SBRT in operable early stage lung cancer patients

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Abstract: Since decades the gold standard for treatment of early stage non-small cell lung cancer (NSCLC) is surgical lobectomy plus mediastinal lymph node dissection. Patients in worse health status are treated with sublobar resection or radiation treatment. With development of stereotactic-body-radiotherapy (SBRT), outcome of patients treated with radiation was substantially improved. Comparison of SBRT and surgical techniques is difficult due to the lack of randomized trials. However, all available evidence in form of case control studies of population based studies show equivalence between sublobar resection and SBRT indicating that SBRT—when performed by a trained and experienced team—should be offered to all high-risk surgical patients. For patients not willing to take the risk of lobectomy and therefore refusing surgery, SBRT is an excellent treatment option.

Keywords: Stereotactic-body-radiotherapy (SBRT); surgical resection; early stage non-small cell lung cancer (NSCLC)

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Background

Malignant neoplasm of the lung is the most frequent cause of cancer related death in males and second in females.

Early stage non-small cell lung cancer (NSCLC) is cured in many cases by local treatment. Unfortunately three quarters of NSCLC cases are detected in a later stage of disease due to a lack of clinical symptoms. Cure is then only achieved in few patients. However, the combination of population aging and oncoming CT-based screenings programs will increase the number of diagnosed early stage lung cancer especially in the elderly patients (1,2).

In the past, surgical lobectomy plus mediastinal lymph node dissection was established as the standard treatment in operable patients. Patients with higher surgical risk due to comorbidity may undergo sublobar resection, although its outcome is inferior based on a randomized study (3). About 80% of stage I disease patients undergo surgical resection (4). However in treatment of elderly patients with increasing numbers of comorbidities, the value of surgery will decrease (5). In the USA the percentage of patients with age >85 years as well as having >3 comorbidities doubled between 1998 and 2007. The number of patients treated with no local therapy at all increased from 14.6% in 1998 to 18.3% in 2007. Looking at these data the decline in use of surgical resection from 75.2% to 67.3%, despite the increasing use of less invasive (6) video-assisted thoracoscopic surgery (VATS), isn't surprising (7). According to data from the Netherlands this proportion even drops <40% in patients >75 years (8). Best supportive care without curative treatment intention is practiced with increasing frequency. Vest *et al*. report of a growing proportion not receiving a curative local treatment from 14.6% in 1998 to 18.3% in 2007 in the USA (7). This number increases in patients >75 years up to 26% (9). Five-year cancer-specific-survival is about 14% (10) in patients undergoing best supportive care indicating the need for a curative and simultaneously minimally or non-invasive treatment option.

For inoperable patients so-called conventional radiation treatment is an established curative treatment option. Conventional radiation in this context usually means applying 60-66 Gy in 2 Gy-fractions over a time period of 6-7 weeks. Overall survival (OS) of about 30% and cancer specific survival (CSS) of about 50% after 3 years

can be achieved in these non-operable patient cohorts (11). However, retrospective studies showed local tumor relapse being the most frequent site of treatment failure and proofed a correlation of dose escalation and OS (12-15).

During the last years improved results were achieved in non-operable patients by introduction of novel radiotherapy concepts and technologies: stereotactic-body-radiotherapy (SBRT). SBRT combines several modern technologies to accurately treat tumors with very high irradiation doses. These irradiation doses are delivered in few radiotherapy fractions or even in one radiosurgical session. Safety of this radical but non-invasive treatment is achieved by confinement of high irradiation doses to the tumor and sparing of healthy normal tissue.

History

SBRT evolved from cranial stereotactic radiotherapy (SRT) by transferring its principles and practice to extracranial sites. Pioneer work done in the mid-1990s at the Karolinska Hospital in Sweden and this concept was quickly adopted and further developed in Japan and Germany (16-19).

Stereotaxy started out as a form of neurosurgery that uses a mechanical head frame and a precise 3-dimensional (3D) coordinate system to align and direct surgical instruments. This combination of a rigid frame and a constitutive 3D-coordinate system was used in radio-oncology for better patient-fixation and treatment planning. With improvement and development of modern imaging systems the coordinates could be referred to the imaging data-sets and non-invasive fixation systems replaced rigid frames. This opened the path for stereotactic radiation therapy to target extracranial tumor sites.

Definition of SBRT

Several work groups have given their version of a definition of SBRT (20-24). A consensus can be described as followed: SBRT is a method of external beam radiotherapy (EBRT) that accurately delivers a high dose of irradiation in one or few treatment fractions to an image-defined extracranial target. Shifting from conventional RT to SBRT is not only a simple modification of techniques, but should be considered as a complete replacement of concepts. More precise methods in terms of localizing and tracking the tumor, fixation of the patient, planning techniques and application of radiotherapy itself, are needed to apply hypo-fractionated doses as used in SBRT. However, by applying the SBRT-concept the whole diagnosis and treatment work flow and not only technical issues have to be adapted (20).

Clinical outcome of SBRT

SBRT in non-operable patients

Conventional radiation therapy has been proven to provide better outcome than best supportive care (25) and was therefore considered to be the first-line therapy in non-operable early stage lung cancer patients. Some years ago this changed in favor of SBRT. NCCN Guidelines as well as the ESMO Clinical Practice Guidelines consider SBRT as first line treatment in medically inoperable patients (26,27).

It's an attractive treatment option for several reasons: non-invasive, outpatient-basis and short overall treatment time of 1-2 weeks.

Compared to best supportive care

Population-based analyses from the Netherlands (8,28) and the US (29) demonstrated an improvement in OS for stage I NSCLC in elderly patients by introducing SBRT.

Haasbeek showed that OS improved in patients treated with radiotherapy by introducing SBRT from 16 months to 24 months between 2001 and 2009 in the Netherlands (8). Palma *et al*. showed a corresponding increase from 16 months to 21 months in elderly patients in North Holland, regardless of treatment modality (28). Furthermore both showed that availability of SBRT reduced the proportion of patients receiving non-curative treatment by 7-12%. Simultaneously, the proportion of patients that underwent surgery remained constant.

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 (29): 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 presence 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.

Compared to conventionally fractionated radiotherapy

Several prospective phase II trials have been conducted

Table 1 Summary of retrospective (n>200) and prospective trials evaluating SBRT-outcomes

Study	Year	No. of cases	Fractionation	Tox. grade pneumonitis/rib fracture [%]	OS 3a (%)	CSS 3a (%)	LC 3a (%)	Median follow up
Retrospective								
Onishi (30)	2004	245		≥2 [6.5/0.8]	56	78	86.5	24
Onishi (31)	2007	257		≥2 [5.4/1.6]	56.8	76.9	86	38
Grills SBRT (32)	2012	505		≥3 [2/1]	48	77	91	30
Senthi (33)	2013	676			55 [2a]	–	95 [2a]	33
Guckenberger (34)	2013	582		≥2 [7/4]	49		80	21
Prospective								
Nagata (35)	2005	45	4×12 Gy (at isocenter)	>3 [0]	72 (stage IB)	–	98	30
Baumann (36)	2009	57	3×15 Gy (67% isodose)	≥3 [29.8]	60	88	92	35
Fakiris (37)	2009	70	60-66 Gy in 3 fractions (80% Isodose)	≥3 [15.7]	42.7	81.7	88.1	50
Timmerman (38,39)	2009	55	3×18 Gy	≥3 [16.3]	55.8	–	97.6	34
Bral (40)	2011	40	60 Gy in 3-4 fractions	≥3 [20]	52 [2a]	64 [2a]	84 [2a]	16
Ricardi (41)	2010	62	3×15 Gy (80% isodose)	≥3 [3.2/1.6]	57.1	72.5	87.8	28

SBRT, stereotactic-body-radiotherapy; OS, overall survival; CSS, cause-specific survival; LC, local control; 3a, 3-year-value; 2a, 2-year-value.

and 2-3 years local tumor control and OS ranged between 84-98% and 43-72%, respectively.

Prospective trials (see *Table 1*) showed 2-3 years local tumor-control rates of 84-98% and OS between 43-72% in non-operable patients suffering from early-stage NSCLC and treated with SBRT (24,35-37,41,42). Even though different SBRT methodologies were used the results were similar and highly consistent.

As better local tumor control was shown to go along with higher OS in patients treated with conventional radiation therapy (12-15), it can also be shown that even further improvement of local control (LC) by applying SBRT transfers into even better OS (29). In a meta-analysis done by Grutters *et al.*, 2-year OS for SBRT was 70% *vs.* 53% for CRT and 2-year CSS was 83% *vs.* 67% (43).

Large retrospective analyses confirmed the good results described above in clinical practice outside of prospective clinical trials. Only studies with >200 patients are included in *Table 1*, which summarizes a total of 2,265 cases. The outcome of 582 patients treated at 13 German and Austrian centers was analyzed (34): it was shown that local tumor control and OS were independent from SBRT-technology used at different time periods and at different centers. Furthermore dose escalation was again shown as a significant factor influencing OS and LC. A biological effective dose BED of at least 106 Gy (2 Gy equivalent) resulted in a 3-year LC rate of 92.5% compared to 79.6% in all patients. three-year OS increased from 47.1% to 62.2%. This dose dependency of local failure was also seen by Onishi *et al*. They reported a cut-off-value at a BED =100 Gy leading to a 3-year OS of 88.9% compared with 69.4% in medically operable patients (30,31). The data collected by Grills *et al*. showed a better tumor control in patients treated with more than a BED of 105 Gy (32). A meta-analysis done by Zhang shows that the outcome gets worse for a BED below 83.2 Gy and a BED that exceeds 146 Gy. Therefore the favorable dose should be in between (44). OS is mainly affected by distant metastases and comorbidities. The probability of distant metastases is up to 20-26% of cases and is correlated to lesion size (33,38,45,46).

Numerous pro- and retrospective studies have confirmed good SBRT results. High consistency between the studies and reproducibility of results in clinical daily routine even in change of clinical setting can be seen. This is a strong indicator for quality and robustness of SBRT treatment.

Compared to radiofrequency ablation (RFA)

RFA alone (47) or in combination with conventional

radiotherapy (48) 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, CSS and OS after SBRT compared to RFA (49). Additionally, toxicity and 30-day mortality (50) 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

First-line treatment in operable stage I NSCLC patients is surgery: lobectomy proved to achieve better outcome than wedge resection (51). Today sublobar anatomical resection (segmentectomy) is discussed as another option (52,53); whether segmentectomy delivers worse (3) or comparable outcome compared to lobectomy is still under investigation (54,55).

Based on the highly promising outcome of SBRT in medically inoperable patients, three randomized trials comparing SBRT with lobectomy (ROSEL, STAR) or sublobar resection (ACOSOG Z4099/RTOG 1021) (56) have been started but all three studies closed very early due to poor accrual: <5% of the planned patients were enrolled leaving us without level A evidence.

Hence level A evidence won't be available in the near future. Several studies compared SBRT to surgery using statistical methods like matched pair analyses and propensity score matching to correct for imbalances in patient characteristics.

Grills *et al*. performed a retrospective single-institution comparison between SBRT and wedge resection. Improved local tumor control in favor of SBRT (5% *vs*. 24%) with no differences in CSS was reported. OS was better in the surgical cohort, which was explained by older age and increased comorbidities in the SBRT patients (57). The previously cited US population based SEER analysis showed no difference in OS and CSS for SBRT versus sublobar resection or lobectomy after propensity score matching (29). Moreover SBRT was shown to be the treatment with best OS up to 6 months in the total of patients, showing its superiority in morbidity and treatment-related mortality.

Puri *et al*. reported identical CSS between SBRT and surgery (lobectomy in 80% of the patients) (58). 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. Verstegen *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. Locoregional control was better after SBRT with no differences in freedom from progression and OS (59). A total of 257 propensity scored patients were analyzed by Crabtree *et al*. and there was again no difference seen between local recurrence, CSS or OS after 3 years (60).

Few studies reported outcome after SBRT when patients were considered suitable for surgical resection but surgery was actively refused by the patients. Two Japanese and one Dutch study described excellent OS of 70% after 5 years (n=87) (61), 86% after 3 years (n=29) (62) and 85% at 3 years (n=177) (63), respectively, results which compare well to OS after lobectomy. Uematsu reported a 3-year OS of 86% in medically operable patients (62). A Markov Model-based decision analysis was developed by Louie *et al*. comparing SBRT and lobectomy. They postulated a comparable OS and quality-adjusted life expectancy (64).

Palma *et al*. reported of comparable outcome in COPD patients undergoing surgical resection or SBRT. However 30-day mortality was significantly higher (0% *vs*. 10%) in surgical patients (65). This compares with a low 30-day mortality rate after SBRT in general (34). Grills *et al*. described no treatment-related death in a nonrandomized retrospective analysis comparing wedge resection with SBRT. Nevertheless a higher 30-day readmission rate in the wedge resection group was conspicuous (57).

Consequently, SBRT appears as 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 live after lung SBRT

The majority of patients treated with SBRT suffer from severe pulmonary or cardiovascular comorbidities and their poor pulmonary status, which does not allow surgical resection. Consequently pulmonary toxicity is an important point of concern in lung SBRT. Radiation induced pneumonitis (RP) is usually seen after a median of 5 months which is longer compared to conventional radiotherapy (66). The treatment of peripherally located tumors <5 cm in diameter causes RP in below 10% of cases. Risk of RP is

reported to be dependent on planned target volume (PTV), mean lung dose and low-dose spread for conventional radiotherapy (67,68). The conclusion that risk factors are similar in SBRT is supported by several papers (66,69-73). RP grade ≥II ranges from below 10% in the majority of reports up to even 28% in one report (66,69,72-80). Development of high grade RP after stereotactic treatment is rarely reported. The two largest retrospective papers show an incidence of RP Tox. Grade ≥2 of below 8% (32,34). Patients with pre-existent pulmonary fibrosis might be at increased risk for RP.

Additionally, pulmonary function is stable after SBRT with a loss of <10% (FEV1, DLCO) within 24 months after treatment (81,82). Pulmonary toxicity was not increased even in patients with very poor pre-SBRT pulmonary function and with severe COPD GOLD III-IV (82). Bishawi *et al.* even postulated a better pulmonary function after four months from SBRT for non-COPD-patients because of tumor shrinkage (83).

Chest wall toxicity (myositis, neuralgia, rip fracture, subcutaneous fibrosis, and skin ulceration) has been reported when tumors are located close to the respective normal tissue structures. Doses >30 Gy (delivered in 3 fractions) 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 (61,84-90). Based on their data, Mutter *et al.* suggest a 30 Gy constraint to a max of 70 cm^3 of the chest wall (2 cm expansion of the lung) to prevent chest wall pain.

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 (91).

Whereas safety of such high single and total doses has been demonstrated for peripheral lung tumors of usually <5 cm size, higher rates of severe toxicity have been reported in centrally located tumors with critical organs like the esophagus and large bronchi close by (92,93). Occurrence of these toxicities is known from conventional radiotherapy to centrally located tumors and therefore not unforeseen (94).

Some reports even mention treatment-related deaths, especially in centrally located tumors (40,95). Senthi *et al.* reported of a treatment-related death rate of up to 2.7%, respectively of 1% if BED below 210 Gy is used. 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 and a lower single-fraction dose (33). Considerable volume definition and avoidance of multiple treatments to the same hilar bronchus is recommended (96) in order to prevent central toxicities like major airway occlusion (97).

Studies consistently reported that SBRT has no detrimental or negative on quality-of-life (QoL) (98-100). 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 (98).

Clinical implemention of SBRT for early stage NSCLC

Before technical details of SBRT will be discussed, it is of fundamental importance that SBRT is practiced by a dedicated multidisciplinary team. All members of this team—radiation oncologists, medical physicists and radiation technologists—should receive specific training and gain experience in SBRT and treatment needs to follow written guidelines.

Several groups and organizations published their recommendation to best practice of SBRT and a short summary is given below.

Clinical evaluation

Evaluation of performance status and pulmonary function is necessary to enable a sensible treatment concept. In surgical series, higher perioperative morbidity and lower quality of life is correlated to higher age (>70 years) and the presence of other comorbidities (5,101,102). To get an impression of the patients risk to suffer from treatment-complications, pulmonary function testing like maximal oxygen uptake (VO_{2max}), forced expiratory volume in 1 second (FEV_1) or diffusion capacity (D_{CO}) is essential for both postoperative and post-radiation performance (102,103). Worse performance status and FEV_1 were proven to correlate with higher side effects in normo-fractioned radiation therapy (104).

Histo-pathological confirmation of lung cancer

Whenever possible and reasonable a biopsy for histopathological confirmation of the cancer diagnosis should be performed. However transbronchial biopsy or transthoracic fine needle aspiration is sometimes impossible

due to unacceptable risks or may fail to prove malignancy.

In this case clinical (age, smoking habit, history of prior malignancy) and radiological criteria (diameter, spiculation, nodule growth rate) are proven to be good prediction or risk factors for malignancy (105-112). The volume doubling time of malignant nodules is somewhere between 20-400 and most often around 120 days (113,114). Nodules, that grow faster or slower have a higher probability to be benign (111). In addition a PET-CT scan might help to evaluate the probability, as higher glucose metabolism is an indicator for malignancy (115).

Repeated imaging to evaluate the growth pattern is an option in patient with intermediate risk of malignancy. However, observation might put the patient at risk of disease progression (116). Although probability of tumor cell dissemination rises with stage of disease, even small primary pulmonary lesions are able to cause disseminated disease (117-120). Therefore the point of time when curative local treatment has the possibility to be successful might be missed.

If malignancy is highly likely based on the described criteria, immediate SBRT without histopathological confirmation is justified (121), as is in this population also standard practice in thoracic surgery (29,122).

As SBRT is also a way of curative treatment of unfit patients that would otherwise have gone to best supportive care, the percentage of histopathological confirmation is already decreasing as the risk for invasive confirmation might be too high (9).

Staging of disease

Correct disease staging is essential for treatment indication because only the primary tumor without elective nodal irradiation is treated in SBRT. Several working groups have given their recommendations referring to staging procedures prior to SBRT (20,21).

Chest-CT-scan using intravenous contrast including the upper abdomen is mandatory.

A whole body FDG-PET/CT-scan might not only improve the malignancy prediction model as mentioned earlier, but there's also evidence of increased detection accuracy of nodal and/or distant metastases (123-125). Even though this is still a subject of discussion for early stage lung cancer (126,127). A FDG-PET/CT scan as part of disease staging is widely postulated (20,21). Furthermore, a PET-CT scan serves to exclude clinically relevant distant metastases or second malignancies.

Pathological FDG uptake in mediastinal lymph nodes should lead to histopathological evaluation in order to prevent overstating (127). Endoscopic (EUS) or endobronchial ultrasound (EBUS) can be used for biopsy guidance. If the situation is still unclear, a mediastinoscopy may be necessary.

Interdisciplinary decision making

SBRT is a local modality that complements other surgical and non-surgical treatments.

As a corollary of this and the big efforts that are made to lay the foundation for high quality treatment, indication for SBRT should be discussed in a multidisciplinary tumor board to offer the patient a therapy concept, that's sensible, individualized and which ensures a high level of quality.

Treatment planning

Imaging for target volume and organ at risk (OAR) definition is a key factor for successful SBRT practice. Only macroscopic targets and small, immediately adjacent volumes of potential microscopic spread are treated in SBRT. 4D-imaging is essential to evaluated breathing induced tumor motion on a patient individual basis. Breathing induced target motion requires motion management strategies to minimize the dose delivered to non-pathological tissue. Several different approaches can be applied and have already been implemented into routine practice (128). In principle, we distinguish between passive 4D motion management strategies and active strategies, where treatment is adapted in real-time to breathing motion. Despite huge technical differences between the strategies, no difference in clinical outcome has been reported.

A minimum dose of at least 100 Gy BED in 3-8 fractions is mandatory as described above. In this context the importance of reassuring the delivery of the prescribed dose was shown by Latifi *et al*. They report of a higher recurrence rate for patients planned with Pencil-Beam compared to collapsed cone convolution (CCC)-algorithm even though the prescribed nominal dose and constraints were identical. This has been conducted to a relative dosimetric underdosing (129).

Patient immobilization and setup

Accurate target localization is essential to apply the conformal radiation dose to the target volume and to spare critical organs at risk. Strict immobilization by patient-

customized systems enable reproducible patient setup and reduce inter- and intrafraction motion of the patients' bony anatomy. To reduce uncertainties to a minimum, daily pretreatment imaging is an essential part of each and every treatment session.

Breathing induced target motion, setup-errors and baseline shifts must be taken into account. Image guidance can be achieved through both: visualization of the lung tumor directly or implanted fiducial markers that act as a surrogate for tumor position. Post- and/or mid-treatment imaging is recommended for quality assurance, particularly in single fraction SBRT.

Follow-up

To confirm and validate efficacy, outcomes and toxicities after SBRT, early and late effects have to be assiduous documented. Special attention has to be brought to potential complications. Differentiation between post-SBRT fibrosis and local recurrence of disease is sometimes difficult. Huang *et al*. published a systematic literature review and proposed an algorithm for this important clinical issue (130). Because of these difficulties, clinical and radiological follow-up should therefore be performed at the treating institution, where all detailed information about the SBRT treatment is available.

Summary

SBRT is an evidence-based and effective treatment option for patients with stage I NSCLC. Superiority to best supportive care and conventional radiotherapy has been documented in prospective and retrospective studies. Local tumor control rates exceeding 90% is consistently achieved and OS is mainly limited by comorbidities. Equivalence to surgery has been consistently reported in matched pair analysis and studies using propensity score matching but level A evidence is missing due to a lack of successfully completed randomized trials: a multi-professional team experienced and trained in SBRT and image guided radiotherapy is essential for safe practice. Discussion in multidisciplinary tumor boards considering the perioperative risk of the patient and patient's preference is important.

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