Because of difficulties with stabilization, breathing motion and dosimetry, stereotactic body radiotherapy for lung cancer has only been practiced for the past 15 years. However, a large amount of case data has rapidly been accumulated in recent years. Stereotactic body radiotherapy for Stage I non-small-cell lung cancer has been actively investigated in inoperable patients since around 1995, and a number of clinical trials have been undertaken. Early studies from 2001 presented a 3-year local control rate of 94% and a 3-year overall survival rate of 66% for patients receiving 50–60 Gy in 10 fractions. Another study in 2005, using 48 Gy in four fractions, presented a 3-year local control rate of 98% and 3-year overall survival rates of 83% for Stage IA patients and 72% for Stage IB patients. A multi-institutional study showed favorable local control and survival rates in a group receiving a biologically effective dose of 100 Gy. A dose-escalation study in the USA suggested a maximum tolerated dose of 60 Gy in three fractions. A Phase II clinical trial (RTOG0236) followed, with a reported 3-year local control rate of 98% and a 3-year overall survival rate of 56% for patients who received 60 Gy in three fractions. A Japanese Phase II clinical trial (JCOG0403) investigated a dose of 48 Gy in four fractions among 165 Stage IA patients, showing a 3-year survival rate of 76% and a 3-year locally progression-free survival rate of 69% for the operable group. An overview of past clinical trials in stereotactic body radiotherapy for Stage I non-small-cell lung cancer and current issues is presented and discussed.

Key words: stereotactic radiotherapy — non-small-cell lung cancer — Stage I — clinical study — review
doses of radiation to the tumor with minimal exposure of surrounding organs. Rapid advances in the capabilities of radiotherapy equipment during the 1990s enabled three-dimensional irradiation. Stereotactic irradiation methods were gradually trialed for lung cancer from around 1995, with increases in stability and precision, and the development of related technologies such as image-guided navigation. Blomgren et al. (2) first reported how to perform stereotactic radiotherapy on body tumors. Uematsu et al. began clinical trials of stereotactic radiotherapy on body tumors in Japan with the development of a combined CT and linear accelerator unit (3) in 1996. Shirato et al. developed a method for tracing a fiducial marker placed near a tumor, installing a device that allowed real-time observation during irradiation in the irradiation room, and applied this method to SBRT (4). As a result of developments like these, SBRT is now showing promise as a radical treatment modality, mainly for lung cancers. Numerous clinical trials are currently underway. SBRT is being applied not only to lung cancers, but also to diverse other body tumors, including the liver, pancreatic, prostate and metastatic cancers, as well as to spinal arteriovenous malformations. Radiotherapy has recently achieved higher levels of accuracy in covering tumors, thanks to advances in respiratory motion management (5) and various image-guidance techniques (6). The Cyberknife, originally designed for use on cranial lesions, is now good enough to also be applied to cervical and body lesions (7).

In 2004, Japanese health insurance policies began to cover SBRT using linear accelerators. Since then, the number of patients receiving SBRT has increased substantially. The specified treatment cost was 630,000 yen (~$8,000 USD), which covered medical services for the entire process, starting from treatment planning. The four conditions the radiotherapy must fulfill are as follows: (1) stability and reproducibility of the focal position of irradiation within 5 mm between treatment planning and actual treatment; (2) measures for preventing respiratory motion error (additional-ly approved for coverage by Japanese health insurance from 2012 in Japan); (3) dose concentration on the tumor by multi-directional, three-dimensional convergence of multiple beams and (4) short treatment period (generally <2 weeks) with a single high-dose treatment (generally ≥5 Gy). For lung cancer, coverage by the Japanese health insurance system is applied for: primary lung cancer with no metastatic lesions and diameter ≤5 cm; and up to three masses of metastatic lung cancer each ≤5 cm in diameter, with no other foci. According to a national survey conducted by Nagata et al., SBRT was being performed at 53 institutions in Japan as of 2005. Overall, 2104 patients had received treatment for lung cancer using stereotactic radiotherapy (including for primary lung cancer in 1111 patients, metastatic lung cancer in 702 patients and unknown histology in 291 patients) (8).

PHASE I (DOSE ESCALATION) STUDY
No rigorous Phase I clinical trial to identify the maximum tolerated dose of SBRT for lung cancer has been conducted in Japan. The results of retrospective study, discussed below, have suggested sufficient local control with biologically effective dose (BED) >100 Gy (9). The prescribed dose for clinical trials or medical practice was established with this trial in Japan. The most frequent SBRT dose fractionation for Stage I NSCLC in the previous survey by Nagata et al. was 12 Gy, administered four times (8).

However, in the USA, the maximum tolerated dose was set at 20 Gy, administered three times, based on a dose escalation study that started from 8 Gy, administered three times (10,11). The dose-limiting toxicities reported at the time included dermatitis, pericarditis, pneumonitis and bronchial necrosis. Some reports have described decreased local control using the Japanese standard SBRT dose for larger lesions (12,13), and a dose escalation study (JCOG0702) is being conducted in Japan for T2N0M0 NSCLC.

RETROSPECTIVE STUDY FOR MEDICALLY INOPERABLE PATIENTS

Needless to say, the standard treatment for Stage I NSCLC is surgery. SBRT was used only for inoperable patients in early phase. Table 1 shows the results of retrospective studies of SBRT for mostly inoperable patients (12,14–17). These studies showed variations in irradiation techniques and prescribed doses, but the results suggested that local control exceeded 90% when treatment doses were sufficient. However, the survival time was not long enough, as discussed below, and insufficient information was obtained regarding local control rates in the long-term follow-up. Survival rates appeared highly variable and were generally inferior to surgical outcomes. This may be partly attributable to a high number of deaths due to other causes, because of the poor health condition of inoperable elderly patients.

RETROSPECTIVE STUDY FOR OPERABLE PATIENTS

A certain proportion of patients are operable but choose to undergo SBRT. One retrospective study extracted operable cases from accumulated multi-institutional data in Japan (13,18). Doses achieving BED >100 Gy showed more favorable local control and survival rates than doses <100 Gy. The 87 operable cases in the group with BED >100 Gy (median age, 74 years) displayed 5-year locally progression-free and 5-year overall survival rates of 90% and 74% for Stage IA and 89% and 58% for Stage IB, respectively, at a median follow-up duration of 58 months. Other illnesses were a major cause of death. Grade 3 toxicity or above was found in only 2% of patients, but the true level of toxicity
PHASE II CLINICAL STUDY FOR MEDICALLY INOPERABLE PATIENTS

Many Phase II clinical trials for medically inoperable regular patients were conducted one after the other based on favorable local control results in early retrospective studies, as shown in Table 1. Table 2 shows the major results of various Phase II trials (19–25). Prescribed doses differ between Japan and the West, but variations in survival rates and local control rates were generally the same as those from retrospective research. A multi-institutional clinical trial undertaken in the USA (Radiation Therapy Oncology Group (RTOG)-0236) found a local control rate of 98%, a 3-year survival rate of 56% and grade 3 or 4 toxicity in 16.3% (24). Some studies showed a higher proportion of grade 3 toxicity and above than the retrospective research. This may be due to regular follow-ups with no missing values in prospective research. In particular, a study of SBRT with 60–66 Gy in three fractions for subjects including patients with centrally located lung tumors near the trachea or lobar bronchi found that 14 of 70 cases (20%) experienced toxicity of grade 3 or above, 6 cases showed grade 5 toxicity (pneumonia, 4 cases; pericarditis, 1 case; hemoptysis, 1 case) and 4 of these 6 cases had centrally located cancers (20). Accordingly, a dose escalation study has been conducted with the prescribed dose for centrally located lung cancer starting from 7.5 Gy administered eight times (JROSG10–1) in Japan and 10 Gy administered five times (RT0G0813) in the USA.

PHASE II STUDY FOR MEDICALLY OPERABLE PATIENTS

In 2004, a Japanese Radiation Treatment Group (representative: Masahiro Hiraoka) was first created in the Japan Clinical Oncology Group (JCOG) and a Phase II clinical trial of SBRT was initiated for NSCLC in clinical Stage IA (JCOG0403). All cases were pathologically confirmed, and two groups were registered, comprising patients with medially operable and inoperable tumors for standard surgery. The medically operable group reached the target number of registrations early and Nagata et al. presented preliminary results after a 3-year follow-up in 2010 at the annual meetings of the American Society for Therapeutic Radiology and Oncology (26) and the Japan Lung Cancer Society. This was the first Phase II clinical trial in the world for a medically operable case group. In JCOG0403, 48 Gy administered in four fractions was prescribed for the isocenter. Sixty-five patients were included between July 2004 and January 2007. The mean age of participants was 79 years (range, 50–91 years), with 45 men and 20 women. The mean tumor diameter was 21 mm (range, 10–30 mm), and histological examination revealed 40 adenocarcinomas, 21 squamous cell carcinomas and 4 others, with performance status (PS) 0 in 43, PS 1 in 20 and PS 2 in 2. The median observation period was 45 months, the 3-year overall survival rate was 76% and the 3-year locally progression-free rate was 69%. Treatment-related toxicities of grade 3 and above included one case of chest pain, two cases of dyspnea, one case of hypoxia and two cases of radiation pneumonitis. No cases of toxicity of grade 4 or above were identified.

PHASE III RANDOMIZED STUDY COMPARING SBRT WITH SURGERY

Two randomized multi-institutional studies comparing SBRT with surgery on operable patients preceded the announcement of JCOG0403. One was a randomized study comparing CyberKnife treatment to surgical resection for Stage I NSCLC (STARS) based in MD Anderson Cancer Center in the United States (27), while the other was a randomized Phase III trial, Radiosurgery or Surgery for operable Early-stage (Stage IA) non-small-cell Lung cancer (ROSEL) based in VU University Medical Center in Netherlands (28). These experimental studies did not have sufficient rationales affirming the randomization process between surgery and SBRT and the registration of patients has encountered difficulties.

Table 1. Results of retrospective studies of stereotactic body radiotherapy for mainly inoperable patients with T1-3N0M0 non-small-cell lung cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Pt. no</th>
<th>Age min–max (median)</th>
<th>Dose Gy/fraction (fx)</th>
<th>Median follow-up (months)</th>
<th>Overall survival rate</th>
<th>Local control</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uematsu (14)</td>
<td>50</td>
<td>54–86 (71)</td>
<td>50–60 Gy/5–10 fx</td>
<td>36</td>
<td>66% (at 3 year)</td>
<td>94%</td>
<td>Rib fracture: 2%</td>
</tr>
<tr>
<td>Wulf (15)</td>
<td>20</td>
<td>58–82 (68)</td>
<td>26–37.5 Gy/1–3 fx</td>
<td>11</td>
<td>32% (at 2 year)</td>
<td>92%</td>
<td>No complications &gt; RTOG grade 2</td>
</tr>
<tr>
<td>Onishi (16)</td>
<td>35</td>
<td>65–92 (71)</td>
<td>60 Gy/10 fx</td>
<td>13</td>
<td>64% (at 2 year)</td>
<td>88%</td>
<td>NCI-CTC (V2) grade 3 pneumonia: 9%</td>
</tr>
<tr>
<td>Onimaru (12)</td>
<td>28</td>
<td>52–85 (76)</td>
<td>48 Gy/4 fx</td>
<td>27</td>
<td>IA 82% IB 32%</td>
<td>64%</td>
<td>NCI-CTC (V3.0) grade 3 pneumonia: 4%</td>
</tr>
<tr>
<td>Takeda (17)</td>
<td>63</td>
<td>56–91 (78)</td>
<td>50 Gy/5 fx</td>
<td>31</td>
<td>IA 90% IB 63%</td>
<td>95%</td>
<td>NCI-CTC (V3.0) grade 3 pneumonia: 3%</td>
</tr>
</tbody>
</table>
CURRENT CLINICAL TRIALS

Over 50 clinical trials on SBRT for early lung cancer are now underway around the world. The major studies are listed in Table 3. RTOG0618 is a Phase II study for medically operable patients with T1-3N0M0 NSCLC, RTOG0813 and JROSG10-1 are dose escalation studies regarding doses for centrally located lung cancer in close proximity to the trachea and lobar bronchus, RTOG0915 is an investigation into the safety and efficacy of single-fraction and four-fraction SBRT for Stage I NSCLC, and the American College of Surgeons Oncology Group (ACOSOG) Z4099/ RTOG1021 is a randomized trial comparing SBRT with partial lung resection with or without brachytherapy in cases with a high risk for receiving lobectomy.

DISCUSSION

The processes used in radiation oncology can be divided into three successive steps: (1) treatment simulation, in which all relevant information on target definition is incorporated; (2) treatment planning, which involves selection of delivery technique and approach for optimizing target coverage and normal tissue avoidance; and (3) radiation delivery and treatment verification. Many technological developments have been made to enable SBRT for small lung tumor, including the following: (a) high precision and speed in calculation algorithms for treatment plans; (b) high dose rate and smaller size of irradiation equipment; and (c) increased precision in respiratory motion management.
New dose-calculation programs more accurately predict the doses to which normal tissues are exposed, thereby overcoming the limitations of older software that over- or underestimated dose distributions in inhomogeneous tissues such as the lungs by more than 10% (29). Accurate dose estimation using these new algorithms will allow for better correlation of dose with toxicity, allowing higher doses to be delivered more safely (30).

Since 2003, four-dimensional (4D) CT scanners have become commercially available, and are increasingly replacing conventional CT for treatment simulation. The use of 4DCT allows organ motions to be observed and quantified (31). When 4DCT information is combined with daily patient position verification, safety margins around tumors can be significantly reduced, thereby decreasing target volumes. In addition, 4DCT allows for the evaluation of strategies such as respiration-gated radiation therapy to minimize target volumes in individual patients (32). When tumors show significant movement, enlargement of the planning target volume (PTV) can be circumvented by limiting treatment to only specific phases of respiration (33) or tracking the beam to the moving tumor (34).

Current approaches to image-guided radiation therapy aim to monitor patient and tumor positions during the course of treatment, an approach that is mandatory when using very small safety margins. Many commercial imaging systems are available for installation in treatment rooms, and are used to verify patient positioning using kilovoltage or megavoltage imaging devices, cameras, external markers or laser tracking systems. Tumor positions can be verified using kilovoltage or megavoltage imaging devices integrated into linear accelerator. The combined use of optimal pretreatment imaging with 4DCT-based target delineation, modern planning techniques and the use of linear accelerators equipped with cone-beam CT scanners allows for smaller safety margins around the tumor (35). In-room imaging in image-guided radiotherapy (IGRT) using CT-on rail (36) or cone-beam CT allows for variations in patient or tumor positions to be identified on a routine basis, and can identify trends in tumor volume and shape, increases or decreases in atelectasis, or changes in patient anatomy due to excessive weight loss.

Although there has been increasing evidence regarding the efficacy and safety of SBRT for patients with Stage I NSCLC, recruitment of further cases and sufficient follow-ups is currently required to create a fair evaluation of treatment outcomes for SBRT. We also have to pay special attention to patients with centrally located tumors or pulmonary fibrosis. SBRT is becoming established as a radical treatment strategy for medically inoperable Stage I NSCLC. Investigation of whether SBRT can also provide a surrogate treatment for surgery in medically operable patients would therefore be meaningful. It is necessary to both wait for progress in ongoing clinical trials and to formulate new clinical trials to more fully elucidate the position of SBRT among other treatment modalities for Stage I NSCLC. If the JCOG0403 study shows long-term, stable, positive outcomes for the operable group, a study of SBRT versus minimal surgery may be justified for patients who have some risks on standard lobectomy, such as due to poor pulmonary condition or overall physical state (the group for whom minimal surgery is considered). A major problem with SBRT is that it does not allow pathological diagnosis of resected subclinical lymph node metastases to determine the necessity of adjuvant chemotherapy. If subjects with a low risk of lymph node metastases can be clarified through the results of the trials currently underway by the lung cancer surgery group in Japan (JCOG0804/WJOG 4507L: case recruitment complete), then groups can be offered SBRT without adjuvant chemotherapy.

Furthermore, many issues (Table 4) remain unresolved and ought to be investigated through long-term follow-up of past clinical trials and the creation of new clinical trials.

**Table 4. Unsolved issues of SBRT**

| Tolerable dose of normal structures |
| Effect of pulmonary fibrosis on SBRT-induced pneumonitis |
| Justice of SBRT for histologically unproven lung tumors |
| Optimal dose fractionation |
| Adjuvant therapy |
| Salvage treatment after recurrence |
| Long-term prognosis (over 10 years) |
| Comparison with surgery |

**CONCLUSION**

Stereotactic radiotherapy administers a concentrated large dose in 3D, over a short time span, with precise targeting of the locations of small tumors. This treatment has been used more widely in recent years on a growing number of cases. Since 1995, SBRT for patients with Stage I NSCLC has mainly seen clinical use on inoperable patients. In addition, various clinical trials have been conducted and have found improved local control and survival rates compared with conventional radiation treatments. SBRT is considered the standard treatment for medically inoperable patients and is selected as a surrogate treatment for operable patients who reject surgery. However, the number of cases and observation periods remain insufficient and many uncertainties need to be clarified related to the tolerable dose to at-risk organs and appropriate dose-fractionation, and several issues related to oncology, such as adjuvant therapy or surgery, etc. It is hoped that SBRT will be used in clinics more properly through obtaining new clinical and long-term follow-up data for Stage I NSCLC.

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Conflict of interest statement
None declared.

References