Chapter 1
GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
Epidemiology of lung cancer
In the Netherlands, lung cancer is one of the most common cancers in both men and women [1]. In 2018, the incidence was 13,262 new cases, of which most were male (55.5%). The incidence of women increased from 2010, reflecting the later onset of smoking among women [1]. Generally, there are two major subtypes of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), accounting for 85% and 15% of the cases, respectively [2]. The research in this thesis focuses on NSCLC-patients only and specifically on locally advanced NSCLC, which is stage III. Twenty-five percent of the patients with NSCLC are diagnosed with stage III [3].

Treatment of locally advanced NSCLC
The standard of care for patients with locally advanced NSCLC is concurrent chemoradiotherapy [4, 5]. Sequential chemoradiotherapy is chosen when co-morbidities and/or the performance status of a patient do not allow for a concurrent regimen. Chemotherapy causes a radiosensitising effect and reduces the incidence in distant metastases. The concurrent use of the two treatment modalities results in a lower local failure rate [4, 6]. Promising five-year OS rates of 32% have been published in patients treated with concurrent chemoradiotherapy [7, 8]. At present, the standard radiotherapy dose consists of 60-66 Gy in 30-33 fractions of 2 Gy, which was established in the 1970s [9]. The chemotherapy regimen differ and may consist of low dose daily cisplatin or high dose cisplatin-doublet.

Radiotherapy and dose-intensification
Since the introduction of the radiotherapy schedule of 60 Gy in 30 fractions, multiple fractionation schemes have been explored to improve the outcome, such as schedules with a higher total radiation dose. Excellent local control has been accomplished by treating early stage NSCLC with hypofractionated stereotactic body radiotherapy (SBRT) [10]. With SBRT, patients are treated in a few fractions with a very high biological effective dose (BED) using a high precision technique that enables maximal sparing of the organs at risk (OAR), such as the lungs, the oesophagus and the heart [11]. Onishi et al. demonstrated a significant difference in local control rate at 36 months with 89% and 62% for respectively >100 Gy and <100 Gy BED [12]. A meta-analysis showed that the optimal BED-range for early stage lung cancer treated with SBRT is between 83 and 146 Gy [13]. It is to be expected that these high local control rates can be reached for more advanced stages as well, because a dose effect relation is anticipated [14].

Phase I/II dose-escalation trials have demonstrated its feasibility in locally advanced NSCLC-patients treated with sequential chemoradiotherapy or radiotherapy alone. Belderbos et al. conducted a phase I/II dose-escalation trial based on the relative mean lung dose (MLD) with a fixed overall treatment time of six weeks [15]. The majority of the patients were treated with 74.3 Gy and 81.0 Gy. The maximum tolerated dose (MTD) was defined as a dose-limiting toxicity (DLT) of ≥ grade 3 pneumonitis in two out of six patients, but this was not reached. Rosenzweig et al. investigated dose-escalation with total doses ranging from 70.2 Gy to 90 Gy in fractions of 1.8-2.0 Gy [16]. The patients treated to a dose of at least 80 Gy showed a better OS compared to patients who were irradiated at a lower dose. The MTD was observed at 84 Gy, since unacceptable pulmonary toxicity occurred at 90 Gy. These results show that treating patients to a high radiation dose is feasible but limited by the OAR (the lungs, the oesophagus, the heart and the spinal cord). The RTOG 0117-study investigated the MTD of
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Radiotherapy with concurrent chemotherapy, using three-dimensional conformal radiotherapy (3D-RT) [17]. The radiation dose was gradually intensified, starting at 75.25 Gy in 35 fractions. Due to two acute treatment-related pulmonary DLT, the dose was de-escalated to 74 Gy in 37 fractions. Subsequently, the phase III RTOG 0617-trial randomized in a 2x2 factorial design 60 Gy (6 weeks) versus 74 Gy (7.5 weeks) with concurrent and consolidation chemotherapy and with or without additional cetuximab [7]. Surprisingly, this trial showed a significantly worse median OS in the high dose arm (HR 1.37, 95%CI 1.09-1.76; p=0.004). This was also the outcome of a meta-analysis on randomized controlled trials using different fractionation schedules for NSCLC: in trials where concurrent chemotherapy was given, a higher dose resulted in a worse OS [18]. However, in case no or sequential chemotherapy was administered, a higher dose resulted in a better OS. It is to be expected that the difference in toxicity caused by the concurrent regimen is responsible for this result.

These outcomes challenge the assumption that dose-escalation will be the solution for inoperable locally advanced NSCLC patients. However, there are limitations regarding the previously described dose-escalation studies. First, it should be emphasized that in the above studies both the primary tumour as well as the lymph nodes were treated with a higher dose. Treating the lymph nodes to a high dose results in a higher dose to the OAR as well, causing an increase in toxicity. Second, the trials often used 3D-RT, while intensity-modulated RT (IMRT) is known to reduce the toxicity rates [19]. Third, in the RTOG-0617 trial, the dose to the heart was among the possible explanations for the worse OS in the 74 Gy-arm. Dose-volume constraints to the heart were not compulsory, however, which dose parameter of the heart is the best predictor is currently unknown. Fourth, in the RTOG-0617 trial, the use of consolidation chemotherapy was allowed consisting of paclitaxel and carboplatin, which is expected to increase the toxicity [20]. Consolidation chemotherapy is no longer part of the standard of care in locally advanced NSCLC-patients since it has failed to improve OS [21]. Last, the majority of the patients included in the RTOG-0617 trial were treated in a low-volume facility: the median was 2 patients per institute (range 1-18). Being treated within a high-volume facilities (≥12-15 patients) is associated with a decreased risk of death [22, 23]. Thus, further research addressing these limitations is necessary to determine eventually the role of dose-escalation in the treatment of locally advanced NSCLC-patients.

Hypofractionated radiotherapy

Hypofractionated radiotherapy can overcome the undesirable effect of a prolonged overall treatment time, by using higher doses per fraction. At the Netherlands Cancer Institute, a schedule of 66 Gy in 24 fractions is used with an overall treatment time of 4.7 weeks (32 days). This is based on the results of two EORTC-trials. The EORTC-08912 trial was a phase II-trial and increased the dose up to 66 Gy in daily fractions of 2.75 Gy [24]. Forty patients were evaluable and the increasing radiation dose was well tolerated in terms of acute and late toxicity. This schedule was subsequently tested in the EORTC-08972 trial, a randomized phase III-trial comparing concurrent chemoradiotherapy using daily low dose cisplatin with sequential chemoradiotherapy (radiotherapy preceded by 2 courses of gemcitabin/cisplatin) [25]. A total of 158 patients were included but the trial was prematurely closed due to poor accrual. Therefore, no significant differences in survival could have been detected, although the 3-year OS was better in the concurrent arm (34% versus 22%). The acute toxicity in this trial was mainly haematological toxicity in the sequential arm (30% versus 6%), while grade 3 and 4 oesophagitis was more frequently observed in the concurrent arm (14% versus 5%).

Another argument in favour of the use of the schedule of 66 Gy in 24 fractions is that the BED increased as well. Converted into an equivalent dose in fractions of 2 Gy (EQD₂) using an α/
$\beta=10$ Gy, the total dose is 70 Gy. Taking into account the short overall treatment time of 32 days as well, the estimated biological equivalent of this schedule is approximately 78 Gy according to the formula: $\text{EQD}_{2,T} = \text{EQD}_{2,t} - (T-t) \times D_{\text{prolif}}$, with $T=32$ days, $t=49$ days and $D_{\text{prolif}}=0.45$ Gy [26]. This dose is substantially higher compared to a conventional fractionated schedule of 60 Gy in 30 fractions.

In conclusion, to determine whether a total dose >60 Gy is beneficial in locally advanced NSCLC further research is necessary. Mild hypofractionated radiotherapy schedules are inevitable as a basis for dose-intensification using high-end radiotherapy techniques, such as image-guided IMRT, to prevent an increase in toxicity. This thesis investigates the optimization of the hypofractionated radiotherapy schedule, which has been used in the Netherlands Cancer Institute since 1997. To further improve the treatment of locally advanced NSCLC-patients, it is necessary to analyse toxicity and outcome in detail which are addressed in the following paragraphs.

Local and regional failures

As previously mentioned, the improved OS associated with concurrent chemoradiotherapy is due to a lower local failure rate. The incidence of locoregional failures is lower in early stage NSCLC than the incidence in locally advanced NSCLC, being respectively 21% versus 41% after 3 years [10, 27]. However, differences between local and regional failure rates after chemoradiotherapy are largely unknown since these are generally analysed together. In clinical practice, both the primary tumour and the involved lymph nodes typically receive the same prescribed radiation dose during concurrent chemoradiotherapy. If a significant difference exists between the failure rate of the primary tumour and the involved lymph nodes, this could be a strong argument to explore new RT treatment strategies with differentiated prescription doses to the primary tumour and the involved lymph nodes. Improvement of local control may be established by escalating the radiation dose to the primary tumour only [28]. The risk of severe pulmonary, oesophageal and cardiac toxicity is mainly determined by the involvement of mediastinal lymph nodes, the size and location of the primary tumour and the total radiation dose. A lower dose to the involved lymph nodes is expected to result in lower acute and late toxicity rates, especially with the use of concurrent chemotherapy.

Acute and late toxicity

The most relevant acute and late toxicity in the treatment of NSCLC patients after concurrent chemoradiotherapy consists of pulmonary and oesophageal toxicity. The rates of acute > grade 3 oesophageal toxicity in patients treated with concurrent chemoradiotherapy ranges between 15% and 21% [5, 7, 29]. We observed severe late oesophageal toxicity in 6% of the patients treated with concurrent chemoradiotherapy [30]. Prognostic factors were the maximal grade of acute oesophagitis, the duration of the radiation oesophagitis and the volume that received a high dose (>76 Gy, EQD.). Acute pulmonary toxicity > grade 3 is observed in 5-10% in case the mean lung dose (MLD) is kept below 20 Gy (preferably below 16 Gy) [31]. Severe late pulmonary toxicity is observed less frequently and might not be a dose-limiting factor anymore in the era of high precision image guided radiotherapy. Since the results of the RTOG-0617 trial demonstrated an association between heart dose and OS, the focus of several research groups is to find valuable heart dose parameters [32, 33].

In dose-escalated radiotherapy trials, the aim is to increase the dose while avoiding pre-defined toxicity rates. Earlier trials on dose-escalation showed no significant increase of grade 3 and higher oesophageal and pulmonary toxicity [34-36]. One of the concerns in treating patients with a higher dose to the
primary tumour is the risk of fatal hemoptysis. Langendijk et al. described an average fatal bleeding risk of 11.3% in 938 patients, treated with palliative radiotherapy and/or brachytherapy [37]. The multivariate analyses showed central location (the presence of endobronchial tumour) as a significant factor, as well as localization of the tumour in the upper lobe and in case hemoptysis present prior to the start of the irradiation. Since the large blood vessels are in close proximity of the bronchi, the presence of hemoptysis could be a possible sign of tumour growth in blood vessels. It should be mentioned that inoperable lung cancer patients often have large and centrally located tumours and belong therefore to a high-risk group. Presently, no dose constraints to the heart, large blood vessels and proximal airways are used in clinical practice in the treatment plan for locally advanced NSCLC-stages.

Incorporating FDG-PET-scans in radiotherapy planning

The incorporation of 18 Fluoro-deoxyglucose positron emission (FDG-PET)-scans in lung cancer diagnostics as well as radiotherapy planning has improved the outcome in locally advanced NSCLC-patients significantly [38]. It reduces inter-observer target delineation variation and allows better target volume definition, based on additional biological information [39]. Computed tomography (CT)-scans showed a significant overestimation in comparison with pathology findings, while FDG-PET-scans provided tumour volume sizes more in agreement with pathology [40]. Additionally, the increased sensitivity compared with CT-scans of involved mediastinal lymph nodes permitted the omission of elective nodal irradiation and supported involved nodal irradiation [41]. These advantages allow more accurate target volume delineations, reduce the radiation treatment volumes and results in a more precise dose delivery. Moreover, FDG-PET-scans incorporated within the radiotherapy planning are valuable in achieving higher radiation doses, while a generated biological target volume can be used to guide dose-escalation [42]. Research showed that local failures for locally advanced NSCLC-patients after concurrent chemoradiotherapy were localized within the metabolic regions of the pre-treatment FDG-PET-scans [43]. It was also shown that patients with residual metabolic areas within the tumour after concurrent chemoradiotherapy or radiotherapy alone had a worse survival rate compared to patients with a complete metabolic response [44]. Following these findings, we designed the randomized phase II PET-boost trial (NCT01024829) based on the hypothesis that an improved local control can be achieved with dose-escalation using the pre-treatment FDG-PET-scan [45]. We investigated dose-escalation using an isotoxic hypofractionated schedule either to the entire primary tumour or redistributed to the regions of high pre-treatment FDG-uptake (SUV$_{\text{max}}$ ≥50%) within the primary tumour.

Response evaluation using FDG-PET-scans

Since concurrent chemoradiotherapy is a curative but toxic treatment, the aim is to identify patients with a good chance of a prolonged treatment response. In order to differentiate patients with a low or high failure risk, biomarkers before and after treatment are important. Many studies have been performed to investigate favourable tumour and/or patient characteristics. General risk factors such as performance status, weight loss, tumour volume and the Charlson Co-morbidity Index are known to affect the prognosis [46, 47]. Other biomarkers are found in metabolic activity imaging of FDG-PET-scans. FDG-PET-scans are essential in lung cancer staging and radiotherapy planning procedures [48]. However, their use in response evaluation is less clear. Metabolic changes due to radiotherapy are observed sooner than morphologic changes on CT-scans [38, 40]. PET-metrics such as the maximum standardized uptake value (SUV$_{\text{max}}$), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) during or shortly after treatment, have been identified as biomarkers for disease recurrence and survival [38, 49-51]. Nevertheless, it is unclear yet what the
ideal time point is to perform response FDG-PET-scans and whether there are differences in the metabolic activity between the primary tumour and the involved lymph nodes.

**Image-guided radiotherapy in locally advanced NSCLC**

Image-guided radiotherapy techniques have been developed and implemented very rapidly over the past years enabling high-precision treatments. Daily online image guided cone beam CT-scans (CBCT) correction strategies were implemented in the Netherlands Cancer Institute since 2012 using vertebral registration, which have improved the position verification and treatment adaptation. The development of four-dimensional CT-scans (4D-CT) in treatment preparation as well as 4D-CBCT on the linear accelerator have allowed for the visualization of individual tumour motion shortly before or even during radiotherapy. Furthermore, 4D-CT allowed for calculating patient-specific planning target volume (PTV)-margins [52]. Previously, Schaake et al. demonstrated that the PTV-margins for the tumour and the lymph nodes can be reduced using a daily online carina registration protocol [53]. This PTV-reduction is expected to result in a decrease of toxicity. However, the implementation of a carina registration protocol and the subsequent reduction of the PTV-margins should not result in an increase of local and regional failures.

In summary, the aim of this thesis is to further improve radiotherapy of locally advanced NSCLC-patients. The acute and late toxicity rates in locally advanced NSCLC-patients determine whether the radiotherapy dose can be escalated. However, much is unknown regarding critical structures as the heart and large blood vessels. Possible differences between the local and regional failure rate might provide evidence for an inhomogeneous dose-prescription in locally advanced NSCLC. In addition, FDG-PET-scans can be very useful to guide dose-escalation to the primary tumour, but may also be able to evaluate the response shortly after finishing the chemoradiotherapy.

**Purpose and outline of this thesis**

This thesis investigates patient selection improvement, response evaluation and treatment optimization of locally advanced NSCLC patients treated with hypofractionated radiotherapy.

**Part I: Predicting the outcome in locally advanced NSCLC-patients**

In chapter 1, local and regional failures were analysed as well as patient and tumour characteristics after concurrent chemoradiotherapy. The value of an early response evaluation using FDG-PET-scans after four weeks was analysed for the primary tumor and lymph nodes separately in chapter 2. Volumetric and intensity imaging biomarkers of both the pre-treatment and post-treatment FDG-PET-scan as well as possible associations with outcome were investigated.

**Part II: Optimizing the treatment for locally advanced NSCLC-patients**

Currently, no dose constraints to the heart are used in clinical practice. In chapter 3, we have investigated potential heart dose parameters as well as patient and tumour characteristics associated with OS. The toxicity rates of the phase II PET-Boost trial are described in chapter 4. An increased dose to the primary tumour or the regions with high FDG-uptake within the primary tumour might improve the local control rates, but may cause an increase in the acute and late toxicity rates as well.

The involved lymph nodes may not need the same dose as the primary tumour due to a difference in the local and regional failure rate. The results of a dose-reduction to the lymph nodes as well as a margin-reduction by a simultaneous implementation of a different daily online correction strategy are described in chapter 5.
REFERENCES


