CHAPTER 7

General discussion and future perspectives

RECENT DEVELOPMENTS IN LUNG SBRT: COMPARISON WITH SURGERY AND OTHER LOCAL THERAPIES

Several phase II trials demonstrated the tolerability and efficacy of SBRT in early stage NSCLC [1-5]. However, there was only one trial that randomized between SBRT and conventionally fractionated radiotherapy. Results of this randomized multi-center phase II trial revealed no difference in disease control and overall survival [6]. However, there was an increased quality of life and less toxicity in terms of radiation pneumonitis and esophagitis in patients treated with SBRT. This study finally confirmed the superiority of SBRT over conventionally fractionated radiotherapy in early stage disease.

With the excellent local control and low toxicity achieved in a frail and elderly patient population [7], the question arose whether SBRT should also be offered to operable patients. The reported overall survival rates of SBRT cohorts are typically lower than surgical cohorts. However, after adjustment for confounders such as age and comorbidity, there are no significant differences between SBRT and surgery [8, 9]. Two prospective phase III studies randomizing between SBRT and surgery were closed early due to poor accrual (ROSEL NCT00687986, STARS NCT00840749). A pooled analysis of both studies showed the highest evidence of non-inferiority with regard to disease control and overall survival thus far [10]. Nevertheless, the non-inferiority of SBRT compared to surgery is still a matter of ongoing debate [11]. In the Netherlands, most patients are informed by both the surgeon and the radiation oncologist prior to treatment, unless the multidisciplinary tumor board has a strong preference for either SBRT or a resection.

With regard to treatment toxicity, Chang *et al*. published the only trial available for direct comparison [10]. Grade 3 toxicity occurred in 10% of patient treated with SBRT and in 40% in patients treated with surgery. No grade 4-5 toxicity was seen after SBRT, whereas 4% of the patients treated with surgery developed grade 4 toxicity and 4% grade 5 toxicity [10].
The Dutch Lung Surgery Audit (DLSA) published 30-day mortality rates of 2% after surgery for early stage NSCLC [12]. Moreover, in 15% of the patients re-surgery was required or a hospital admission for >14 days was deemed necessary [12]. In patients with severe Chronic Obstructive Pulmonary Disease (COPD GOLD III or IV) 30-day mortality rates increase to 10% in patients after surgery, whereas after SBRT the mortality rate is 0% [13].

When comparing regional control between both treatment modalities, the 10% rate of regional recurrences after SBRT appears to be similar in patients who underwent lobectomy [14-16]. Even though the latter includes a lymph node dissection with reported hilar and mediastinal lymph node metastases of 13-32% (despite negative lymph nodes with FDG PET staging) [17-19]. There are several reasons that could explain this discrepancy. First, incidental dose of the primary tumor to the lymph nodes could sterilize microscopic disease

in neighboring lymph nodes [20, 21]. Second, SBRT might elicit an abscopal effect, which is a phenomenon where local irradiation of a particular tumor site causes a tumor response at a site distant to the irradiated volume [22]. Third, although an intraoperative systematic lymph node dissection should routinely be performed, in daily practice only 4% is performed according to The European Society of Thoracic Surgeons (ESTS) guideline for intraoperative lymph node staging in NSCLC [23]. This guideline states that a systematic lymph node dissection should consist of at least six lymph nodes including the interlobar, hilar and lobe specific mediastinal lymph nodes and should always include the subcarinal node [24]. However, daily practice revealed that 35% of the mediastinal lymph node stations explored were sampled instead of a complete resection of the entire station [23].

Patient reported outcomes have become increasingly important in the evaluation of treatment modalities. Quality of life after SBRT for patients with early stage lung cancer unfit for surgery or who refused surgery, was evaluated in a recent meta-analysis of nine prospective studies, which overall revealed good tolerance of SBRT [25]. Most studies analyzed tumors smaller than 5 cm that were located peripherally in the lung, i.e., not located within 2 cm of mediastinal critical structures, e.g. the main bronchus, vessels, esophagus and heart. In two studies a detrimental effect on dyspnea and fatigue was demonstrated one year after SBRT [26, 27]. These results compare favorably with surgery. A review of 19 studies showed that the majority of patients had worse physical function the first six months after surgery for NSCLC, in some patients even persisting two years after surgery [28]. The most prevalent complaints were pain, cough, fatigue and dyspnea predominantly occurring within the first months after surgery, and three studies reported higher levels of fatigue and dyspnea after two years.

In recent years, surgery for early stage NSCLC has witnessed new techniques to reduce toxicity and improve treatment outcome. Video Assisted Thoracic Surgery (VATS) lobectomy is a less invasive surgical approach showing better quality of life and less pain for the first year after surgery compared to patients treated with a thoracotomy [29]. A more lung parenchyma sparing approach is a segmentectomy, which yields similar results in selected patients with tumors < 2 cm. Prospective randomized trials are underway to draw final conclusions about lobectomies versus sublobar resections [30, 31]. Interestingly, results from the DLSA revealed that parenchyma-sparing techniques are rarely applied, with segmentectomies performed in only 2% of all anatomical lung parenchyma resections in 2015 [12].
Alternative minimal invasive local therapies are wedge resections and radio frequency ablation (RFA). During the latter technique a needle is placed inside the tumor with radiofrequency waves passing through the probe, leading to an increasing temperature with tumor destruction as a consequence [32]. However, in both approaches local control rates are inferior and toxicity higher when compared to SBRT [20, 33].

In conclusion SBRT in early stage NSCLC is a very effective treatment, with high local control rates and lower toxicity compared to fractionated radiotherapy [6]. Moreover, as the number of fractions is low, the overall treatment time is short compared to conventional radiotherapy regimens of typically five to seven weeks. Therefore it is a patient friendly treatment, also reflected by the improved quality of life compared to fractionated regimens [6]. Although SBRT was first developed for frail patients unfit for surgery, due to the excellent results SBRT is nowadays offered to operable patients as well with less side effects compared to surgery. The goal of this thesis was to further optimize SBRT treatment and to expand the current SBRT indications by detailed toxicity analysis aiming at a larger proportion of patients benefitting from the excellent local control.

PART ONE OPTIMIZATION OF SBRT IN EARLY STAGE NSCLC

Toxicity reduction in lung SBRT

Prospective studies of SBRT for peripheral NSCLC smaller than 5 cm, reported 2-year local rates of 90% or more and low toxicity [1, 3-5]. The margins used in those studies were typically 5-10 mm, while tumor motion was measured with fluoroscopy as online volumetric imaging was often not available. The development of four-dimensional imaging in both treatment preparation and online volumetric image guidance (e.g. cone beam CT [CBCT]) increased accuracy considerably, enabling a decrease in margins [34-37]. As discussed in **chapter 2**, delineation variability is an important but often unknown and ignored systematic error. We examined the delineation variability in candidates for SBRT among an international group of experts. A relatively small tumor delineation uncertainty of 1.2 mm was found. The corresponding margin to obtain 90% coverage of the delineated contours was 3.4 mm. When using the margin recipe [38] and taking into account other geometric uncertainties (e.g. localization accuracy and respiratory motion), our GTV-PTV margins are 5-7 mm with a non-linear increase depending on respiratory amplitude as discussed in **chapter 3**. In retrospect, margins in the early-published cohorts were relatively small [1, 3, 4]. However, the high biological effective dose (BED) delivered with SBRT might have compensated for geographical misses in some patients. Nowadays with the excellent results of SBRT for peripheral early stage NSCLC smaller than 5 cm, there is little to gain with regard to toxicity in the majority of patients. For example, radiation pneumonitis grade 2 was reported in approximately 6% and grade 3 in only 2% [14, 39]. However, there are certain patient groups with an increased risk of developing lung toxicity. In a pooled analysis of 7752 patients, older age, larger tumor size and higher lung dose were associated with higher risks of grade 2 or higher radiation pneumonitis and lung fibrosis [40]. Another risk factor is the presence of interstitial lung disease like pulmonary fibrosis, being associated with a higher incidence of radiation pneumonitis and more extensive radiation pneumonitis, i.e., extending outside of the irradiated lung tissue [41, 42]. Another often reported toxicity for peripheral tumors is chest wall pain, with grade 2 or

higher occurring in 7-39% up to 36 months of follow-up [43-47]. In two studies the maximum dose to the rib or chest wall was the most important predictor for symptomatic rib fractures [43, 46]. Typically chest wall pain cannot be explained by rib fractures only, but may also be due to injury of the neurovascular bundle and musculoskeletal structures [48]. Several normal tissue complication probability modeling studies reported that the volume of the chest wall receiving 30 Gy was significantly associated with pain [43-45, 49]. Also patient characteristics are associated with increased risk such as high body mass index, diabetic state and osteoporosis [47, 50]. There is general agreement that the Planning Target Volume (PTV) coverage should not be compromised to spare the chest wall, as this will negatively impact local control. The risk of developing chest wall toxicity can relatively easily be reduced by a more fractionated radiotherapy regimen and the avoidance of a high maximum dose in the chest wall [43, 46, 51]. In addition, for tumors closely related to the chest wall but not touching the chest wall, higher accuracy and thus margin reduction could ameliorate the risk of developing chest wall pain. Finally, another interesting approach to reduce toxicity could be to decrease the prescribed total dose. Typically in lung SBRT the smallest tumors receive the highest dose. There are several reports describing a clear dose-response relationship with regard to local control [52-54]. Based on these studies, a BED >100 Gy is recommended, whereas slightly lower doses seem to be sufficient for T1-tumors [52-55]. However, others questioned this dose response relationship in lung SBRT and suggested dose de-escalation [56]. In fact, very high doses in lung SBRT can have a detrimental effect, which was supported by results of a meta-analysis showing that the overall survival decreased when delivering a very high biological effective dose (BED) of more than 146 Gy (e.g. 3x18 Gy), compared to milder fractionation regimens with a BED of 83-149 Gy [57]. This was possibly related to a higher incidence of adverse events in the higher dose groups. A recent pooled analysis of 46 studies confirmed the existence of a steep biological effective dose (BED) response relationship [58]. The authors concluded that a BED of 90 Gy was sufficient to achieve a TCP of ≥95% for T1 tumors, whereas T2 tumors require an additional 1 Gy dose per fraction to achieve the same tumor control probability (TCP) [58]. Altogether, several TCP models were proposed and recently there seems to be a tendency to decrease the BED. However, it should be kept in mind that the utility and suitability of these linear-quadratic (derived) biophysical models is still under debate [59, 60]. With the increasing use of SBRT, more data will become available and further research to improve TCP models in lung SBRT should be encouraged.

In conclusion, to further reduce the toxicity of lung SBRT, specific risk groups can be identified (e.g. close relation with the chest wall). In these cases higher accuracy and thus smaller margins besides dose de-escalation are valid treatment options.

SBRT for central lung tumors

Apart from patients with tumors closely related to the chest wall or with interstitial lung disease there are other high-risk SBRT indications that can be identified. In tumors larger than 5 cm or multiple lung tumors treated simultaneously, treatment volumes are larger and hence more normal tissue is exposed to these extremely high radiation doses. These indications will be further elaborated in the second part of the discussion. Another high-risk treatment is SBRT for central tumors, i.e., tumors within 2 cm of the mediastinal critical structures, where an increased risk of toxicity after SBRT was reported compared to peripheral tumors [61-64]. Critical structures include the proximal bronchial tree, but also great vessels, esophagus and brachial plexus. In addition, since recently heart dose has emerged as a cause of concern; heart dose reduction may improve overall survival for both lung SBRT and fractionated concurrent chemoradiotherapy for stage III NSCLC [65, 66]. Taken together for centrally located tumors a margin reduction is certainly appealing.

There are two major challenges with SBRT for central tumors. First, with CBCT imaging quality of the soft tissue/mediastinum is suboptimal. Second, normal tissue constraints of mediastinal structures in lung SBRT are currently unknown. There are however options to overcome these issues. Magnetic resonance imaging (MRI) provides superb tissue contrast, although in lung MRI imaging is challenging due to moving tissues and needs further development to overcome blurry imaging. If solved it could greatly enhance tumor and normal tissue visibility during treatment. Currently, MRI guided radiotherapy is being investigated by several groups [67-70]. In addition, MRI could also improve the accuracy of gated radiotherapy, i.e. beam delivery at a specific phase of the breathing cycle [71]. Gating typically requires an external marker to generate a respiratory signal to trigger the radiation beams if the respiratory phase is within the gating window [72]. However, external anatomy does not always correspond well with tumor motion [73]. MRI enables real time feedback of the tumor location, thus increasing accuracy and potentially reducing toxicity. Several groups are currently investigating the use of MRI-gating [74-76]. Another potential application of MRI-guidance is tumor tracking during treatment delivery [77]. Previously, due to the poor soft tissue contrast of fluoroscopy, invasive marker implantation was performed. However, marker implantation is sometimes complicated by a pneumothorax or marker migration [78, 79]. To overcome these problems marker-less tracking was investigated, but appeared not to be robust for all gantry angles, where during fluoroscopy the tumor might be hidden behind normal tissue. Especially in these cases MRI seems promising to optimize tumor guidance during treatment of centrally located tumors [77, 80]. It is therefore a promising tool to increase delivery accuracy and consequently decrease margins.

To investigate the normal tissue constraints of mediastinal structures in lung SBRT, three prospective phase II trials are currently accruing (RTOG 0813 NCT00750269, EORTC Lungtech trial NTC01795521, Nordic Hilus trial). All these phase II trials investigate the safety of SBRT for

central tumors. The RTOG 0813 is a dose-escalation trial of 10-12 Gy delivered in five fractions. Accrual is completed and preliminary results reveal that grade 3 or higher toxicity was 16% in the 5x11.5 Gy risk group and 21% in the 5x12 Gy risk group [81]. Moreover, grade 5 pulmonary bleeding occurred in 4%, with three out of four patients being treated in the highest risk groups of 11.5 and 12 Gy per fraction [82]. No optimal fractionation schedule was assigned yet. In the EORTC Lungtech trial, tumors are treated with a more fractionated schedule of 8x7.5 Gy [83, 84]. The study is currently accruing and results are to be awaited. In the Nordic HILUS trial patients with centrally located primary lung tumors or lung metastases were treated with 8x7 Gy stratified by tumor location close to the main bronchus or lobar bronchus [85]. Preliminary data revealed 28% grade 3-5 toxicity and 9% grade 5 toxicity consisting of pulmonary hemorrhage in six patients (86%) and radiation pneumonitis in one patient (14%) [85]. Five out of six patients with grade 5 pulmonary bleeding had tumors close to the main bronchus. Normal tissue complication probability (NTCP) modeling of these trials can hopefully provide us with the urgently needed dose constraints for normal tissue. However, anticipated caveats are the limited number of severe events reported thus far, e.g. bleeding grade 5, making a NTCP model less robust as in general a high number of events and multi-institutional data will build the best model. Several NTCP modeling studies were performed to find constraints in lung SBRT for esophagus [86-88], brachial plexus [89], bronchus [63] and spine (derived from spine SBRT cases) [90, 91]. While waiting for more prospective data, these constraints may give some guidance in daily practice.

In conclusion, more toxicity has been reported very recently in SBRT for centrally located lung tumors and should therefore be performed within the context of a trial. More knowledge on normal tissue constraints is essential and three prospective clinical trials will hopefully provide us with dose volume constraints that will guide the safe delivery of SBRT in centrally located lung tumors. MRI pre-treatment online imaging, MRI-gating and MRI-tracking is expected to increase accuracy, which could possibly lead to a margin reduction and reduced toxicity.

All previously discussed results are based on photon beam radiotherapy. By using multiple beam directions and segments, i.e. Intensity Modulated Radiotherapy (IMRT), a steep dose gradient can be achieved with a conformal dose distribution. This dose distribution can be even further improved by using protons compared to IMRT photons [92]. As a consequence, critical structures may be better spared, possibly decreasing treatment toxicity. However, treatment delivery in lung tumors is less robust than in photons with respect to tumor motion and changes in anatomy [93, 94]. There are three prospective studies of Stereotactic Body Proton Therapy (SBPT) in early stage NSCLC, of which two were closed early due to low accrual and no data were reported thus far (NCT01511081, NCT01525446, NCT00875901). Given the already excellent results for early stage peripheral NSCLC, the possible advantage of proton therapy in this setting is questionable [95]. Proton therapy might be beneficial in

the previously mentioned high-risk SBRT treatments for centrally located tumors, tumors > 5 cm or in conventionally fractionated radiotherapy for locally advanced NSCLC [93, 96].

Detection of disease recurrence

Treatment response evaluation after radiotherapy for NSCLC is typically performed with CT and/or PET-CT scans. Local recurrences after SBRT are difficult to distinguish from infiltrative or fibrotic changes in the lung parenchyma, occurring up to years after the irradiation [97-99]. These infiltrative or fibrotic changes might cause false positive FDG PET results, making it unsuitable for standard follow-up [100]. In this thesis previously reported High-Risk Features (HRFs) based on repeated CT-scans after SBRT, were successfully validated in a large data pool (**chapter 4**). Presence of ≥4 HRFs or the combination of the two HRFs bulging margin and cranio-caudal growth resulted in the highest sensitivity and specificity to detect a local recurrence. Although analyzing CT features on repeat CT scans is currently the best procedure to detect a local recurrence, salvage therapy may unnecessarily be delayed for several months, hence decreasing survival rates.

Instead of using relatively simple tumor measurements such as tumor diameter, recent developments allow for more advanced image analysis methods. This is referred to as 'radiomics': the use of a large amount of quantitative image features to decode the tumor phenotype [101]. Texture analysis of ground glass opacities on CT-scan following SBRT for early stage NSCLC demonstrated the ability to predict local recurrence within five months after SBRT and outperformed size measures [102]. Although this approach might improve the sensitivity to detect a recurrence, a relatively large number of tumor cells must be present, before it can be detected on CT-scan.

A major improvement would be to detect disease recurrence after SBRT in a very early stage when there is potentially a very small tumor load. Currently, many groups are investigating a new generation of biomarkers, such as circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) [103-108]. Circulating tumor cells are intact, often viable tumor cells separated from the primary site or metastatic lesion, whereas ctDNA is composed of small fragments of nucleic acid not associated with cells or cell fragments [109-111]. Both biomarkers can be obtained from blood and are promising examinations that can be used as for prognosis prediction, post treatment monitoring, therapeutic response and detection of mutations causing resistance to therapy. Some studies suggest that ctDNA may be more sensitive than CTCs in detecting tumor tissue and mutational status [103, 112]. Preliminary data of the Stanford group revealed that ctDNA can detect minimal residual or recurrent disease after concurrent chemoradiation and hypofractionated radiotherapy, on average 4 months prior to progression detected with traditional RECIST scoring using CT-scans [113]. Another interesting finding of the same group is that KEAP1/NRF2 mutational status is associated with tumor aggressiveness, metastasis and resistance to oxidative stress and radiotherapy

in lung squamous cell carcinomas. Therefore, this marker is expected to predict the risk of local recurrence in NSCLC patients treated with radiotherapy and might enable personalized treatment [114].

In conclusion, biomarkers in peripheral blood may be used for a variety of clinical applications, such as early detection of disease recurrence. Although very promising, the utility of these biomarkers are currently being tested in prospective clinical trials and results need to be awaited.

PART TWO EXPANDING THE USE OF SBRT

SBRT for advanced disease

Currently, mostly peripheral tumors smaller than 5 cm are being treated with SBRT. Apart from previously discussed central tumors, it could also be a very effective treatment for other indications. Reirradiation with SBRT as salvage treatment was investigated and reported in **chapter 5**. Another indication relatively unexplored yet is SBRT for peripheral tumors larger than 5 cm. There are limited retrospective articles reporting acceptable toxicity with grade 3 or higher toxicity of 7% including one fatal radiation pneumonitis [115, 116]. Two-year local and regional control were approximately 90%, but distant failure was 30% and markedly higher than the 20% at five years reported in tumors smaller than 5 cm [15, 117]. From a biological perspective, it is not surprising that large tumors have a higher chance of spread and thus have a poorer overall survival [118]. On the other hand, large lymph node negative tumors remain quite uncommon, suggesting that these tumors have a less aggressive biological behavior supporting a curative local treatment. In these large tumors, appropriate lymph node staging is even more important and could be improved. Currently the accuracy of PET-CT for mediastinal lymph node staging is limited, with a sensitivity of 76% and a specificity of 88% [119]. To decrease the false negative rate, the STAGE-study was initiated, investigating the use of Endobronchial Ultrasound (EBUS) or Endoesophageal Ultrasound (EUS) in determining loco-regional lymph node status compared with FDG-PET alone in patients eligible for SBRT.

The VOLUMES trial is the first prospective international phase I/II trial of SBRT for peripheral lung tumors larger than 5 cm initiated by the Netherlands Cancer Institute (NCT01543672). As radiation pneumonitis is most likely the dose limiting toxicity and the Mean-Lung Dose (MLD) is a good predictor for radiation pneumonitis, we designed a MLD escalation trial [120]. Primary endpoint is to define the MLD associated with a 20% chance of radiation pneumonitis ≥ grade 3 or severe unexpected Serious Adverse Events (SAEs). Secondary endpoints are disease control, overall survival and quality of life. The first patient was accrued in 2011 and the trial closed in April 2016 after the total accrual of 30 patients was reached. First results are

expected in May 2017 and will provide important results about safety and disease control of large, node negative lung tumors.

In a second treatment arm of the VOLUMES trial, patients with two or more lung tumors treated with SBRT are investigated. Retrospective analyses reveal 5-10% grade 3 toxicity and 2-year local control rates of 84-95% [121, 122]. Again, there are no prospective studies available, which is important since extrapolating results from single lung tumors or consecutively irradiated tumors might underestimate toxicity compared to simultaneously treated tumors. Currently this arm in the VOLUMES trial is still accruing with an estimated remaining accrual period of about one year.

Yet another unexplored area is the use of SBRT in the setting of locally advanced NSCLC. Although a phase III dose-escalation study using conventional fractionated radiotherapy failed to demonstrate a survival benefit, SBRT is a more rational strategy for dose escalation, because the overall treatment time is short [65, 123]. Another issue raised is the increased toxicity seen in dose-escalation trials with concurrent chemoradiation compared to radiotherapy only, possibly leading to a detrimental effect on overall survival [124]. As in SBRT volumes and margins are generally smaller than in fractionated radiotherapy, toxicity may decrease if refraining from high-risk SBRT treatments (e.g. central tumors). Therefore we developed a strategy for dose escalation by treating the peripheral primary tumor with SBRT in combination with fractionated concurrent chemoradiation to the lymph nodes. There are few reports about the combination of SBRT with concurrent chemotherapy [125, 126], although concurrent chemoradiation is the standard treatment in locally advanced NSCLC [127]. Hence, we initiated the phase I single-center Hybrid trial, investigating the feasibility and the safety of combined SBRT to the primary tumor and concurrent chemoradiation to the lymph nodes in locally advanced NSCLC (NCT01933568). Preliminary data show feasibility (**chapter 6**) and low toxicity [128]; final results are expected in 2017.

SBRT and oligometastases

Oligometastatic disease is a concept first described by Hellman and Weichselbaum in 1995, and defined by a limited state of metastasized disease with potentially curative treatment options [129]. De Ruysscher *et al.* conducted the first non-randomized prospective trial of radical treatment of NSCLC patients with oligometastatic disease [130]. Patients were treated with systemic therapy followed by radical local radiotherapy or surgery of all oligometastatic sites showing a small but a significant group of long-term survivors: 15% of the patients had no disease progression after two years [130]. Although in this study only one patient was treated with SBRT (all other patients received conventionally fractionated radiotherapy or stereotactic radiotherapy in case of brain metastases), several prospective and retrospective trials have shown excellent local control and low toxicity of SBRT for oligometastases, both in lung as well as other primary tumors and metastatic sites such as adrenal gland,

liver and bone [131-136]. In order to select the patients most likely to benefit from radical treatment in oligometastatic disease, several patient characteristics were identified. In NSCLC metachronous presentation of oligometastases and lymph node negative disease had a significantly better overall survival than patients with synchronous presentation and lymph node positive disease [137]. In studies about SBRT for oligometastatic disease of various primary tumors (breast, prostate, colorectal, renal cell, head & neck, esophagus and lung), patients with breast cancer histology, smaller metastases and a limited number of 1-3 metastases had a more favorable overall survival [131, 136]. However, all these studies are non-randomized and the possible benefit of radical local treatment over chemotherapy could be attributed to selection bias. Recently the first randomized prospective multi-center phase II study for oligometastatic NSCLC patients was published [138]. Forty-nine patients with ≤3 metastases were randomized between local consolidative therapy ((chemo)radiotherapy or resection of all sites) with our without subsequent maintenance treatment. An impressive increased progression free survival was reported of 11.9 months in the local consolidative arm versus 3.9 months in the chemotherapy alone arm. Due to the large disease free survival difference in favor of the consolidative arm (48% received SBRT), the study closed early. There was no grade 4-5 toxicity and grade 3 toxicity was observed in 20% of the consolidation arm and 8% in the maintenance group alone. In 2011 another phase II randomized trial was initiated (SABR-COMET NCT 01446744) and results are awaited [139].

In conclusion, also in the setting of oligometastases, SBRT results are excellent with regard to local control and toxicity. Although results of phase II studies are promising, exploration in phase III trials is necessary to assess if the addition of SBRT to oligometastatic sites after systemic treatment results in an overall survival improvement.

Another interesting application of SBRT in advanced NSCLC is in so called oligoprogressive disease, i.e., progression in one tumor site while in other locations the disease seems stable [140]. Oligoprogression was a rare event in the past, but due to the identification of genetic alterations, the so-called driver mutations, selective pathway directed systemic therapy became available [141]. In patients with Epidermal Growth Factor Receptor (EGFR)-mutations (prevalence of about 12%), treatment with tyrosine kinase inhibitors (TKI's) (e.g. Gefitinib, Erlotinib, Afatinib) has resulted in improved progression free survival (PFS) and quality of life compared to platinum based chemotherapy in the first line treatment [142, 143]. For patients with Anaplastic Lymphoma Kinase (ALK)-rearrangements (prevalence of about 5%), an ALK tyrosine kinase inhibitor (Crizotinib) became available, increasing PFS compared to standard chemotherapy [144]. Unfortunately, most patients receiving targeted therapy progress within one year due to drug resistance. However, if only a limited number of disease sites become resistant to targeted therapy, SBRT can be delivered to the progressive sites for local control without significant side effects, enabling continuation of the drug [140]. Whether delay of systemic treatment switch results in improved overall survival needs to be

investigated in future trials. Moreover, the number of targeted therapies for advanced NSCLC is increasing rapidly and a potential concern is the development of severe side effects due to the interaction with SBRT [145-147].

SBRT and immunotherapy

A very promising new development in cancer treatment is immunotherapy. Cancer immunotherapy was called breakthrough of the year for 2013 and harnesses the body's immune system to combat tumors [148]. Normally, tumor cells suppress the immune system, however immunotherapy is sometimes able to release this brake. There is growing evidence that in combination with immunotherapy, local radiotherapy generates an in situ individualized tumor vaccine by inducing release of antigens that trigger the immune system to activate tumor-specific T cells [149]. As a result, there may be an anti-tumor immune response that mediates the so-called abscopal effect. The abscopal effect is a phenomenon where local irradiation of a particular tumor site causes a tumor response at a site distant to the irradiated volume. There are several case reports describing an abscopal effect, but altogether it is rather uncommon [22, 150]. A very promising approach seems to be the combination of local radiotherapy with immunotherapy. There is some evidence that hypofractionated radiation therapy leads to a stronger local and systemic anti-tumor immune stimulation that normal fractionation [151]. If confirmed in future studies, a Hybrid treatment strategy (SBRT to the primary tumor and fractionated radiotherapy to the lymph nodes) could be delivered concurrently with immunotherapy in locally advanced NSCLC. Another promising strategy would be to use SBRT as a boost after concurrent chemoradiation prior to adjuvant immunotherapy. However, the recommended SBRT dose, fractionation regimen and timing for achieving the optimal response are unknown. There are currently more than 80 prospective trials testing the combination of radiotherapy and immunotherapy [152].

In conclusion, with the excellent results achieved in early stage NSCLC, SBRT is now offered to selected patients with advanced stage NSCLC as well. In combination with immunotherapy SBRT shows a synergistic systemic effect, which is a fantastic new area of research. Also in locally advanced NSCLC, SBRT is expected to play an important role as a promising strategy for dose escalation. Further research in these new areas is warranted.

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