment regimen is often helpful for patients with haemoptysis, pain, neurological complaints and sometimes dyspnoea.

4. New treatment strategies
To date, targeted therapies are introduced which attack the tumour cells without affecting healthy tissue. Altered cell signalling and survival pathways are often overexpressed or mutated in tumour cells and are identified as potential therapeutic targets. Also tumour associated antigens are a potential target for immunotherapy. Consequently, small molecule inhibitors, immunotherapy and gene therapy are of great interest to improve outcome of lung cancer patients. The introduction of targeted therapies has shown favourable results in the treatment of lung cancer. One example is the administration of a recombinant humanized monoclonal antibody
(bevacizumab) that binds vascular endothelial growth factor (VEGF) and thereby preventing its interaction with the VEGF receptor [27]. Another example is the inhibition of the epidermal growth factor receptor (EGFR) pathway with small molecule tyrosine kinase (TK) inhibitors (gefitinib, erlotinib) [28]. These molecules have shown significant benefit in second line and are investigated in first line treatment. Also combinations of small molecules with conventional chemotherapy and radiotherapy are under clinical investigation.

5. Radiotherapy and Lung Cancer

5.1 Target Definition and Imaging
The definition of the target (tumour) and the position of the target is critical before and during the irradiation. Consequently, appropriate imaging is of great importance for RT. Computer tomography (CT) scans are often used to define and delineate the tumour and to design the treatment plan. However, because CT images are based on tissue density, discrimination of the tumour surrounded by other non-tumour tissue with similar density (e.g. atelectasis, vasculature, mediastinum) is difficult. Consequently, the probability of observer delineation variability and anatomical misses (e.g. too small or too large irradiation volumes) is increased. The introduction of the positron emission tomography (PET) scan, visualizing metabolic active tissue using a radioactive labelled glucose analogue ([18F]fluorodeoxyglucose, FDG), proved to have a major impact for staging and RT target definition for lung cancer patients [29,30].

5.2 Irradiation Technique
Technical developments of irradiation equipment and treatment planning systems improved the possibility to irradiate lung tumours more precise. In the early eighties, CT-assisted 2-D treatment planning was introduced and proved to have significant impact on the treatment planning [31]. 2-D planning was followed by 3-D treatment planning later in the eighties. First, patients were treated with two (AP-PA) beam directions whereby an additional boost was given to the tumour by oblique fields. Subsequently, according to the 3-D planning system more advanced treatment plans could be made using multiple beams resulting in the possibility to increase the dose in the tumour [32]. Nowadays, Intensity Modulated Radiotherapy (IMRT) is used in an increasing number of institutes. This treatment is given by multiple segments (i.e. individually modified treatment fields created by multi leaf collimators) per beam whereby many different beam angles are used according to coplanar and non-coplanar (off-axis of the patient) gantry positions. Consequently, the high dose can be better given to the defined target whereby the dose in the vicinity of the target can be spread to surrounding tissue [33].
5.3 Dose Delivery and Setup Correction
Indispensable for good tumour dose coverage during irradiation is knowledge concerning the position of the tumour during the treatment, which is often based on surrogate markers on (or bony anatomy of) the patient and on imaging prior to the start of the irradiation. For decades, setup verification was performed using the 2-D images (electronic portal image device, EPID) made by the linear accelerator (linac). Nowadays, more advanced techniques are introduced improving the patient setup variability and knowledge of the tumour position. For example, fiducial markers inserted around the tumour can be imaged or ideally the tumour itself can be localised using fluoroscopy [34]. An increasing number of radiotherapy departments do have a linac equipped with a Cone Beam CT (CBCT) scan. A CBCT is an integrated kV-source and imager enabling acquisition of radiographs, fluoroscopy and CBCT scans (3-D/4-D images) [35-37]. Another technique is based on infra-red reflecting markers on the patient and a stereoscopic X-ray imaging device placed in the floor and two detectors mounted at the treatment room ceiling [38]. Other techniques are the cyberknife [39] (whereby the accelerator is mounted on a robotic arm and X-ray imaging cameras are located around the patient) and tomography [40] whereby a small megavoltage X-ray source is mounted in a similar way to a CT X-ray source.

6. Normal Tissue Complications after Radiotherapy
6.1 Normal Tissue Complication Probability
In the decision whether to treat a patient, with what intent, and which treatment would be feasible, the (possible) benefits are weighted against the (possible) negative side effects. Therefore, a reliable estimation of the probability that a specific toxicity occurs is important. Normal tissue complication probability (NTCP) models are helpful in the daily clinic but also in the design of new treatment strategies to formulate dose constraints. From clinical data, NTCP curves are fitted as a function of the dose and/or volume. To develop robust NTCP models, objective well defined endpoints, sufficient number of patients and events and coverage of a wide dose range are needed.

6.2 Radiation Induced Lung Toxicity
Radiation pneumonitis (RP) is a serious side effect which might be life threatening. For lung cancer patients treated with conventional fractionated RT (CFRT) the relation between the lung dose and the incidence of radiation pneumonitis (RP) is known [41,42], however, for patients treated with hypofractionated schemes this relation is unknown. Because lung cancer patients are often suffering from pulmonary co-morbidities it is a challenge to discriminate whether an increase of pulmonary complaints is due to the
irradiation or is due to an exacerbation of a pre-existing pulmonary disease. Therefore, comprehensive collaboration with the pulmonologist is needed. Moreover, long term follow up, pulmonary function tests, and comprehensively described clinical and dosimetric characteristics might help to reveal the predictive and prognostic factors to identify the patients at high risk for severe radiation induced lung toxicity.

6.3 Radiation Dose

From cell survival data it is known that the relation between dose and cell kill is not linear and dependent on multiple factors. Cellular recovery (repair), cell-cycle progression (redistribution), proliferation (repopulation), hypoxia (reoxygenation) influences the response (i.e. radiosensitivity) of normal tissue and tumour after irradiation. Clinically, the physical irradiation dose is converted into a biological equivalent dose according to a mathematical model (i.e. the linear quadratic (LQ) model) derived from the log cell survival as function of the dose. This model uses a linear ($\alpha$) and a quadratic ($\beta$) component to describe the radiosensitivity as function of the dose. Thames et al. [43] published a survey of iso-effect curves for various normal tissues in animals; the response of various normal tissues was plotted for a range of doses per fraction. They showed that the LQ model can be used to describe the relationship between the the total iso-effective dose and the total physical dose, the dose per fraction and the tissue specific radiosensitivity parameter ($\alpha/\beta$ ratio).

However, the bending curve of log cell survival as function of the dose as described by the LQ-model becomes a linear line for higher dose levels [44]. Consequently, it should be questioned whether the LQ-model can be applied for RT schedules using a high dose per fraction. The consequences of these hypofractionated dose schedules for the toxicity are still uncertain.

7. The purpose of this thesis

As described above, RT is an important treatment modality for lung cancer patients but the prognosis of irradiated patients remains poor. To improve the prognosis better patient selection, development of high accuracy irradiation techniques and the optimization of predictive toxicity models are needed. These topics are subject of studies included in this thesis.

I. Pre-RT PET scans are obtained primarily for tumour staging and can be helpful for target delineation. The amount of FDG uptake in the primary tumour is correlated with the metabolism of the tumour cells. If higher uptake of FDG is correlated with worse outcome, the quantification of the FDG can be of great interest for patient selection and future treatment strategies. We evaluated the prognostic value of FDG in pre-RT scan for inoperable lung cancer patients (Chapter 2).
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II. The use of NTCP models is an important but complicated subject in the treatment of lung cancer patients. Previous (validated) studies found a dose-response analysis for RP after conventional fractionated RT. However, the variability within the prediction of RP is substantial. We evaluated whether the prediction of RP can be improved by the addition of pulmonary function test parameters (Chapter 3).

III. In contrast to conventional fractionated RT, for hypofractionated RT the relation between dose and RP is still unknown. Moreover, the incidence and period of risk of RP after hypofractionated RT is uncertain and are also evaluated (Chapter 4).

IV. Long term consequences of irradiation of large lung volumes is poorly studied since clinical data is scarce because of the bad prognosis. The pulmonary function of a group of lung cancer patients fortunate with a long term disease free survival is indicative of what can be expected if the prognosis of lung cancer patients is improving (Chapter 5).

V. The LQ model and NTCP calculations are important in the daily clinic to estimate the complication probabilities after conventional fractionated RT. The relation between the physical and biological lung dose (and the applicability of the LQ and the NTCP model) after hypofractionated RT is evaluated in Chapters 4 and 6.

VI. More sophisticated irradiation techniques delivering higher doses to the tumour are dependent of better imaging techniques to visualize the regions of interest. The introduction of linear accelerators equipped with a CBCT was a major improvement for safe and accurate RT treatment. Nevertheless, older verification techniques are still in widespread use. Consequently, differences between the patient setup verification using the CBCT and the EPID are of great interest (Chapter 7).
References

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