Chapter 1

Introduction
**EPIDEMIOLOGY OF LUNG CANCER**

Lung cancer is the most common cancer worldwide and the leading cause of cancer related death. In the Netherlands, more than 12,000 patients were diagnosed with lung cancer in 2016, accounting for 11% of all malignancies. The global incidence of cancer is expected to increase, which is mainly a consequence of population aging. In the Dutch lung cancer population, 46% of patients are 70 years or older at the time of diagnosis. Between 2010 and 2030, an increase of 67% in the cancer incidence is expected for patients aged 65 years or older in the United States. The most important risk factor for lung cancer is smoking, and 90% of patients were current or former smokers.

The histology of lung cancer is classified by the guidelines of the World Health Organization (WHO). About 15% of patients are diagnosed with small cell lung cancer (SCLC), and 80% have non-small cell lung cancer (NSCLC), which is further divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The adenocarcinoma is the commonest histologic type.

The overall prognosis of patients with lung cancer is poor, with a median survival of less than a year. European lung cancer analyses predicted a death rate of 275,700 in both sexes for 2017, which corresponds to about 20% of total cancer deaths. NSCLC is subdivided into disease stages with each of them having a specified prognosis. Using size and extension of the tumor (T), involvement of regional lymph nodes (N), and the presence of distant metastases (M), a TNM classification has been defined by the International Association for the Study of Lung Cancer (IASLC). Based on this TNM classification, a disease stage could be established. The TNM classification has recently been updated (Table 1 and 2). According to this new eighth edition of the TNM classification, stage I disease has a five year overall survival ranging from 68% to 92%, being the stage with the best prognosis. However, stage I disease, which frequently is unassociated with symptoms, is present in only 15% of NSCLC patients at the time of diagnosis. More than half of Dutch patients with NSCLC are diagnosed with stage IV disease, which has a five year survival of about 0 to 10%.

**TREATMENT OF LUNG CANCER**

The treatment of lung cancer depends on the disease stage at the time of diagnosis, as well as the general condition of the patient. All cases should be evaluated within an experienced multidisciplinary tumor board. The guideline specified treatment of early stage (stage I A-II B) and potentially resectable NSCLC is an anatomical surgical resection, defined as a lobectomy with systemic mediastinal lymph node assessment. Locally advanced (stage IIIA)
Table 1 - Proposed changes in the eighth edition of the TNM classification for lung cancer

<table>
<thead>
<tr>
<th>T: Primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tx</strong> Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy</td>
</tr>
<tr>
<td><strong>T0</strong> No evidence of primary tumor</td>
</tr>
<tr>
<td><strong>Tis</strong> Carcinoma in situ</td>
</tr>
<tr>
<td><strong>T1</strong> Tumor 3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*</td>
</tr>
<tr>
<td><strong>T1a(m)l</strong> Minimally invasive adenocarcinoma*</td>
</tr>
<tr>
<td><strong>T1a</strong> Tumor ≤1 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>T1b</strong> Tumor &gt;1 cm but ≤2 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>T1c</strong> Tumor &gt;2 cm but ≤3 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>T2</strong> Tumor &gt;3 cm but ≤5 cm or tumor with any of the following features: involves main bronchus regardless of distance from the carina but without involvement of the carina, invades visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung.</td>
</tr>
<tr>
<td><strong>T2a</strong> Tumor &gt;3 cm but ≤4 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>T2b</strong> Tumor &gt;4 cm but ≤5 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>T3</strong> Tumor &gt;5 cm but ≤7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, and parietal pericardium.</td>
</tr>
<tr>
<td><strong>T4</strong> Tumor &gt;7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N: Regional lymph node involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nx</strong> Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td><strong>N0</strong> No regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>N1</strong> Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
</tr>
<tr>
<td><strong>N2</strong> Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td><strong>N3</strong> Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M: Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M0</strong> No distant metastasis</td>
</tr>
<tr>
<td><strong>M1</strong> Distant metastasis present</td>
</tr>
<tr>
<td><strong>M1a</strong> Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusionsd</td>
</tr>
<tr>
<td><strong>M1b</strong> Single extrathoracic metastasis e</td>
</tr>
<tr>
<td><strong>M1c</strong> Multiple extrathoracic metastases in one or more organs</td>
</tr>
</tbody>
</table>

Abbreviations: TNM = tumor, node, and metastasis. Changes to the seventh edition are in bold. *The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a. 2Solitary adenocarcinoma, ≤3 cm with a predominately lepidic pattern and ≤ 5 mm invasion in any one focus. 4T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension. 4Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor. 5This includes involvement of a single distant (nonregional) lymph node.
**Introduction**

NSCLC has been subdivided into a potentially resectable and unresectable disease. Multi-modality treatment strategies with induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or surgery followed by adjuvant chemotherapy should be considered in patients with potentially resectable stage IIIA disease. Concurrent definitive chemoradiotherapy is the treatment of choice for patients with unresectable stage IIIA disease and patients with stage IIIB disease. Sequential approaches of induction chemotherapy followed by definitive radiotherapy is the alternative treatment option if concurrent therapies are not possible for any reason. Treatment of metastatic (stage IV) NSCLC depends on factors like histology, molecular pathology, age, performance status, and comorbidities. Systemic therapies should be offered to all patients with metastatic disease and a WHO performance status of ≤2.

**COMORBIDITIES IN LUNG CANCER PATIENTS**

As lung cancer patients generally have a smoking history or are elderly patients, the prevalence of smoking-induced or age-related comorbidities is high. In a population-based cohort study among 5,683 lung cancer patients, comorbid diseases were present in more than 70%, and chronic pulmonary diseases (53%), diabetes mellitus (16%), and congestive heart failure (12%) were the most common comorbidities. The presence of comorbidities can significantly impact the treatment options and outcomes for patients with lung cancer.
tive heart failure (13%) were the most frequent comorbidities. The percentage of elderly patients with stage I disease having three or more comorbidities increased from 15% to 30% between 1998 and 2007.

One of the most frequently used methods to objectify comorbidities is the Charlson comorbidity index (CCI) scoring system (1987), which is a weighted index that reflects both the number and seriousness of comorbid diseases. The scale has been validated to predict mortality risk over a period of a few weeks to 10 years for a variety of diseases. In the validation of the CCI, age was also found to be an independent risk factor for death from a comorbid condition. The 1 year mortality rates for the CCI scores 0, 1-2, 3-4, and ≥5 were defined as 12%, 26%, 52%, and 85%, respectively. A frequently used adaptation of the CCI score is the Charlson-Deyo method, which utilizes International Classification of Disease (ICD) codes to calculate the comorbidity index.

Aging and comorbid conditions may involve the prognosis of lung cancer patients in different ways, by having an independent negative effect on survival, preventing complete diagnostic evaluation leading to less accurate staging, or being a reason for less aggressive lung cancer treatment. Up to 20% of patients with early stage NSCLC were considered to be medically inoperable due to comorbidities or general frailty. A SEER (Surveillance, Epidemiology and End Results) Medicare analysis in elderly patients with stage I NSCLC showed that the proportion of patients not receiving any local treatment increased from 15% to 18% between 1998 and 2007, despite the introduction of the less invasive video-assisted thoracoscopic surgery (VATS). In the Netherlands, less than 20% of patients aged 80 years or older received surgery, and radiotherapy was by far the most frequently used treatment modality (± 60%) between 2010 and 2013. The five year survival rate of untreated patients with stage I disease is very poor with 6%. For stage III disease, the SEER Medicare database showed that 62% of all patients aged 65 years or older received radiotherapy alone instead of the guideline recommended combined treatment with chemoradiotherapy. In the Dutch stage III population aged 80 years or older, between 2010 and 2013, chemoradiotherapy was given in approximately 10% of patients, and about 30% received radiotherapy alone. A poor median survival of 6.9 months is observed for untreated stage III disease in a large population study among elderly patients.

STEREOTACTIC ABLATIVE RADIOTHERAPY FOR EARLY STAGE NSCLC

Traditionally, in patients who are medically inoperable or decline surgery, conventional radiotherapy has been given in 30 to 35 daily fractions to a total dose around 60-70 Gy. Since 2013, stereotactic ablative radiotherapy (SABR or SBRT), a high precision delivery of total doses around 60 Gy, generally given in 3 to 8 fractions with image guidance, is
the guideline-specified treatment of choice for patients with peripherally located stage I disease who are medically inoperable or unwilling for surgery.\textsuperscript{17} The fundamental principle of SABR is hypofractionation. The larger the total delivered dose and the fewer the used fractions (hypofractionation), the higher the biologically effective dose (BED).

Local, regional, and distant recurrence rates in large SABR databases were 4-9%, 6-12%, and 12-21%, respectively.\textsuperscript{18,19} Compared to conventional radiotherapy, SABR resulted in superior overall survival and local control rates in a recent multicenter trial including 101 patients with inoperable stage I NSCLC who were treated between 2009 and 2015.\textsuperscript{20} The latter was in line with a recent meta-analysis in early stage lung cancer patients.\textsuperscript{21} In addition, both treatment toxicity and health related quality of life were significantly better in the SABR arm of a randomized study in 102 patients with medically inoperable stage I NSCLC treated between 2007 and 2011.\textsuperscript{22}

Since the implementation of SABR as an alternative for surgery, the proportion of elderly patients with stage I NSCLC not receiving any curative treatment decreased significantly in the Netherlands.\textsuperscript{23} Compared to untreated patients, a significant improvement of the overall survival was observed in elderly Dutch and American patients receiving SABR for an early stage NSCLC.\textsuperscript{23,24} In the absence of prospective comparative data, other forms of comparative effectiveness research have been performed in the Dutch population, and results of two prospective SABR trials, both terminated due to poor accrual, are combined, all of these showing a clinical equipoise between a surgical resection and SABR for early stage NSCLC.\textsuperscript{25–29} Based on these findings, SABR is now increasingly being evaluated as a treatment option even in operable patients with early stage NSCLC, and more than half of the Dutch clinicians consider outcomes of surgery comparable to SABR.\textsuperscript{25,30} Current research increasingly focuses on the development of tools for shared decision making in this patient population.\textsuperscript{31,32}

**STEREOTACTIC ABLATIVE RADIOThERAPY FOR HIGH RISK LUNG TUMORS**

Further improvements and advances in treatment techniques in recent years allowed for the use of SABR in a variety of clinical scenarios. Although SABR has achieved a well-defined role within the treatment of peripherally located early stage NSCLC, its role in the treatment of patients with “higher risk lung tumors” is not well established. Historically, clinical trials tend to exclude patients with tumors near to the central critical organs in the chest, patients with tumors larger than 5 cm in diameter, and patients having multiple lung tumors, all of which has led to a lack of data about toxicity in these patient populations. Due to this lack, SABR using three fractions was contra-indicated for these patients, and more conventional or accelerated schedules were recommended by international guidelines.\textsuperscript{33}
Among these high risk groups, most of the attention has been paid to patients with centrally located tumors. Concerns about these tumors arose in the early years of SABR, when a prospective phase II trial in medically inoperable early stage NSCLC observed an 11-fold higher risk to develop severe (grade 3 to 5) adverse events in patients with tumors located in the proximal bronchial tree (PBT) zone compared to peripherally located tumors (NCT00087438). The PBT zone has been defined as a volume within two centimeters in all directions around the proximal bronchial tree (i.e. the carina, right and left main bronchi, right and left upper lobe bronchi, intermediate bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi) (Figure 1). Based on these findings, the PBT region was called the “no fly zone”, and SABR delivered in just three fractions was considered contraindicated for patients with a central lung tumor. Subsequently, the RTOG 0813 phase I/II dose-escalation study aimed to establish the toxicity rate and maximum tolerated dose for a 5 fraction SABR regimen in centrally located stage I NSCLC, and expanded the definition of central lung tumors by also including tumors adjacent to the mediastinal or pericardial pleura (NCT00750269). While the full results from this trial are awaited, more and more centers explored the safety of SABR in patients with central tumors, leading to a diversity of definitions used for central lung tumors and many variations in treatment fractionation. Findings of 20 studies in patients with a central lung tumor were summarized in a recent systematic review. A total of 563 patients, consisting of mainly patients with early stage NSCLC, were analyzed, which showed that local control rates were more than 85% after SABR delivery of a biologically effective dose (BED$_{10}$) of $\geq 100$ Gy to the tumor. Grade 3 or grade 4 toxicity was observed in less than 9% of patients, and treatment-related mortality (grade 5 toxicity) occurred in 3% of patients.

As compared to surgery, larger tumors were associated with an increased use of radiation therapy in elderly patients in the SEER medicare database. SABR might be a good treatment option in unfit patients who are less likely to tolerate or accept long conventional schedules for between 5 to 6 weeks. Unfortunately, less data is available about the long-term clinical outcomes of SABR in patients with tumors measuring more than 5 cm, as these patients are generally not included in SABR trials.

In recent years, as a result of improvements in thoracic imaging, an increasing number of patients with multiple primary lung cancers are being identified. In addition, as the lung is a common site of metastatic disease from many solid tumors, patients presenting with multiple metastatic lung lesions are common in clinical practice. Synchronous SABR delivery to two or more lesions might be convenient for patients. However, as a result of concerns about the risks of lung toxicity, SABR has generally been delivered to one lesion at a time, or patients with multiple tumors were excluded from treatment with SABR.
LUNG SABR AT THE VU UNIVERSITY MEDICAL CENTER

At the VU University Medical Center (VUmc), a lung SABR protocol with “risk adapted” fractionation schemes based on tumor size and tumor location was introduced in 2003 (Table 3). Peripherally located small tumors were treated with 3 fractions of SABR, and for higher risk groups, schedules with more fractions were used. In the case of broad chest wall contact and/or a tumor diameter between 3 to 7 centimeters, a schedule with 5 fractions was used. For centrally located tumors adjacent to and/or with minimal overlap with the brachial plexus, hilus, stomach, pericardium, or mediastinum, 8 fractions of SABR was applied. Early
results for this central tumors schedule with multiple fixed conformal beams, a pencil-beam
dose calculation, and a spine-based set up, were encouraging as significant toxicity was not
observed, and clinical outcomes were comparable with those for peripheral lesions.\textsuperscript{35} With
accumulating institutional experience, and after the introduction of volumetric modulated
arc therapy (VMAT, RapidArc, Varian Medical Systems, Palo Alto, CA) for treatment delivery,
Anisotropic Analytical Algorithm (AAA, Varian Medical Systems) for dose calculation, and
online tumor-setup with cone beam CT (CB-CT) scans, SABR was also increasingly used for
other high risk tumors including the simultaneously treatment of multiple tumors. In 2010,
an adapted hypofractionated schedule with 12 fractions of 5 Gy was introduced to be used
for tumors with a substantial overlap with mediastinal structures and/or tumors measuring
more than 7 centimeters.

### Table 3 - SABR and hypofractionated radiotherapy for lung tumors at the VU University Medical Center

<table>
<thead>
<tr>
<th>Tumor characteristics</th>
<th>Fractionation schedule</th>
<th>Year implemented</th>
<th>BED\textsubscript{10}</th>
<th>Overall treatment time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor &lt;3 cm</td>
<td>3 fractions of 18 Gy</td>
<td>2003</td>
<td>151 Gy</td>
<td>1.5 weeks</td>
</tr>
<tr>
<td>Tumor &lt;3 cm and broad contact with chest wall and/or Tumor &gt;3 cm, but &lt;7 cm</td>
<td>5 fractions of 11 Gy</td>
<td>2003</td>
<td>116 Gy</td>
<td>1.5-2 weeks</td>
</tr>
<tr>
<td>Central tumor adjacent to and/or with minimal overlap with plexus, hilus, stomach, pericardium, or mediastinum</td>
<td>8 fractions of 7.5 Gy</td>
<td>2003</td>
<td>105 Gy</td>
<td>2.5 weeks</td>
</tr>
<tr>
<td>Tumor &gt;7 cm and/or Central tumor with a substantial overlap with mediastinal structures and/or Presence of pathological ipsilateral mediastinal nodes</td>
<td>12 fractions of 5 Gy</td>
<td>2010</td>
<td>90 Gy</td>
<td>3 weeks</td>
</tr>
</tbody>
</table>

Abbreviations: BED\textsubscript{10} = biological effective dose in Gy with an \( \alpha/\beta \) ratio of 10; SABR = stereotactic ablative radiotherapy.
THESIS OUTLINE

The aim of this thesis was to report on the outcomes, and specifically to explore the risks of using SABR and hypofractionated high dose radiotherapy in patients with high risk lung tumors, defined as patients with centrally located tumors, patients with large volume tumors, and patients simultaneously presenting with multiple lung tumors.

We start in Chapter 2 with an overview of all available Dutch comparative effectiveness research studies comparing a surgical resection with SABR in the treatment of peripherally located early stage NSCLC.

The following five chapters of this thesis focus on centrally located tumors. In this thesis, we have classified central tumors into two groups: “moderately central” when the planning target volume was located within two centimeter in all directions of the proximal bronchial tree (the proximal bronchial tree was defined above) and “ultracentral” for tumors with a planning target volume overlapping the trachea or main stem bronchi (Figure 1).

In Chapter 3, we analyzed the quality of institutional treatment plans in patients treated for so-called moderately central tumors using 8 fractions of SABR, and assessed compliance with institutional dose guidelines. In addition, clinical treatment plans were benchmarked against dose criteria and guidelines defined in prospective SABR trials for central lung tumors. Long-term toxicity outcomes were described, and survival outcomes were compared with those in patients with a peripherally located tumor treated in the same period using SABR in 3 or 5 fractions. Chapter 4 reports on institutional outcomes of the use of high dose hypofractionated radiotherapy in 12 fractions for patients with an ultracentral tumor location. Chapter 5 clarifies in a letter to the editor our institutional approach for treatment planning, and especially the use of dose guidelines for SABR and hypofractionated high dose radiotherapy, in the treatment of centrally located lung tumors.

In the lack of long-term outcomes form prospective trials, large population studies are needed to perform comprehensive statistical analyses in order to identify toxicity predictors for centrally located tumors. We combined dosimetric and clinical data of patients with a moderately central or ultracentral tumor treated with SABR or hypofractionated radiotherapy at the VUmc and Erasmus Medical Center (EMC, Rotterdam, The Netherlands). Both a multivariable logistic regression analysis and a normal tissue complication probability (NTCP) modeling were performed in Chapter 6 to identify factors predicting clinical and radiographic pulmonary toxicity. Slightly different inclusion criteria were used in Chapter 7 to select patients with a moderately central or ultracentral tumor from both institutions in order to evaluate the incidence of esophagus toxicity after SABR and hypofractionated
radiotherapy, and to perform a multivariable analysis and NTCP model including both clinical and dosimetric toxicity predictors.

The last two chapters deal with two additional clinical scenarios considered to be high risk for the use of SABR. Chapter 8 reports on long-term clinical outcomes for SABR with 5 or 8 fractions in patients with primary or recurrent NSCLC measuring more than 5 centimeters. All analyzed patients were treated at the VUmc. Chapter 9 describes the outcomes of SABR delivery using volumetric modulated arc therapy (VMAT) in the synchronous treatment of two or more lung tumors. Patients from both the VUmc and the London Health Sciences Centre (LHSC, Ontario, Canada) were studied. A practical scheme for approaching treatment planning in such patients was developed, and a multivariable analysis was performed to identify predictors for toxicity.

Finally, the main findings of this thesis and future perspectives are discussed in Chapter 10.
REFERENCES

19. Senthi S, Lagerwaard FJ, Haasbeek CJA, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-


34. Senthi S, Haasbeek CJa, Slotman BJa, Senan S. Outcomes of stereotactic ablative radiotherapy for central lung cancers: