GENERAL DISCUSSION AND FUTURE PERSPECTIVES
Chapter 7

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Non-small cell lung cancer (NSCLC) is one of the most frequently diagnosed cancers in the Netherlands [1]. Twenty-five percent of the patients are diagnosed with stage III (locally advanced) NSCLC [2, 3]. The patients with a good performance status are preferably treated with concurrent chemoradiotherapy with curative intent [2, 3]. Following this treatment, promising 5-year overall survival (OS) rates of 32%-40% have been published, which is considerably higher than previously reported [4-6]. In 2018, Antonia et al. demonstrated that after concurrent chemoradiotherapy, in patients without progression, adjuvant Durvalumab for 1 year significantly improves OS from 55.6% to 66.3% at two years [7]. Recently, an update of the OS was presented demonstrating an ongoing significant clinical benefit after 3 years (57.0% versus 43.5%) [8]. Radiotherapy is an essential part of the treatment of lung cancer patients, as 60% of these patients need it at least once during the course of their disease [9]. Due to the development of new systemic therapies, such as immunotherapy and targeted therapies, the treatment of distant metastases has improved significantly [10, 11]. The need to control the primary tumour and the involved lymph nodes therefore becomes even more important. Without local control no long term OS can be achieved.

The aim of this thesis was to improve the prediction of recurrence and survival as well as to improve the radiation therapy. A new treatment strategy was investigated to improve the local control rate while reducing the acute and late toxicity rates by applying an inhomogeneous dose prescription using a mild hypofractionated regimen. The first part focused on analysing prognostic factors of patient and tumour characteristics. The second part focused on optimizing the radiotherapy dose to the organs at risk (OAR), the primary tumour as well as the involved lymph nodes.

PART I
Predicting the outcome in locally advanced NSCLC-patients

Although the long-term OS rates have improved after chemoradiotherapy, over a third of the patients develop a locoregional failure after 2 years [4]. Several analyses of prognostic factors have been performed in the past, but this has not been done separately for the primary tumour and the lymph nodes. In chapter 2, we demonstrated that a differential analysis supported an improved prediction of the local and regional control rates. The recurrence rate differed between the primary tumour and the lymph nodes based on a difference in tumour volume. We also analysed the prognostic value of an early 18F-Fluoro-deoxyglucose positron emission (FDG-PET)-scan (4 weeks) after chemoradiotherapy (chapter 3). As in chapter 2, the primary tumour and the lymph nodes were analysed independently of each other. Our research aimed to answer the question whether an early FDG-PET-scan was useful to predict the location of the recurrence and which PET-parameters were the most useful.

Finding specific and reliable prognostic and predictive factors has been the subject of several other research strategies. The minimally invasive liquid biopsies are very promising as potential biomarkers in NSCLC-patients [12]. Circulating tumour cells or tumour DNA (ctDNA) from the blood is particularly useful when the tumour biopsy location is inaccessible. ctDNA can provide “real-time” tumour information due to a short half-life and can be deployed to measure early treatment response [12, 13]. Currently, liquid biopsies are mainly used to guide targeted therapies for stage IV NSCLC-patients. Due to its promising results, the research has shifted to stage I-III lung cancer as well and even to the early detection of NSCLC in asymptomatic individuals [12]. In addition, ctDNA
might also be useful to predict treatment response or toxicity due to radiotherapy [14]. A recently published study suggested that ctDNA may be used as a predictive factor for the development of oral mucositis in patients with head and neck cancer treated with radiotherapy [15].

In oncology, patients undergo many diagnostic and evaluation imaging modalities, such as CT-scans and/or FDG-PET-scans. We estimate that every oncologic patient yields 0.1-10 Gb of data [16]. In 2018, over 13,000 new patients were diagnosed in the Netherlands, producing large amounts of data, together also called “Big Data” [17]. Radiomics, a concept introduced in 2012, is the computerized extraction of quantitative features from medical images [18]. It has the potential to discover imaging features that the human eye is not able to detect. Imaging analysis algorithms can be used to quantify specific features from the CT-scan and FDG-PET-scan: e.g. intensity, shape and texture [19]. Subsequently, machine learning optimizes a multivariable prediction model using these features in order to maximally individualize cancer treatments. For example, Ramella et al. analysed radiomic features from the planning CT-scan in 91 locally advanced NSCLC-patients and identified a signature that was prognostic of tumour reduction during concurrent chemoradiotherapy [20]. Similarly, other studies have been able to demonstrate the potential of radiomics in response assessment in NSCLC, both early stage as locally advanced stage [21]. Radiomics obtained by FDG-PET-scans are also promising: textural features seem to perform better than the conventional uptake parameters such as SUV<sub>max</sub> used in the clinic [19]. It is to be expected that radiomics will play a role in improving the patient and tumour selection.

FDG-PET-scans are indispensable in the staging of lung cancer patients. However, false-positive and false-negative findings are possible since it represents tissue glucose metabolism. Lung tumours are very heterogeneous and responses do not only depend on energy metabolism. Therefore, the value of other PET-tracers has been analysed that characterized other, more specific aspects of the tumour biology, such as tumour proliferation, hypoxia and angiogenesis [22-24]. Tumour proliferation can be measured by using radiolabelled thymidine, 18F-fluorothymidine (18FLT-PET). Thymidine kinase is a key enzyme in the DNA-synthesis and is related to intracellular accumulation of 18FLT. It has a high sensitivity for primary pulmonary lesions, but is less reliable in the detection of nodal metastases and distant metastases than FDG-PET. The accuracy in staging was 67% versus 85% for FDG-PET in NSCLC [23]. Hypoxia is associated with resistance to radiotherapy and the hypoxic regions within the tumour might require a 2-3 times higher radiotherapy dose to achieve a comparable therapeutic effect. Several PET-tracers are available to detect hypoxia, such as 18F-fluoromisonidazole (FMISO), fluoromycin arabinoside (FAZA) and 2-nitroimidazole nucleoside analog (18F-HX4). Currently, the prognostic value of such tracers is being investigated in several trials for NSCLC-patients treated with radiotherapy (NCT02490696; NCT02701699). Furthermore, hypoxia tracers might also be used to segment hypoxic regions for dose painting, similarly as the FDG-PET-scans in the PET-boost trial (chapter 5) [24]. Also worth mentioning is the possibility of visualizing new blood vessel formation, or angiogenesis, which is associated with tumour growth by radiolabeled integrin antagonists. Nevertheless, the alternative PET-tracers representing the heterogeneity of the tumour biology need further investigation and validation before applying these in routine clinical practice.

In summary, great effort has been made to improve the patient selection using various minimal invasive and non-invasive methods. These methods estimate the probability for a given patient on developing local, regional and/or distant failures and may be able to guide treatment decisions at different time points (pre-treatment, mid-treatment, post-treatment). In any case, all modalities contribute to personalizing the treatment of lung cancer patients.
PART II
Optimizing the radiotherapy for locally advanced NSCLC-patients

This part of the thesis investigated the optimization of the treatment of locally advanced NSCLC-patients. Although the long-term OS rates have been improved significantly in recent years, there is certainly room for optimization. The interest in identifying relevant heart dose parameters increased exponentially after the unexpected results of the phase III RTOG 0617-trial showing a significantly worse median OS within the 74 Gy-arm than the 60 Gy-arm [4]. Locally advanced NSCLC-patients are treated with a (mild) hypofractionated radiotherapy schedule combined with daily low dose cisplatin in the Netherlands Cancer Institute, which is different from the international standard. Therefore, we pursued an analysis of this hypofractionated schedule and demonstrated in chapter 4 a significant association between OS and the volume of the heart receiving 0.1 Gy-45 Gy. Our results add to the growing amount of evidence that radiation to the heart does have a significant impact on OS in these patients.

Both chapters 5 and 6 demonstrated that an inhomogeneous dose-prescription is an interesting and promising strategy in locally advanced NSCLC-patients. Achieving local control is vital since the treatment of distant metastases improved in recent years due to the development of targeted therapies and immunotherapy [10]. Dose-escalation in locally advanced NSCLC-patients may improve local control, but concerns about the increase in acute and late toxicity hampers its clinical implementation. We have demonstrated that individualized dose-escalation to the primary tumour as a whole or to the high FDG-avid regions within the primary tumour that the toxicity rates indeed increased, although the rates were within the pre-defined boundaries. Reduction of toxicity to the heart and oesophagus is possible by decreasing the mediastinal dose and the PTV-margins. Future dose-escalation trials should aim at the primary tumour only, while the involved lymph nodes can be treated to a standard dose. The challenge is finding the balance between improved locoregional control and the acute and late toxicity rates.

Further improvements of the radiation dose distribution as described in chapters 4-6 may be possible with relatively new developments as magnetic resonance guided radiotherapy and proton therapy. In the last decades, image guided radiotherapy has evolved very rapidly as well as its implementation into the clinic. However, the images obtained by CBCT-scans have inferior soft-tissue contrast and are therefore suboptimal for image-guided radiotherapy. Due to the development of magnetic resonance guided radiotherapy, the visualization of the primary tumour and organs at risk improved significantly [25]. The MR-Linac allows the implementation of adapted and inhomogeneous dose prescriptions in lung cancer as demonstrated in this thesis. The improved visualization and reduced margins might support in a safer delivery of a high dose per fraction to the primary tumour, which will very likely result in lower toxicity rates as demonstrated in chapter 6. A recently published planning study showed that both strategies (dose-escalation and reduced margins) are possible using a 1.5T MR-Linac for locally advanced NSCLC [26]. Ten patients were replanned using conventionally fractionated radiotherapy with standard margins or isotoxic dose-escalation comparing standard and reduced margins. The treatment plans using reduced margins demonstrated that increased sparing of the organs at risk was possible as well as delivering a higher dose. Analogous to chapter 6, we calculated the effect of rather small PTV-margins of only 5 mm that might be achievable when a patient is treated on the MR-Linac (Table 1A-C). A significant decrease of the MLD can be obtained due to these reduced margins. Furthermore, the mean heart dose and the V_{50} of the oesophagus decreased as well. It can be expected that the acute and late toxicity rates will subsequently
decrease. As a result, magnetic resonance guided radiotherapy can support the application of dose-escalation strategies expecting that toxicity rates remain within acceptable limits.

Table 1A-C. The mean lung dose (1A), the mean heart dose (1B) and the $V_{50}$ of the oesophagus (1C) in 6 different radiotherapy conditions (A-F) of the involved lymph nodes in 10 patients to gain more insight in the toxicity profile of the reduction of the mediastinal dose and the margins, separately. The difference of the mean ($\Delta$ Mean) between A and the five other conditions are specified as well as the standard deviation (SD).

A= Dose of 70 Gy (EQD$_2$) and large margins using a bone anatomy based correction strategy.
B= Dose of 70 Gy (EQD$_2$) and intermediate margins using a carina based correction strategy.
C= Dose of 60 Gy (EQD$_2$) and large margins using a bone anatomy based correction strategy.
D= Dose of 60 Gy (EQD$_2$) and intermediate margins using a carina based correction strategy.
E= Dose of 70 Gy (EQD$_2$) and small margins when treated on the MR-Linac.
F= Dose of 60 Gy (EQD$_2$) and small margins when treated on the MR-Linac.

**Table 1A. Mean lung dose**

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**Table 1B. Mean heart dose**

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**Table 1C. V$_{50}$ of the oesophagus**

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Another approach to optimize the radiotherapy of lung cancer patients is the use of proton therapy. Protons in contrast to photons deliver the large majority of the dose in a small region, the so-called Bragg peak, at a depth that depends on their energy [27]. Protons therefore have the potential to deliver the dose precisely to the target while the dose at the proximal and distant side of the tumour is reduced compared to photons. This enables a maximal sparing of the organs at risk, such as the heart and the lungs. Promising studies have been published regarding the sparing of cardiac substructures [28]. The lower radiation exposure of the organs at risk is expected to result in lower acute and late toxicity. However, a recently published phase III-trial randomizing locally advanced NSCLC-patients between proton and photon therapy did not show an improvement in ≥ grade 3 radiation pneumonitis or local failure [29]. This might be due to the proton technique used in the trial, which consisted of passive scattering protons, while pencil-beam scanning proton therapy delivers more conformal dose distributions [30]. Nevertheless, due to the unique features of proton therapy, there are many possible indications, some of which have been discussed in this thesis, in which maximal sparing of the organs at risk should be pursued [31]. For instance, proton therapy might play a role in enabling dose-escalation to the primary tumour while simultaneously decreasing the acute and late toxicity. Also, it might be considered in case of reirradiation for an in-field local recurrence, since 26% of the locally advanced NSCLC-patients develop a local failure 2 years after concurrent chemoradiotherapy (as was demonstrated in this thesis, chapter 2).

The rapid evolvement of new techniques and treatments is very promising for locally advanced NSCLC-patients. There have been successful developments involving targeted therapies and immunotherapy for locally advanced and stage IV NSCLC [7, 10, 11]. In particular, the interaction between immunotherapy and radiotherapy is very promising as was demonstrated in the recently published phase II PEMBRO-RT trial [32]. Currently, adjuvant immunotherapy is part of the standard treatment in patients responding to chemoradiation following the results of the Pacific-trial [7]. Other combinations, for example neo-adjuvant immunotherapy, are currently being tested. In 2018, a phase I-trial opened for accrual in our hospital that investigates the safety of induction immunotherapy consisting of tremelimumab and durvalumab followed by chemoradiotherapy in locally advanced NSCLC. In addition, the phase II ETOP-Nicolas trial demonstrated that concurrent nivolumab with radiotherapy is safe [33]. Subsequently, the 1-year progression-free survival will be evaluated. Immuno-radiotherapy is an exciting field that will provide new treatment strategies for locally advanced NSCLC-patients in the coming years.

As demonstrated in chapter 2, FDG-PET-scans performed early after completing chemoradiotherapy might be valuable to evaluate the response. However, adaptive radiotherapy is not possible using this strategy. Therefore, several research groups investigated the value of a mid-treatment FDG-PET-scan. Gensheimer et al. analysed 77 patients who underwent an FDG-PET-scan 3-4 weeks after the first fraction (at a median of 34 Gy) [34]. Over 90% was treated with concurrent chemoradiotherapy and the total median radiation dose was 66 Gy (range, 60-80.4 Gy). The authors demonstrated that both intensity and volumetric PET-parameters were associated with local, regional and/or distant failure. However, none were associated with OS. Interestingly, the tumour volume changes (consisting of both the primary tumour and the involved lymph nodes) as appreciated on the CT-scan were associated with local, regional and/or distant failure. Recently, the results of a PET-adapted radiotherapy (PART) dose-escalation regimen were published by Kong et al. [35]. The 102 patients were treated to 60-74 Gy in fractions of 2 Gy or up to 88 Gy in fractions of 2.2-3.8 Gy (based on lung NTCP of ≤17.2%). Several factors were associated with an improved survival: female gender, adenocarcinoma, higher Karnofsky performance status, higher
In the coming years, new results and treatment strategies on patient selection and optimization of the radiotherapy can be expected. One of the main topics of this thesis was the exploration of dose-escalation for locally advanced NSCLC-patients. As demonstrated in chapter 5 (the PET-boost trial), a high dose to the primary tumour or to the FDG-avid regions within the primary tumour was feasible. Yet, subsequent research topics can be devised from this trial. First, was the (individualized) escalated dose to the primary tumour sufficient or is an even higher dose required? Although the physical dose to the primary tumour of ≥ 72 Gy was very high, being comparable to a BED of ≥ 86 Gy, to achieve local control rates of >90%, a BED > 100 Gy is necessary according to the SBRT-data [36]. A strategy to enable the delivery of a very high dose to the primary tumour is to implement SBRT in the treatment of locally advanced NSCLC-patients. Several regimens using SBRT to escalate the dose to the primary tumour are currently investigated. At our department, a phase I-trial was performed to assess the safety of SBRT to the primary tumour combined with hypofractionated radiotherapy to involved lymph nodes (NCT01933568). Other trials investigate the safety and efficacy of SBRT before or after concurrent chemoradiotherapy (NCT02262325; NCT01345851). Also, SBRT combined with adjuvant Durvalumab after concurrent chemoradiotherapy will be tested (NCT03589547). Second, the development of specific dose-volume constraints of the heart, the airways and the large vessels, will help to optimize the radiotherapy treatment planning in the coming years. In the PET-boost trial, we developed the mediastinal envelope consisting of all mediastinal structures and did not allow hotspots or overlap with the escalated dose to the primary tumour, which probably resulted in a limited increase in toxicity. The toxicity was evaluated at pre-specified time points and therefore, we were able to adjust the study protocol. For instance, an important amendment to the study protocol was performed that excluded centrally located tumours with increasing pulmonary artery invasion and/or encasement [37]. A single dose-constraint was applied to the mediastinal envelope, however, the organs at risk, e.g. the large vessels or the airways, may have different dose constraints in relation to a specific volume [38]. After the analysis of the primary endpoint (freedom from local failure at 1 year), which is expected in the near future, the preferred treatment arm should
be compared with a conventional fractionated schedule within a randomized phase III-trial.

As previously discussed, the role of Big Data and artificial intelligence technology in oncology is increasing and promising. Deep learning is part of machine learning methods based on artificial neural networks [39, 40]. Currently, the delineation of the primary tumour, the involved lymph nodes and the organs at risk are performed manually. This process potentially induces systematic errors evolving into geographically misses or harmful side effects. This is worrying in the era of high precision radiotherapy and the application of smaller margins. Machine learning and deep learning may be able to auto-delineate the target volumes and reduces the uncertainty of manual delineations [39]. Additionally, deep learning may play a role in improving the prediction of the prognosis of lung cancer patients. Currently, the prognosis is based on patient and tumour characteristics. The results of prognostic imaging features identified using deep learning methods were recently published in >1100 patients treated with radiotherapy or surgery [41]. The authors demonstrated that deep learning networks were able to identify with a low and high mortality risk. Deep learning performed better than the tumour characteristics including tumour volume, although the results were only significant in lung cancer patients treated with surgery. At any case, this paper demonstrates the promise of deep learning for improving the patient selection in the future.

The potential of adaptive radiotherapy has been discussed using mid-treatment FDG-PET-scans to adapt and possibly escalate the radiotherapy dose. However, image-guided radiotherapy using daily CBCT-scans performed prior to each fraction allows adaptive radiotherapy as well [42]. In case of significant anatomical changes, such as weight loss, atelectasis and/or tumour regression, adaptation of the treatment plan can be considered. One of the possible strategies is the calculation of the delivered dose by recalculating the treatment plan using daily images and the accumulated dose [43]. Patients that might need adaptive replanning may be identified due to a difference between planned and delivered dose. This strategy has the potential to increase the accuracy of the radiotherapy and may eventually result in an improvement of the locoregional control rates.

For patients with locally advanced NSCLC, real-world data is essential to be able to balance treatment toxicity and treatment outcome. The Dutch lung cancer Audit-Radiotherapy (DLCA-R) is a national lung cancer registration that started in 2013 for patients treated with radical or curative intent radiotherapy [44]. The three major disciplines within thoracic oncology (pulmonology, thoracic surgery and radiotherapy) have joined forces within this registry to evaluate the quality of the lung cancer care within the Netherlands.

In conclusion, new radiation techniques and treatment strategies will be explored in the coming years, ensuring that radiation oncologists have an exciting time ahead. However, in addition to the efforts described here, it is essential to invest in the prevention of lung cancer. It is estimated that smoking leads to the early death of approximately 6 million people worldwide [45]. We should keep in mind that the most effective strategy to decrease the lung cancer incidence is to prevent (young) people from smoking [46].
GENERAL DISCUSSION AND FUTURE PERSPECTIVES

REFERENCES


