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CLINICAL INVESTIGATION

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

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Purpose: To review treatment outcomes for stereotactic body radiotherapy (SBRT) in medically operable patients with Stage I non–small-cell lung cancer (NSCLC), using a Japanese multi-institutional database.
Patients and Methods: Between 1995 and 2004, a total of 87 patients with Stage I NSCLC (median age, 74 years; T1N0M0, $n = 65$; T2N0M0, $n = 22$) who were medically operable but refused surgery were treated using SBRT alone in 14 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. Total dose was 45–72.5 Gy at the isocenter, administered in 3–10 fractions. Median calculated biological effective dose was 116 Gy (range, 100–141 Gy). Data were collected and analyzed retrospectively.
Results: During follow-up (median, 55 months), cumulative local control rates for T1 and T2 tumors at 5 years after SBRT were 92% and 73%, respectively. Pulmonary complications above Grade 2 arose in 1 patient (1.1%). Five-year overall survival rates for Stage IA and IB subgroups were 72% and 62%, respectively. One patient who developed local recurrences safely underwent salvage surgery.
Conclusion: Stereotactic body radiotherapy is safe and promising as a radical treatment for operable Stage I NSCLC. The survival rate for SBRT is potentially comparable to that for surgery.

Stereotactic body radiotherapy, Lung cancer, Non–small-cell, Operable, Stage I.

INTRODUCTION

With the popularization of computed tomography (CT) screening, lung cancers are increasingly detected at an early stage. For patients with Stage I (T1 or 2, N0, M0) non–small-cell lung cancer (NSCLC), resection of the set of full lobar and systemic lymph nodes represents standard treatment. Five-year overall survival rates for clinical Stage IA and IB treated surgically are approximately 60–75% and 40–60%, respectively (1–3). However, a proportion of patients who meet the criteria for surgery refuse such intervention for various reasons. Radiotherapy offers a therapeutic alternative in such cases, but the effects of conventional radiotherapy in patients with Stage I NSCLC are unsatisfactory, with local control rates of approximately 50% during a short 5-year survival period in 15–30% of patients (4–7). Survival rates for conventional radiotherapy for a statistically sufficient number of cases of operable Stage I NSCLC have not been reported, because most

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patients receiving radiotherapy are inoperable. The poor local control rates with conventional radiotherapy have been attributed to doses of conventional radiotherapy that are too low to control the tumor. Mehta *et al.* (8) provided a detailed theoretical analysis of NSCLC responses to radiotherapy and a rationale for dose escalation. They concluded that higher biologically effective doses (BED) irradiated during a short period must be administered to achieve successful local control of lung cancer. To provide a higher dose to the tumor without increasing adverse effects, three-dimensional conformal radiotherapy techniques have been used, and better local control and survival have recently been reported (9–11). Over the last decade, hypofractionated high-dose stereotactic body radiotherapy (SBRT) has been actively performed for early-stage lung cancer, particularly in Japan (12–17). We have previously reported preliminary results for a Japanese multi-institutional review of 257 patients with Stage I NSCLC treated with SBRT (18). The results showed that local control and survival rates were better with BED $\geq$100 Gy than with <100 Gy, and survival rates were much better for medically operable patients than for medically inoperable patients. These results were encouraging, but the duration of follow-up for the study was somewhat short (median, 38 months), and we have not presented a detailed analysis of medically operable patients as a distinct subgroup. Although the standard therapy for operable Stage I NSCLC remains surgery, the effect of SBRT on medically operable patients is an issue of great concern. We provide herein detailed and matured results of SBRT (BED $\geq$100 Gy) for medically operable patients with Stage I NSCLC, using a retrospectively collected Japanese multi-institutional database.

PATIENTS AND METHODS

Eligibility criteria

All patients who satisfied the following eligibility criteria were retrospectively collected from 14 major Japanese institutions in which SBRT for lung cancer was actively performed: (*1*) identification of T1N0M0 or T2N0M0 primary lung cancer on chest and abdominal CT, bronchoscopy, bone scintigraphy, or brain magnetic resonance imaging; (*2*) histopathologic confirmation of NSCLC; (*3*) medically operable cancer but selection of SBRT after refusal to undergo surgery. Medical operability was discussed within the multidisciplinary tumor board of each institution according to respiratory function, age, and complicating diseases. Basic cutoff values for medical operability were World Health Organization performance status $\leq$2, pressure of arterial oxygen $\geq$65 mm Hg, predicted postoperative forced expiratory volume in 1 s $\geq$800 mL, no heart failure requiring pharmacotherapy, no diabetes requiring insulin, no severe arrhythmia, and no history of cardiac infarction. Positron emission tomography was not essential in the staging procedures.

Patients were informed of the concept, methodology, and rationale of this treatment, which was performed in accordance with the 1983 revision of the Declaration of Helsinki.

Table 1. Patient characteristics

Number (14 institutions)	87
Male	63
Female	24
Age (y), median (range)	74 (43–87)
ECOG performance status	
0	51
1	30
2	6
Histology	
Adenocarcinoma	54
Squamous cell carcinoma	25
Other	8
Stage	
IA	64
IB	23
Tumor diameter (mm), median (range)	25 (7–50)
IA	21
IB	39
Chronic lung disease	
Positive	38
Negative	49

Abbreviation: ECOG = Eastern Cooperative Oncology Group.
Values are number unless otherwise noted.

Patient characteristics

A summary of patient pretreatment characteristics is given in Table 1. From April 1995 to March 2004, a total of 87 medically operable patients with primary NSCLC were treated using hypofractionated high-dose SBRT in 14 major Japanese institutions. Each of these 87 cases was judged medically operable, and surgery was initially recommended, but the patients declined surgery and selected SBRT as a radical treatment. Pathology of all tumors was confirmed as NSCLC by transbronchial or CT-guided percutaneous biopsy. The 14 participating institutions were these: Hokkaido University; Kyoto University; Cancer Institute Hospital; Tokyo Metropolitan Komagome Hospital; Kitasato University; Tohoku University; Hiroshima University; Tokyo Metropolitan Hiroo Hospital; Sapporo Medical University; Institute of Biomedical Research and Innovation; International Medical Center of Japan; Tenri Hospital; Kitami Red Cross Hospital; and Yamanashi University.

Treatment methods

Although the techniques to accomplish stereotactic methods differed among these institutions, all "stereotactic radiotherapy techniques" fulfilled the following five requirements: (*1*) reproducibility of the isocenter (setup error $\leq$5 mm), as confirmed by image guidance for every fraction; (*2*) respiratory motion (internal margin) suppressed using as much as possible, to <5 mm; (*3*) slice thickness on CT $\leq$3 mm for three-dimensional treatment planning; (*4*) irradiation with multiple noncoplanar static ports or dynamic arcs; and (5) single high dose $\geq$5 Gy.

Gross target volume (GTV) was delineated on CT images displayed with a lung window level. Clinical target volume (CTV) marginally exceeded GTV by 0–5 mm as judged by the individual radiation oncologist. Internal margin was calculated and set around the CTV by 2–5 mm according to the individual measurements for respiratory motion of each institution. Internal margin caused by respiratory motion was reduced by gating, tracking, breath-hold technique, or abdominal compression. Planning target volume (PTV) comprised the CTV, a proper internal margin measured in each patient, and a 5-mm safety margin. The total margin between PTV and GTV was thus 7–15 mm. The irradiated port marginally exceeded PTV by 3–5 mm to secure the surface dose of PTV. Dose calculation was performed using the Clarkson algorithm and heterogeneity correction. A total dose of 45–72.5 Gy (mean, 58.7 Gy) at the isocenter in 3–10 fractions with single doses of 6.25–15 Gy was administered with 6-MV X-rays within 20% heterogeneity in the PTV dose. Minimum dose in the PTV corresponded to 85–95% of the prescribed dose in most cases. Typical dose/fractionation schedules were 75 Gy in 10 fractions for 42 patients and 48 Gy in 4 fractions for 38 patients. In principal, patients were treated on consecutive days, but some patients were treated every other day. No chemotherapies were administered before or during radiotherapy.

To compare the effects of various treatment protocols with different fraction sizes and total doses, BED was utilized in a linear-quadratic model (19). Biologically effective dose was here defined as $nd(1 + d/\alpha/\beta)$, with units of Gy, where n is fractionation number, d is daily dose, and α/β is assumed to be 10 for tumors. Biologically effective dose was not corrected with values for tumor doubling time or treatment term. Biologically effective dose was calculated at the isocenter in this study. Median calculated BED was 116 Gy (range, 100–141 Gy).

No restriction was placed on whether the tumor was located peripherally or centrally in the lung, but dose for the spinal cord was limited. Biologically effective dose limitation for spinal cord was 80 Gy (α/β was assumed to be 2 Gy for chronic spinal cord toxicity). Doses for other organs were not restricted.

Evaluation

The objectives of this study were to retrospectively evaluate toxicity, local control rate, and survival rate. Follow-up examinations were performed 4 weeks after treatment first, then patients were seen every 1–3 months. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors by CT (20). Chest CT (slice thickness, 2–5 mm) was usually obtained every 2 to 3 months for the first year and repeated every 4–6 months thereafter. Complete response indicated that the tumor had completely disappeared or was judged to have been replaced by fibrotic tissue. Partial response was defined as a ≥30% reduction in maximum cross-sectional diameter. Distinguishing between residual tumor tissue and radiation fibrosis was difficult. Any suspicious residual confusing density after radiotherapy was considered evidence of partial response, so actual complete response rate may have been higher than presented herein. Distinguishing between local recurrence and inflammatory change was also difficult. Here, local recurrence was considered to have occurred only when enlargement of the local tumor continued for >6 months on follow-up CT, obviously positive findings were identified on positron emission tomography, or histologic confirmation was acquired. Findings on CT were interpreted by two radiation oncologists in each case. Absence of local recurrence was defined as locally controlled disease. Lung, esophagus, bone marrow, and skin were evaluated using version 2 of the National Cancer Institute–Common Toxicity Criteria.

Statistical analysis

Cumulative rates of progression-free status at local, regional lymph node, and distant sites and survival were calculated and drawn using Kaplan-Meier algorithms, with day of treatment as the starting point. Subgroups were compared using log–rank statistics. Values of $p < 0.05$ were considered statistically significant. Statistical calculations were conducted using StatView version 5.0 software (SAS Institute, Cary, NC).

RESULTS

All patients completed treatment without obvious complaints. Median durations of observation for all patients and survivors as of final follow-up were 55 and 63 months, respectively.

Local tumor response

Complete response was achieved in 28 patients (32.2%), and partial response was seen in 43 patients (49.4%).

Toxicity

Radiation-induced pulmonary complications of National Cancer Institute–Common Toxicity Criteria (version 2.0) Grade 0, 1, 2, and 3 were noted in 21 (24.1%), 61 (70.1%), 4 (4.6%), and 1 patient (1.1%), respectively. Rib fracture and Grade 3 dermatitis were observed in 4 (4.6%) and 3 patients (3.4%), respectively. All tumors bordered the chest wall. Grade 3 radiation-induced esophagitis was produced in 1 patient, in whom the tumor slightly bordered the esophagus. Maximum esophageal dose in this case was 30 Gy in 5 fractions. No vascular, cardiac, or bone marrow complications had been encountered as of last follow-up. In total, Grade 3 toxicities were identified in 8 patients (9.2%).

No definite second malignancies were found during follow-up, but 1 patient died of acute myelogenous leukemia 3.7 years after completing SBRT.

Recurrence

Local recurrence, lymph node metastases, and distant metastases occurred in 8 (9.2%), 13 (14.9%), and 19 cases (21.8%), respectively.

Cumulative local progression–free rate curves according to stage are shown in Fig. 1. Cumulative local progression–free rate after 5 years was 86.7% (95% confidence interval [CI], 78.3–94.9%) for total cases. Cumulative local progression–free rate at 5 years was 92.0% (95% CI, 83.8–99.6%)

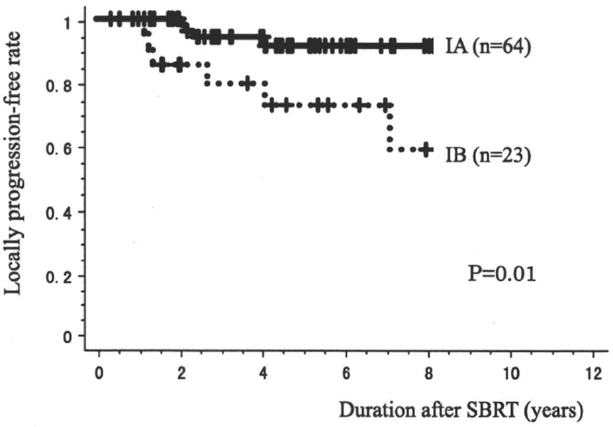

Fig. 1. Cumulative local progression–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

for the Stage IA subgroup, significantly superior ($p = 0.01$) to that for the Stage IB subgroup (73.0%; 95% CI, 52.2–93.7%). Five-year local progression–free rates were not significantly different between adenocarcinoma (80.9%; 95% CI, 68.7–93.1%) and squamous cell carcinoma (95.5%; 95% CI, 86.7–100.0%). One patient who developed local recurrence underwent surgery and has remained healthy for more than 3 years after operatively. The operation method was upper lobectomy and mediastinal lymphadenectomy, and they were performed safely without any trouble.

Cumulative curves of regional lymph node and distant metastases–free rates according to stage are shown in Figs. 2 and 3, respectively. The 5-year lymph node metastasis–free rate and distant metastasis–free rate for total cases was 85.3% (95% CI, 77.6–93.0%) and 75.1% (95% CI, 64.8–85.4%], respectively. No significant difference was identified between Stage IA and IB subgroups.

In patterns of regional nodal recurrence, 8 patients (61.5%) showed nodal failure alone, 2 patients (15.4%) had nodal failure combined with local failure, and 3 patients (23.1%) showed nodal failure combined with distant metastases.

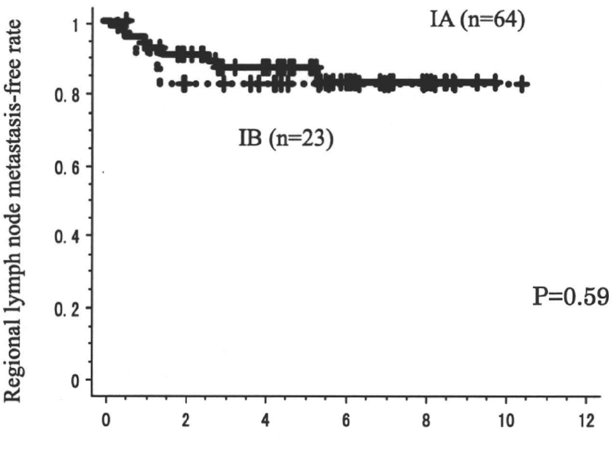

Fig. 2. Cumulative regional lymph node metastasis–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

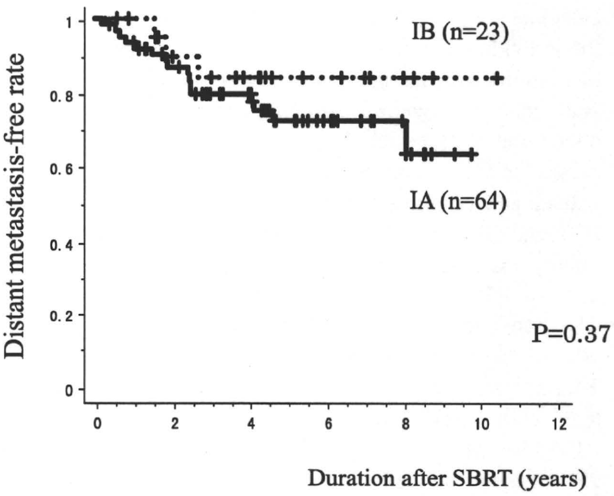

Fig. 3. Cumulative distant metastasis–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

Survival

Overall and cause-specific 5-year survival rates for total cases were 69.5% (95% CI, 58.8–80.1%) and 76.1% (95% CI, 65.9–86.3%), respectively. Overall and cause-specific survival curves according to stage are shown in Figs. 4 and 5, respectively. Five-year overall survival rate was 72.0% (95% CI, 59.6–84.4%) in Stage IA patients and 63.2% (95% CI, 42.7–83.6%) in Stage IB patients. A marginal but nonsignificant ($p = 0.14$) difference was found between overall survival rates of Stage IA and IB groups. In terms of histology, overall 5-year survival rate was 72.2% (95% CI, 59.2–85.2%) in the adenocarcinoma subgroup and 60.8% (95% CI, 38.4–83.2%) in the squamous cell carcinoma subgroup.

DISCUSSION

Exposing a tumor to a higher dose of radiation without increasing adverse effects can be achieved using stereotactic techniques. Stereotactic irradiation is an approach using

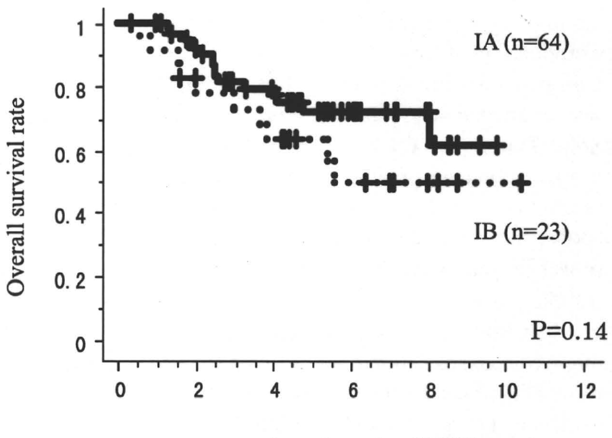

Fig. 4. Cumulative overall survival rate curves, according to stage. SBRT = stereotactic body radiotherapy.

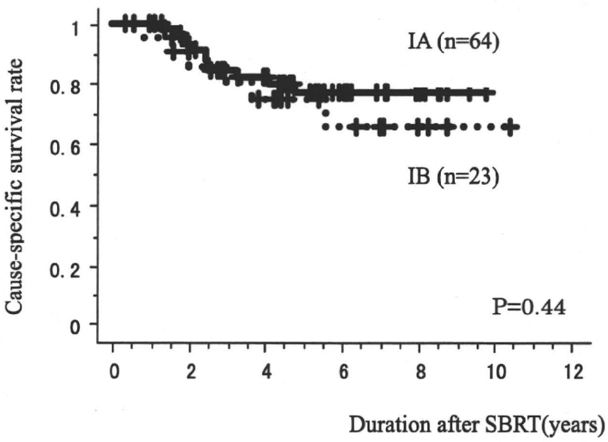

Fig. 5. Cumulative cause-specific survival rate curves, according to stage. SBRT = stereotactic body radiotherapy.

multiple noncoplanar convergent beams, precise localization with a stereotactic coordinate system, rigid immobilization, and single high-dose treatment, maximizing delivery to the tumor and minimizing the exposure of normal tissue. This approach can also substantially reduce overall treatment time from several weeks of conventional radiotherapy schedule to a few days, offering an important advantage to the patient. Stereotactic irradiation techniques are well established for the treatment of intracranial malignancies, but use in extracranial malignancies has been considered problematic because of the issues of fixation and internal motion. In 1994, Blomgren *et al.* (21) described a technique of SBRT using a custom-made body cast and stereotactic coordinates. In 1996, Uematsu *et al.* (22) reported a CT–linear accelerator unit sharing a common couch, enabling image-guided fractionated SBRT without rigid immobilization. Since verification of the effects and safety of SBRT for lung cancer (12), this treatment method has rapidly been adopted in many institutions (Table 2) (12–17, 23, 24). Although various fractionation schedules are undergoing evaluation around the world, a frequently used BED prescribed for tumors with SBRT for Stage I NSCLC in Japan has been set at a little over 100 Gy, as recommended in our previous study (18). However, concerning determination of the truly optimal dose of SBRT for Stage I NSCLC, many problems and controversies remain, such as dose-calculation algorithms (16), inhomogeneity corrections, essential dose for tumor control (24), and dose constraints for organs at risk (25, 26).

Although a number of articles on SBRT for Stage I NSCLC have been published, duration of follow-up in most cases has not been sufficiently long, and almost all treated patients were medically inoperable. The present study thus provides data on two important areas.

One was cumulative local recurrence and metastatic rates with a long duration of follow-up after SBRT. Rates of local control and metastases depend largely on the duration of follow-up and generally deteriorate as the duration of follow-up increases. Furthermore, recurrence rates have been reported in numerous articles, but most of them were crudely calculated rate. We have presented 5-year cumulative local control, regional lymph node recurrence–free and distant metastasis–free rates, calculated using Kaplan-Meier methods. The local progression–free rate in our results was unsatisfactory, particularly for the T2 tumor subgroup. The Japanese Clinical Oncology Group (JCOG) has thus started a multi-institutional dose-escalation study for Stage IB NSCLC patients (JCOG 0702).

Another meaningful result was the overall survival rate with a longer follow-up duration, allowing comparison between SBRT and surgery. Although the survival rate in this study was less than in our previous reports, we consider this information worth reporting, because median duration of follow-up was almost 5 years. Uematsu *et al.* (12) reported a 3-year overall survival rate of 86% in 29 medically operable patients with Stage I NSCLC, but the number of patients was small, and follow-up duration was relatively short. Because the number of medically operable patients treated with SBRT was very small in individual institutions, the present study collated the data of operable patients from multiple institutions. Whether the survival rate of SBRT was lower than that of surgery could not be clarified from our results. Representative 5-year overall survival rates of surgery for clinical

Table 2. Reports of SBRT for Stage I NSCLC

First author (reference)	*N*	Total dose (Gy)	Single dose (Gy)	BED (Gy)	Median follow-up (mo)	Local recurrence (%)	3-y overall survival (%)
Uematsu (12)	50	72	7.2	124	60	6*	6
Nagata (13)	42	48	12	106	52	3*	82
Onimaru (14)	28	48	12	106	27	36†	82 (Stage IA) 32 (Stage IB)
Onishi (15)	26	72	7.2	124	24	8*	75
Takeda (16)	63	50	10	100	31	5†	90 (Stage IA) 63 (Stage IB)
Koto (17)	31	45–60	7.5–15	105–113	32	29*	72
Hof (23)	10	19–26	19–26	55–94	15	40*	37
Fakiris (24)	47	60–66	20–22	180–211	50	12†	43

Abbreviations: SBRT = stereotactic body radiotherapy; NSCLC = non–small-cell lung cancer; BED = biologically effective dose ($\alpha/\beta = 10$).
* Crude data.
† Cumulative data calculated with Kaplan-Meier method.

Table 3. Comparison of 5-y overall survival rate between surgical series and SBRT

Clinical stage	United States (1)	Japanese National Cancer Center (2)	Japanese National Survey (3)	SBRT
IA	61	71	77	76
IB	40	44	60	64

Abbreviation: SBRT = stereotactic body radiotherapy.
Values are percentages.

Stage IA and IB NSCLC are listed in Table 3 (1–3), ranging approximately 60–75% for Stage IA and 40–60% for Stage IB. We cannot conclude that the survival rate for SBRT is equivalent to that for surgery, because the present data for SBRT are based on a retrospective study and small sample size. However, the background of patients treated by SBRT in this study seems likely to have included worse prognostic factors than those in patients treated surgically. Concerning the size and characteristics of tumors, good prognostic factors such as smaller tumor size (27) or lower-density mass (so-called ground-glass opacities) (28) might be more frequently included in patients treated with surgery, because the determination of histological malignancy before SBRT was difficult for such tumors. In addition, median age of patients treated by surgery was approximately 10 years younger in the surgical series (median, 60–65 years) than in the SBRT series (median, 75 years). We therefore believe that survival rates for SBRT in medically operable patients are potentially comparable to those for surgery.

Regarding treatment-related toxicity, the rate of severe (Grade ≥3) acute and short-term chronic complications after SBRT was very low and acceptable, despite the high age of those patients (median, 74 years) in our experience. In results for pulmonary lobectomy, Deslauriers *et al.* (29) reported much higher mortality and morbidity rates that increased with aging. In other reports, mortality rates for patients aged >70 years old after pulmonary lobectomy were 7.6% (30). Even though improvements of mortality and morbidity of surgery may have recently been achieved (31), in particular under a technique of video-assisted thoracoscopic lobectomy (32), we consider SBRT as a safer and less invasive treatment modality than surgery, at least for peripherally located lung tumor up to 5 years after treatment. However, reports of SBRT for centrally located lung tumor have shown a comparably high risk (25, 26), and long-term chronic toxicity remains unclear. A longer and larger follow-up of SBRT is needed.

We thus consider that SBRT may offer a useful option for initial radical treatment of at least peripheral Stage IA NSCLC, not only for medically inoperable patients but also for operable patients. However, regarding centrally located or large T2 tumors, surgery must still be recommended as the first choice of treatment until further data can be accumulated. Although we encountered only 1 case in the present study, pulmonary lobectomy and mediastinal lymph node resection were performed without difficulty for a locally recurring tumor after SBRT. Surgery might be an option as salvage therapy for locally recurrent cases after radical SBRT for Stage I NSCLC.

In Japan, the number of patients treated with SBRT has exploded, especially since SBRT for lung cancer has been covered by the national health insurance since 2004. A Phase II multi-institutional study of JCOG researching the efficacy and toxicity of SBRT for both medically operable and inoperable Stage IA NSCLC patients (JCOG 0403) started in 2004, and patient entry was completed in October 2008. A total of 90 medically inoperable and 65 operable patients have been enrolled. In the United States, a Phase II multi-institutional study of SBRT for only medically inoperable Stage I NSCLC patients (Radiation Therapy Oncology Group 0236) has been ongoing.

Even multi-institutional Phase II studies of SBRT for Stage I NSCLC may have inevitable selection bias compared with surgical series. A prospective randomized trial is essential to conclude whether outcomes of SBRT for medically operable patients are truly comparable to those of surgery. A protocol for randomized studies comparing SBRT with surgery for Stage I NSCLC has been initiated (33) but has not progressed. Such a randomized study is likely to prove very difficult to perform, because most patients may hope for more minimally invasive therapy, such as SBRT. Many more experiences for more patients with a longer follow-up duration are thus needed to confirm the safety and effects of SBRT as a radical treatment for operable Stage I NSCLC. If the experience of SBRT for medically operable Stage I NSCLC matures and produces no poor results in future, SBRT will have a marked impact on standard treatment procedures for lung cancer and provide good news for Stage I lung cancer patients, the prevalence of whom is likely to increase.

In conclusion, treatment results of SBRT reviewed from a Japanese multi-institutional database showed that SBRT is safe and promising as a radical treatment for operable Stage I NSCLC. The survival rate of SBRT is potentially comparable to that of surgery.

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CRITICAL REVIEW

STEREOTACTIC RADIOTHERAPY OF PRIMARY LUNG CANCER AND OTHER TARGETS: RESULTS OF CONSULTANT MEETING OF THE INTERNATIONAL ATOMIC ENERGY AGENCY

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To evaluate the current status of stereotactic body radiotherapy (SBRT) and identify both advantages and disadvantages of its use in developing countries, a meeting composed of consultants of the International Atomic Energy Agency was held in Vienna in November 2006. Owing to continuous developments in the field, the meeting was extended by subsequent discussions and correspondence (2007–2010), which led to the summary presented here. The advantages and disadvantages of SBRT expected to be encountered in developing countries were identified. The definitions, typical treatment courses, and clinical results were presented. Thereafter, minimal methodology/technology requirements for SBRT were evaluated. Finally, characteristics of SBRT for developing countries were recommended. Patients for SBRT should be carefully selected, because single high-dose radiotherapy may cause serious complications in some serial organs at risk. Clinical experiences have been reported in some populations of lung cancer, lung oligometastases, liver cancer, pancreas cancer, and kidney cancer. Despite the disadvantages expected to be experienced in developing countries, SBRT using fewer fractions may be useful in selected patients with various extracranial cancers with favorable outcome and low toxicity. © 2011 Elsevier Inc.

Stereotactic body radiation therapy, Non–small-cell lung cancer, Lung metastases, Liver cancer, Pancreatic cancer, Kidney cancer.

INTRODUCTION

Cancer is one of the major health concerns worldwide. The burden of cancer is increasing globally, with 20 million new cases expected per year in 2020, half of which will be in developing countries (1). The inability to cope with the growing economic and societal burden of cancer is emblematic of the tremendous health disparities reflected in developing countries, which have only 5% of the global resources spent on cancer (2–3).

The proportion of cancer patients in developing countries requesting radiotherapy (RT) is likely higher than in regions of high income because of the types of cancers and the stages at which these tumors are diagnosed (4). Moreover, patients in developing countries are dealing with some issues that are not common in the developed world. They include patient transportation to the facility (5), social support, accessible local housing, and noncompliance with treatment. It was shown (6) that the use of short courses in selected patients could be cost effective and convenient, especially for patients coming from remote areas.

Although many countries have not yet established RT service, others have aging RT services, which are usually restricted to a few centers, mainly concentrated in large urban areas. RT is affordable for developing countries with large populations, but some regions with small populations have not invested in RT (7–10). Emerging new technologies for cancer treatment, however, are spreading widely, in both developed and developing countries. One of these, stereotactic body radiotherapy (SBRT), has been increasingly used in recent decades.

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The International Atomic Energy Agency (IAEA) has a crucial role in both developing new RT facilities and upgrading existing facilities, including equipment and human resources in developing countries. By organizing meetings of experts, the IAEA gathers advice in RT to establish RT facilities in member states. With such an aim, a meeting of consultants was held in Vienna in November 2006 to advise the IAEA on the state of the art of the use of SBRT in primary lung tumors and other body tumors. This article represents a summary of that meeting and subsequent (2007–2010) communication between experts on the recent developments in SBRT deemed necessary because of the fast developments in the field.

Stereotactic radiation characteristics

Characteristics attractive to developing nations. Several characteristics would make SBRT attractive to developing nations. Shortened treatment time with fewer fractions than usually used in developing countries would be a major consideration. This in turn would generally enable improved access to RT treatments in departments worldwide. In addition, shorter treatment (outpatient or inpatient) would also be more cost effective for both patients and hospitals. This would be realized by lessening travel from prolonged distances to and from hospitals, and secondly for hospitals having limited inpatient capabilities. Other attractive characteristics would include improved overall results such as local control, overall survival, and disease-specific survival. Lower toxicity, in addition, would also be an important issue from the standpoint of both better quality of life and less costly symptomatic care (including frequent hospitalization in a patient population having a notorious record of having excessive comorbidities) needed in such cases.

Obvious barriers to implementation in developing nations. There may be several barriers for successful implementation of SBRT of lung cancer in developing countries. They can be broadly separated into pretreatment and treatment issues, including low incidence in certain regions such as sub-Saharan Africa. The lack of modern and comprehensive diagnostic tools, such as computed tomography (CT) and positron emission tomography, would largely jeopardize appropriate diagnosis and staging of potential candidates. In addition, the vast majority of patients would fall into a locally advanced or metastatic category because of a lack of screening and early detection programs that may result in identification of suitable cases, *i.e.,* those having Stage I non–small-cell lung cancer. Of treatment-dependent obstacles, capital costs for obtaining an immobilization system would be the major issue, assuming that existing external-beam RT machines (primarily linear accelerators) have been properly maintained. Lack of previous exposure and experience with three-dimensional RT, seen as the logical parent of SBRT, may be an important obstacle. Barriers to successful implementation of SBRT also include insufficient staffing, inadequate training of personnel, and lack of a dedicated team for introducing and implementing this technique.

CURRENT STATUS OF SBRT DELIVERY IN THE DEVELOPED WORLD

Historical aspects and early experience

Intracranial stereotactic radiosurgery (SRS) was a novel treatment method when introduced in the middle of the 20th century, with conceptual parallels to brachytherapy in regard to the tight spatiotemporal distribution in dose delivery. The clinical experience with intracranial SRS, together with the technical developments in conventional RT, initiated the development of SBRT characterized by a very high dose per fraction, delivered in a short time. This was started at the Swedish Karolinska University hospital in 1991 with tumors in the liver and lungs (11, 12). In parallel the method was developed in Japan and clinically introduced in 1994 for lung tumors. During the last 5 years of the 1990s, SBRT was introduced in several centers in Europe, Japan, and the United States (13–19). The early reports had already shown very promising results with regard to local control and toxicity for the hypofractionation schedules that were adopted, with 10 to 15 Gy per fraction given in a few fractions during a short time (15, 20). However, owing to the new aspects introduced in SBRT, clinical experience was initially gathered at a very slow rate, and it was only during the past decade that outcome data from several centers were available to confirm the initial promising results.

Experience in primary lung tumors

Many studies with SBRT were conducted around the world in treating both primary and metastatic cancers within the lungs because of their high prevalence, the high rates of cancer-associated deaths, and the desire for more effective treatments. The experience in treating primary lung cancer using SBRT has been obtained mainly in patients unfit for surgical resection (*i.e.,* medically inoperable patients). Furthermore, nearly all reports described outcomes in patients with Stage I disease, particularly for peripheral tumor locations. Inasmuch as medically inoperable lung cancer patients are at risk for death of other causes, survival in these patients is ultimately compromised. Still, the benefits of SBRT were demonstrated by dramatically improved rates of local control.

Local tumor response. The local control rates of primary lung cancer with SBRT have been previously reported by several authors (Table 1): 94 % (47/50) for 50 to 60 Gy in five fractions with a median follow-up time of 36 months (21, 23); 92 % (22/24) for 60 Gy in eight fractions with a median follow-up time of 24 months (22, 24) 87 % (30/37) for 60 Gy in three fractions with a median follow-up time of 15 months (19); 85% for 48 to 60 Gy in eight fractions with a median follow-up time of 17 months (25); 95% for 45 to 56.2 Gy in three fractions with a median follow-up time of 10 months (26); 90% for 30 to 40 Gy in

Table 1. Local control rates of stereotactic radiotherapy for primary lung cancer

Study	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control	Median follow-up time
Uematsu *et al.*, 2001 (21, 23)	50–60	10	80% margin	94%(47/50)	36 months
Arimoto *et al.*, 1998 (24)	60	7.5	Isocenter	92%(22/24)	24 months
Timmerman *et al.*, 2003 (19)	60	20	80% margin	87%(30/37)	15 months
Onimaru *et al.*, 2003 (25)	48–60	6–7.5	Isocenter	80%(20/25)	17 months
Wulf *et al.*, 2004 (26)	45–56.2	15–15.4	80% margin	95%(19/20)	10 months
Nagata *et al.*, 2005 (28)	48	12	Isocenter	97%(44/45)	30 months
Lee *et al.*, 2003 (27)	30–40	10	90% margin	90%(8/9)	21 months
Fakiris *et al.*, 2009 (29)	60–66	20–23	80% margin	88%(70)	50 months
Baumann *et al.*, 2009 (30)	45	15	67% margin	92%(57)	35 months
Timmerman *et al.*, 2010 (31)	60	20	80% margin	98%(54/55)	36 months

four fractions with a median follow-up time of 21 months (27); 97% (44/45) for 48 Gy in four fractions with a median follow-up time of 22-30 months (28); 88% for 60 to 66 Gy in three fractions with a median follow-up time of 50 months (29); and 92% for 45 Gy in three fractions with a median follow-up time of 35 months (30). The Radiation Therapy Oncology Group (RTOG) 0236 demonstrated a very good 3-year local control rate that was as high as 98% (31). Even though the definition of local control is different between each trial, a biologic effective dose (BED) larger than 100 Gy may be effective for SBRT of solitary lung cancers with a local control rate above 85%.

Survival. In a series of Stage IA disease (T1N0M0), the 1-year and 5-year local relapse-free survival rates were 100% and 95%. The disease-free survival rates after 1, 3, and 5 years were 80%, 72%, and 72%, respectively, and the overall survival rates were 93%, 83%, and 83%, respectively. In the Stage IB (T2N0M0) series of Nagata *et al.* (28), local relapse-free survival rates were 100%. The disease-free survival after 1, 3, and 5 years were 92%, 71%, and 71%, respectively, and the overall survival rates were 82%, 72$, and 72%, respectively. Onishi *et al.* (32) reported the results for 13 institutions in Japan, which summarized 245 patients: 155 with Stage IA lung cancer and 90 with Stage IB lung cancer. There were 87 operable and 158 inoperable patients, and their results showed that the intercurrent death rate was especially high in the inoperable patient group. Moreover, the 5-year survival rates of operable patients irradiated with more than BED = 100 Gy were 90% for Stage IA and 84% for Stage IB disease, and their clinical results were as good as those obtained by surgery.

Toxicities. The great concern of pulmonary toxicity with SBRT treatment was moderated by the very low rates of complications in early studies. Most pulmonary complications are less than Grade 2 according to the National Cancer Institute Common Terminology Criteria version 2.0. It is not uncommon for patients to experience rib fracture or chest wall pain months after SBRT, especially if tumors adjacent to the chest wall have been treated. Some of these patients, but not all, will have pleural effusions associated with the chest wall pain. The problem seems mostly to be self limited, and conservative management with over-the-counter analgesics or anti-inflammatory medicines is typically effective.

However, a few serious complications have recently been reported by several institutions in Japan (33). These include Grade 5 pulmonary complications, radiation pneumonitis, hemoptysis, and radiation esophagitis. Most cases of Grade 5 radiation pneumonitis were accompanied with interstitial pneumonitis.

Another concern of toxicity was the effects on the central bronchus, pulmonary artery, esophagus, heart, and spinal cord, for which a hypofractionated dose had not been followed up for a sufficiently long time. Lethal pulmonary bleeding and esophageal ulcer have been previously reported (33). Timmerman *et al.* also reported a series of complications with SBRT (34). Chang *et al.* reported on safely treating central tumors considering dose constraints with the SBRT technique (35). Nonetheless, central tumors adjacent to mediastinal organs should be carefully considered (36). Toxicities as reported in several articles are shown in Table 2.

The most important issue is to maintain the dose constraints of organs at risk (OAR) to avoid serious complications. The dose constraints of the OAR, including the spinal cord, pulmonary artery, bronchus, and heart under the Japan Clinical Oncology Group (JCOG) 0403 protocol, are shown in Table 3. The RTOG has enacted normal tissue

Table 2. Clinical toxicities after stereotactic radiotherapy for primary lung cancer

Study	Number of cases	Lung ≥Grade 3	Lung Grade 5	Other Grade 5
Uematsu *et al.*, 2001 (23)	50	0%	0%	
Arimoto *et al.*, 1998 (24)	24	NA	0%	
Lee *et al.*, 2003 (27)	28	0	0%	
Onimaru *et al.*, 2003 (25)	45	2%	0%	Esophagus
Wulf *et al.*, 2004 (26)	61	0	0%	
Nagata *et al.*, 2005 (28)	45	0	0	
Timmerman *et al.*, 2006 (34)	70	20%	9%	Hemoptysis, pericarditis
J-CERG, 2009 (33)	2,106	NA	0.6%	Esophagus, hemoptysis

Table 3. Dose and volume constraints for organs at risk in stereotactic body radiotherapy of lung tumors according to Japan Clinical Oncology Group 0403

Organ	Dose	Volume	Dose	Volume
Lung	40 Gy	≤100 cc	MLD	≤18 cc
	V_{15}	≤25%	V_{20}	≤20%
Spinal cord	25 Gy	Maximum		
Esophagus	40 Gy	≤1 cc	35 Gy	≤10 cc
Pulmonary artery	40 Gy	≤1 cc	35 Gy	≤10 cc
Stomach	36 Gy	≤10 cc	30 Gy	≤100 cc
Intestine	36 Gy	≤10 cc	30 Gy	≤100 cc
Trachea, main bronchus	40 Gy	≤10 cc		
Other organs	48 Gy	≤1 cc	40 Gy	≤10 cc

Abbreviation: MLD = Mean Lung Dose, Other organs do not include chest wall & liver.

constraints for RTOG 0618 treating operable patients with early-stage primary lung cancer (Table 4).

Clinical trials. Prospective Phase II testing of SBRT in operable patients is currently ongoing in Japan (JCOG 0403) and the United States (RTOG protocol 0618). In medically inoperable patient groups, a Nordic multi-institutional consortium is comparing three-fraction SBRT to conventional RT in an ongoing randomized Phase II study. The RTOG has finished a Phase II study of three-fraction SBRT for peripheral tumors and is planning a Phase I study with five fractions in patients with central tumors. Finally, the JCOG is finishing a Phase II study using a four-fraction treatment for peripheral tumors and is starting a Phase II study using a higher dose specifically for T2 tumors as JCOG 0701.

Experience in metastatic lung tumors

The experience in treating lung metastasis has been mostly with oligometastases. In contrast to patients with primary lung cancer, patients with metastases do not inherently have poor pulmonary function secondary to tobacco abuse. As such, the toxic effects of treatment would not be expected to be identical between these differing populations. In addition, there is increasing evidence that it may be more difficult to attain local control in metastatic tumors than in primary lung cancer. This would argue for a higher treatment dose (controlled for tumor volume) for metastatic tumors than for primary presentations. Unfortunately, the results of treating lung metastases were frequently included in the reports of patients treated with primary lung cancers, making interpretations of the results more difficult (20, 37–39). Recently a few articles were published that focused on lung metastases (40, 41). Still, SBRT has a relatively high rate of local control per lesion, making it an effective treatment for selected patients with oligometastases.

Table 4. Dose constraints for normal tissue related to steepness of dose gradients from target according to Radiation Therapy Oncology Group 0618 for stereotactic body radiotherapy in operable patients with lung cancer

Organ	Volume	Dose (cGy)
Spinal cord	Any point	18 Gy (6 Gy/fraction)
Esophagus	Any point	27 Gy (9 Gy/fraction)
Ipsilateral brachial plexus	Any point	24 Gy (8 Gy/fraction)
Heart/pericardium	Any point	30 Gy (10 Gy/fraction)
Trachea and ipsilateral bronchus	Any point	30 Gy (10 Gy/fraction)
Whole lung (right & left)	V_{20}	Less than 5–10% of total lung volume
Skin	Any point	24 Gy (8 Gy per fraction)

Experience in liver tumors

Treatment of liver tumors is the second highest indicator for SBRT. Surgical data have shown that local treatment of liver tumors—mostly hepatocellular carcinoma and metastases—can be curative in up to 25–30% of patients if patient selection is appropriate (42). Nevertheless a significant proportion of patients will not be suitable for surgery because of age, medical comorbidity, or intrahepatic localization of the tumor (bilobar, adjacent to large vessels/portal structures). For these cases, SBRT is completely noninvasive and compares favorably with actuarial local control rates of at least 80% after 2 years (16, 20, 43, 44). Acute toxicity is mild. Clinically relevant subacute or late toxicities are not reported, if OAR have been kept out of the high dose area. Nevertheless, local control is dependent on dose, with recurrences occurring even after years, (*e.g.,* with single doses below 26 Gy/isocenter or 3 × 10 Gy/planning target volume [PTV] enclosing 65% isodose) (45, 46). By contrast, some authors have shown that significantly higher doses can be applied safely, such as single doses above 30 Gy/isocenter or 3 × 20 Gy/PTV enclosing 80% isodose, if the normal tissue dose constraints are respected (46–49).

Experience in retroperitoneal (pancreas and kidney) tumors

Abdominal retroperitoneal tumors pose a difficult challenge in view of their proximity to the poorly tolerant bowel. In the case of pancreas tumors, trials have shown conflicting results about the benefit of therapy. Although Hoyer *et al.* indicated little benefit and increased toxicity in patients treated with 45 Gy in three fractions (50), Koong *et al.* used a single dose ranging from 15 to 25 Gy and were able to control tumors in most patients with acceptable toxicity (51, 52).

Although renal cancers are thought to be radioresistant when treated with conventional fractionation schedules, Wersaell *et al.* found extremely high rates of local control with a three- to four-fraction SBRT regimen (53). These results concurred with the high local control rates observed when SRS with a large dose per fraction was used to treat brain metastases of the same histology.

Biology of dose delivery to tumor and normal tissues

Unlike normofractionated RT, the biologic purpose of SRT is for lethal rather than sublethal cell damage in the high-dose area without repair. Additionally, because of the short overall treatment time (single dose, hypofractionation within 1 to 3 weeks), avoiding the repopulation of tumor cells is another advantage. On the other hand, the presumption is that reoxygenation and redistribution of cells in the cell cycle will not occur with the prescribed dose. The OAR are prevented from serious damage by sparing these tissues from the high-dose area.

Besides dose escalation trials for lung and liver tumors (47, 49), prospective institutional-based reports on the clinical results of SBRT have been published. Unfortunately, comparison of these results is difficult because different dose fractionation schedules have been used, and there is lack of uniformity in normalization and prescribed doses. To overcome this problem, some authors used the BED based on the formula BED (Gy) = dose/fraction × fraction number (1 + fraction dose / α/β using an α/β of 10 Gy for tumor tissue (54, 55). They found a BED of about 100 Gy to be appropriate to achieve a tumor control probability of about 90% for lung tumors. Because it has not been proved that the LQ (linear quadratic) model will be reliable at such high fraction doses, other radiobiologic models might be better suited to predict the effect of SBRT, including modifications of the multitarget model (56).

MINIMUM METHODOLOGY/TECHNOLOGY REQUIREMENTS

Imaging for planning

Imaging for treatment planning is usually based on CT data, whereas magnetic resonance imaging or positron emission tomography can assist this purpose. Before 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 performed to determine the appropriate margins for PTV definition). This can be done by either four-dimensional CT, multislice CT, dynamic scans (repeated scans at the same couch position), or evaluation of the target position during maximum inspiration and expiration. Although this approach is based on slices, which show the scanned tumor position in a very short (<1 second) time, resulting in a sharp image, the target can also be scanned by slow CT. With this technique the tumor is scanned very slowly (*e.g.,* scan time for a slice of 3 seconds). The image shows a blurred shape of the target, including and depending on internal motion (57), which represents the orbit of the moving target. This technique might have advantages, especially when cone-beam CT is used for target verification before irradiation, because the slow scan time (about 1 minute) will cause the shape of the target to also seem blurred (58).

Planning processes

Clinical experience from SBRT has indicated that geometric errors (of a magnitude that is not too uncommon in RT) may lead to more severe consequences than errors in dose delivery. Thus, if priorities need to be determined, geometric aspects should be emphasized more than dose aspects in the planning and delivery processes of SBRT.

Treatment planning in SBRT is done on commercial treatment planning systems, which are also used for RT planning in general. The CT data must account for the different densities in the body for the dose calculation. For dose calculation of tumors in the lungs, pencil beam algorithms have a limited accuracy but are acceptable for use (59). Point kernel–based superposition/convolution algorithms give a more accurate estimate of the dose to the tumor and surrounding lung tissue (60). The error in the dose calculation for tumors in the lungs is reduced if the photon energy is restricted a maximum of 6 MV. Small field sizes are often used in SBRT because of the small size of the PTV. Thus, accurate beam modeling is important (both profiles and depth doses) for field sizes down to 3 cm × 3 cm, preferably down to 2 cm × 2 cm. Image registration tools for the geometric verification process, dose–volume histogram calculation tools, and tools (for example rulers) to calculate the position of the isocenter in the reference system defined by the fiducials must be included.

Radiation beam delivery equipment

Clinical experience with SBRT stems primarily from the use of conventional linear accelerators, and to a lesser extent from more specialized accelerators, but not from the use of conventional cobalt units. The latter is not recommended for SBRT because of the lack of clinical experience and the inferior physical characteristics of the beams.

The following recommendations are given for the linear accelerator for SBRT: Photon energies of 6 MV (or close to that) for tumors in the lungs. For tumors below the diaphragm (not passing through lung tissue), 6 to 20 MV. It is important to keep the treatment time reasonably short, preferably in the range of half an hour per target, as a maximum. The reason is mainly to avoid geometric errors from patient motion during a very long treatment time, but also to some extent to avoid a possible dose–rate effect. The following aspects are related to a short treatment time. A multileaf collimator (leaf width maximum 1 cm) should preferably be used to shape the beams, but customized blocks may be acceptable. The preferred dose rate should be at least 400 MU/min, but at least 250 MU/min can be acceptable Motorized wedges should preferably be used, but manual wedges may be acceptable. The size of the mechanical isocenter sphere should be within 1 mm in radius. Equipment (*e.g.,* lasers, video cameras, X-ray sources) in the treatment room used for setup should be accurately adjusted to the isocenter. The deviation of the actual isocenter point from the planned one should be aimed to be within 1 mm in the reference system defined by the fiducials (Figure). The mechanical sag on the treatment couch with the patient in treatment position and CT couch must be checked, and should be of the same order. This is of primary importance for targets extended in the cranial-caudal direction.

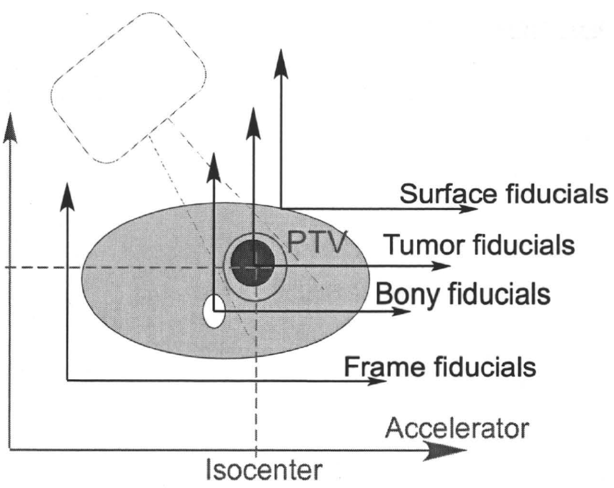

Fig. Patient treatment in the stereotactic body frame (ELEKTA Instr.). The correct isocenter position of the target and adequate suppression of breathing mobility by increased abdominal pressure is proved on the treatment couch by a mobile computed tomography device with gantry movements (Tomoscan M, Philips, Inc.).

Immobilization

Immobilization of the patient should be comfortable and also rigid to avoid intrafractional motions to ensure accurate repositioning of the patient between treatment planning and irradiation sessions. Both goals are usually achieved by tightly moulded vacuum pillows, which are attached to a stereotactic frame (e.g. SBF) or are used frameless (*e.g.,* BodyFix). Specific attention should be directed to providing comfortable support for the arms and legs/knees, because they are most prone to become uncomfortable during a long treatment procedure (verification and irradiation might last up to 60 min).

Geometric verification

Geometric verification is a very important issue for SBRT because its single dose is usually more than 10 Gy and therefore constitutes 20–33% of the whole dose. A single misalignment will result in local failure or severe complication. The most simple verification method widely accepted is an anterior–posterior portal film taken before each session to compare with DRR (Digitally reconstructed radiographs) to check bony anatomy. EPID (Electronic portal imaging device) images can be used alternatively, but the sensitivity to detect setup error may be inferior to portal film. A more useful method is using the CT on rails. It is possible for CT images taken before and after SBRT to detect not only intertreatment setup error but intratreatment setup error. Recently, a couple of image-guided RT machines have been developed. With either the on-board or the in-room imaging apparatus, the position of a patient can be confirmed before every treatment day.

Target volumes and margins

Ideally, both gross tumor volume (GTV) and clinical target volume (CTV) should be geometrically defined in an unambiguous way in the reference system used. In clinical practice, however, there will always be some degree of breathing motion during imaging (even with gating there will be a residual motion) and differences in tumor position during imaging and treatment. ICRU 62 defines an internal margin (IM) and an internal target volume (ITV) for the physiologic movements and variations of the CTV during therapy. One way to get an estimate of the IM is to do the imaging during several breathing cycles (see Imaging for Planning, above). In the clinical practice of SBRT, ITV is not always defined explicitly, but PTV is usually drawn with standard margins to a CTV that has been defined by normal dose-planning imaging. The standard margins are determined from geometric verification imaging of patient cohorts and basically are valid only for the use of a particular set of conditions like patient fixation and breathing reduction, and also choice of reference system and method for setup and geometric verification. However, owing to similar geometric requirements using different methods for SBRT, a relatively narrow range of margins between CTV and PTV is currently 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 5 mm and up to 10 mm. Table 5 shows the margins used at different centers (16,18,19, 32,36,44,48–50,65,66).

Training requirements

The process of SBRT differs greatly from general RT in method and, more importantly, regarding patient selection, dose prescription/fractionation, target definition, and as a consequence toxicity patterns. Thus, training in SBRT is of major importance, and the following recommendations have been made: General methods for SBRT should be studied by RO (Radiation oncologist), medical physicist (MP), and radiation therapy technologist (RTT); patient selection criteria by RO; patient immobilization and accounting for internal organ motions by MP and RTT; imaging acquisition technique by MP and RTT; target definitions by RO; dose planning by MP; dose prescription by RO and MP; geometric verification by MP and RTT; treatment by RTT; toxicity patterns by RO; and follow-up by RO.

Personal experience is important not only in patient selection but also in proper use of the equipment, target definition, three-dimensional treatment planning, and follow-up of patients. Some vendors offer practical teaching courses with experienced faculty after the purchase of SBRT equipment.

QUALITY ASSURANCE REQUIREMENTS

General recommendations on quality assurance (QA) in RT also apply to SBRT. QA recommendations focused on SBRT have also been published (61), as have practice guidelines for the performance of SBRT (62). However, some aspects of QA that are of particular importance for SBRT are given below.

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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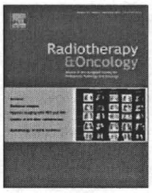

PET imaging in lung cancer

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

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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.

Radiotherapy and Oncology 97 (2010) 200–204

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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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 the semi-quantitative analysis, we calculated the maximum standardized uptake value (SUVmax) after setting regions of interest. For three scans, although qualitative analysis was pos-

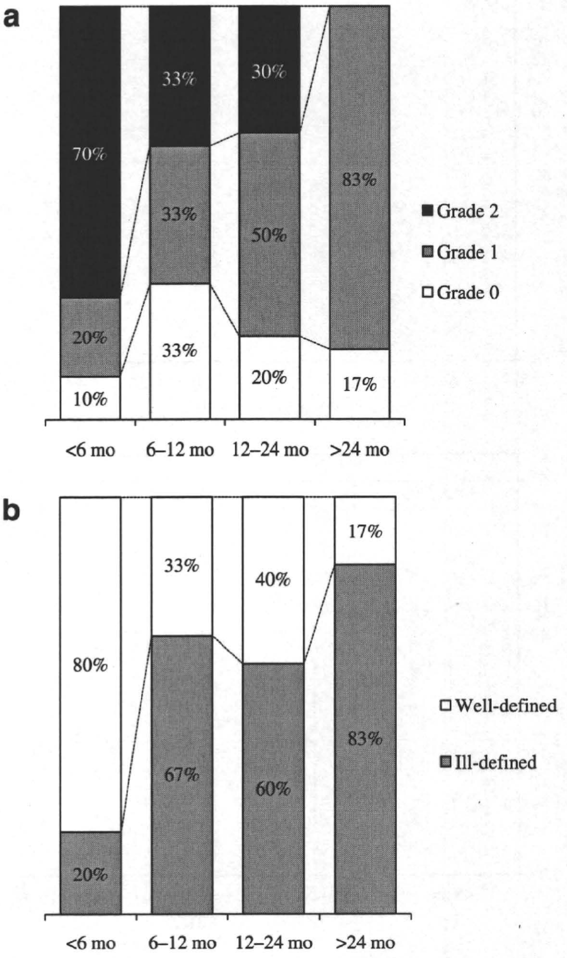

Fig. 1. Visual analysis of FDG uptake regarding intensity (a) and demarcation (b). Intensity was classified into three grades: 0, none or faint uptake; 1, mild uptake, comparable to that in the blood pool; and 2, moderate to intense uptake, greater than that in the blood pool. The prevalence of intense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

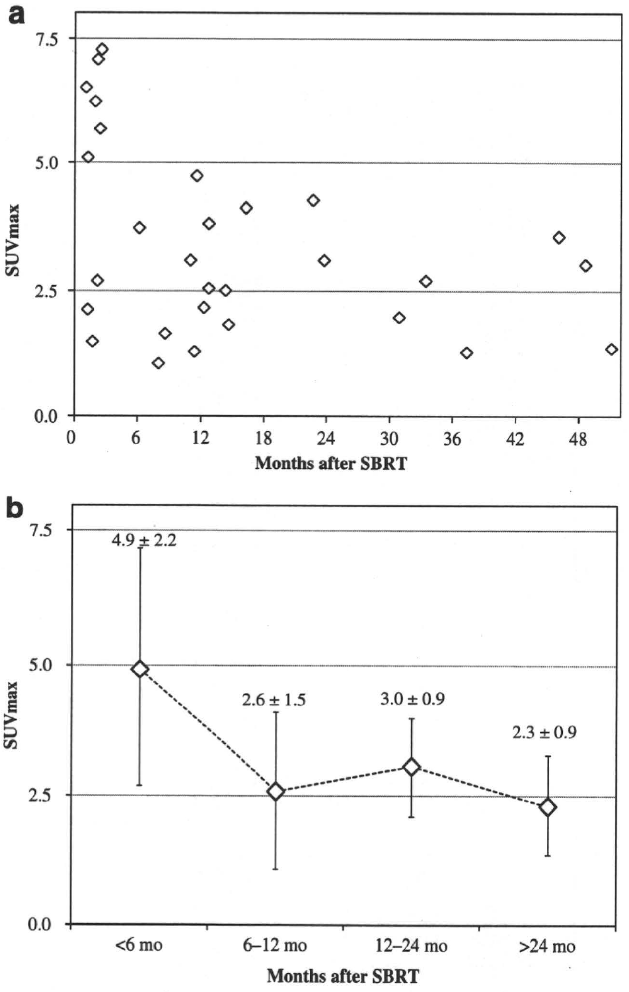

Fig. 2. SUVmax in FDG-PET and the time duration between SBRT and FDG-PET. (a) Scatter plot of SUVmax versus time after SBRT, showing a moderately negative correlation coefficient of −0.388. (b) Mean (diamond) and SD (vertical bar) of SUVmax for FDG-PET performed at different times after SBRT: <6 months,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