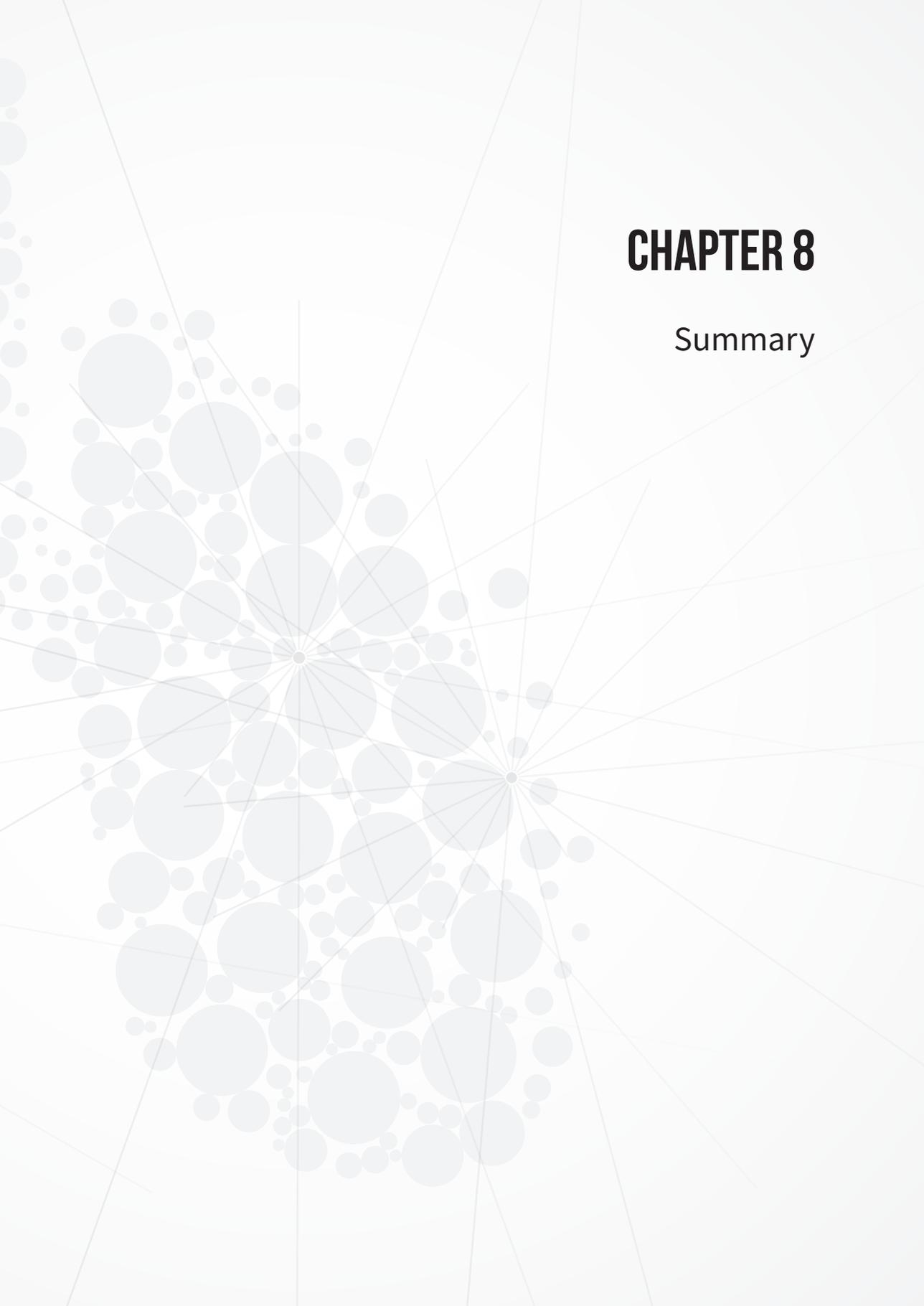




# CHAPTER 8

## Summary



Lung cancer is among the most common cancers and the leading cause of cancer death in both men and women. There are broadly two different subtypes based on histology: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In NSCLC approximately 60% present with local or locoregional disease and most of these patients are offered radiotherapy as single treatment modality or as part of a multimodal approach. The work presented in this thesis focuses mainly on radiation treatment of local NSCLC, but also on (locally) advanced NSCLC. In patients with local disease, cornerstone of treatment used to be surgery. However, only a minority of patients is operable due to pulmonary and/or cardiac co-morbidities. Hence, Stereotactic Body Radiotherapy (SBRT) was developed in the early nineties as an alternative to surgery. Stereotactic Body Radiotherapy is a high precision treatment taking into account tumor motion and delivering a high dose in a few fractions with a short overall treatment time using image guidance during treatment. Due to the high local control and low toxicity in SBRT for early stage NSCLC, SBRT has been rapidly introduced in several parts of the world. Given the excellent results, it is now also offered to operable patients.

The goal of this thesis is to further optimize SBRT treatment and to expand the current SBRT indications by detailed toxicity analysis allowing more patients to benefit from the excellent local control. In **chapter 1** a general introduction on the epidemiology, staging and standard treatment of NSCLC is provided. Furthermore, basic principles of SBRT are explained followed by an outline of the thesis. This thesis consists of two parts, which are summarized below. In the first part optimization of treatment preparation for lung SBRT and follow-up after SBRT for early stage NSCLC will be discussed. The second part of this thesis concerns novel treatment strategies with the use of SBRT in early stage NSCLC as well in locally advanced NSCLC and pulmonary metastasized disease.

## **PART ONE OPTIMIZATION OF SBRT IN EARLY STAGE NSCLC**

To compensate for tumor motion, patient set-up and delineation variability, a margin around the tumor is generated to avoid tumor miss during irradiation. Tumor motion and patient set-up can be corrected for using image guidance during treatment (e.g. kV-CBCT). However, delineation errors cannot be managed by image guided radiotherapy and therefore persist during treatment. This so-called ‘systematic error’ can have a large impact on final dose delivery and can be accounted for by an increase in Planning Target Volume (PTV) margin. In **chapter 2** tumor delineation variability in 16 patients with early stage NSCLC, delineated by 11 radiation oncologists from four different institutes was evaluated. The overall target delineation variability of all patients was small with 2.1 mm, quantified by the root-mean-square of the local standard deviation relative to the median tumor surface. Institutes I-III delineated significantly smaller volumes than institute IV, yielding delineation variabilities of 1.2 mm and 1.8 mm respectively. Corresponding margins to obtain 90% coverage of

the delineated contours were 3.4 mm and 5.9 mm respectively, ignoring other sources of geometric uncertainties. In conclusion, there is low interobserver variability in delineation of early stage NSCLC.

As described earlier there are different strategies to take into account tumor motion for delineation and treatment planning. **Chapter 3** describes the clinical result of the Mid-ventilation approach, where margins increase non-linearly as opposed to the Internal Target Volume (ITV) approach, resulting in smaller margins in case of large tumor motion. We retrospectively analyzed 297 patients with 314 peripheral early stage lung tumors treated with SBRT. After a median follow-up of 22 months, the two-year local control rate was 98%. The median tumor motion amplitude vector for all patients was 6.5 mm and patients who had larger tumor amplitudes did not have more local failures or poorer overall survival. Surprisingly, in the six patients with a local recurrence, the amplitude vector was significantly smaller with 3.0 mm. Although the Gross Tumor Volume (GTV) was significantly larger in local recurrences, there was no correlation between GTV and smaller tumor motion amplitude. The median tumor amplitude vector of 6.5 mm roughly reflects the cut-off point from which the ITV approach results in larger PTV margins compared with the Mid-ventilation approach. Assuming that 50% of the tumors were 'potentially at risk' of developing a local recurrence, smaller margins did not influence local control and overall survival if the tumor amplitude vector was  $\geq 6.5$  mm. This provides clinical support to incorporate respiratory motion directly into the PTV instead of using an ITV concept, leading to a margin reduction in case of large tumor motion with potential toxicity reduction and a potential increase in number of patients eligible for SBRT.

Response evaluation after SBRT is compromised due to extensive fibrotic scar tissue that can mimic tumor recurrence on repeated CT-scans. This may lead to unnecessary salvage thoracotomies. In **chapter 4** we present a validation study of previously reported High Risk Features (HRFs) based on serial CT-scans to detect a local recurrence after SBRT for early stage NSCLC. The HRFs are: enlarging opacity, sequential enlarging opacity, enlarging opacity after 12 months, bulging margin, linear margin disappearance, loss of air bronchogram and cranio-caudal growth. From a multicenter database, 13 patients with a biopsy-proven local recurrence were matched 1:2 to 26 patients without a local recurrence based on dose, PTV, follow-up time and lung lobe. All HRFs were significantly associated with a local recurrence except for loss of air bronchogram. Receiver operating characteristic (ROC) analysis of the number of HRFs to detect a local recurrence had an area under the curve (AUC) of 0.97, which was identical to the performance described in the original report. Presence of  $\geq 4$  HRFs or the combination of the two HRFs bulging margin and cranio-caudal growth resulted in the highest sensitivity and specificity. In conclusion, we successfully validated CT-based HRFs for the detection of a local recurrence after SBRT for early stage NSCLC. As an alternative to

number of HRFs, we propose a simplified model with the combination of the two best HRFs: bulging margin and cranio-caudal growth based on serial CT-scans.

## **PART TWO EXPANDING THE USE OF SBRT**

In case a local recurrence develops after SBRT, local treatments options are scarce as patients are very often inoperable. **Chapter 5** describes the results of an analysis of reirradiation with SBRT of primary lung tumors or lung metastases after a previous course of SBRT. In total 29 patients were reirradiated with SBRT on 32 lung tumors. The median interval between the first SBRT course and the reirradiation was 14 months. After a median follow-up of 12 months, grade 3-4 toxicity was scored 14 times in eight patients and three patients died of massive bleeding. There was no correlation between the Mean-Lung Dose and lung toxicity or dose to the large vessels and bleeding. All patients with grade 4-5 toxicity had centrally located tumors and central tumors were larger than peripherally located tumors. These data show that reirradiation with SBRT is feasible, although higher toxicity was seen in central tumors.

The combination of SBRT to the primary tumor and fractionated radiotherapy to the lymph nodes with concurrent chemoradiation has not been explored yet. Therefore we initiated the phase I Hybrid trial (NCT01933568), assessing the safety of combined SBRT to the primary tumor and fractionated radiotherapy to the lymph nodes with concurrent chemoradiation in locally advanced NSCLC using a Mean-Lung Dose escalation design. Prior to start of the Hybrid trial we performed a treatment planning study, investigating the technical feasibility of a Hybrid treatment. Results of this treatment planning study are presented in **chapter 6**. Eligible patients had stage III NSCLC with a peripheral primary tumor smaller than 5 cm in diameter. In ten patients three treatment plans were compared: the standard fractionated treatment plan of 24x2.75 Gy to the primary tumor and lymph nodes and two Hybrid plans. In the Hybrid plans dose to the primary tumor was either 3x14 Gy (Hybrid low) or 3x18 Gy (Hybrid high), while the lymph nodes received 24x2.75 Gy in both plans. The EQD<sub>2</sub> corrected normal tissue dose parameters were compared and dosimetric analysis of the Hybrid treatment was performed in five patients. For all Hybrid low and Hybrid high plans, the average Mean-Lung Dose increased with 1.0 Gy (p=0.050) and 3.1 Gy (p=0.005), and the average spinal cord Dmax decreased with 11.3 Gy (p=0.01) and 10.6 Gy (p=0.03) respectively. For Hybrid low the average esophagus V35 decreased with 4 Gy (p=0.03). All other dose parameters did not significantly change. Altogether, in eight out of ten patients a Hybrid treatment was feasible. Average pass rates were > 95% for both electronic portal imaging device (EPID) dosimetry and Octavius. In conclusion the combination of SBRT and fractionated radiotherapy is feasible at the cost of an increased Mean-Lung Dose. The safety of this treatment will be assessed in the phase I Hybrid trial.

Finally, **chapter 7** provides the discussion of this thesis. In the first part of the discussion SBRT is compared with surgery and other local therapies. Thereafter, strategies to further optimize SBRT in early stage NSCLC are discussed and novel treatment perspectives are highlighted.