Table 5. Margins used for planning target volume definition for stereotactic body radiotherapy of different targets

Study	Organ	Margin transverse (mm)	Margin long (mm)	Comment	Method for breathing reduction
Timmerman *et al.*, (19)	Lung	5	10		Different methods
Bauman *et al.*, (66)	Lung	5, 10	10		Abd. comp
Zimmermann *et al.*, (65)	Lung	Individual	Individual		Abd. comp
Joyner *et al.*, (36)	Lung	5	10		
Okunieff (67)	Lung	7	10		Resp. gating
Paludan (68)	Lung	Minimum 5	10		Abd. comp
Hoyer *et al.*, (50)	Liver	Minimum 5*	10	*Later ind. margin	Abd. comp
Mendez-Romero *et al.*, (44)	Liver	5	10		Adom. comp
Wulf *et al.*, (16)	Liver	5	5, 10		Abd. comp
Kavanagh *et al.*, (48)	Liver	Minimum 5	10		Abd. comp or breath hold
Dawson *et al.*, (49)	Liver	Minimum 5*	min 5*	*Ind. margin	ABC
Svedman (69)	Liver, lung	5, 10	10		Abd. comp
Wurm (70)	Liver, lung	5	5		Adaptive gating
Hodge (71)	Lung	6	6*	*Margin to ITV	Abd. comp
Guckenberger (58)	Lung	5*	5*	*Margin to ITV	Abd. comp
Nagata *et al.*, (18)	Lung	5*	8–10*	*Margin to ITV	Abd. comp
Onishi *et al.*, (32)	Lung	0–5*	0–5*	*Margin to ITV	Different methods

Abbreviations: Resp. = respiratory; Abd. = abdominal compression. ABC = Automatic breezing control.

Treatment planning QA

Important aspects of treatment planning are adequate definitions of GTV, CTV, PTV, and OAR; conformity to dose requirements for target volumes; dose restrictions for OAR; practical aspects on a deliverable dose plan; isocenter coordinates; and accuracy in dose calculation.

The selection of adequate target volumes and an appropriate dose prescription are key factors in SBRT. Margins between GTV and CTV should be based on image information and clinical experience. The margin to PTV depends on the particular method used for SBRT, including the method for reducing internal target motion.

Evaluation of the conformity of the planned dose distribution to that intended is very important and generally requires a careful look-through of isodoses in the irradiated volume and also evaluation of dose–volume histogram data for the different volumes.

The practical aspects of the dose plan, in terms of the time for dose delivery and the possibility to reach the different beam directions, should be considered in the evaluation of the plan.

The accuracy of the dose calculation depends on the particular dose calculation algorithm used in the treatment planning system (59) and on the quantity and quality of the input data used for modeling the particular beam (radiation quality). It is important that the modeling of beam data accurately describes the beam profiles, especially with regard to geometry in the penumbra region.

Setup and geometric verification QA

The QA aspects of the geometric dose delivery are of great importance in SBRT. This can be divided into aspects of setup and geometric verification. Of importance for setup at the accelerator is that procedures for patient positioning on the treatment unit couch are the same as on the CT. Procedures to assure that the correct isocenter coordinates are used should be implemented. Preferably, this can be done with double-checking. Lasers, video cameras, imaging devices, or other equipment used for setup must be accurately aligned to the coordinate system of the accelerator (usually the mechanical isocenter (Figure). This should be checked with a phantom. The mechanical isocenter should also be checked periodically and preferably be within 0.5 mm in radius.

An important characteristic of SBRT is that direct geometric verification of the target image is used instead of imaging of surrogates for the target position, as in conventional RT. Today, several different geometric imaging methods are used in SBRT. These are CT on a device separate from the treatment unit, CT (with slit-beam or cone-beam) on a device built into the treatment unit, and projection imaging of gold markers in the tumor or of a bony tumor. For all these methods, procedures must be implemented to ensure that a proper image registration method is used to align the reference system in the geometric verification images with the same reference system in the reference image set. This procedure should be based on imaging of a phantom.

ECONOMIC CONSIDERATIONS

From the economic perspective, SBRT is more cost beneficial than surgery. In 2004, SBRT for lung tumor and liver tumors was approved by the government for insurance coverage in Japan. The charge for SBRT is only 630,000 Yen. By contrast, the surgical fee for lobectomy is approximately 900,000 Yen. The surgical fee for video-assisted thoracoscopic surgery requires both surgical and instrumental fees of 960,000 to 980,000 Yen. Other costs

including hospital charges and drug fees are higher for surgical and video-assisted thoracic surgery cases than for SBRT cases. Although similar cost comparisons for treatment in the United States and Europe have not been reported, to our knowledge, it follows that similar differences would be seen as in Japan.

SUMMARIES AND RECOMMENDATIONS

Accumulated evidence coming from the developed world strongly favors SBRT for various lung and other body tumors as an effective treatment option with acceptable toxicity (63, 64). It is expected that ongoing clinical trials will further refine its approach in selected populations of patients who are not surgical candidates for various reasons. In particular, it seems that the absolute indication of SBRT is the inoperable patient with peripheral histologically confirmed T1–3N0M0 (<5 cm) lung cancer.

However, in practice, other indicators for SBRT are encountered. Examples are an elderly patient with peripheral histologically confirmed T1–3 N0M0 (<5 cm) lung cancer who declines surgery; a patient with peripheral histologically unconfirmed (<5 cm) but radiologically diagnosed lung tumor who also declines surgery; or a patient with oligometastatic lung cancer. Other patients with primary liver cancer, oligometastatic liver cancer, pancreatic cancer, and kidney cancer could be candidates for SBRT when clinically applicable. Finally, when the patient who does not want surgery has been considered operable, SBRT can be an alternative choice.

These recommendations apply for both developed and developing countries. Moreover, several advantages inherent in the latter, such as preferred short treatment courses, fewer hospitalizations, and transport to and from hospitals, all make the cost effectiveness of this method favorable. However, certain disadvantages also exist, including high capital costs, lack of supporting (pretreatment and treatment) services, and, regardless of region, fewer patients than are usually seen in the developed world. Despite the latter, SBRT has recently been introduced in several developing countries with adequate logistics and infrastructure, which constitutes an important step toward the improvement of RT results that has been awaited for many years.

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Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

PET imaging in lung cancer

Characterization of FDG-PET images after stereotactic body radiation therapy for lung cancer

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ARTICLE INFO

Article history:
Received 4 January 2010
Received in revised form 16 March 2010
Accepted 5 April 2010
Available online 27 April 2010

Keywords:
FDG-PET
Stereotactic body radiation therapy
Lung cancer

ABSTRACT

Background and purpose: The purpose was to characterize ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) findings after stereotactic body radiation therapy (SBRT) for lung cancer.
Materials and methods: This was a retrospective review of 32 FDG-PET scans from 23 patients who underwent SBRT for lung cancer and who showed no evidence of local recurrence. The FDG uptake by lesions was assessed visually using a 3-point scale (0, none or faint; 1, mild; or 2, moderate to intense), and the demarcation (ill- or well-defined) was evaluated. For semi-quantitative analysis, the maximum standardized uptake value (SUVmax) was calculated.
Results: Grade 2 intensity was observed in 70%, 33%, 30%, and 0% of PET scans performed <6, 6–12, 12–24, and >24 months, respectively, after SBRT; well-defined demarcation was observed in 80%, 33%, 40%, and 17%, respectively, and the respective means of the SUVmax were 4.9, 2.6, 3.0, and 2.3. The SUVmax was significantly higher for scans performed at <6 months than at 6–12 or >24 months.
Conclusions: FDG uptake tended to be intense and well-defined at early times after SBRT, especially within 6 months, and was faint and ill-defined at later periods. Moderate to intense FDG uptake observed soon after SBRT does not always indicate a residual tumour.
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Stereotactic body radiation therapy (SBRT) is an important option for the treatment of solitary lung cancer, especially in inoperable patients. Initial studies on SBRT were reported by Blomgren et al. [1] and Uematsu et al. [2]. Thereafter, many promising outcomes have been reported for SBRT of solitary non-small cell lung cancer (NSCLC). We reported our experience in SBRT for primary lung cancer [3]. The local control rates for stage I NSCLC were 96.7% for T1a, 84.5% for T1b, and 78.1% for T2a, respectively. The excellent rates for local control of stage I NSCLC after SBRT were also reported by several authors, and they ranged from 77% to 95% [4–7].

When SBRT is applied to operable patients, the early detection of local recurrence after SBRT is vital for those who may be salvaged with surgery [8]. However, it is difficult to detect local recurrence based on computed tomography (CT) alone [9,10], because consolidations representing radiation-induced inflammation or fibrosis [11] can overlap the tumour and prevent evaluation of local tumour status.

As a diagnostic imaging tool, positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) reveals metabolic changes. FDG-PET currently plays important roles in not only staging [12] and restaging [13] but also the prognostic assessment of lung cancer [14]. The clinical significance of FDG-PET after conventional radiotherapy for NSCLC has been described [15–18], but FDG-PET findings after SBRT are limited [19,20]. Even with FDG-PET, it may be difficult to differentiate between recurrence and inflammatory changes. Nevertheless, the recognition of the uptake patterns and frequency of FDG accumulation owing to inflammatory processes after SBRT would be helpful in interpreting PET images during follow-up.

The objective of this study was to characterize the FDG-PET findings in patients with lung cancer treated by SBRT.

Materials and methods

Patients

Inclusion criteria for this study were as follows: (1) availability of at least one FDG-PET scan performed 1 or more months after SBRT and attenuation-corrected PET images reconstructed by

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doi:10.1016/j.radonc.2010.04.011

iterative algorithms; (2) follow-up duration of >12 months; and (3) no local recurrence for at least 6 months after the FDG-PET scan. Local recurrence was diagnosed based on histological confirmation or continuous enlargement of local tumour on CT for 6 months or more. Among 96 patients who underwent SBRT for primary lung cancer at our institution between September 1998 and November 2005, 58 patients, 9 patients, and 6 patients were excluded based on the criteria (1), (2), and (3), respectively. The remaining 23 patients were eligible for this study. All patients provided written informed consent for SBRT and associated researches which were approved by the institutional review board. Characteristics of the patients were shown in Table 1. Fifteen patients were male; eight were female. The median age of the patients was 77 years (range 64–89). The histological findings were adenocarcinoma in 14 patients and squamous cell carcinoma in six patients, with unconfirmed diagnoses in three patients. The post-SBRT median follow-up duration was 51 months (range 13–113).

SBRT technique

Details of the SBRT technique used in the present study have been described in our previous study [21]. The patient's body was immobilized using a stereotactic body frame (Elekta AB, Stockholm, Sweden). SBRT was planned using a commercial treatment planning system (CADPLAN or Eclipse; Varian Medical Systems, Inc., Palo Alto, CA). The planning target volume (PTV) was defined as the internal target volume, which was delineated on long scan-time CT images, with a 5-mm margin for setup uncertainty. Multiple non-coplanar static ports (5–8 ports) were arranged for the PTV. The prescription dose was 48 Gy, administered in four fractions at the isocenter. Irradiation was performed with 6-MV X-ray beams from a linear accelerator (Clinac 2300 CD; Varian Medical Systems). The median overall treatment time was 11 days (range 4–14) in this cohort.

PET scanning

^{18}F-FDG was synthesized by the nucleophilic substitution method, using an ^{18}F-FDG synthesizing instrument (F-100; Sumitomo Heavy Industries, Tokyo, Japan) and a cyclotron (CYPRIS-325R; Sumitomo Heavy Industries, Tokyo, Japan). Patients fasted for $\geqslant$4 h before the intravenous injection of approximately 370 MBq of FDG. Whole-body PET images with attenuation correction were acquired about 50 min later, using a whole-body PET scanner with an 18-ring detector arrangement (Advance; GE Healthcare, Milwaukee, WI). The system permitted the simultaneous acquisition of 35 transaxial images with a 4.25-mm interslice spacing. The transaxial resolution was 4.2 mm at full width at half maximum, allowing for multidirectional reconstruction of the images without loss of resolution. The field of view and pixel size of the reconstructed images were 128 mm and 4 mm, respectively. The images were reconstructed by ordered-subsets expectation maximization algorithm.

Table 1
Patient characteristics.

Sex	
Male	15
Female	8
Age (median; range)	77; 64–89
Histology	
Adenocarcinoma	14
Squamous cell carcinoma	6
Unconfirmed	3

Evaluation and analysis

There were a total of 32 FDG-PET scans for the 23 patients, because nine patients each had two PET scans. For the analysis, the PET scans were divided into four groups according to the time duration between the completion of SBRT and the PET scan, which ranged from 1 to 51 months with a median of 12 months: <6 months, 10 scans; 6–12 months, six scans; 12–24 months, 10 scans; and >24 months, six scans. The intensity and pattern of the FDG uptake were evaluated qualitatively and semi-quantitatively in the pulmonary region, which received a high dose.

For the qualitative evaluation, the intensity of the FDG uptake was assessed visually using a 3-point scale: 0, none or faint uptake; 1, mild uptake, comparable to that in the blood pool; and 2, moderate to intense uptake, greater than that in the blood pool. The demarcation of the tracer uptake was categorized as well- or ill-defined. The qualitative evaluations were determined by a board-certified radiologist and nuclear medicine physician (Y.N.) and a board-certified radiation oncologist (Y.M.) on consensus without any information about time duration between SBRT and FDG-PET. For three scans, although qualitative analysis was pos-

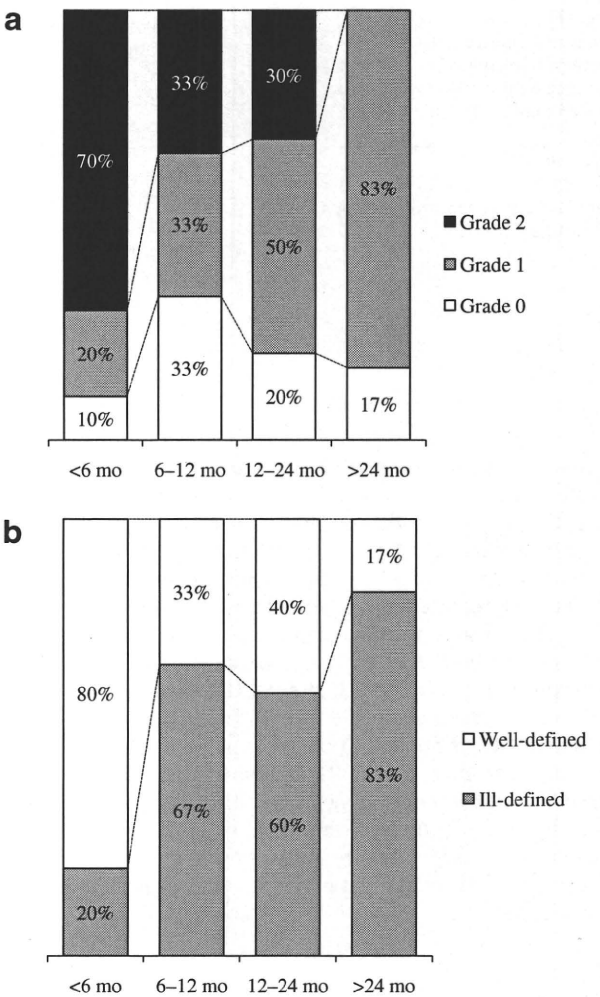

Fig. 1. Visual analysis of FDG uptake regarding intensity (a) and demarcation (b). Intensity was classified into three grades: 0, none or faint uptake; 1, mild uptake, comparable to that in the blood pool; and 2, moderate to intense uptake, greater than that in the blood pool. The prevalence of intense and well-defined uptake gradually decreased with time after treatment.

sible, a reliable SUVmax could not be obtained because of artifacts. Thus, a total of 29 PET scans were analyzed semi-quantitatively. The SUVmax was calculated as follows:

SUV = $FDG_{region}/(FDG_{dose}/WT)$, where FDG_{region} is the decay-corrected regional ^{18}F-FDG concentration in Bq/ml, FDG_{dose} is the injected ^{18}F-FDG in Bq, and WT is the body weight in grams.

Statistical significance was defined as $p < 0.05$.

Results

Qualitative evaluation (Fig. 1)

The numbers of PET scans showing FDG uptake intensity grades of 0, 1, and 2 for each time category were: 1 (10%), 2 (20%), and 7 (70%) for scans performed at <6 months; 2 (33%), 2 (33%), and 2 (33%) at 6–12 months; 2 (20%), 5 (50%), and 3 (30%) at 12–24 months; and 1 (17%), 5 (83%), and 0 at >24 months. Uptakes with ill- and well-defined demarcations were observed in 2 (20%) and 8 (80%) scans at <6 months; 4 (67%) and 2 (33%) scans at 6–12 months, 6 (60%) and 4 (40%) scans at 12–24 months, and 5 (83%) and 1 (17%) scans at >24 months. The FDG uptake tended to be intense and well-defined at early times after SBRT.

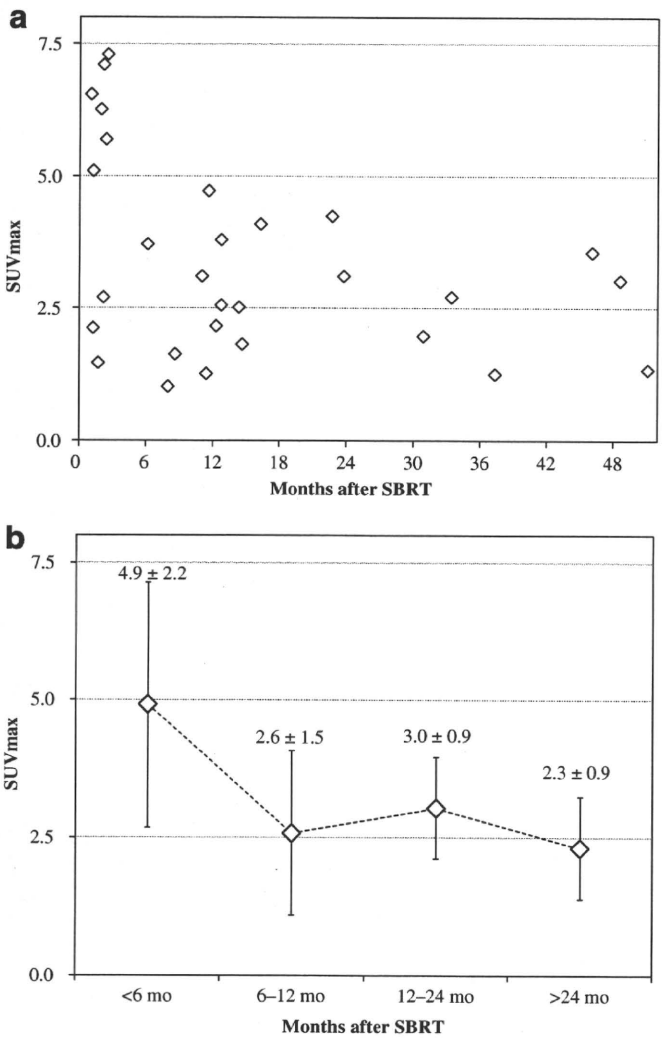

Fig. 2. SUVmax in FDG-PET and the time duration between SBRT and FDG-PET. (a) Scatter plot of SUVmax versus time after SBRT, showing a moderately negative correlation coefficient of −0.388. (b) Mean (diamond) and SD (vertical bar) of SUVmax for FDG-PET performed at different times after SBRT: <6 months, 6–12 months, 12–24 months, and >24 months. The SUVmax at <6 months was significantly higher than that at 6–12 or >24 months.

Semi-quantitative evaluation (Fig. 2)

A moderate negative correlation was observed between the SUVmax and time after SBRT (Pearson's product–moment correlation coefficient = −0.388; $p = 0.038$). The SUVmax (mean ± SD) was 4.9 ± 2.2 at <6 months, 2.6 ± 1.5 at 6–12 months, 3.0 ± 0.9 at 12–24 months, and 2.3 ± 0.9 at >24 months. The SUVmax at <6 months was significantly higher than that at 6–12 months or >24 months ($p = 0.042$ or 0.020, Tukey HSD test). Differences in the SUVmax were not significant between 6–12 months, 12–24 months and >24 months.

Changes in FDG uptakes between two scans

Table 2 shows FDG-PET findings in the nine patients who had two PET scans. FDG uptakes in three of the nine patients (Patients A, D, and F in Table 2) changed into typical findings (i.e. faint intensity, ill-defined demarcation, and less SUVmax) in the later periods. A representative case is demonstrated in Fig. 3. No significant change was observed in two patients (Patients B and C). The remaining four patients (Patients E, G, H, and I) showed a higher grade of intensity or a higher SUVmax in the second scan than in the first scan.

Discussion

Two previous reports have described FDG-PET findings after SBRT for lung cancer. Ishimori et al. investigated the feasibility of PET with ^{18}F-FDG and ^{11}C-methionine (MET) in nine patients treated with SBRT [19]. The SUV decreased gradually with time in five patients, whereas it increased at 2 weeks after SBRT in two patients and at >3 months after SBRT in the remaining two patients. Radiation pneumonitis was thought to be the cause of this increase; the addition of MET-PET did not supply any information beyond that provided by FDG-PET. Hoopes et al. also evaluated FDG-PET in patients treated with SBRT [20]. PET analysis was performed in 28 patients after a median post-SBRT time of 17.3 months (range 4–48). Four of the 28 patients showed a high SUV (2.5–5.87) without evidence of local, nodal, or distant failure. In the present study, the SUVmax remained high (mean 2.7; range 1.3–4.3) at ⩾12 months

Table 2
FDG-PET findings in patients who received PET scan twice.

Patient	Months after SBRT	Intensity grade	Demarcation	SUVmax
A	37	1	Well	1.3
	51	1	Ill	1.3
B	21	1	Ill	NA
	46	1	Ill	3.6
C	2	0	Ill	1.5
	9	0	Ill	1.6
D	2	2	Well	7.1
	49	1	Ill	3.0
E	13	1	Ill	2.6
	24	1	Ill	3.1
F	1	2	Well	5.1
	14	1	Well	2.5
G	1	1	Well	2.1
	13	2	Well	3.8
H	2	1	Ill	2.7
	12	2	Ill	4.7
I	11	1	Ill	3.1
	23	2	Ill	4.3

Abbreviations: SBRT, stereotactic body radiation therapy; SUVmax, maximum standardized uptake value; NA, not available.
Intensity grades were the same as in Fig. 1.

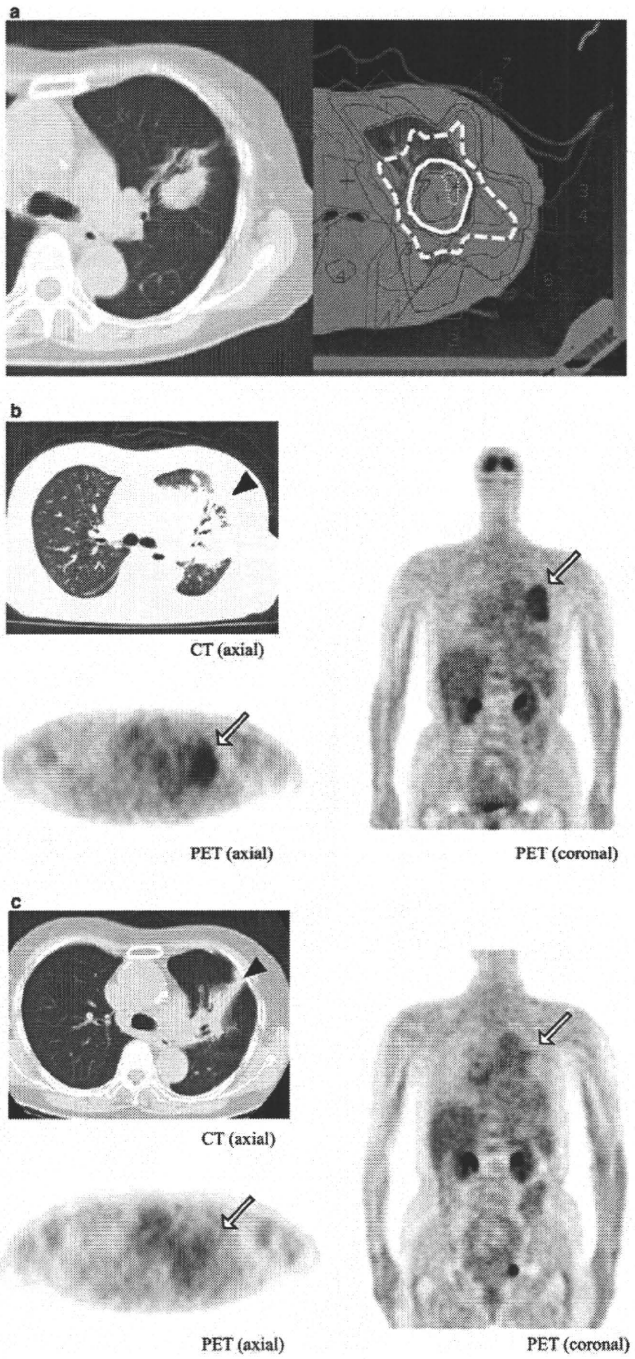

Fig. 3. 79-year-old woman (Patient D in Table 2) with cT2N0M0 primary lung adenocarcinoma, who underwent SBRT with a prescription dose of 48 Gy administered in four fractions at the isocenter. (a) CT image before treatment (left) and dose distribution of SBRT (right). The inner thin dashed, solid, and outer dashed lines indicate 48-, 40-, and 20-Gy isodose lines, respectively. (b) CT and FDG-PET images 2 months after SBRT. Radiation pneumonitis is observed upon CT (arrowhead). The FDG-PET scan shows well-defined and intense (grade 2) uptake (arrows) with the SUVmax of 7.1. (c) CT at 52 months and FDG-PET at 49 months; CT shows a scar-like shadow (arrowhead). Ill-defined and mild (grade 1) uptake is seen upon FDG-PET (arrows). The SUVmax was 3.0.

after SBRT, which is consistent with the results of Hoopes et al. [20].

It is important to detect local recurrence soon after SBRT, but this is difficult based on CT alone. We have previously evaluated post-irradiation changes and local recurrence after SBRT, based on CT [9]. However, in the previous study, we could not detect any significant CT differences between radiation-induced inflammatory changes and local recurrence. We concluded that early detection of local recurrence is difficult using CT because of the dense consolidation, called mass-like consolidation, which was observed at a median post-SBRT time of 5 months in 68% of the cases. Most cases (89%) of consolidation were confirmed as radiation-induced lung injury, although a few (11%) were local recurrence. Takeda et al. reported that 20 of 50 patients had abnormal opacity that was suspicious for local recurrence at a median of 20.7 months after SBRT [10]. However, only three patients had recurrence, and the remaining 17 patients were free from recurrence or were considered equivocal. They also concluded that it was difficult to distinguish radiation fibrosis from local tumour recurrence.

The value of FDG-PET in detecting residual or recurrent NSCLC after conventional radiotherapy has been evaluated by Frank et al. [15] and Bury et al. [16], who found a sensitivity and specificity of 100% and 89–92%, respectively. Inoue et al. have suggested a threshold SUV of 5.0 for the differential diagnosis between local recurrence of lung cancer and post-treatment changes [17]. Indeed, our study had no case in which the SUVmax was >5.0 at $\geqslant$6 months after SBRT. According to Takeda et al. [10], a patient with a SUVmax of 5.0 at 12 months after SBRT developed local recurrence, and three patients with a SUVmax of 2.2–3.13 showed no evidence of local recurrence. However, Hoopes et al. [18] reported that two patients with a SUV > 5.0 at 23–26 months were free from local recurrence. Further studies are needed to investigate an optimal SUV for distinguishing local recurrence from post-SBRT changes. As far as we are aware, there have been no studies to date regarding FDG-PET detection of local recurrence after SBRT.

The present study has some limitations. First, the study was not prospective but was a retrospective review. FDG-PET was performed in a limited number of patients, some of whom had a suspicious consolidation upon CT, which might have caused selection bias. Second, local control was not based on pathological confirmation but on CT images. Therefore, FDG uptake demonstrating recurrent tumours might have been included with that owing to inflammation caused by irradiation. However, clinically suspicious recurrent cases were not included, and a median follow-up duration of 51 months was sufficient to establish no recurrence of local tumours.

In conclusion, this study showed that FDG uptake tended to be high and well-defined during an early time period after SBRT, especially within the initial 6 months, and became lower and ill-defined during later periods. Moderate to intense FDG uptake observed during an early period after SBRT does not always indicate residual or recurrent tumour. These findings may help in interpreting FDG-PET data for follow-up in patients with NSCLC after SBRT.

Conflict of interest notification

Yukinori Matsuo: none; Yuji Nakamoto: none; Yasushi Nagata: none; Keiko Shibuya: none; Kenji Takayama: none; Yoshiki Norihisa: none; Masaru Narabayashi: none; Takashi Mizowaki: none; Tsuneo Saga: none; Tatsuya Higashi: none; Kaori Togashi: none; Masahiro Hiraoka: none.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research Nos. 20229009 and 21791188 of the Ministry of Education, Culture, Sports, Science and Technology, and by Grants-in-Aid Nos. H20-S5 and H20-020 of the Ministry of Health, Labour and Welfare in Japan.

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Heide J, Schmittel A, Kaiser D, Hinkelbein W (eds): Controversies in the Treatment of Lung Cancer.
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Stereotactic Body Radiation Therapy for Early Non-Small Cell Lung Cancer

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Abstract

For patients with early stage non-small cell lung cancer (NSCLC) unsuitable for resection local high-dose radiotherapy is the treatment of choice. In modern series even with escalated conformal radiotherapy local control rates of about 55% remain disappointing. Within the last years, stereotactic radiotherapy has been shown an effective treatment approach for early stage malignant lung tumors, combining the accurate focal dose delivery by stereotactic techniques with the biological advantages of dose escalated hypofractionated radiotherapy. Typical treatment regimens include three to five fractions over 1–2 weeks or 1 single fraction as radiosurgery. With adequate staging procedures including FDG-PET-CT scan and a low probability of subclinical involvement of unsuspicious locoregional lymph nodes, the concept is to irradiate the primary T1/2 tumor alone. Recent data report local control rates of up to 90%, with favorable results especially for patients in good general condition. Less than 10% of all patients develop isolated tumor recurrences in regional lymph nodes. Three-year survival is significantly improved to more than 80% when biological effective doses of more than 100 Gy are applied to patients in good conditions. Systemic tumor recurrence still is a major problem, making an additional systemic chemotherapy interesting for selected patients after hSRT, such as those younger than 75 years.

Cancer is one of the major health concerns worldwide. The burden of cancer is increasing globally, with an expected 20 million new cases per year in 2020, half of which will be in low and middle income countries [1].

In stage I non-small cell lung cancer (NSCLC) standard treatment is still surgery, in younger patients sometimes followed by systemic chemotherapy [2, 3]. At 3 years, mean overall survival rates of about 70% in stage IA and of less than 50% in stage IB were published [4–6]. Local tumor control is about 90% and depends on the type of resection. Lobectomy and pneumonectomy are superior to atypical resection [5]. It is reported that the worse outcome with atypical resection is not only influenced by an increased local failure rate but mainly by perioperative morbidity and mortality. For these patients in early NSCLC stages with pre-existing comorbidity, advanced age or refusal of operation, definitive local high dose radiotherapy alone may be the standard treatment option. Unfortunately, with conventionally fractionated and even moderately accelerated or hyperfractionated schedules, the results are still less favorable than those obtained with surgery alone. The reported 5-year survival rates are as low as 18% (5–42%), but it became obvious that the highest doses achieved a better local control than the standard 60 Gy in 30 fractions commonly used in practice. Furthermore, local failures continue to occur even at the highest dose levels, possibly owing to the very protracted overall treatment times [7–10].

Among many technologically advanced treatments that new informatic technologies brought to the field of radiation oncology, such as the use of sophisticated treatment planning systems and radiation therapy using three-dimensional software programs, stereotactic radiotherapy has been increasingly used in recent years [11, 12]. Combining the accurate focal dose delivery of stereotactic radiotherapy with the biological advantages of hypofractionated radiotherapy has been shown to be an effective treatment approach for both malignant and nonmalignant brain tumors. High biologically effective radiation doses are generally of advantage with regard to tumor cell kill and local tumor control. Patients with clinically T1–2 N0 tumors seem to be the ideal candidates for investigation of these new technologies of SBRT [11, 13–16]. This paper summarizes the current technique of SBRT and recent clinical data on local tumor control, overall survival and early and late toxicity of SBRT in early NSCLC.

Definitions of Stereotactic Body Radiation Therapy

SBRT evolved from the clinical experience of intracranial stereotactic radiosurgery and the technical development of radiotherapy in general. Today, SBRT is an accepted acronym for Stereotactic Body Radiation Therapy, which previously commonly was called extracranial stereotactic radiotherapy. The following essential components are collectively unique to SBRT [17–19]:

- The use of a well-defined reference system for localization of the target and for set-up at the accelerator. The reference (stereotactic) system is a 3D coordinate

system as referenced to fiducials, which are 'markers' whose position can be confidently correlated both to the target and the treatment delivery device. A stereotactic treatment is one directed by such fiducial references.
- Direct geometrical verification of the target position in the reference system, as opposed to verification of surrogate markers in conventional radiotherapy.
- Secure immobilization and repositioning of the patient, as well as proper accounting for the internal organ motion.
- Small margins to PTV.
- Spatial dose distribution very conformal to and commonly intentionally heterogeneous within the PTV with a very rapid fall off to surrounding normal tissues.
- Treatment of solid tumors.
- Prescription of biologically very potent target doses, with a few fractions of very high dose delivered in a short time.

SBRT is thus used to treat well-demarcated visible gross tumors. It is not intended for prophylactic (adjuvant) treatment, independent of the technique used for SBRT (Linac, Protons, Cyberknife e.o.).

Different reference systems defined by fiducials in use in SBRT exist (fig. 1). The reference system relates both to the target (CTV) and to the treatment unit. *Set-up* is the alignment of the reference system used, to the coordinate system of the accelerator, according to what is determined during the dose planning, and the set-up margin is the margin used for the set-up error [20]. Characteristic for SBRT is a small set-up error, usually of less than 5 mm. To account for variations in position, shape and size of the CTV in the reference system used, a margin is added, an internal margin [20]. *PTV* is a geometrical concept used in treatment planning to ensure that the prescribed dose is delivered to the CTV, and includes both the set-up margin and an internal margin [20]. *Geometrical verification* aims at making confident that the volume of the CTV will be within the PTV during the treatment. This can be optimized by image guidance within the treatment room (IGRT) with conventional X-ray, CT scan or cone-beam CT as well, which is not necessarily obligat for SBRT. With a small set-up error (within 1 mm), the geometrical verification will be essential to make it confident that the volume of the CTV will be within PTV in the reference system used.

In some SBRT methods, set-up and geometrical verification are two separate steps in the process. However, when reference systems defined by tumor fiducials are used (for example, gold markers in the tumor and projection imaging or the tumor itself and cone-beam CT) the two steps are generally integrated to a single procedure, as the set-up also includes an on-line correction as a result of the geometrical verification.

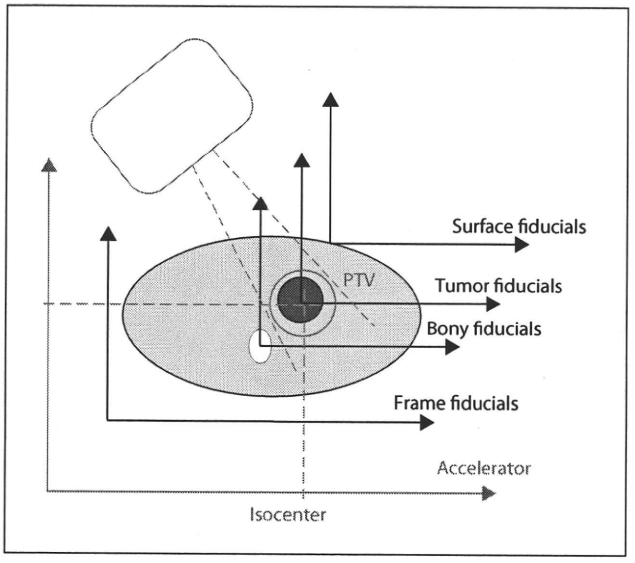

Fig. 1. Different reference systems defined by fiducials used in SBRT.

Staging Procedures before SBRT

Accurate clinical staging is critical in the evaluation of any patient with NSCLC. The clinical stage as determined by all available clinical, radiographic, and biopsy data, has to be performed as accurately and comprehensively as possible. Newer technologies such as autofluorescence bronchoscopy, narrow banding imaging, endoscopic ultrasound, endobronchial ultrasound and electromagnetic navigation are used to define the local tumor extension [21].

Mediastinoscopy remains the gold standard for regional nodal staging. Due to the fact that most patients presented for SBRT were not amenable for operative staging procedures due to poor functional status of lung and/or heart, CT scans have been used in principle to define both local and regional tumor extension. Invasive procedures can be omitted in patients with peripheral tumors and negative mediastinal positron emission tomography images [22]. Based on recent knowledge on the superiority of FDG-PET scan to CT scanning alone, with a 91% sensitivity and a 86% specificity for mediastinal staging and a negative predictive value of about 98%, nowadays, FDG-PET-CT scan is recommended in general [22, 23].

In SBRT, the concept to irradiate the primary tumor (T1 or T2) alone is based on the well-known observation that in these early T stages the probability of involvement of locoregional lymph nodes after adequate staging procedures, including a

negative FDG-PET-CT scan for regional lymph nodes, is comparatively low, usually below 10% [24]. In all modern series, FDG-PET-CT is applied as the basic staging procedure and for radiation treatment planning to define target volume, especially in tumors causing subsequent atelectasis.

Unfortunately, data sets on overall survival with a longer follow-up after initial staging with FDG-PET-CT are still limited. In centrally located, undifferentiated carcinoma, MRI of the brain may be added to ascertain the staging of the brain [25, 26].

Implementation of Techniques in Clinical Routine

The clinical issue of SBRT is high local tumor control with low acute and late toxicity. Both goals are achieved by very high fraction doses applied to a small volume. Because the CTV is given, volume reduction can only be achieved by increased precision of treatment, which covers both – setup accuracy and target mobility. For this purpose two strategies are available: a frame-based stereotactic approach (external fiducials) and a frameless procedure, usually with internal markers (i.e. implanted in the tumor by CT punction or endoscopic techniques). In the latter, imaging is used for guidance, and in the previous situation, IGRT can be used additionally but is not needed in principle.

In both situations, patient fixation is required using a stereotactic body frame (SBF; ELEKTA, Inc.), BodyFix (Medical Intelligence/ELEKTA, Inc.) or comparable devices [13, 17, 27, 28]. In all devices, the patient is fixed by a tight vacuum pillow, which again can be related to an external (stereotactic) reference system. Breathing mobility can be easily decreased mechanically by abdominal pressure or – more advanced – controlled by gating techniques such as the active breathing control (ABC; ELEKTA, Inc.) or real-time positioning management (PRM, Varian, Inc.). Oxygen-assisted shallow breathing or JET ventilation are also in use, but its value is not yet proven.

In all scenarios setup accuracy and breathing mobility of the target have to be assessed for treatment planning and prior to irradiation. This can be performed by the use of fluoroscopy (if the target can be seen or is strongly related to bony structures) or by CT (if the target cannot be identified by conventional X-ray equipment). Recent advances in technology allow target verification and assessment of breathing mobility directly on the treatment couch using cone-beam CT. With the use of cone-beam CT prior to treatment stereotactic coordinates can be abandoned, because the isocenter position can be directly assigned to the appropriate position (image-guided radiotherapy).

Treatment planning is usually based on CT data. Further imaging modalities such as MRI or FDG-PET can be included, too. The scanned volume should not

only cover the target but also the complete organs at risk, e.g. the lung and heart for pulmonary tumors. If non-coplanar irradiation techniques might be used, this should be regarded when determining the scanned volume. While slice thickness obviously depends on the size of the tumor, under normal conditions 3–5 mm will be appropriate in the majority of cases. Intravenous contrast will be helpful in central lung tumors. Prior to definite scanning potential breathing mobility has to be evaluated. Depending on the method used to decrease breathing mobility the amount of motion should be analyzed (it has to be regarded to determine appropriate margins for PTV definition). This can either be done by multislice CT, dynamic scans (repeated scans at the same couch position) or evaluation of the target position in maximum in- and expiration. While this approach is based on slices, which show the scanned tumor position in a very short (<1 s) period of time resulting in a 'sharp' image, the target also can be scanned by a slow CT. With this technique the tumor is scanned very slowly (e.g. scan time for a slice 3 s). The image shows a 'blurred' shape of the target including and depending on internal motion (ITV) [29], which represents the 'orbit' the target is moving in. This technique might have advantages especially when a cone-beam CT is used for target verification prior to irradiation, because due to the slow scan time (about 1 min) the shape of the target will also appear 'blurred' [30].

Ideally, both GTV and CTV should be geometrically defined in an unambiguous way in the reference system used. In clinical practice, however, there will always be more or less breathing motions during imaging (even with gating there will be a residual motion) as well as differences in tumor position during imaging and treatment. ICRU 62 [20] defines an internal margin (IM) and an internal target volume (ITV) for the physiologic movements and variations of the CTV during therapy (fig. 1). One way to get an estimate of the IM is to do the imaging during several breathing cycles (cf. Imaging for planning above). In clinical practice of SBRT, ITV is relatively seldom defined explicit, but PTV is usually drawn with standard margins to a CTV which has been defined by normal dose-planning imaging (table 1). Current clinical experience is basically based on this way of target definitions. The standard margins are determined from geometrical verification imaging of patient cohorts and basically only valid for the use of a particular set of conditions like methods for patient fixation, breathing reduction as well as choice of reference system and method for set-up and geometrical verification. However, due to similar geometrical requirement using different methodology for SBRT there is today a relatively narrow range of margins between CTV and PTV used in clinical practice. With the immobilization equipment and methods for reduction of the target motion described in this report, the longitudinal margin is generally 10 mm. In the transverse plane, margins are usually of the order of 5 mm up to 10 mm (table 1) [15, 30–40]. Even though the margins reported are relatively

Table 1. Margins for definition of planning target volume used in different recent trials of SBRT in early NSCLC

First author (year)	Margin trans mm	Margin long mm	Comment	Method for breathing reduction
Timmerman (2006) [19]	5	10		different methods
Baumann (2006) [31]	5, 10	10		Abd. Comp
Zimmermann (2006) [32]	individual	individual		Abd. Comp
Joyner (2006) [74]	5	10		
Okunieff (2006) [35]	7	10		Resp gating
Hoyer (2006) [34]	min 5	10	later ind. marg.	Abd. Comp
Wulf (2005) [33]	5	5, 10		Abd. Comp
Wurm (2006) [36]	5	5		adaptive gating
Hodge (2006) [37]	6	6	Marg. to ITV	Abd. Comp
Guckenberger (2007) [30]	5	5	Marg. to ITV	Abd. Comp
Nuyttens (2006) [38]	5	5		tracking
Nagata (2005) [39]	5	8–10	Marg. to ITV	Abd. Comp
Onishi (2007) [15]	0–5	0–5	Marg. to ITV	different methods
Hata (2007) [40]	5	5–10	Marg. to ITV	different methods

similar, it is important that the margins used should be based on experience from the particular methodology used at each center.

Treatment planning in SBRT is done on commercial treatment planning systems (TPS) used also for radiotherapy planning in general. Pencil beam algorithms have a limited accuracy, but acceptable to use [41]. Point kernel-based superposition/convolution algorithms give a more accurate estimate of the dose to the tumor and surrounding lung tissue [41]. The error in the dose calculation for tumors in the lungs is reduced if the photon energy is restricted to a maximum of 6 MV. Comparing different publications, these effects should be taken into account.

There are two different concepts of treatment planning for SBRT. One concept is to maintain dose homogeneity within the target derived from conventional radiotherapy. In this case, the homogeneity index (HI) is an important index and the dose is usually prescribed at the isocenter. The other concept is not to maintain

Table 2. Dose-volume constraints of various organs at risk, used in RTOG trial 0618 treating operable patients with early stage primary NSCLC

Organ	Volume	Dose, cGy
Spinal cord	any point	18 Gy (6 Gy per fraction)
Esophagus	any point	27 Gy (9 Gy per fraction)
Ipsilateral brachial plexus	any point	24 Gy (8 Gy per fraction)
Heart/Pericardium	any point	30 Gy (10 Gy per fraction)
Trachea and ipsilateral bronchus	any point	30 Gy (10 Gy per fraction)
Whole lung (right and left)	V-20	less than 5–10% of total lung volume
Skin	any point	24 Gy (8 Gy per fraction)

dose homogeneity derived from cranial stereotactic radiotherapy. In this case, the conformity index (CI) is an important index and the dose is prescribed at the PTV margin. To avoid serious complications, the most important issue for RTP of SBRT is to maintain the dose constraints of OAR, including the spinal cord, pulmonary artery, bronchus, and heart (table 2).

Biological Basis of Hypofractionated SBRT

Different to normofractionated radiotherapy, the biological purpose of stereotactic irradiation is lethal rather than sublethal cell damage in the high dose area without repair. Additionally due to short overall treatment time (single dose, hypofractionation within 1–3 weeks) avoidance of repopulation of tumor cells is another advantage. On the other hand the prescription of the amount of dose has to respect that re-oxygenation and re-distribution of cells in the cell cycle will not occur. Organs at risk are prevented from serious damage by sparing these tissues from high dose area. This is in accordance to the practice in intracranial stereotactic radiotherapy. The optimal amount of dose required to achieve local tumor control and the tolerance doses for normal tissue are a subject of evaluation [11, 16].

Besides dose escalation trials [13, 42, 43], a lot of prospective institutional-based reports on clinical results of SBRT have been published. Unfortunately, comparison of these results is difficult, because different dose fractionation schedules have been used and normalization and prescription of dose (PTV-enclosing isodose vs. isocenter, homogeneous vs. inhomogeneous dose distribution) is also very non-uniform. To overcome this problem, some authors used the biological effective

dose (BED) based on the formula: BED (Gy) = dose/fraction × fraction number (1 + fraction dose/α/β) using an alpha/beta of 10 Gy for tumor tissue. Analyzing their data they found a BED of about 100 Gy to be appropriate to achieve a TCP of about 90% for lung tumors [15, 33]. Nevertheless, this approach can be criticized, because it is not proven that the LQ model will be reliable at such high fraction doses. Therefore eventually other radiobiological models might be better to predict the effect of ESRT including modifications of the multitarget model [44].

Historical Aspects and Early Clinical Experience in SBRT of Lung Cancer

The clinical experience from intracranial stereotactic radiosurgery introduced in the middle of the 20th century, together with the technical development in conventional radiotherapy, initiated the development of stereotactic radiotherapy with very high dose per fraction, delivered in a short time to targets in the body. This started at Karolinska University hospital, Sweden in 1991 with tumors in the liver and lungs [17]. In parallel, the method was developed in Japan and clinically introduced in 1994 for lung tumors [45]. During the last 5 years of the 1990s, SBRT was introduced at several centers in Europe, Japan and USA [28, 42, 46, 47]. Early reports already showed very promising results both with regard to local control and toxicity for the hypofractionation schedules adopted with 10–15 Gy/fraction given in a few fractions during a short time [27, 45]. However, due to the new aspects introduced in SBRT, clinical experience was gathered at a very slow rate at the beginning and it was not until the end of the 1990s and the first years of the 21st century that outcome data from several centers were at hand to confirm the initial promising results.

Clinical Experience

Considerable investigation of SBRT to treat both primary and metastatic cancers of the lungs has been carried out around the world. With the high prevalence of such tumors, the high rates of cancer-associated deaths, and the desire for more effective treatments, it is no wonder that lung tumors have been the most common site of SBRT treatment. In addition, the large volume and inherent functional redundancy of pulmonary tissue has allowed stereotactic treatments to be carried out effectively and with acceptable toxicity for many tumor presentations especially in the periphery of the lung.

So far, the experience in treating primary lung cancer using SBRT has mostly occurred in patients who were unfit for surgical resection (medically inoperable patients). Furthermore, nearly all reports describe outcomes in patients with stage I disease, particularly for peripheral tumor locations. As medically inoperable

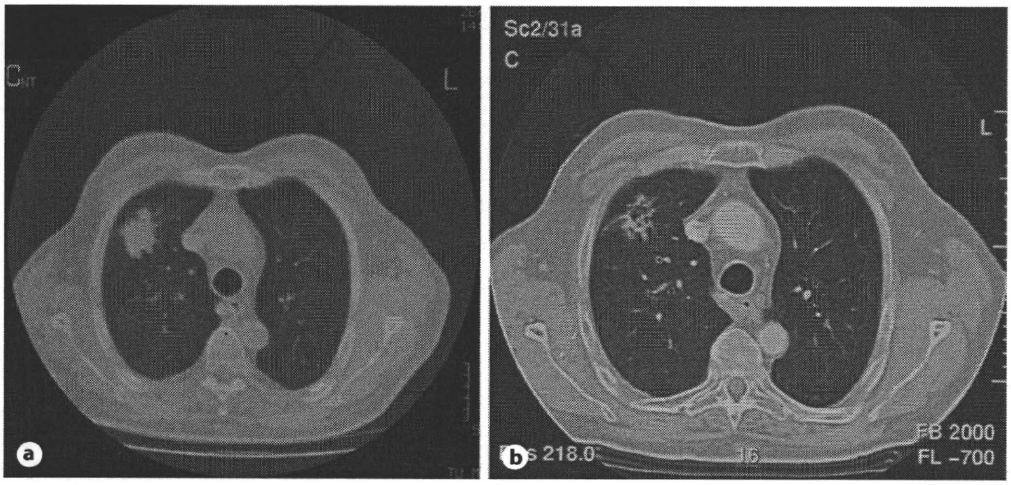

Fig. 2. NSCLC of the right upper lobe. T1 tumor. Before SBRT. 18 months after SBRT with 3 × 12.5 Gy (calculated on the 60%-isodose). Local lung fibrosis. Complete remission.

patients are at risk of dying from more causes than just their lung cancer, survival in these patients is ultimately compromised. On the other hand, initial data report on local control rates of up to 90%, with favorable results especially for patients in good general condition [15], asking for a further spread of this technique to new indications.

Local Tumor Response

Still the benefits of SBRT can be quantified by assessing local control (especially if reported as an actuarial rate). Numerous reports show dramatically improved rates of local control compared to results published using conventional radiotherapy methods and schedules. Historically, local control at 2 years from radiation treatment was only 30–45% with conventional schedules, yet with SBRT rates of 70–98% are reported in numerous phase II institutional protocols [15, 18, 27, 31, 32, 40, 42, 47–68] (fig. 2; table 3).

Unfortunately, a broad spectrum of fractionation schedules with different dose prescription resulting in various biologically effective doses have been used (tables 3, 4). The number of fractions have been 1 to more than 10, and the size of fractions 5–30 Gy at the PTV-surrounding isodose.

From the first clinical trials starting in the 1990s, local control rates of primary lung cancer with SBRT have been reported by to be 94% (47/50) for 50–60 Gy in 5 fractions with a median follow-up of 36 months [51], and 92% (22/24) for 60 Gy

Table 3. Local tumor control rates from different recent trials of SBRT in early NSCLC

First author (year)	Number of patients	Fraction	Total dose	Isodose	LC	CSS	OS	Comment
Ng (2008) [59]	20	3–4	45–54	85–90	94.7	77.6	73.3	
Salazar (2008) [62]	60	1–6	40	76	98	87 82	74 62	 3 years data
Takeda (2009) [63]	63 38 25	5	50	80	95 93 96	92 100 81	79 90 63	 3 years stage IA 3 years stage IB
Onishi (2007) [15]	257	1–14	30–84	100	76.2	73.2	47.2	5 years data
Onimaru (2008) [60]	41	4	32–38.4	80	73	73	64	no consequent margins
Guckenberger (2007) [30]	38	1–8	26–56	65–80	89 83	n.g. 59	n.g. 37	 3 years data
Timmerman (2007) [57]	70	3	60–66	80	95	n.g.	56	
Brown (2007) [64]	57	1–5	15–67.5	57–81	<75	~90	84	1.5 years data, indirect calculation
Fritz (2008) [58]	40	1	24	80	94 81	71 57	66 53	 3 years data
Hof (2007) [47]	42	1	15.2–24	80	67.9	n.g.	65.4	
Baumann (2006) [31]	57	3	45	67	96	n.g.	n.g.	
Uematsu (2001) [51]	50	5–10	50–60	80	94	88	66	3 years data; 36% combined with CRT
Zimmermann (2006) [32]	68	3–5	24–40	60	88 88	82 73	71 53	 3 years data
Wulf (2005) [33]	20	1–3	45–56.2	80	92	n.g.	32	
Nagata (2005) [39]	45	3	38.4	80	98	n.g.	83 72	stage IA stage IB
Hata (2007) [40]	21	10	50–60	90	96	86	74	proton therapy
Beitler (2006) [14]	75	5–40	30–90	70–95	n.g.	n.g.	45	some patients with prior chemotherapy

TD = Total dose, LC = local control, CSS = cause-specific survival, OS = overall survival. Isodose = PTV-encompassing isodose. n.g. = Not given.
All data are at 2 years of follow-up when not stated differently.