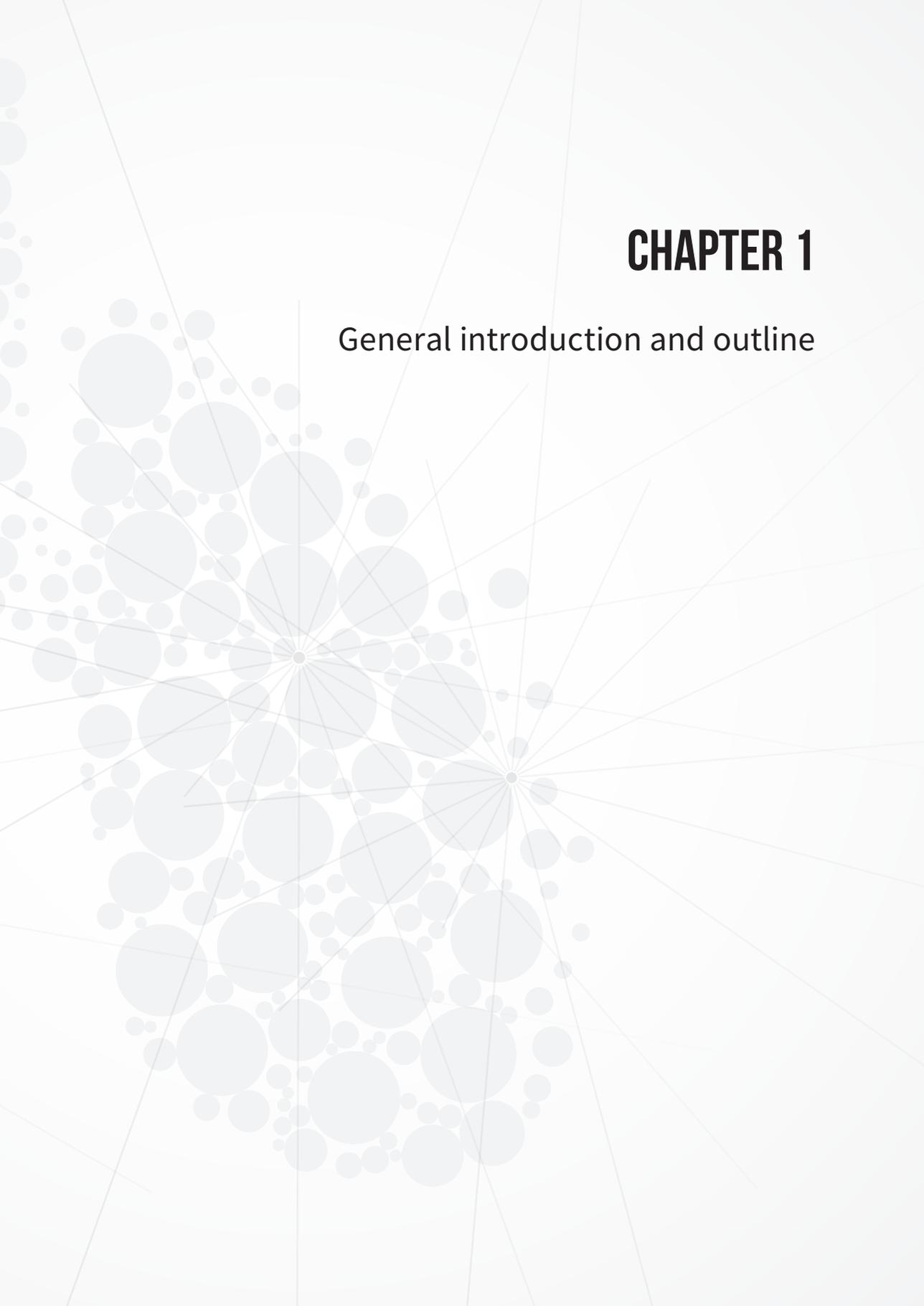




# CHAPTER 1

## General introduction and outline



## **Epidemiology**

Lung cancer is among the most common cancers and the leading cause of cancer death in both men and women, causing 353.000 deaths in Europe and approximately 1.4 million worldwide [1]. The most important cause of lung cancer is smoking: people who smoke tobacco are 11 times more likely to develop lung cancer than those who do not smoke. The lung cancer risk increases when people smoke more cigarettes a day and for a longer period of time. People who are exposed to passive smoke are 1.4 times more likely to develop lung cancer [2]. Between the 1970's and 90's lung cancer mortality among males in the Western countries has declined, whereas countries where the smoking epidemic began more recently, including low- and middle-income countries such as South America and Asia, mortality rates continue to rise [3]. The incidence of female mortality is increasing worldwide due to a later onset of smoking in women [3].

In the Netherlands, the incidence in 2015 was 12.000 new cases, with a decrease in males and an increase in females, although the steepness of the slope in females is declining the last two years [4]. From 2010-2014 the numbers of death stabilized with 10.000 per year, with 60% being male, but again the same trend with a decrease in males and an increase in females. Although survival has increased the last decades, five-year survival rates are still poor with approximately 18% [5].

Lung cancer is divided in broadly two different subtypes based on histology: non-small cell lung cancer (NSCLC) accounting for approximately 85% of the cases and small cell lung cancer (SCLC) accounting for 15% of the cases. The latter has a more aggressive behavior with 62% having metastasized disease at diagnosis [6]. Therefore the cornerstone of treatment is systemic therapy. In NSCLC approximately 60% present with local or locoregional disease and most of these patients are offered radiotherapy. The work presented in his thesis focuses on radiation treatment of NSCLC only.

## **Stages of lung cancer**

There are four stages in lung cancer, classified by the TNM staging system [7]. It defines the anatomical tumor extension (T), lymph node involvement (N) and the presence of metastases (M). Goal of the international TNM classification is to specify prognosis, allocate treatment and to compare treatment outcome. The staging system is regularly evaluated and updated. In this thesis the 7<sup>th</sup> TNM classification is used. The standard diagnostic work-up for stage I-III lung cancer includes: bronchoscopy, diagnostic CT-thorax and FDG PET/CT and in case of suspicion of lymph node metastases Endobronchial Ultrasound (EBUS) or Endoesophageal Ultrasound (EUS) and a MRI-brain. With the introduction of FDG PET/CT and MRI-brain scanning in the first decade of this century, more patients were diagnosed with stage IV disease [8], which lead to an increase in the overall survival in all stages. This is called the 'Will Rogers' phenomenon; the paradox observed when moving one element to another group

and the average in both groups increase [9]. This thesis will concern early stage NSCLC (stage I-II) and locally advanced NSCLC (stage III).

### **Treatment of early stage NSCLC**

Approximately 26% of all lung cancer patients present with stage I disease and 8% with stage II disease, which is considered resectable [8]. Corner stone of treatment has been lobectomy with local control rates of 90% and three-year overall survival rates of 78% [10, 11]. However, a large group of patients are at high-risk for surgery, due to high age or comorbidities, such as poor lung function, cardiac problems or general frailty. For this group of inoperable patients, conventional fractionated radiotherapy is an acceptable alternative, although it has inferior survival rates compared to lobectomy or pneumonectomy with poor local control rates of 30% [12]. Moreover, patients with large tumors have a higher probability of local and distant failure, which can be reduced if treated with doses above 65 Gy, especially for T1 tumors [12]. In general, dose escalation is associated with increased risk of normal tissue toxicity. But then in the early nineties stereotactic body radiotherapy (SBRT) of the lung was developed in Sweden, which was initiated after the successful introduction of stereotactic brain radiotherapy [13-15]. Stereotactic body radiotherapy is a high precision treatment, where a very high dose in few fractions is delivered to the tumor, while maximally sparing the surrounding normal tissue [16]. With this new strategy, excellent local control can be achieved with remarkably low toxicity, as demonstrated by several prospective trials [17-21].

### **Treatment of locally advanced NSCLC**

Twenty-eight percent of the lung cancer patients present with mediastinal lymph node metastases. For these stage III NSCLC patients and for inoperable stage II NSCLC, concurrent chemoradiation is standard of care in case of a good performance score. A meta-analysis with treatment doses in the range of 56-66 Gy given in fractions of 2-2.75 Gy showed superiority of concurrent chemoradiation compared to sequential treatment with three-year overall survival rates of 24% and 18% respectively [22]. However, acute esophagus toxicity (grade 3-4) increased from 4% to 18% for sequential and concurrent treatment respectively. Since there was no difference in distant progression between the two treatment arms (39% at three years), increased survival in the concomitant treatment arm can be attributed to increased local control. Apart from chemotherapy as radiosensitizer, other strategies have been applied to improve local control. One strategy was to overcome proliferation of tumor cells by use of hyperfractionated accelerated radiotherapy (CHART), which resulted in a two-year local control increase from 16% to 22% and an improvement of two-year survival from 20 to 29% at the expense of more acute esophagus toxicity [23]. Multiple institutes investigated the safety and efficacy of dose-escalation in phase I/II trials, which revealed improved local control and overall survival [24-27]. However, higher radiation doses are associated with increased risk of normal tissue toxicity with dose-limiting toxicity reported above 90 Gy [28].

Although local control rates have improved, three-year locoregional failures rates remain high with 30% [22]. In pancoast tumors, a trimodality approach of concurrent chemoradiation followed by a resection results in higher local control rates and an improved overall survival [29]. However, in a randomized phase III study the addition of surgery to concurrent chemoradiation in stage III NSCLC did not improve overall survival [30]. Several chemotherapy regimens have been used with concurrent chemoradiation, such as 3-weekly doublet chemotherapy and also daily low dose cisplatin. No preferred regimen has been identified, but daily low dose cisplatin has a more favorable hematological toxicity profile and is therefore preferred at the Netherlands Cancer Institute [31].

### **Basic principles of SBRT**

Stereotactic body radiotherapy is a high precision irradiation of the primary tumor, characterized by a high dose given in few fractions with a short overall treatment time and a high degree of precision, rigorously taking into account tumor motion using image guidance during treatment [16, 32].

Dose in SBRT is typically expressed in Biological Effective Dose (BED), taking into account the true biological effect when delivering a very high dose in a few fractions. A BED of  $\geq 100$  Gy has shown to result in a significantly higher local control rates and overall survival compared to a BED  $< 100$  Gy [33]. Frequently used fractionation regimens in agreement with this principle are 3x18 Gy, 4x12 Gy, 5x11 Gy and 8x7.5 Gy.

Respiratory tumor motion should be accounted for in treatment planning and during delivery. In the early days fluoroscopy was used and diaphragm motion was registered as a surrogate for tumor motion [15]. With the development of a four-dimensional CT-scan [34], the tumor motion trajectory could be reconstructed and motion artifacts could be reduced [35]. This greatly improved the accuracy of tumor delineation, treatment planning and delivery [36]. For tumor delineation, the maximum intensity projection (MiP) can be used, which is a single image created by the 4DCT data set, reflecting the highest density value encountered in each pixel throughout the respiratory cycle [37]. As an alternative, the time weighted average tumor position can be generated (Mid-ventilation and Mid-position approach) and used for contouring [38, 39].

Furthermore, pre-treatment positioning verification was developed. Previously patients were positioned in a custom fitted pillow placed in a frame with a stereotactic coordinate system for treatment preparation and treatment delivery [15]. Before every treatment fraction a CT-scan was made to correct for tumor misalignments, where after the patient was moved to the treatment couch. Later kilo-Volt Cone-beam Computed Tomography (kV-CBCT) became available, which could visualize soft tissue/tumors during treatment [40, 41]. Online treatment verification enabled geometrically accurate dose delivery during free breathing, making a

frame-based patient set-up no longer necessary [32]. But also other strategies to account for tumor motion during treatment were developed such as tracking, gating and breath hold techniques [42-44].

Finally, treatment planning in SBRT was optimized to increase accuracy. Standard fractionated treatment plans generally consisted of 5-7 beam directions. In SBRT treatment plans were refined by using multiple ( $\geq 10$ ) collimated (non-coplanar) beams and by allowing dose inhomogeneity in the Planning Target Volume (PTV), creating a steep dose fall-off at the edge of the PTV [14, 15]. Dose conformity was further improved with the introduction of Intensity Modulated Radiotherapy (IMRT), hence further decreasing dose to organs at risk [45]. In recent years volumetric modulated arc therapy (VMAT) emerged, significantly decreasing delivery time compared to IMRT without compromising the treatment plan quality [46].

In conclusion, SBRT in NSCLC relates to a very high and accurate dose delivery achieved by taking into account baseline shifts and respiratory tumor motion in pre-treatment imaging, treatment planning and dose delivery. As this results in more sparing of normal tissue, increased tumor dose can be delivered without necessarily increasing toxicity.

### **SBRT in early stage NSCLC**

Several prospective phase II trials of early stage lung SBRT showed two-year local control rates of more than 90% and two-year overall survival rates of 50-60% [17-21]. In the Netherlands the introduction of SBRT decreased the number of untreated elderly patients, resulting in an increase in overall survival in the province of North Holland [47].

Toxicity after SBRT is generally mild and the majority of patients do not experience any toxicity at all during the course of treatment [33, 48, 49]. Grade 3 toxicity is reported in 10-28%, grade 4 is rare with 2-4% and no grade 5 toxicity has been reported [17, 20, 50]. Even in patients aged 75 years or higher with significant co-morbidities grade 3-5 toxicity was observed in <10% [51]. The most commonly seen acute toxicities are dyspnea, cough, skin reactions, chest wall pain and fatigue [52]. Late toxicity is mostly composed of pulmonary toxicity, such as radiation pneumonitis, chest wall pain and rib fractures, the latter two being associated with tumors closely located to the chest wall [33, 49]. Bleeding and bronchial stenosis are rarely seen and are associated with centrally located tumors, i.e., tumors within 2 cm of the mediastinal critical structures [53-55]. However, this was contradicted by others reporting no severe toxicity when treating centrally located tumors when using a modest fractionation regimen of 8x7.5 Gy [56]. Stereotactic body radiotherapy can be safely delivered to patients with poor pulmonary function and multiple studies have shown that pulmonary function tests are relatively unaffected [57-61].

In conclusion, SBRT results in excellent local control with low toxicity and has become the standard treatment for inoperable early stage NSCLC.

### **Margins and respiratory motion in lung SBRT**

A variety of geometrical uncertainties such as setup error [40], baseline variation [62] and respiratory motion [63], limit the precision of radiation therapy for lung cancer. To compensate for these uncertainties, the target volume, also Gross Tumor Volume (GTV), is expanded with a margin [64]. In contrast with conventionally fractionated radiotherapy, in SBRT the GTV is directly expanded to the Planning Target Volume (PTV), therefore not applying a margin for microscopic disease extension, i.e., the Clinical Target Volume (CTV). It is thought that the very high dose delivered in SBRT, results in sufficient dose in the first millimeters surrounding the PTV, eradicating possible microscopic disease extension. This hypothesis is supported by the high local control rates achieved in several prospective lung SBRT trials as previously described [17-21]. At the Netherlands Cancer institute, we apply margins expansions from GTV to PTV based on the margin recipe of van Herk *et al.* [65]. This margin recipe consists of two components: systematic errors and random errors. Systematic errors consist of treatment preparation variations propagated throughout the treatment such as baseline tumors shifts and delineation variation. Random errors occur due to daily variations, such as set-up and breathing motion. Following this margin recipe, a larger margin is required for systematic errors than for random errors [65]. Moreover, errors are summed up quadratically and not linearly, because it is unlikely that all errors occur in the same direction at the same occasion.

There are different ways to account for respiratory motion during treatment delivery. A common method is to generate an Internal Target Volume (ITV) from the 4D CT-scan. The ITV concept covers the entire tumor motion and therefore effectively treats all respiratory motion as a systematic error. Hence, patients with considerable tumor motion consequently have larger margins, resulting in an increased exposure of normal tissue to high doses. At the Netherlands Cancer Institute, we use the Mid-ventilation CT for treatment planning, which is the frame of the 4D CT with the tumor closest to its time-weighted mean position [38]. Due to better image quality the Mid-position CT scan was introduced, which generates a motion compensated CT scan from the 4D CT data set and comprises all internal structures in their time-weighted mean position over the respiratory motion [39].

As previously mentioned, advanced image guided systems like in-room CT [66], cone beam CT [41] and Tomotherapy [67] have the ability to visualize the tumor and organ at risk in 3D or 4D just prior to treatment. These systems enable online corrections, aligning the time weighted mean target position with the planned position through a couch shift, thereby increasing the accuracy and precision of radiotherapy delivery. This correction strategy is highly suitable for lung SBRT, given the small number of fractions and the very high dose per fraction. By using these advanced online image guidance systems, systemic and random errors can be reduced

which can lead to a margin reduction and possibly toxicity decrease. Already a small margin reduction yields a substantial reduction of the volume, which was so clearly demonstrated by Verellen *et al.* [68]. The authors compared the treatment volume with an orange, showing that after removal of the zest, the volume of the core equals the zest.

Generally toxicity in lung SBRT for early stage peripherally located NSCLC is low [33, 48, 49]. Therefore a clinically relevant decrease in toxicity due to reduction of the PTV margins for this group of patients is questionable. However, there are indications where a margin reduction is certainly relevant. For example, the previously mentioned centrally located tumors [54, 55] and patients who receive a second course of irradiation (re-irradiation). Or in case of SBRT for larger tumors (> 5 cm), who have a higher local failure rate and rarely receive SBRT due to toxicity concerns [69, 70].

In conclusion, in these high-risk treatments margin decrease may lead to significant toxicity reduction. Therefore, there is need for higher treatment accuracy in lung SBRT.

In summary, due to the excellent local control and low toxicity SBRT has become the treatment of choice for inoperable early stage NSCLC or patients that refuse surgery. As a result, SBRT was rapidly introduced in several parts of the world. The success of SBRT for small peripherally located tumors caused a shift towards higher-risk treatments. As increased toxicity is seen in these patients, there is need for higher treatment accuracy. Moreover, new treatment indications arise such as SBRT for operable patients with early stage NSCLC [71]. But also in the setting of salvage re-irradiation and in more advanced staged disease, such as pulmonary metastases [72]. Especially in patients that are eligible for other local salvage therapies such as surgery and radio-frequent ablation, follow-up to detect local recurrences at an early stage becomes crucial [73-75]. However, local recurrences after SBRT are difficult to distinguish from infiltrative or fibrotic changes in the lung parenchyma, occurring in the majority of patients up to years after the irradiation [76, 77]. Therefore, a reliable method for detection of local recurrences is urgently needed to prevent unnecessary harm to the patient with futile biopsies or resections.

### **Purpose and outline of this thesis**

The goal of this thesis is to further optimize SBRT treatment and to expand the current SBRT indications by detailed toxicity analysis facilitating that more patients will benefit from the excellent local control.

In the first part of this thesis 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, not only in early stage NSCLC but also 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. In **chapter 2** we investigate the tumor delineation variability between different observers and how this variability affects the margins.

As described earlier there are different strategies to take into account tumor motion for tumor delineation and treatment planning. **Chapter 3** describes the clinical result of the Mid-ventilation approach, where margins increase non-linearly as opposed to the ITV approach, resulting in smaller margins in case of large tumor motion.

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 based on serial CT-scans and propose a simplified model.

## **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.

Given the excellent results of SBRT in early stage NSCLC, the phase I Hybrid trial was initiated to investigate the safety of SBRT combined with concurrent chemoradiation in locally advanced NSCLC. In **chapter 6** we present the results of a treatment planning study prior to start of the Hybrid trial, investigating the technical feasibility of a Hybrid treatment.

**Chapter 7** provides a review of SBRT versus surgery or other local therapies. Furthermore, a general discussion and future developments of optimization of SBRT are provided. Finally new treatment strategies using SBRT will be explored.

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