

Chapter 4

Stereotaxic Body Radiotherapy for Stage I NSCLC

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Rational for Stereotactic Body Radiotherapy

Globally, lung cancer represents the leading cause of cancer death in males, and is the second leading cause in females. High rates of cure are only achieved if the diagnosis of non-small cell lung cancer (NSCLC) is made at an early stage of disease; however, this is accomplished only in about one quarter of the patients due to the indolent nature of early stage NSCLC. Two current developments will result in substantially higher numbers of NSCLC patients and especially elderly patients with stage I NSCLC. (1) An aging population will increase the number of NSCLC patients by 50 % in the US and the majority of these patients will be older than 65 years [1]. (2) CT based screening of patients at high risk for lung cancer has recently been approved in the US and is expected to increase the number of stage IA by a factor of two [2].

Treatment of this increasing number of elderly patients with early stage NSCLC will pose a challenge to all disciplines involved in lung cancer treatment. Despite surgical resection – lobectomy and systematic lymph node dissection – is the standard of care, its use is declining. Of all patients with stage I disease, >80 % are treated with surgical resection [3], but resection rates drop in the elderly Western population due to comorbidities and the associated risk of increased operative mortality and morbidity [4]. In the US population older than 65 years, the proportion of patients treated with open or laparoscopic surgery decreased from 75.2 to 67.3 % between 1998 and 2007 [5] and this proportion drops to <40 % in patients older than 75 years based on data from the Netherlands [6].

These numbers illustrate the need for non-surgical options offering safe and effective treatment for elderly comorbid patients with stage I NSCLC. Best

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supportive care without any curative treatment is practiced with increasing frequency: life expectancy of elderly patients with (severe) comorbidities is assumed being too short to justify a potentially toxic and cumbersome curative treatment. Based on the California Cancer Center registry, 7 % of all stage I NSCLC patients remain treated with best supportive care [3] and this proportion of untreated patients increases to 30 % in the elderly population >75 years old [6, 7]. However, lung cancer specific survival (CSS) is <20 % after 5 years in these untreated patients indicating the need for a curative treatment option.

Conventionally fractionated radiotherapy is an established curative treatment option for medically inoperable patients with stage I NSCLC. The term “conventional” radiotherapy refers to the technique and fractionation of radiotherapy: uncertainties in tumor extension and tumor targeting require large safety margins and result in large volumes of normal tissue irradiated. Therefore, radiotherapy is delivered in multiple small irradiation fractions of usually 2 Gy per day (conventional fractionation) to total doses of 60–66 Gy, delivered over a period of 6–7 weeks. This treatment has been the standard of care for medically inoperable patients and achieved 3-years OS rates of about 30 % and 3-years CSS of about 50 %, better than best supportive care [8]. However, local tumor relapse is the most frequent site of treatment failure after irradiation with conventional radiotherapy and retrospective studies have demonstrated a dose-response relationship for local tumor control and disease specific survival [9–11]: higher irradiation doses are associated with better local tumor control, which improves OS [8, 12]. These data indicate the need for a methodology making safe intensification of radiotherapy possible.

SBRT Background and Definitions

Principles and practice of Stereotactic Body Radiotherapy (SBRT) were transferred from cranial stereotactic radiotherapy/radiosurgery in the mid-90s by pioneering work at the Karolinska Hospital in Sweden and this concept was quickly adopted and further developed in Japan [13] and Germany [14, 15]. Several national and international bodies [16–19] have defined stereotactic Body Radiotherapy (SBRT) as a method of external beam radiotherapy (EBRT) to accurately deliver a high dose of irradiation in one or few treatment fractions to an extra-cranial target.

SBRT can be adequately performed with either traditional linear accelerators equipped with suitable image-guidance technology, accelerators specifically adapted for SBRT and dedicated delivery systems. Additionally, the principles of SBRT apply for both photon and particle therapy. It is of fundamental importance that the whole work-flow of SBRT – the medial and technical parts – are systematically optimized and appropriate quality assurance procedures are implemented. SBRT is therefore a multi-professional teamwork involving the Radiation Oncologists, Medical Physicists and Radiation Technologists. Targeting the tumor with daily image guidance is most important to avoid its missing and to avoid delivery of high irradiation doses to critical normal structures. This high accuracy allows

safe treatment with irradiation doses, which are at least equivalent to radical doses in conventional fractionation. The full SBRT irradiation dose is delivered in few fractions, usually but not necessarily in maximum 3–10. Adjustment of single-fraction dose and total dose to size and location of the target is essential.

Outcome After SBRT for Early Stage NSCLC

SBRT in the Elderly Population Compared to Best Supportive Care

Two population-based analyses from the Netherlands [6, 7] and the US [20] demonstrated an improvement in OS for stage I NSCLC by the introduction of SBRT into the elderly patient population. SBRT represents an attractive treatment option for this elderly patient population because of its non-invasive nature, practice on an outpatient basis and short overall treatment time of 1–2 weeks: these factors might improve patient referral to a curative treatment and improve patient compliance.

In the Dutch study of patients older than 75 years, OS survival was improved in the total patient population from median 16 months to median 21 months by the introduction of SBRT between 1999 and 2007 [7]. Availability of SBRT reduced the proportion of patients treated with (non-curative) best supportive care from 38 to 28 % and increased the proportion of patents treated with (curative) radiotherapy from 26 to 42 %. The proportion of patients treated with surgery remained constant during the analyzed time periods.

The US study is based on the SEER database of patients older than 65 years and compared five different treatment options for patients with stage I NSCLC [20]: best supportive care, conventional radiotherapy, SBRT, sublobar resection and lobectomy. Propensity score matching between SBRT and non-SBRT treatment was performed to correct for imbalances of race, sex, education level, median income, comorbidity score, histology, tumor grade, tumor size, and receipt of lymph node sampling. SBRT achieved improved OS compared to best supportive care and conventional radiotherapy and differences were not significant compared to sublobar resection and lobectomy. Safety of SBRT in this elderly population is expressed in 30- and 90-days mortality rates of 0 and 0.8 %, respectively; 90-day mortality rates were 4.1 % for sublobar resection and lobectomy.

Two studies focused on safety and efficacy of SBRT in patients older than 80 years. A Japanese study about 109 patients with a median age of 83 years (maximum 91) reported 3-years OS of 53.7 % [21]. One patient suffered from a grade 5 radiation induced pneumonitis: this patients was medically inoperable because of interstitial pneumonia associated with antineutrophil cytoplasmic antibody-related vasculitis. Sandhu et al. described treatment of 24 patients with a median age of 85 years and 2-years OS was 74 % after SBRT with a median dose of 48 Gy delivered in 4–5 fractions. No patient developed early or late grade 3+ toxicity. A Dutch study reported SBRT in 193 patients older than 75 years, median 79 years [22]: all

patients but one finished their treatment resulting in 3-years OS of 45 %. No grade 4+ toxicity was observed. Summarizing these data, SBRT was safe with only one treatment related death in 326 patients and with small numbers of grade 3 and 4 toxicity despite median age ranged between 79 and 85 years. SBRT data appear favorable compared to surgical series, where mortality in octogenarians approaches 10–15 % in some series and postoperative morbidity is consistently reported in >20 % of the patients [23].

Another concern is safety of SBRT in patients with very poor pre-treatment pulmonary function. Palma et al. analyzed SBRT in 176 patients with chronic obstructive pulmonary disease (COPD) at stage Global Initiative for Chronic Obstructive Lung Disease (GOLD) III/IV [24]. Patients were treated with a risk-adapted fractionation of 60 Gy delivered in 3–8 fractions. Three-year OS was 47 % and no patient developed any grade IV or V toxicity. Guckenberger et al. analyzed post-SBRT pulmonary function changes in 270 patients treated at five international centers [25]. In the patient cohort with worst pre-SBRT values (FEV1 <40 %), pulmonary function was stable over a 24 months period indicating safety of SBRT in this high-risk cohort of patients with severe pulmonary comorbidities. Stable or only small loss of pulmonary function after SBRT has been reported by other groups as well [26–29] and is explained by the parallel structure of the lung and restriction of high SBRT doses to small volumes.

There certainly exists a cohort of patients with severe comorbidities and very limited OS, which will not benefit from curative SBRT. However, such patient selection criteria are not available. Consequently, SBRT should be offered to all patients irrespective of old age and pre-existing pulmonary comorbidities unless they will not tolerate the procedure of SBRT planning and delivery.

SBRT in Medically Inoperable Patients Compared to Conventionally Fractionated Radiotherapy

Local tumor control rates of 84–98 % are reported by several prospective phase II trials of SBRT in medically inoperable stage I NSCLC patients [30–35]. This improved local tumor control compared to conventional radiotherapy [8] transfers into an improved OS as demonstrated in a meta-analysis [36] and a population based analysis [20]: 3-years OS is approximately 50 % after SBRT with pre-treatment comorbidities being a strong predictor for OS [37].

Large single- and multi-institutional studies confirm results from the prospective studies described above, highly consistent results despite differences in the methodology of SBRT (Table 4.1). A patterns-of-care and outcome study analyzed SBRT in 582 patients treated at 13 German and Austrian academic centers [38]: local tumor control and OS was independent from the SBRT technologies used at different time periods and used at different centers and no learning curve or procedure volume effect was observed. This again confirms the robustness of SBRT.

Table 4.1 Prospective and large retrospective studies of SBRT for stage I NSCLC

Study	Year	# patients	OS @ 2–3a (%)	LC @ 2–3a (%)
Nagata et al. [30]	2005	45	75	98
Baumann et al. [31]	2009	57	60	92
Fakiris et al. [32]	2009	70	43	88
Ricardi et al. [33]	2010	62	57	88
Timmerman et al. [34]	2010	55	56	98
Bral et al. [35]	2011	40	52	84
Prospective studies		329	56.2	91.2
Senthi et al. [70]	2012	676	55	95
Guckenberger et al. [38]	2013	582	47	80
		164 ^a	62 ^a	93 ^a
Grills	2013	859	51.5	94
Retrospective studies		2,049	51.3	91

^aCohort of patients treated with >106 Gy BED

Based on these findings, the 1.2013 version of the NCCN Guidelines [39] as well as the ESMO Clinical Practice Guidelines [40] consider SBRT as superior to conventionally fractionated radiotherapy and as the standard of care for medically inoperable patients.

SBRT in Medically Inoperable Patients Compared to Radiofrequency Ablation

Radiofrequency ablation (RFA) has been introduced as a minimally invasive option into the treatment of stage I NSCLC. No study performed a direct comparison between SBRT and RFA but a recent literature review reported improved local tumor control, cancer specific survival and overall survival after SBRT compared to RFA [41]. Additionally, toxicity and 30-day mortality [42] were lower after SBRT resulting in the conclusion, that SBRT should be proposed as the first non-surgical treatment to high-risk patients.

SBRT in Medically Operable Patients Compared to Surgery

Lobectomy is the evidence-based standard of care for operable stage I NSCLC patients: a randomized trial described improved local tumor control and OS after lobectomy compared to wedge resection [43]. Whether sublobar anatomical resection (segmentectomy) is equivalent to lobectomy is discussed controversially [44] but results of segmentectomy appear comparable especially in stage IA patients [45].

Based on the promising outcome of SBRT in medically inoperable patients, three randomized trials comparing SBRT with lobectomy (ROSEL, STAR) or sublobar resection (ACOSOG Z4099/RTOG 1021) have been started but all three studies closed early due to poor accrual: only 68/2,410 (2.8 %) patients were enrolled leaving us without level I evidence.

Because of this lack of level I evidence, several studies used statistical methods like matched pair analyses and propensity score matching were performed to correct for imbalances in patient characteristics between SBRT and surgery. Grills et al. performed a single-institution comparison between SBRT and wedge resection and reported improved local tumor control after SBRT with no differences in cancer specific survival; OS was better in the surgical cohort, which was explained by older age and increased comorbidities in the SBRT patients [46]. The previously cited US population based analysis showed no difference in OS and cancer specific survival for SBRT versus sublobar resection and SBRT versus lobectomy [20]. Puri et al. reported identical cancer specific survival between SBRT and surgery (lobectomy in 80 % of the patients) [47]. OS appeared better after surgery compared to SBRT but was not statistically significant and this potential difference was explained by increased pulmonary comorbidities in the SBRT cohort, which was not corrected in the propensity score matching. Versteegen et al. compared SBRT and VATS lobectomy in 128 patients after propensity score matching of gender, age, clinical tumor stage, tumor diameter, location of the tumor, pretreatment tumor histology, lung function (FEV1%), Charlson comorbidity score and WHO performance score [48]. Locoregional control was better after SBRT with no differences in freedom from progression and OS.

Few studies reported outcome after SBRT when patients were considered as suitable for surgical resection but surgery was refused. Two Japanese and Dutch studies described excellent OS of 70 % after 5 years (n=87) [49] and 85 % at 3 years (n=177) [50], respectively, results which compare well to OS after lobectomy.

Consequently, SBRT is a viable treatment option in the situation, when lobectomy is refused by the patients. Additionally, SBRT appears equivalent to sublobar resection and both options with their specific pros and cons should be discussed with the patient.

Toxicity and Quality of Life After Lung SBRT

The majority of patients are referred for SBRT because of severe pulmonary comorbidities and their poor pulmonary function does not allow surgical resection. Consequently, pulmonary toxicity is a concern in lung SBRT. The incidence of symptomatic radiation induced pneumonitis is consistently below 10 % in SBRT of lung tumors <5 cm in diameter and peripherally located. Higher mean lung doses and a larger low-dose spread have been reported to be correlated with the risk of radiation-induced pneumonitis [51, 52]. Additionally, pulmonary function is stable after SBRT with a loss of <10 % (FEV1, DLCO) within 24 months after treatment [25]. Pulmonary toxicity was not increased even in patients with very poor pre-SBRT pulmonary function [25] and with severe COPD GOLD III-IV [53].

Patients with pre-existent pulmonary fibrosis might be at increased risk for radiation induced pneumonitis

Chest wall toxicity (myositis, neuralgia, rip fracture, subcutaneous fibrosis, skin ulceration) has been reported when tumor are located close to the respective normal tissue structures. Doses >30 Gy to the chest wall haven been correlated with these toxicities and the volume of the chest wall exposed to these doses should be minimized by conformal treatment planning [54–56].

Severe toxicity to the brachial plexus (neuropathic pain, motor weakness, or sensory alteration), large bronchi (stenosis with pulmonary atelectasis) and esophagus (ulceration, perforation, fistula) has been reported but these toxicities are rare. Limiting the total dose to the plexus to <26 Gy in 3–4 fractions can minimize the risk of toxicity [57]. The issue of SBRT for centrally located tumors close to the esophagus and large bronchi is discussed below.

Studies consistently reported that SBRT has no detrimental or negative on quality-of-life (QoL) [58–60]. Overall QoL as well as subdomains of dyspnea and cough were stable after SBRT in all studies and one study described significantly improved emotional functioning [58].

Clinical Practice of SBRT for Early Stage NSCLC

Lung SBRT is a multi-disciplinary task, involving all disciplines dealing with the diagnosis and treatment of lung cancer. Within the radiotherapy department, SBRT needs to be implemented and practiced by a multi-professional team consisting of the Radiation Oncologists, Medical Physicists and Radiation Technologists: all members of the team should have undergone dedicated training in SBRT. The development of written protocols is an essential component of the quality assurance.

Any treatment of NSCLC should be discussed within an interdisciplinary tumor board and this applies to SBRT as well. A careful assessment of the performance status is important to provide a sensible therapy concept. Perioperative morbidity is associated with older age and the presence of co-morbidities [4, 61]. Therefore, pulmonary function tests, cardiac assessment and performance status are recommended clinical assessments before estimating the operative risk and adjusting the treatment to the patient individual medical and personal situation.

In the following part, some clinical and technical issues of SBRT for stage I NSCLC will be discussed

SBRT Without Histopathological Confirmation of Disease

Histological confirmation of disease is recommended prior to any treatment for NSCLC. Transbronchial biopsy or transthoracic needle aspiration are primary methods. Nevertheless sometimes it is impossible or at high risk to prove malignancy because of the medical and/or pulmonary co-morbidities. In such cases radiological

criteria of malignancy should be consulted. Swensen et al. [62] described a prediction model to estimate the probability of malignancy in solitary pulmonary nodules: clinical and radiographic characteristics are used to estimate the likelihood of malignant disease. Inclusion of FDG-PET imaging might further improve the accuracy of the prediction model [63, 64]. If malignancy is highly likely based on the described criteria, immediate SBRT without histopathological proof is justified [65], which is also standard practice in thoracic surgery [66]. Repeated imaging to evaluate the growth pattern is an option in borderline risk-of-malignancy patients but might put the patient at risk for disease progression in the time interval [67].

Staging of Disease

In SBRT, only the primary tumor is treated with high irradiation doses and no elective nodal irradiation is performed. Consequently, a whole body FDG PET scan should be performed in all cases for exclusion of nodal metastases. The added value of FDG PET lies in the higher diagnostic accuracy for the detection of nodal metastases compared to CT-based staging (negative predictive value 90 %) [68, 69]. The FDG PET scan should be not older than 6 weeks to avoid disease progression in the interval between staging and treatment. In case of pathologic FDG uptake in mediastinal lymph nodes, further evaluation, e.g. by EBUS/EUS are mandatory. If the situation is still unclear, a mediastinoscopy may be necessary. After FDG PET based staging and exclusion of nodal disease, lymph node metastases are observed in about 10 % of the patients [70].

Technology of SBRT Planning and Delivery

Because lung tumors can move by several centimeters due to breathing of the patient, a motion management strategy is required for all patients [71]. This starts at treatment planning, where patient individual tumor motion is assessed by 4-dimensional CT (4D-CT), also known as respiration-correlated CT [72, 73]. Additionally, 4D-CT reduces motion artifacts and systematic errors introduced due to the non-representativeness of the captured breathing position [74, 75]. Various motion compensation techniques have been developed and are available in clinical practice – gating, tracking, breath-hold irradiation mid-ventilation concept, internal target volume concept – all with specific pros and cons [76]. It is of utmost importance, that breathing motion is consistently integrated into all steps of SBRT planning and delivery, especially into the image-guidance procedure. Though patient-specific motion management is strongly recommended, no benefit for advanced motion management strategies like gating or tracking has been found for patients with tumors moving <10–15 mm in amplitude, the majority of the patients [76, 77].

Treatment planning can be performed using 3D-conformal radiotherapy (3D-CRT), Intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). All published prospective trials have used 3D-CRT but IMRT and VMAT have the potential to increase dose conformity and homogeneity and reduce treatment delivery times [78]. Type B algorithms achieve accurate dose calculation especially at the interface of lung tissue and soft tissue and their use is highly recommended [79]. Monte Carlo dose calculation algorithms achieve most accurate results but differences to collapsed cone algorithms appear small.

The position of lung tumors within the patient varies from day to day and is different between the time of treatment planning and treatment delivery. This variation of the tumor position is not caused by patient misalignment but is rather a relative motion of the pulmonary tumor within the lung. The magnitude of this variability is 5–7 mm on average and up to several centimeters in individual patients [80, 81]. To avoid missing the tumor at the time of treatment delivery with the consequence of decreased local tumor control, daily pre-treatment image-guidance (IGRT) is mandatory [77]. Various IGRT technologies are available, which can be broadly categorized into planar and volumetric imaging. Major advantage of planar imaging is the possibility to perform repetitive verification during treatment delivery; however, implanted fiducial markers are required for visualization of the soft-tissue tumor with the associated risk of pneumothorax. Major advantage of volumetric imaging is the possibility not only to verify the tumor position but also the position of critical organs at risk close to the tumor, e.g. the spinal cord.

SBRT Irradiation Dose and Fractionation

Because of large differences in single-fraction doses between studies, comparison of physical doses is less meaningful but doses are converted to biological effective doses (BED) to account fractionation effects [82]. Independently, several groups demonstrated a clear dose-effect relationship for local tumor control [83–86]: a minimum PTV dose of >100 Gy BED (biological effective dose; α/β ratio 10 Gy) achieved local tumor control >90 %. It could be demonstrated that this dose-dependent increase in local control translates into improved OS [83, 87]. A recent meta-analysis reported best OS for medium-to-high SBRT doses of 83.2–146 Gy BED; OS was worse after SBRT with >146 Gy BED indicating a detrimental effect of excessively high SBRT doses [88].

This dose of minimum 100 Gy BED is usually delivered in 1–10 fractions but reimbursement rules have resulted in a widespread use of 5 or fewer fractions in the United States. The most frequently used fractionation scheme is 3 fractions of 18 Gy as PTV encompassing dose [89]. Whereas safety of such high single and total doses has been demonstrated for peripheral lung tumors of usually <5 cm size, high rates of severe toxicity have been reported in centrally located

tumors with critical organs like the esophagus and large bronchi close by [90, 91]. In contrast, safety of SBRT for centrally located tumors has been reported if the total dose is delivered using a larger number (5–10) of treatment fractions of a lower single-fraction doses [92], a concept which is called risk adapted fractionation. Eight fractions of 7.5 Gy as PTV encompassing dose is the most frequently used and best-evaluated fractionation scheme for centrally located tumors [93].

Response Assessment and Follow-Up

Regular chest CT follow-up every 3–6 months for 2–3 years and annually thereafter is recommended for early detection of secondary primary lung tumors and local recurrences amenable for salvage therapy. Localized acute (asymptomatic) pneumonitis and late pulmonary fibrotic changes are regularly observed in the follow-up CT images and the radiological appearance of the fibrotic changes may remain dynamic for several years [94]. Anyone involved in the response assessment should be aware of these normal tissue reactions to SBRT doses to avoid misinterpretation as local recurrence. An algorithm for follow-up has been proposed, which identified high-risk CT morphological features of local recurrence: enlarging opacity at primary site, sequential enlarging opacity, enlarging opacity after 12-months, bulging margins of the opacity, loss of a linear margin, and loss of air bronchograms [95]. In the presence of such high-risk CT features, an FDG-PET should be acquired and a SUVmax ≥ 5 is predictive for local recurrence.

Salvage treatment of isolated local recurrences has been performed very rarely and both salvage surgery and SBRT have been described. Salvage surgery was reported as safe in two studies with 5 [96] and 7 [97], where significant SBRT-related adhesions were found in none of the patients; re-SBRT should be restricted to peripherally located tumors [98].

Summary

SBRT is an evidence-based treatment option for patients with stage I NSCLC. Prospective and retrospective studies reported consistent results of SBRT for stage I NSCLC: local tumor control exceeding 90 % and overall survival mainly limited by the comorbidities of the patients. Safe practice of SBRT requires, that it is performed by a multi-professional team experienced and trained in SBRT and image-guided radiotherapy. It is essential that patient selection to SBRT treatment is discussed in multi-disciplinary tumor boards considering the perioperative risk of the patient and patient preference.

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