Chapter 10

General discussion and future perspectives
Weeks after Wilhelm C. Röntgen discovered X-rays in 1895, Emil H. Grubbe treated the first cancer patient with radiation in Chicago. In the 1930s, protracted courses of ionizing radiation had been started to be delivered to a tumor in multiple fractions. Since that time, radiotherapy has become a major component of cancer treatment. Today, more than half of the cancer patients will receive radiotherapy at some point during their treatment.

The first stereotactic radiotherapy was delivered to an intracranial target, also known as “stereotactic radiosurgery”, by the Swedish neurosurgeon Lars Leksell. In 1995, the Swedish Karolinska Hospital described the first 31 patients treated with extracranial stereotactic ablative radiotherapy (SABR), and several clinical applications had been explored thereafter. In the past decade, implementation of lung SABR has led to a decrease in the proportion of untreated elderly patients in the Netherlands, and evidence has been accumulated for the clinical equipoise between SABR and a surgical resection in patients with peripherally located stage I NSCLC. A majority of the Dutch clinicians consider outcomes of surgery and SABR comparable to each other for this indication, and SABR is being increasingly used as a treatment option for even operable patients with early stage NSCLC.

While SABR has proven its efficacy and safety in the treatment of peripherally located early stage NSCLC, its role in the treatment of patients with high risk lung tumors is less well established. The aging patient population, higher rates of comorbidities, developments in image guidance, and advanced treatment techniques gave rise to look beyond the “limits” of high dose radiotherapy and refine the indications. This thesis focuses on the risks and outcomes of SABR and high dose hypofractionated radiotherapy in patients with a high risk lung tumor, defined as a centrally located tumor, a large volume tumor measuring more than 5 cm, and multiple lung tumors synchronously presented (Figure 1).
Figure 1 - Examples of patients with high risk lung tumors and their dose distributions. The planning target volumes are shown in red. (A) A patient with a moderately central tumor who has been treated with 8 fractions of SABR. (B) An example of an ultracentral and endobronchial tumor treated with 12 fractions of 5 Gy. (C) A patient with a large tumor measuring approximately 7 cm (greatest dimension) treated with 8 fractions of 7.5 Gy. (D) An example of two synchronously presented lung tumors, which were simultaneously treated during one treatment session using separate treatment plans with 8 fractions of 7.5 Gy.

CENTRALLY LOCATED EARLY STAGE LUNG TUMORS

A number of different definitions of central lung tumors have been used in the literature, and this lack of consistency has made it difficult to accurately estimate the risks of toxicity. An early paper defined central location to include all tumors located within or touching the 2 cm zone of the proximal bronchial tree.\textsuperscript{8,9} Subsequently, the RTOG 0813 dose escalation
study enlarged this definition by including tumor locations adjacent to the mediastinal or pericardial pleura (NCT00750269). Investigators of the Nordic multicenter HILUS trial defined central tumors as either being within or touching the 1 cm zone of the proximal bronchial tree. This trial also specified subgroups of central tumors located close to the main stem bronchi and those closer to a lobar bronchus. Finally, the term “ultracentral” was introduced to define gross tumor volumes abutting the trachea or the proximal bronchial tree, as opposed to other central lesions. The varying definitions used have contributed to differences between centers in patient selection for SABR, as well as differences in reported toxicity.

In this thesis, we have classified centrally located tumors into two groups. Tumors are defined as being “moderately central”, when the planning target volume was located within 2 cm in all directions of the proximal bronchial tree, whereas “ultracentral” tumors had a planning target volume overlapping the trachea or main stem bronchi. However, we would argue that the key issue here is less about the nomenclature used, as it is about the true radiation tolerance doses of the proximal airways, heart, and esophagus.

**Toxicity of the trachea and proximal bronchi**

Radiation damage to the bronchi can manifest as stenosis, occlusion, atelectasis, haemoptysis, or pulmonary haemorrhage. Grade 3 or higher bronchial toxicities and fatal lung haemorrhage were observed in up to 25% and 27% of patients, respectively, depending on the treatment schedule and definition of central tumor location that has been used. Following the initial experience using three fractions of SABR for central tumors, alternative risk-adapted fractionation schedules have been studied in order to limit toxicity rates. Based on recent data, SABR in four or more fractions is now recommended for moderately central tumors in some guidelines, and 77% of European centres treat central tumors with SABR. However, limited data is available on outcomes for ultracentral tumors. In the HILUS trial, six out of the 7 fatal toxicities were observed after delivery of 8 fractions of SABR in tumors close to the main bronchi. In our pooled analysis of data from two centers, PTV overlap with trachea or main stem bronchi was identified as a significant clinical predictor for severe clinical and radiographic bronchial toxicity.

An important point to note is that fatal lung haemorrhage is not necessarily a consequence of anti-cancer treatment, as it is often caused by the tumor itself and a common cause of death in patients with NSCLC. Prospective, retrospective, and autopsy studies in patients with NSCLC have all identified specific tumor-related factors associated with higher risks of haemoptysis or fatal lung haemorrhage. Besides a central tumor location, a histologic diagnosis of squamous cell carcinoma, baseline tumor cavitation, and endobronchial tumor involvement have been identified as predictive factors for pulmonary haemorrhage after.
surgery, chemotherapy, brachytherapy, or conventional radiotherapy. In patients for whom the risks of SABR are deemed too high, such as ultracentral tumors, the American Society for Radiation Oncology (ASTRO) and European Society for Medical Oncology (ESMO) now recommend the use of alternative regimens with more fractions.29,31

A concern with the use of hypofractionated schedules is the potential for more local failures due to the lower biologically equivalent dose (BED) delivered to the tumor. Our institutional experience with the 12 fraction schedule for ultracentral tumors observed excellent local control rates. Other hypofractionated schedules using more than 8 fractions have also reported local control rates in central tumors exceeding 90%.38,39 A recent systematic review explored the relationship between local control rate and planning target volume (PTV) doses.40 Analysis of 15 studies with at least 30 months of follow-up, revealed no significant relation between freedom from local progression and doses delivered to the periphery of the PTV, suggesting that lower or more uniform doses within the PTV may be sufficient for local control. These new insights are of particular relevance for ultracentral tumor locations, where a more homogeneous dose distribution within the PTV appears necessary in order to spare the central airways. However, in the context of shared decision-making, potential risks of both toxicity and disease failure should be carefully discussed with patients.41

Besides appropriate patient selection and dose fractionation, future research should focus on obtaining more reliable normal organ tolerance doses. Long-term results from prospective dose-escalation trials are awaited, and comprehensive dose-response analyses in large study populations are lacking. In addition, delineation of target volumes and organs at risk, margins used for the clinical target volume (CTV) and PTV, dose prescription, dose calculation algorithms, treatment planning techniques, and treatment delivery vary considerably between studies. Consequently, the reported doses and correlations with clinical outcomes are not comparable between series. Until more data becomes available, international guidelines recommend the use of point dose and volume dose limits from the 5 fractions RTOG 0813 trial (Table 1). These were defined as a point dose maximum of 105% of the prescription dose and a volume maximum of <4 cc receiving 18 Gy for the non-adjacent wall of both the trachea and the ipsilateral proximal bronchial tree. Dose constraints used in this trial are, however, based on expert opinion, somewhat arbitrarily chosen, and not yet validated in larger populations.

Our initial assessment of clinical treatment plans of 80 patients treated for a moderately central tumor revealed that in the majority point dose limits derived from the RTOG 0813 were exceeded, whereas toxicity rates were acceptable, and survival comparable with that seen with peripheral tumors.13 Another study in central lung SABR did not find any significant difference in toxicity results between patients meeting the RTOG 0813 dose constraints versus those exceeding them.11 These findings underline the need to continue
to accrue larger patient datasets to derive normal organ tolerance doses, and to not accept in a uncritical fashion recommendations derived for clinical trials.

Table 1 - Normal organ tolerance doses for a 5 fractions regimen of SABR in the RTOG 0813 study

<table>
<thead>
<tr>
<th>Normal organs</th>
<th>Maximum point dose (Dmax)</th>
<th>Volume maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea and ipsilateral proximal bronchial tree, non-adjacent wall</td>
<td>105% of prescription dose</td>
<td>&lt;4 cc = 18.0 Gy</td>
</tr>
<tr>
<td>Heart or pericardium</td>
<td>105% of prescription dose</td>
<td>&lt;15 cc = 32.0 Gy</td>
</tr>
<tr>
<td>Great vessels, non-adjacent wall</td>
<td>105% of prescription dose</td>
<td>&lt;10 cc = 47.0 Gy</td>
</tr>
<tr>
<td>Esophagus, non-adjacent wall</td>
<td>105% of prescription dose</td>
<td>&lt;5 cc = 27.5 Gy</td>
</tr>
</tbody>
</table>

The volume maximum column shows limits for treatment planning purposes. Exceeding these limits is not a protocol violation. However, exceeding the maximum point dose limit is a violation. Abbreviations: SABR = stereotactic ablative radiotherapy.

A general limitation of dose-escalation studies and retrospective dosimetric analyses is the potential discrepancy between planned and delivered doses due to uncertainties about the day-to-day location of the normal organs. More accurate estimates of the delivered dose may be possible by imaging studies during beam-on, which will lead to more reliable dose constraints. A promising development is the introduction of magnetic resonance imaging (MRI) guided radiotherapy which has a lot of potential in lung radiotherapy as it provides means to manage tumor motion and daily deformation, but clinical implementation has had to surmount some technical challenges. Similarly, markerless lung tumor tracking using fluoro-CBCT scan reconstructions of kV images acquired during breath-hold lung SABR may allow for smaller PTV margins, although it remains to be seen if kV images are useful for verifying positions of central normal organs. Proton therapy, by allowing for very steep dose gradient at the distal end of the tumor, may result in reduced normal organ doses. Volumetric image guidance is not available in the most current proton centers, and a prospective trial (NCT01511081) comparing SABR using photons versus protons in patients with centrally located tumors has been terminated recently due to poor accrual. The advantages of proton therapy in central lung SABR remains therefore questionable.

Toxicity of the heart

Cardiac side effects include radiation-induced damage to the pericardium, impulse conducting system, myocardium, endocardium, coronary arteries, and the heart valves. High grade cardiac toxicities are infrequently reported after the use of 4 or more fractions of SABR. For tumors adjacent to the heart or large vessels, the ASTRO guidelines recommend the use of 45–50 Gy SABR delivered in 4 to 5 fractions, with adherence to point dose and volume dose limits from prospective trials and the literature. The RTOG 0813 maximum point doses for the heart and great vessels were both defined as 105% of the prescription dose, and recommendations are being made to limit the volume of the heart receiving 32 Gy to <15 cc and the volume of the great vessels receiving 47 Gy to <10 cc (Table 1). Due to
the intra-fractional motion of the heart and the surrounding vessels, true tolerance doses remain unknown.

Retrospective multi-institutional analyses have been used in an attempt to identify dosimetric predictors of “cardiac toxicity”. However, a key limitation of these studies is the considerable variation in underlying risks for heart disease in patients who present with lung cancer. Chronic obstructive pulmonary disease (COPD) is estimated to affect between 40 and 70% of patients with lung cancer.\textsuperscript{50,51} A systematic review and meta-analysis revealed that patients with COPD had a two to five-fold higher risk of ischaemic heart disease, cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation, and diseases of the arteries, when compared with the non-COPD population.\textsuperscript{52} Furthermore, sub-groups of patients with COPD have a five to eight-fold higher risk of mortality from cardiovascular disease, including a 34% higher risk for sudden cardiac death.\textsuperscript{53,54} The failure to account for differences in baseline cardiac risk factors in the SABR populations, can confound study conclusions. For example, a recent analysis of early stage NSCLC patients suggested that the maximum dose delivered to the left atrium and the dose to 90% of the superior vena cava had the highest correlation with non-cancer death.\textsuperscript{55} Another retrospective study in early stage NSCLC found no correlations between cardiac doses and overall survival rates after SABR.\textsuperscript{56} In a patient population where cardiac, pulmonary, and other comorbidities are commonly present and preclude surgical treatment, correlating survival rates or non-cancer death with cardiac doses is questionable.\textsuperscript{57}

Toxicity of the esophagus

Esophageal toxicities include painful inflammation (esophagitis), stricture, or perforation of the esophagus. Although acute esophageal toxicity occurs frequently after conventional (chemo)radiotherapy, severe esophageal toxicities are uncommon in patients treated with SABR.\textsuperscript{23,24,49,58,59} The largest SABR study to date had a median follow-up time of 55 months, and reported an incidence of 0% for grade ≥2 esophagitis after 4 or 10 fractions of SABR in 772 patients, in whom 17% had a central lung tumor.\textsuperscript{57} Given the serial character of the esophagus, both point dose and volume parameters should be constrained in order to limit toxicities.\textsuperscript{60,61} Guidelines recommend the use of RTOG 0813 limits, which were defined as a volume dose maximum of 27.5 Gy to 4 cc of the esophagus, and a point dose limit of 105% of the PTV dose (Table 1).\textsuperscript{29} As high grade esophageal toxicities are uncommon, it may not be appropriate to compromise PTV coverage in order to minimise risk of self-limiting low grade toxicities in patients eligible for a curative treatment. Caution is nonetheless recommended in patients where high risk factors are present, such as prior radiotherapy and concurrent or sequential systemic therapies.
LUNG TUMORS MEASURING MORE THAN 5 CM

Increasing tumor size has an adverse impact on treatment outcomes in patients with NSCLC, as larger tumors are associated with poorer survival and more distant recurrences.\textsuperscript{62,63} Analysis of the IASLC database showed that for tumors measuring from 1 to 5 cm, each centimeter increase resulted in worse survival, and that tumors measuring more than 5 cm had a prognosis comparable with stage T3 or T4 (TNM 7\textsuperscript{th}).\textsuperscript{64} These findings have led to changes in the T descriptors of the 8\textsuperscript{th} edition of the Tumor, Node, and Metastasis (TNM) classification of NSCLC (Table 2).\textsuperscript{64}

Eighteen percent of patients with early stage NSCLC, and 27\% of elderly patients with locally advanced NSCLC did not receive any curative treatment.\textsuperscript{65,66} For untreated stage III NSCLC, a mean survival of about 7 months has been reported in a meta-analysis among 5,449 patients.\textsuperscript{67} Although SABR is an established treatment for unfit and poor-risk patients with small volume early stage NSCLC, its efficacy and safety for tumors exceeding 5 cm was unclear as these patients were generally excluded from earlier trials. Data from the few recent retrospective studies in patients with tumors exceeding 5 cm have reported median survivals of 17 to 28 months, high local control rates (85-95\%), and acceptable toxicity rates ranging from 5 to 30\%.\textsuperscript{68–72} Updated guidelines consider SABR now as an appropriate treatment for tumors exceeding 5 cm if normal organ constraints are adhered to.\textsuperscript{29,30} SABR outcomes in this patient group will be examined by a prospective trial, now accruing high risk patients, including those with tumors exceeding 5 cm (NCT01543672).

Distant recurrences represent the predominant pattern of failure in patients with tumors measuring more than 5 cm, a finding observed in between 19\% to 33\% of such patients treated with SABR.\textsuperscript{68–72} SABR alone may therefore be insufficient for these patients. However, the feasibility of combined treatment modalities is doubtful in patients with a poor general condition that contraindicates use of surgical resection or chemotherapy. These patients should be carefully counseled about the risks of regional or distant failure.\textsuperscript{29}

Table 2 - Proposed changes in the 8\textsuperscript{th} edition of the TNM classification

<table>
<thead>
<tr>
<th>Tumor diameter</th>
<th>Previous TNM (7\textsuperscript{th})</th>
<th>New TNM (8\textsuperscript{th})</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 cm</td>
<td>T1a</td>
<td>→ T1a</td>
</tr>
<tr>
<td>1 - 2 cm</td>
<td>T1a</td>
<td>→ T1b</td>
</tr>
<tr>
<td>2 - 3 cm</td>
<td>T1b</td>
<td>→ T1c</td>
</tr>
<tr>
<td>3 - 4 cm</td>
<td>T2a</td>
<td>→ T2a</td>
</tr>
<tr>
<td>4 - 5 cm</td>
<td>T2a</td>
<td>→ T2b</td>
</tr>
<tr>
<td>5 - 7 cm</td>
<td>T2b</td>
<td>→ T3</td>
</tr>
<tr>
<td>&gt;7 cm</td>
<td>T3</td>
<td>→ T4</td>
</tr>
</tbody>
</table>

Abbreviations: TNM = tumor, node, and metastasis.
Adjuvant systemic therapies may be considered in patients with a good performance status. A very promising development in the treatment of NSCLC is the role of immunotherapy. Evidence is rapidly accumulating that radiation therapy also has effects outside the treated volume, and quantitatively augments the immune system by different pathways, including increased antigen presentation and T-cell activation. These systemic effects have been described as the non-targeted, “abscopal” effects of radiotherapy. At this moment, knowledge about the optimal fractionation schedule and doses are lacking. In patients with advanced NSCLC, improved overall survival has been observed with T-cell checkpoint inhibitors, such as anti-PD-1 and anti-PD-L1 antibodies, which maintain T-cell activation by blocking inhibitory signaling pathways. A trial exploring the neo-adjuvant use of Nivolumab (an anti-PD-1 inhibitor) in early-stage resectable NSCLC, reported a major pathological response in 43% of patients, with ‘major’ defined as <10% viable tumour cells in a subsequent resection specimen (NCT02259621). All these findings have led to a growing interest to further translate these benefits into the treatment of patients with early stage NSCLC, and to combine immunotherapy with radiotherapy to improve the systemic control. (Neo)adjuvant anti PD(L)-1 checkpoint inhibitors are currently being evaluated in early stage NSCLC as an addition to current standard of care, and as a consolidation therapy after chemoradiation. Future studies will explore if a combination therapy of SABR with immune checkpoint inhibitors is safe and efficacious in patients with larger tumors.

An additional consideration in patients with tumors exceeding 5 cm is whether more invasive mediastinal lymph node staging has a role when PET-CT scans reveal no metastases. Data from two large reports totaling more than 1,500 patients treated with SABR have reported 5-year regional recurrence rates of between 12-13%. In patients with tumors measuring more than 5 cm, these rates were ranged from 6 to 13%, and occult mediastinal lymph nodes were found in approximately 12% of patients staged cT2N0 at PET-CT. First results from the prospective, multicenter STAGE study reported a rate of 11% of upstaging for patients with cN0 NSCLC disease after complete endoscopic staging by EBUS or EUS. Additional prospective clinical trials are ongoing to evaluate the routine use of endoscopic staging in patients intended to be treated with SABR (NCT01786590, NCT02719847).

## TWO OR MORE SYNCHRONOUSLY PRESENTED LUNG TUMORS

Two or more synchronous lung lesions were present in 15% of all surgical patients. The IASLC Staging and Prognostic Factors committee identified four patterns of presentation in patients with multiple pulmonary sites of disease: (1) second primary lung cancers; (2) separate tumor nodules with the same histological type (intrapulmonary metastasis); (3) multifocal lung adenocarcinoma with prominent ground glass or lepidic (GG/L) features;
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(4) pneumonic-type lung adenocarcinoma. Distinguishing between these sub-types is difficult, and recent guidelines recommend to evaluate these patients in a multidisciplinary team including a thoracic surgeon, radiation oncologist, medical oncologist, pulmonologist, thoracic radiologist, and pathologist.

While the 7th edition of the TNM introduced a new classification for multiple synchronous nodules, and defined nodules in the same lobe as T3, synchronous ipsilateral lesions in different lobes as T4, and synchronous bilateral lesions as M1a disease, no changes are proposed in the 8th edition of the TNM regarding this subgroup of patients.

Fit patients with multiple primary lung tumors should be considered for guideline-specified curative treatments, and invasive mediastinal staging, whole-body PET scan, and brain MRI are recommended to rule out metastatic disease. Recent guidelines also consider SABR as a curative treatment option for patients with synchronous primary or multifocal tumors.

Outcomes of SABR in this patient group show similar survival and disease control as in surgical series, and toxicity rates are comparable to what is reported for single lesion SABR. However, the majority of these studies included patients with two or three tumors, and bilateral lesions were uncommon. More data in patients with more than three lesions are awaited to show the efficacy and safety of SABR in such patients with synchronous lung tumors.

PATIENTS WITH CO-EXISTING INTERSTITIAL LUNG DISEASE

In addition to patients with a high risk lung tumor, patients with co-existing lung cancer and interstitial lung disease (ILD) are now recognized to constitute another high risk population for radiation-related toxicity. ILD results in a restrictive defect on pulmonary function testing, causes irreversible lung fibrosis, and is subdivided in entities based on histological criteria, with each of them having a characteristic CT pattern. Idiopathic pulmonary fibrosis (IPF) is the most common entity, and is characterized by the morphologic pattern of usual interstitial pneumonia (UIP). Guidelines recommend a multidisciplinary evaluation by a panel involving a pulmonologist, radiologist, and pathologist for an accurate diagnosis and an appropriate determination of the prognosis. Patients with IPF have an increased risk to develop lung cancer, with a prevalence ranging from 4.4 to 13%, and cumulative incidence rates of 3.3%, 15.4%, and 54.7% after 1, 5, and 10 years of follow-up, respectively. Retrospective review of pre-treatment imaging of our patients with a moderately central, ultracentral, or >5 cm measuring tumor, revealed that ILD was present in 5%, 9%, and 13% of patients, respectively (Table 3).
Table 3 - VUmc experience with SABR in patients with co-existing interstitial lung disease

<table>
<thead>
<tr>
<th>Study group</th>
<th>Patients</th>
<th>Fractionation</th>
<th>Grade ≥3 toxicity</th>
<th>Grade 5 toxicity</th>
<th>Patients with ILD (%)</th>
<th>Toxicity in ILD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderately central</td>
<td>n = 80</td>
<td>8 x 7.5 Gy</td>
<td>11%</td>
<td>7.5%</td>
<td>n = 4 (5%)</td>
<td>≥G2 RP: 75%</td>
</tr>
<tr>
<td>tumors</td>
<td>2008-2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultracentral tumors</td>
<td>n = 47</td>
<td>12 x 5 Gy</td>
<td>38%</td>
<td>21%</td>
<td>n = 4 (9%)</td>
<td>≥G3 toxicity: 75%</td>
</tr>
<tr>
<td></td>
<td>2010-2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumors measuring &gt;5 cm</td>
<td>n = 63</td>
<td>5 x 11 or 12 Gy</td>
<td>30%</td>
<td>19%</td>
<td>n = 8 (13%)</td>
<td>≥G3 toxicity: 63%</td>
</tr>
<tr>
<td></td>
<td>2003-2014</td>
<td>8 x 7.5 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Three ILD patients included in the third study, were also included in the first publication. However, for two of these patients, the diagnosis of ILD was only recognized during imaging reviews performed for the third study. Abbreviations: ILD = interstitial lung disease; n = number; RP = radiation pneumonitis.

Acute exacerbations, characterized by suddenly progressive and severe respiratory failure, have an incidence of 5 to 19% per year in patients with IPF, and anti-cancer treatments are the most common triggers of a fatal acute exacerbation. IPF patients are considered at high risk for surgical resections, and in patients who do undergo surgery, the weighted proportions of treatment-related mortality and ILD-specific toxicity were 2.2% and 12%, respectively. These rates were 15.5% and 25%, respectively, for medically inoperable patients treated with SABR. At our institution, SABR was increasingly recognized as a relative contra-indication for patients with ILD in recent years, and high priority planning objectives were generally used to minimize lung irradiation in such patients. For our subgroups with a moderately central, ultracentral, or >5 cm measuring lung tumor, grade 2 or higher toxicity was observed in 63% to 75% of patients with co-existing ILD, and a substantial part of the reported G5 toxicity was observed in patients with ILD (Table 3). Figure 2 shows two patients with IPF who were treated with SABR at our department, and who developed fatal radiation pneumonitis.

As radiation pneumonitis is the commonest severe toxicity in patients with ILD, several studies have explored clinical and dosimetric factors predictive for the development of radiation pneumonitis in patients treated with SABR. Radiological grade or the clinical severity of ILD, pretreatment lung function, and the presence of emphysema may refine the risks of severe radiation pneumonitis. While several dosimetric predictors have been identified for radiation pneumonitis in the general SABR population, a systematic review in IPF patients failed to identify any significant correlations between SABR dose or dosimetric parameters and treatment-related toxicity. A subgroup analysis revealed nonetheless that a $V_{20Gy}$ ≤6.5% and a mean lung dose ≤4.5 Gy were both associated with reduced treatment mortality.
It is important to note that ILD patients have a poor prognosis with median survival rates ranging from 2.5 to 3.5 years even without lung cancer. SABR may therefore be considered as an acceptable treatment option, provided that such patients are evaluated by experienced clinicians before the start of treatment, and that treatment plans are adapted to limit lung doses. More studies in patients with various severities of ILD are needed to define safe thresholds. Carefully counseling about the treatment-related risks is recommended, and referral to more experienced centers should be considered when treating these patients with high dose thoracic radiotherapy.

**SURVEILLANCE & SURVIVORSHIP**

Improved treatment techniques have led to longer life expectancies for patients with lung cancer. Data from the Surveillance, Epidemiology, and End Results (SEER) registries estimated a total number of 526,510 for lung cancer survivors in 2016. Better survivorship programs are needed for follow-up of these patients, and these should include the following aspects: surveillance for recurrences or second primary lung cancers; assessment of treatment-related complications and quality of life; healthy lifestyle promotion and counseling for smoking cessation; screening for second malignancies other than lung cancers; referrals to
cancer support groups, psychosocial counseling, or specialists for management of comorbid conditions; and communication with primary care physicians.\textsuperscript{31,103}

**Surveillance for recurrences or second primary lung cancers**

Local recurrences can be observed for up to five years after SABR, and survivors of a primary lung cancer have a risk of 8% to develop a second primary lung cancer (SPLC) in the following 10 years.\textsuperscript{104,105} The optimal follow-up regimen has not been established yet, but the ESMO guidelines recommend surveillance with a visit including history, physical examination, and a chest CT scan every 6 months for the first two years after treatment, and annual visits with CT imaging thereafter.\textsuperscript{31} When an intrathoracic recurrence is suggested on CT scans, the use of FDG-PET scans is advised, and a confirmatory biopsy should be performed in all patients who are suitable for salvage therapy. A modified follow-up schedule may be used for patients ineligible for salvage treatment. Suspicious findings detected through history, physical examination and/or follow-up imaging usually needs to be discussed in an experienced multidisciplinary tumor board.

Detection of local recurrences or second primaries in patients treated previously with SABR may be difficult as radiation-induced lung changes are common after SABR. These changes can persist and continue to evolve up to 4 years after treatment, and occasionally may mimic the appearance of a recurring tumor, especially in patients with mass-like fibrosis.\textsuperscript{106} While “Response Evaluation Criteria in Solid Tumors” (RECIST criteria) are widely used in the general lung cancer population to assess tumor response after treatment, it is of limited utility in patients treated with SABR. A recent expert consensus guideline for surveillance after SABR recommended the use of a formal scoring system including high risk imaging features (HRFs) predictive of a local recurrence.\textsuperscript{107} The following CT-findings were therefore specified: infiltration into adjacent structures, bulging margins, sustained growth, mass-like growth, spherical growth, craniocaudal growth, and loss of air bronchograms. A validation study of these HRFs in an independent patient cohort concluded that features such as a bulging margin, linear margin disappearance, and craniocaudal growth were the best predictors of recurrence, and combining these features resulted in higher sensitivity and specificity.\textsuperscript{108,109} A recent study in patients without a local recurrence after SABR showed that three or more HRFs were present in approximately 25% of patients.\textsuperscript{110} Inter- and intra-observer variability of HRFs are not well established, and the applicability of these features in routine clinical practice merits further investigation.

A complicating factor in the follow-up for locoregional recurrences is the risk of a fatal lung bleeding after biopsies or even brushings in the central airways in patients treated with high dose radiotherapy.\textsuperscript{111} The VUmc policy recommends that the indication for a bronchoscopy and biopsy should first be discussed at a multidisciplinary tumor board, where the potential
risks and benefits of the procedure should be argued (dr. J.M.A. Daniels, pulmonologist, personal communication). A recent contrast-enhanced CT scan and any available PET-CT scans should be reviewed, and the proximity to large blood vessels assessed. During the bronchoscopy, saline lavage and suctioning at the site of suspicious lesions is preferred before any biopsy is performed. If necrotic or unidentified tissue remains visible after the preceding step, a biopsy is not recommended. However, if a bulky or exophytic tumor becomes visible, and a recent CT scan shows no large blood vessels in the proximity, a biopsy can be considered.

An upcoming alternative approach for the early detection of local recurrences is the use of radiomics and texture analyses, where quantitative image features from regions of interest on pre- or post-treatment images are used to predict or detect a local recurrence. These “radiomics decision support tools” are also being investigated in combination with standardized uptake values (SUV) on FDG-PET imaging, and it remains to be determined if they can improve the detection of recurrences.

Assessment of treatment effects
The American Society of Clinical Oncology (ASCO) have stated that “clinical benefit” also integrates assessment of quality of life besides disease-specific treatment effectiveness, and recommended to include patient reported outcome measurements (PROMs) in future clinical trials. In the assessment of treatment effects, in particular treatment toxicity, physician reports are preferably combined with the patients’ perspective using PROMs. These measurements generally include questionnaires evaluating acute and late effects of treatment and the quality of life. The ESMO has developed a validated tool to assess the magnitude of clinical benefit of anti-cancer interventions, the “ESMO Magnitude of Clinical Benefit Scale” (ESMO-MCBS), which can be used in clinical trials. Analyses of these data will facilitate shared decision making in the future.

Smoking cessation
The association between smoking history and the development of lung cancer or an SPLC has been well recognized. Smoking cessation should be encouraged by physicians, as several studies report significantly worse survival for patients who were smoking at the time of NSCLC diagnosis compared to former smokers. In a surgical series of 1,484 patients, smoking history was found to be the only independent risk factor for the development of an SPLC on multivariable analysis (hazard ratio 1.08; 95% CI 1.02-1.16, p = 0.031), corresponding to an 8% increased risk per 10 year exposure, and current smokers had a significantly worse survival compared to former or never-smokers. A survival benefit for smoking cessation has also been observed after SABR for early stage NSCLC, with an improved two year survival of 78% compared to 69% in current smokers. These findings emphasize the
significance of paying attention to smoking cessation in lung cancer survivors during follow-up. Specialized behavioral support and the use of pharmacotherapy may be necessary to maximize the success of smoking cessation.
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