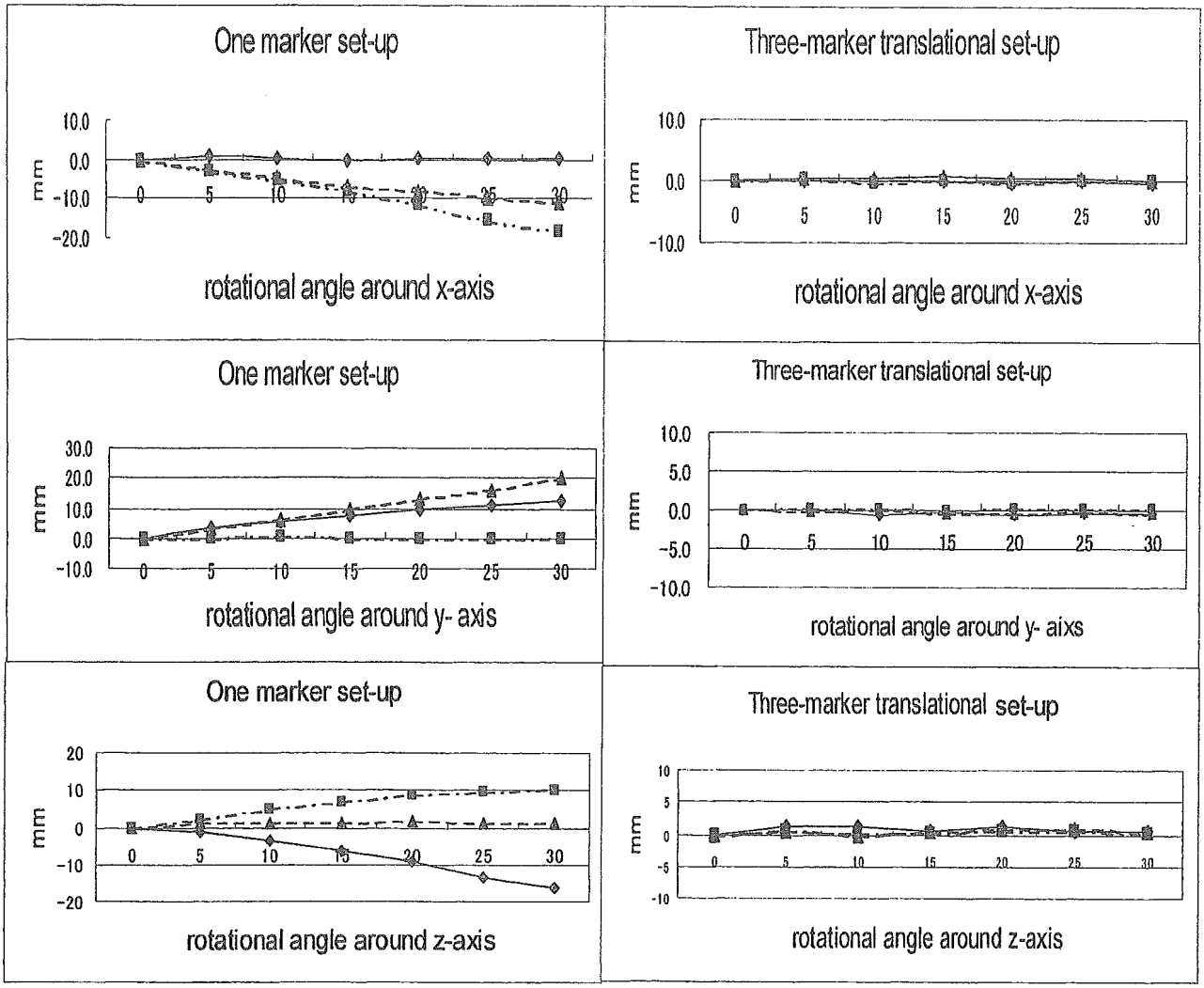

Fig. 3. Discrepancy between the planned position and the actual position of the gravity center of the phantom in (left) one-marker translational setup and (right) three-marker translational setup in the x (upper row), y (middle row), and z (lower row) directions. The discrepancy of coordinates in x-direction (squares), y-direction (triangles), and z-direction (diamonds) is shown in mm.

of the gravity center of the phantom was as large as 20 mm when the rotation angle was 30 degrees in one-marker translational setup for the 6.0 × 6.0 × 6.0 cm^3 cubic phantom. Using three-marker translational setup, the discrepancy was 0.9 ± 0.3 mm (mean ± standard deviation [SD]), 0.4 ± 0.2 mm, and 0.6 ± 0.2 mm throughout the rotation angle in the range from 0–30 degrees for the x, y, and z axes, respectively, in the gravity center of the phantom.

The differences in the treatment fields between no correction, one-marker translational setup and 3D-CSU were shown from 10–30 degrees around the x, y, and z axes (Fig. 4). The experiment showed us that a one-marker setup may reduce the rotational setup error around the y (β) and z (γ) axes in Fig. 4. However, one-marker setup may result in an alignment worse than the alignment without any correction that is seen with the rotational setup error around x axis (α) in Fig. 4. This is because the displacement of one marker can be larger than the displacement of the gravity center of the target volume in the rotational setup error. If we use the marker that moved more than the gravity center of the target volume in translational "correction," the gravity center of the target volume may be "overcorrected." Three-dimensional conformal setup was able to reduce the error due to rotation without any deterioration in translational alignment (α, β, γ; Fig. 4).

Table 1 shows the mean and SD of the angles measured with the 3D-CSU system. The mean ± SD was −0.4 ± 0.4, −0.2 ± 0.4, and 0.0 ± 0.5 degrees for α, β, and γ, respectively, from 0–90 degrees.

DISCUSSION

The setup system using two orthogonal diagnostic fluoroscopies and one internal fiducial marker has been shown to be useful for reducing translational setup error (4). However, this system was vulnerable to misalignment due to

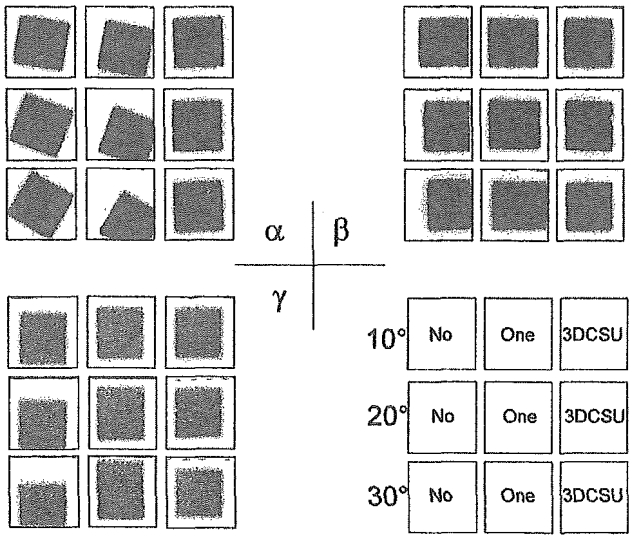

Fig. 4. The differences in dose distribution at the surface of the phantom, which was rotated from 10–30 degrees around the x (α), y (β), and z axes (γ). The dose distribution was measured without correction, with one-marker translational setup of the phantom, and with three-dimensional conformal setup (3DCSU) of the phantom.

rotation of the CTV, as we have seen in this study. The present study showed that three-marker translational setup using the gravity center of three markers is better than one-marker setup for reducing the translational setup error when there is some rotational error. The three-dimensional conformal setup system is expected to be useful for correcting the rotational setup error by adjusting the gantry, couch, and collimator of the linear accelerator to the calculated rotational angles.

Table 1. Mean and standard deviation of the rotation around the $x(\alpha)$, $y(\beta)$, and $z(\gamma)$ axes as estimated by three-dimensional conformal setup

	Average			SD		
Degrees	α	β	γ	α	β	γ
0	−0.3	−1.1	0.6	0.4	0.2	0.3
5	0.4	−0.3	0.0	1.4	0.7	1.4
10	−0.5	0.5	0.8	0.6	0.1	0.7
15	−0.5	0.1	0.6	0.2	0.6	0.4
20	−0.5	0.2	0.7	0.4	0.7	0.5
25	−0.3	0.3	0.4	0.4	0.5	0.6
30	−0.7	0.2	0.6	0.6	0.5	0.6
35	−0.5	−0.2	0.3	0.3	0.1	0.5
40	−0.6	−0.6	0.3	0.2	0.8	0.4
45	−0.7	−0.4	0.2	0.4	0.6	0.6
50	−0.7	−0.2	−0.1	0.2	0.3	0.5
55	−0.4	−0.2	−0.1	0.2	0.1	0.3
60	−0.7	−0.4	0.0	0.4	0.6	0.6
65	−0.3	−0.8	−0.3	0.2	0.3	0.2
70	−0.4	−0.4	−0.6	0.6	0.6	0.2
75	−0.1	−0.7	−0.7	0.5	0.2	0.3
80	−0.6	0.2	−0.3	0.2	0.3	0.5
85	−0.2	−1.1	−1.0	0.9	0.4	0.8
90	−0.2	1.4	−0.7	0.5	0.3	0.1
	−0.4	−0.2	0.0	0.4	0.4	0.5

The present study showed that 3D-CSU is sufficiently accurate for clinical usage provided that the rotating subject is rigid and there is no migration of the markers. However, there are several possible shortcomings of this method. First, the tumors are soft and deformable, so the effect of deformation may mimic the rotation of the subject. Second, migration of the markers can influence the calculation of the rotation angle. Third, if the organ motion in the body is too large, the distance between the skin surface and the tumor's center of gravity changes significantly from the planned beam. In other words, even when 3D-CSU corrected the beam angle's relation to the surface of the tumor, it did not correct the beam angle in relation to the skin surface. Thus, the depth from the skin to the surface of the tumor will change, resulting in a change in dose distribution. The dose to the organs at risk close to the target volume can also change when the corrected beam passes the organs at risk after 3D-CSU. Three-dimensional conformal setup is applicable only when these uncertainties are controllable or taken into account in treatment planning.

Even though its clinical application has limitations, implanting three gold markers method may be useful for certain situations if careful quality control is employed. In practice, the deformation of the tumor and migration of the marker can be estimated based on the distance among three markers to avoid uncertainty. Because the effect of a few millimeters' difference in depth on the absorbed dose is negligible in the case of a megavoltage MV X-ray, the dose to the target volume may not change significantly. Spinal or paraspinal lesions are reasonable candidates for the present version of 3D-CSU since the distance between the skin and the spine does not change significantly. Three markers were attached to the vertebrae during the surgical operation. The steadiness of the marker fixation has been reported previously (2, 6). We have used 3D-CSU for 2 patients with spinal schwannoma in the last year. It was necessary to monitor the disease for more than 3 years to judge the clinical outcome, but there has been no relapse and no adverse effect.

Previous studies have suggested that intrafractional organ motion is negligible in prostate cancer patients in the supine position but can be large in prone position (7). The distance among the three markers was useful to detect the possible migration and deformation of the prostate gland in our previous study (6). Previous studies have suggested that inter-fractional rotational movement of the prostate gland can be so large that 3D-CSU may be usable for prostate cancer (1, 9, 10). Head-and-neck tumors may also benefit from 3D-CSU, as it is often difficult to correct the rotation of the head in the plastic mask attached to the treatment table (11). Uterine cervical cancers may benefit from 3D-CSU as well. For these tumors, reduction of rotational error by 3D-CSU would lead to the reduction in adverse effects and increase in local control rates. For lung tumors, the

intrafractional movement is so large that the benefit of 3D-CSU may be limited unless real-time tumor-tracking of the marker is used during the delivery of the therapeutic beam as well (12).

There have been several attempts to fix the imaging tools onto the gantry of the linear accelerator (13, 14). Although these technologies are promising for the purpose of improving precision radiotherapy, 3D-CSU may not be practical with these configurations because the imaging tools would be obstacles to rotating the table. Our system uses imaging tools on the floor and ceiling so that there is no obstacle to the performance of 3D-CSU as well as to 3D noncoplanar irradiation.

In conclusion, phantom studies showed that 3D-CSU is useful for rotational correction of the target volume without correcting the position of the patient. This method can improve the accuracy of external radiotherapy. However, the uncertainty regarding the deformation of the tissue, migration of the marker, and the change of distance between the surface of the body and the center of gravity of the target volume must all be estimated for this method to be used in clinical practice.

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Stereotactic Hypofractionated High-Dose Irradiation for Stage I Nonsmall Cell Lung Carcinoma

Clinical Outcomes in 245 Subjects in a Japanese Multiinstitutional Study

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BACKGROUND. Stereotactic irradiation (STI) has been actively performed using various methods to achieve better local control of Stage I nonsmall cell lung carcinoma (NSCLC) in Japan. The authors retrospectively evaluated results from a Japanese multiinstitutional study.

METHODS. Patients with Stage I NSCLC (n = 245; median age, 76 years; T1N0M0, n=155; T2N0M0, n=90) were treated with hypofractionated high-dose STI in 13 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. A total dose of 18–75 gray (Gy) at the isocenter was administered in 1–22 fractions. The median calculated biologic effective dose (BED) was 108 Gy (range, 57–180 Gy).

RESULTS. During follow-up (median, 24 months; range, 7–78 months), pulmonary complications of National Cancer Institute-Common Toxicity Criteria Grade > 2 were observed in only 6 patients (2.4%). Local progression occurred in 33 patients (14.5%), and the local recurrence rate was 8.1% for BED ≥ 100 Gy compared with 26.4% for < 100 Gy ($P < 0.05$). The 3-year overall survival rate of medically operable patients was 88.4% for BED ≥ 100 Gy compared with 69.4% for < 100 Gy ($P < 0.05$).

CONCLUSIONS. Hypofractionated high-dose STI with BED < 150 Gy was feasible and beneficial for curative treatment of patients with Stage I NSCLC. For all treatment methods and schedules, local control and survival rates were better with BED ≥ 100 Gy compared with < 100 Gy. Survival rates in selected patients (medically operable, BED ≥ 100 Gy) were excellent, and were potentially comparable to those of surgery. ***Cancer* 2004;101:1623–31.**

KEYWORDS: stereotactic, radiotherapy, altered fractionation, nonsmall cell lung carcinoma, Stage I, dose escalation, multicenter study, local control, survival rate.

Nonsmall cell lung carcinoma (NSCLC) represents a leading cause of mortality worldwide. Lung carcinomas are being detected increasingly early, thanks to routine use of computed tomography (CT)

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scans. For patients with Stage I (T1N0M0 or T2N0M0) NSCLC, full lobar or greater surgical resection represents a treatment choice that promises local control rates ≥ 80% and overall survival rates > 50% after 5 years.[1] However, surgical resection is often not feasible or involves excessive risk for some patients with lung carcinoma with tobacco-related illness, severe cardiovascular disease, or other medical conditions. A small proportion of patients who are eligible for surgery may refuse procedures for personal reasons. Radiotherapy can offer a therapeutic alternative for these patients, but outcomes for conventional radiotherapy are unsatisfactory, and are potentially amplified by selection bias, with local control rates of 40–70% and 5-year survival rates of only 5–30%.[2–4] Doses of conventional radiotherapy to treat NSCLC have been suggested to be too low to achieve tumor control. However, providing a higher dose to the tumor without increasing adverse effect was previously impossible, due to technical uncertainties over focusing irradiation only on the tumor-bearing area of the lung.

With the increasing accuracy of localization for tumor-bearing areas using various imaging techniques, hypofractionated or single high-dose stereotactic irradiation (STI) has been actively investigated for Stage I NSCLC in Japan.[5–8] STI can also substantially reduce overall treatment time from several weeks for a conventional radiotherapy schedule to a few days, offering important advantages to the patient. A landmark study by Uematsu et al.,[5] one of the pioneers of STI for extracranial lesions, revealed excellent survival rates for medically operable patients, approximating those for full lobar surgical resection. Under the guidelines of the Japanese Society of Radiation Oncology study group,[9] Stage I NSCLC has been treated using small-volume STI in numerous Japanese institutions since the late 1990s, with far fewer symptomatic adverse effects than conventional radiotherapy. Although optimal STI techniques and schedules for Stage I NSCLC remain unclear, the number of patients with Stage I NSCLC treated nationwide using small-volume, high-dose STI has accumulated rapidly. Although differences in techniques and schedules may vary widely, retrospective investigation of the results of STI for Stage I NSCLC from the many institutions that have used small-volume, high-dose irradiation in this short period should yield some meaningful data. The current study retrospectively evaluated Japanese multiinstitutional results for high-dose STI for Stage I NSCLC, and sought to answer the following questions: 1) What is the optimal dose to limit toxicity and still obtain local control? 2) Are the results from single-institution studies reproducible? 3) Are STI results comparable to those of surgery?

TABLE 1
Patient Characteristics

Total no. of patients	245
Age	35–92 yrs (median, 76 yrs)
PS	PS 0, 94; PS 1, 104; PS 2, 47
Pulmonary chronic disease	Positive, 196; negative, 96
Histology	Squamous cell carcinoma, 110; adeno carcinoma, 109; others, 26
Stage	Stage IA, 155; Stage IB, 90
Tumor diameter	7–58 mm (median, 28 mm)
Medical operability	Inoperable, 158; operable, 87

PS: performance status.

MATERIALS AND METHODS

Eligibility Criteria

All patients enrolled in the current study satisfied the following eligibility criteria: 1) identification of T1N0M0 or T2N0M0 primary lung carcinoma on chest and abdominal CT scans, bronchoscopy, bone scintigraphy, or brain magnetic resonance imaging scans; 2) histologic confirmation of NSCLC; 3) tumor diameter < 60 mm; 4) performance status ≤ 2 according to World Health Organization guidelines; and 5) inoperable tumor due to poor medical condition or refusal to undergo surgery.

No restrictions were utilized concerning the location of eligible tumors, irrespective of whether they were located adjacent to a major bronchus, blood vessel, chest wall, or the esophagus or spinal cord. However, the spinal cord was kept out of the high-dose area.

Patients were informed as to the concept, methodology, and rationale of this treatment. Written informed consent was obtained from all patients. The study was approved by the ethics committee of each institution and was performed in accordance with the 1983 revision of the Helsinki Declaration.

Patient Characteristics

A summary of patient characteristics is provided in Table 1. From April 1995 to February 2003, 245 patients with primary NSCLC were treated with hypofractionated high-dose STI in 13 institutions. Of the 245 patients, 158 (65%) were considered to be medically inoperable, due predominantly to chronic pulmonary disease, advanced age, or other chronic illness. The remaining 87 patients (35%) were considered to be medically operable, but had refused surgery or had been advised to select STI by medical oncologists.

Treatment Methods

All patients were irradiated using stereotactic techniques. For the purposes of the current study, all ste-

TABLE 2
Treatment Schemes

Beam energy	6-MV X-ray, 12; 4-MV X-ray, 1
Measures for respiratory motion	Respiratory gating, 5; breath hold, 2; non, 6
Fixation of patients	Vacuum pillow, 5; body frame, 4; non, 4
Irradiation port shape	Regular, 4; conformal, 9
Fraction numbers	1–25 (multiple, 11; single, 2)
Irradiation mode	Multiple (6–20) static ports, 7; dynamic arc, 6
Single dose (at the isocenter)	3–35 Gy
Total dose (isocenter) of stereotactic irradiation	20–69 Gy
Conventional radiotherapy	30–44 Gy/15–20 fractions in 27 patients; non, 218 patients
BED = nd(1+d/a/b) at the isocenter	57–180 Gy (median, 108 Gy)

BED: biologic effective dose; Gy: gray.

reotactic techniques fulfilled three requirements: 1) reproducibility of the isocenter ≤ 5 mm, as confirmed in every fraction; 2) slice thickness on CT scan ≤ 3 mm for three-dimensional (3D) treatment planning; and 3) irradiation with multiple noncoplanar static ports or dynamic arcs. Table 2 summarized various techniques and instruments introduced to achieve STI in 13 institutions. To fulfill the first requirement, a CT scan or two-directional portal graph was undertaken before every treatment regimen in 12 institutions, whereas real-time tumor tracking using a gold marker inserted around the tumor[10] was performed in 1 institution. A CT scanner sharing a common couch with the linear accelerator was placed in an irradiation room in two institutions.[11,12]

Treatment planning with irregularly shaped beams using noncoplanar multiple (3–10) dynamic arcs or multiple static ports (6–20 ports) was established with the help of a 3D treatment-planning computer. Beam shaping was performed in some institutions using an integrated motorized multileaf collimator with 0.5–1-cm leaf width at the isocenter. Furthermore, various techniques using breathing control or gating methods and immobilization devices such as a vacuum cushion with or without a stereotactic body frame were utilized to reduce respiratory internal margins. Respiratory gating or breath-hold methods were used in seven institutions.

Planning CT scans were performed with 2 or 3-mm slice thickness and displayed using a window level of −700 Hounsfield units (HU) and a window width of 2000 HU. In some institutions, irradiation and planning CT scans were performed under breath-hold conditions. In other institutions, irradiation and planning CT scans were performed under free shallow breathing, with images taken using slow scanning (4 seconds per slice).

The clinical target volume (CTV) marginally exceeded the macroscopic target volume by 0–5 mm. The planning target volume (PTV) comprised the CTV, a 2–5-mm internal margin, and a 0–5-mm safety margin. An example of an STI dose distribution for Stage I lung tumors is shown in Figure 1. A high dose was concentrated on the tumor-bearing area while sparing surrounding normal lung tissues using STI.

Irradiation schedules also differed among institutions. The number of fractions ranged between 1 and 25, with single doses of 3–12 Gy. A total dose of 18–75 Gy at the isocenter in 1–25 fractions was administered with 6-MV X-rays within 20% heterogeneity in the PTV dose. Twenty-seven patients had received conventional irradiation doses of 30–44 Gy in 15–20 fractions before STI due to physician preferences. No chemotherapy regimens were administered before or during radiotherapy.

To compare the effects of various treatment protocols with different fraction sizes and total doses, a biologic effective dose (BED) was utilized in a linear-quadratic model.[13] BED was defined as $nd(1+d/\alpha/\beta)$, with units of grays, where n is the fractionation number, d is the daily dose, and α/β is assumed to be 10 for tumors. BED was not corrected with values for tumor-doubling time or treatment term.

The median BED at the isocenter was 108 Gy (range, 57–180 Gy). BED was ≥ 100 Gy in 173 patients and < 100 Gy in 72 patients.

Dose constraints were set for the spinal cord only. The BED limitation for the spinal cord was 80 Gy (α/β was assumed to be 2 Gy for chronic spinal cord toxicity). This dose constraint for the spinal cord was achieved in all patients who satisfied all eligibility criteria.

Evaluation

The objectives of the current study were to retrospectively evaluate toxicity and the local control and survival rates according to BED. Follow-up examinations were performed by radiation oncologists for all patients. The first examination took place 4 weeks after treatment, and patients were subsequently seen every 1–3 months. Tumor response was evaluated using previously published National Cancer Institute (NCI) criteria.[14] Chest CT scans (slice thickness, 2–5 mm) were usually obtained every 3 months for the first year, and repeated every 4-6 months thereafter. A complete response (CR) indicated that the tumor had completely disappeared or was replaced by fibrotic tissue. A partial response (PR) was defined as a ≥ 30% reduction in the maximum cross-sectional diameter. Distinguish-

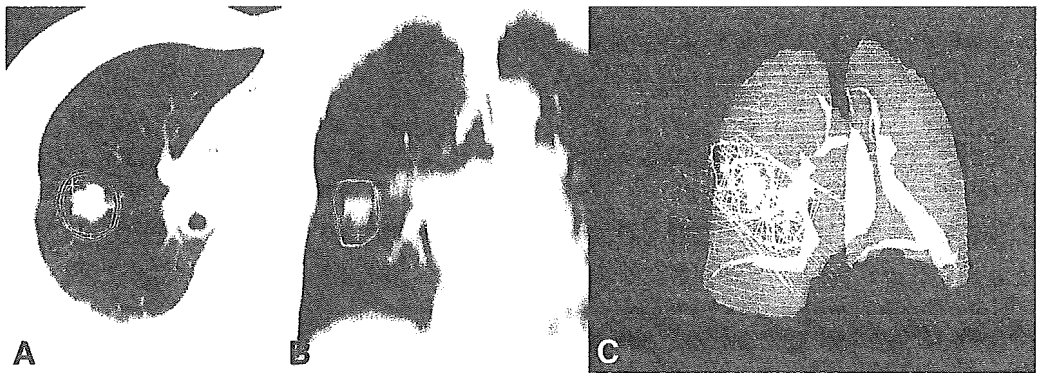

FIGURE 1. An example of three-dimensional treatment planning. (A) Isodose curves on axial CT through the center of the PTV. (B) Isodose curves on a coronal reconstructed image through the center of the PTV. (C) Three-dimensional image showing all radiotherapy arcs and isodose curves.

ing between residual tumor tissue and radiation fibrosis was difficult. Any suspicious residual confusing density after radiotherapy was considered to be evidence of PR, so the actual CR rate may be higher than presented in the current study. Local disease recurrence was considered to have occurred only when enlargement of the local tumor continued for > 6 months on follow-up CT scans. Findings on CT scans were interpreted by two radiation oncologists. Absence of local disease 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 (NCI-CTC).

Statistical Analysis

Local disease recurrence rates in the two groups were compared using the chi-square test. BED among patient groups at each pulmonary toxicity grade was compared using Kruskal–Wallis tests. Cumulative survival curves were calculated and drawn using Kaplan–Meier algorithms with the day of treatment as the starting point. Subgroups were compared using log-rank statistics. Values of $P < 0.05$ were considered to be statistically significant. Statistical calculations were conducted using Version 5.0 StatView software (SAS Institute Inc., Cary, NC).

RESULTS

All patients completed treatment with no particular complaints. The median period of follow-up was 24 months (range, 10–78 months). BED (α/β is assumed to be 2 Gy for chronic toxicity of the spinal cord) did not exceed 80 Gy in any of the patients.

Local Tumor Response

Of the 245 patients evaluated using CT scans, CR and PR were achieved in 57 (23.3%) and 151 (61.6%) patients, respectively. The overall response rate (CR+PR) was 84.8%. Overall response rates for tumors with BED $\geq$ 100 Gy ($n = 173$) and < 100 Gy ($n = 72$) were 84.5% and 83.3%, respectively. An example of a CR is shown in Figure 2.

Toxicity

Treatment toxicities are summarized in Table 3. Symptomatic radiation-induced pulmonary complications (NCI-CTC criteria Grade > 1) were observed in 17 patients (6.9%). No significant differences in BED were identified among patient groups at each pulmonary toxicity grade. Pulmonary fibrosis or emphysema before treatment was observed in 15 (88%) of the 17 patients with pulmonary complications > Grade 1. Pulmonary symptoms resolved in most patients with or without steroid therapy, but continuous oxygen supply was required in three patients who displayed poor respiratory function before irradiation. Chronic segmental bronchitis and wall thickening causing atelectasis on the peripheral lung was observed in one patient. Grade 3 esophagitis was temporarily observed in two patients with tumors adjacent to the esophagus. Grade 3 or 4 dermatitis was observed in two patients with tumors adjacent to the chest wall. No vascular, cardiac, or bone marrow complications had been encountered as of the last follow-up.

Disease Recurrence

Local disease recurrence occurred in 13.5% of all patients, with rates being significantly lower for BED $\geq$ 100 Gy (8.1%) compared with < 100 Gy (8.1% vs. 26.4%, $P < 0.01$). Patients with Stage IB disease displayed significantly higher rates of local disease recurrence compared with patients with Stage IA disease. However, no differences in the local disease recurrence rate were observed between patients with Stage IA disease and patients with Stage IB disease for BED

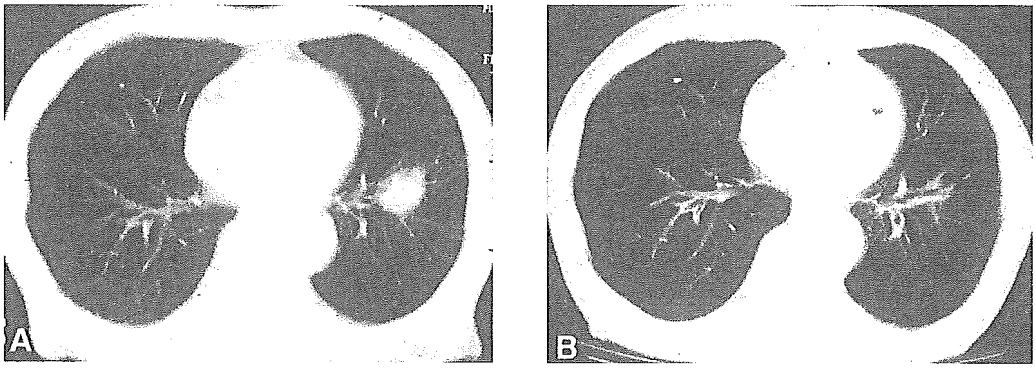

FIGURE 2. An example of a patient with a complete response (CR). The patient was an 80-year-old male with T2N0 adenocarcinoma. (A) Computed tomography scan (CT) before stereotactic irradiation (STI) of 70 gray/10 fractions/5 days. (B) CT scan 6 months after STI. CR was acquired and no radiation-induced pneumonia was apparent.

TABLE 3
Toxicity

Pneumonitis[a]	
Grade 0, 32.8%	
Grade 1, 59.6%	
Grade 2, 4.1%	
Grade 3, 1.2%	
Grage 4, 1.2%	
Esophagitis[a]	
Grade 0, 95.6%	
Grade 1, 2.4%	
Grade 2, 1.2%	
Grade 3, 0.8%	
Dermatitis[a]	
Grade 0, 98.0%	
Grade 1, 0.8%	
Grade 2, 0.4%	
Grade 3, 0.4%	
Grade 4, 0.4%	
Pleural effusion (1.6%)	
Rib fracture (0.8%)	
Bone marrow suppression (0.0%)	

[a] Graded according to National Cancer Institute-Common Toxicity Criteria (Version.2.0).

≥ 100 Gy. Rates of local disease recurrence were also significantly lower in the total group and Stage IA and Stage IB subgroups for BED ≥ 100 Gy compared with < 100 Gy. In particular, when BED was < 100 Gy, the local disease recurrence rate in patients with stage IB disease was 41.4% (12 of 29) compared with 16.3% (7 of 43) for patients with Stage IA disease. For BED ≥ 100 Gy, the local disease recurrence rate was 7.5% for BED ≥ 120 Gy (n = 80) and 9.8% for BED ≥ 140 Gy (n = 40). The local disease recurrence rates for adenocarcinoma and squamous cell carcinoma were 13.6% (15 of 110) and 13.8% (15 of 109), respectively.

The patterns of first disease recurrence are listed in Table 4. Some sites of disease recurrence overlapped, and isolated local, lymph node, and distant disease recurrences were observed in 8.6%, 3.3%, and 9.8% of patients, respectively. The local disease recurrence rate of patients with Stage IB was twice that of patients with Stage IA disease, whereas lymph node and distant disease recurrence rates were basically identical in the two subgroups.

Survival

The overall 3 and 5-year survival rates were 56% and 47%, respectively. The cause-specific 3 and 5-year survival rates were both 78%. Overall survival rates differed significantly according to medical operability. For example, intercurrent deaths occurred in 19.1% of inoperable patients and in 3.4% of operable patients (Fig. 3). Overall survival rates according to BED in all patients revealed significant differences between the subgroups for BED < 100 Gy and ≥ 100 Gy (Fig. 4). Overall survival rates according to BED in operable patients revealed identical 3 and 5-year survival rates of 88% for BED ≥ 100 Gy (Fig. 5). Overall 5-year survival rates according to stage in operable patients irradiated with BED ≥ 100 Gy were 90% for patients with Stage IA disease and 84% for patients with Stage IB disease (Fig. 6).

DISCUSSION

Surgical resection remains the standard management for patients with Stage I NSCLC. The 5-year overall survival rates for patients undergoing resection range from 55% to 72% for Stage I NSCLC.[15–17] Results for treating early-stage NSCLC using conventional radiotherapy are disappointing. Qiao et al.[18] reviewed 18 studies on Stage I NSCLC treated using conventional radiotherapy alone, and reported that the 3-year overall and cause-specific survival rates were 34 ± 9% (mean ± standard error of the mean) and 39±10%, respectively. Although CR represents an important

TABLE 4
Patterns of First Disease Recurrences According to Stage and BED

Site of disease recurrence[a]	Total no. of patients (%)	Stage IA (%)	Stage IB (%)	BED < 100 Gy (%)	BED ≥ 100 Gy (%)
Local disease recurrence	33/245 (13.5)	15/155 (9.7)	18/90 (20.0)	19/72 (26.4)	14/173 (8.1)
Regional lymph node recurrence	20/245 (8.2)	12/155 (7.7)	8/90 (8.9)	8/72 (11.1)	12/173 (6.9)
Distant metastasis	36/245 (14.7)	23/155 (14.8)	13/90 (14.4)	14/72 (19.4)	22/173 (12.7)

BED: biologic effective dose; Gy: gray.
[a] Some of the disease recurrences overlapped each other.

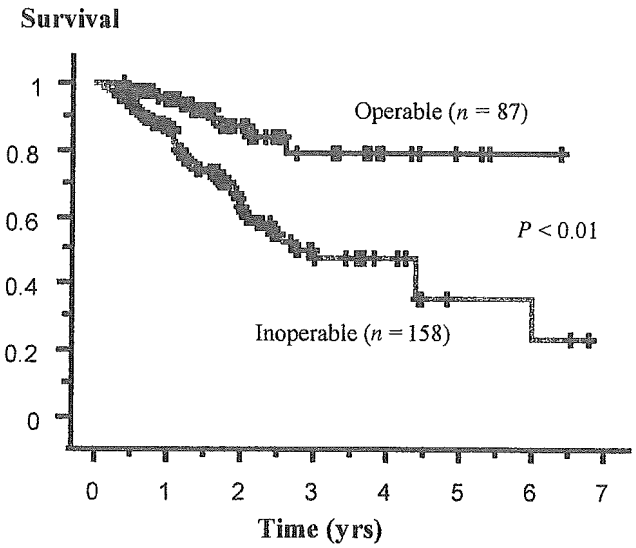

FIGURE 3. Overall survival rate according to medical operability.

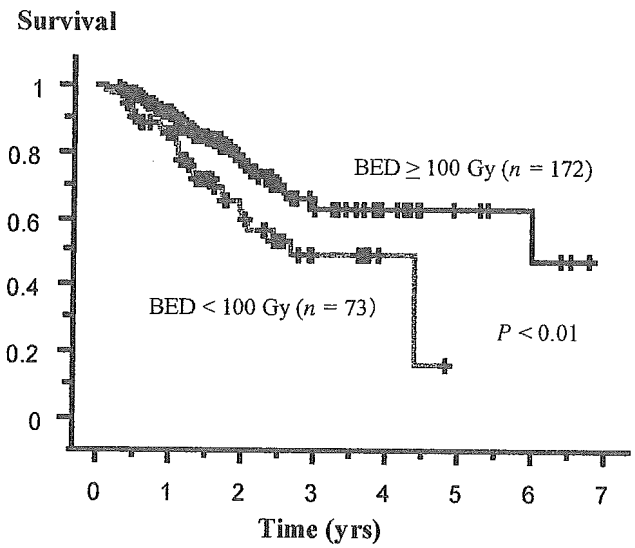

FIGURE 4. Overall survival rate according to the biologic effective dose in all patients.

prognostic factor, particularly for tumors < 5 cm in diameter,[19,20] local disease recurrence is common after conventional radiotherapy for early-stage NSCLC.[18,21,22] Several studies have shown the value of dose escalation in Stage I NSCLC.[18–20] Although increased radiation dose to the tumor is essential, escalating the dose is difficult under conventional radiotherapy techniques, given the relatively large amount of normal lung tissue enclosed in the high-dose region, including internal and safety margins to accommodate respiratory movements and daily setup errors. The most common reactions caused by radiation dose escalation are pneumonitic changes, which can induce acute symptoms of fever and cough, leading to interstitial fibrosis and subsequent reduction in lung capacity. In patients with already compromised respiratory function, such reductions can prove fatal.

Because excessive dose escalation, which improves local control in patients with NSCLC,[18,23,24] is so hard to obtain using conventional techniques, new approaches must be taken to improve outcomes. In 1995, Blomgren et al.[25] introduced a new STI technique for extracranial radiotherapy that was analogous to cranial radiosurgery. The advantages of this radiotherapeutic technique include narrow X-ray beams, concentrated in such a manner as to provide intense irradiation to small lesions at high doses, and a small number of treatment fractions. The ability to concentrate radiotherapy on a small tumor while sparing surrounding tissues had already been made possible using STI. Results from treating small brain metastases are excellent, with local control rates of approximately 90%. Application of STI techniques to the treatment of small lung tumors is reasonable, as the ratio of high-dose radiation volume to normal tissue volume should be smaller than that for the brain. Moreover, the limited volume of radiation damage on the lung or adjacent structures is unlikely to result in the severity of symptoms possible with damage to cerebral tissues. The current data reveal that Grade 3 or 4 radiation pneumonitis was observed in few patients (4%). Acute esophagitis, dermatitis, and chronic bronchitis were also observed in relatively few patients for whom tumors bordered on these organs. No other life-threatening toxicities were encountered.

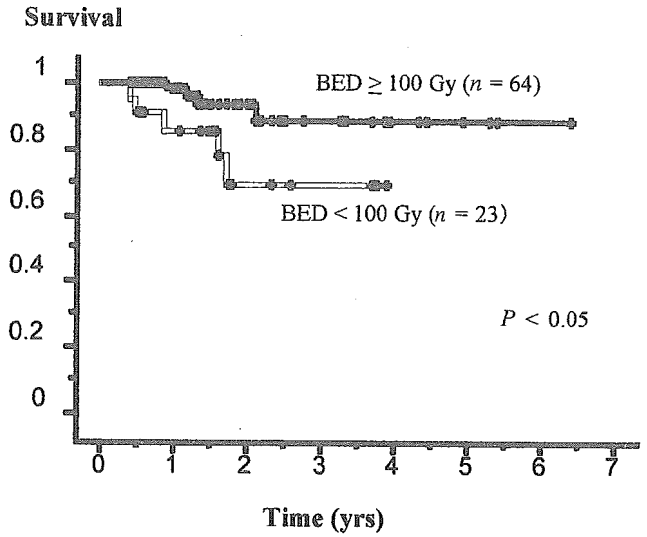

FIGURE 5. Overall survival rate according to the biologic effective dose in medically operable patients.

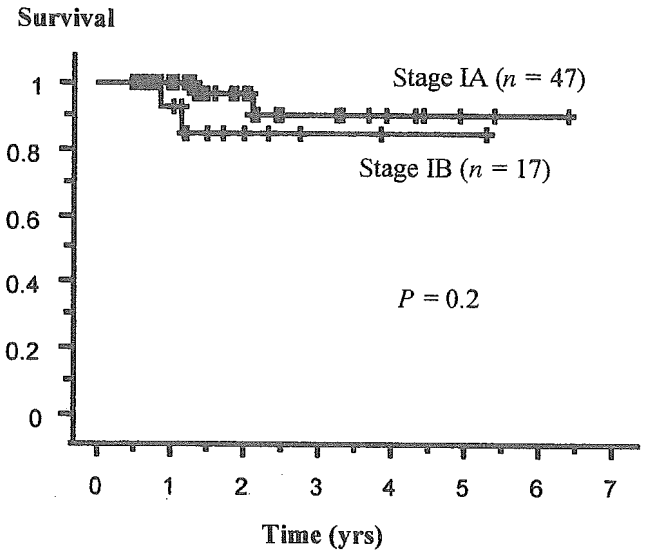

FIGURE 6. Overall survival rate according to stage in medically operable patients irradiated with biologic effective dose ≥ 100 gray.

However, the chronic effects of hypofractionated irradiation on major vessels, bronchus, esophagus, heart, and spinal cord remain unknown. Lethal pulmonary bleeding has been reported after a schedule of 24-Gy single-dose irradiation (BED = 81.6 Gy).[26] Long and careful follow-up is therefore warranted.

Recently, STI for small lung tumors using a linear accelerator has gained acceptance as an effective treatment modality. Irradiation methods and local disease recurrence rates from several institutions in which STI has been performed for primary Stage I NSCLC are listed in Table 5.[5–7,27–29] Although BED analysis using the linear-quadratic model is not quite appropriate for radiotherapy with a large single dose or short treatment period,[30] the model is useful to compare outcomes from a variety of treatment schedules using different single doses and number of fractions. Cheung et al.[31] summarized several clinical studies. In their study, crude local recurrence rates with conventional radiotherapy were 36–70%, with BED of 59.6–76.4 Gy at an α/β ratio of 10. They recommended dose escalation to increase the local control rate. STI appears to represent an ideal modality for dose escalation. Local tumor recurrence rates of Stage I NSCLC after STI with a BED of 99–137 Gy were 0–6% for a median follow-up period of 19–60 months.[5–7,27,28] The comparatively high local disease recurrence rate reported by Hof et al.[29] may be attributable to lower BED. In the current study, the local control rate was 91.9% for BED ≥ 100 Gy. For BED < 100 Gy, the local control rate was poor, particularly in patients with Stage IB disease. Given our clinical results, additional dose escalation studies may be possible. However, patients receiving BED ≥ 120 Gy or ≥ 140 Gy did not display significantly better local control rates than patients receiving lower BED, even for patients with Stage IB disease. Satisfactory BED to achieve local control for Stage I NSCLC is approximately 100 Gy. Representative examples of dose regimens performed in the current study that provided approximate BEDs > 100 Gy were 48 Gy/4 fractions or 50 Gy/5 fractions. However, treatment outcomes for patients who received conventional irradiation before STI in our study were not significantly different from those of other patients. Although a longer follow-up is necessary to determine final control rates of tumors in our study, local control rates for STI may be equivalent to surgical results, as most local disease recurrences generally occur within 3 years after treatment.[18]

In our study, the overall survival rates were excellent for limited patients considered operable before treatment and with BED ≥ 100 Gy. The 88% three-year overall survival rate in operable patients treated with BED ≥ 100 Gy was consistent with single institutional results (a 3-year overall survival rate of 88% in 29 medically operable patients) reported by Uematsu et al.[5] The patients in that study (from the Medical Defense College, Saitama, Japan) were not included in the current multiinstitutional study. Survival rates after STI for BED ≥ 100 Gy may well match those after lobectomy for Stage I NSCLC. We believe that good treatment outcomes from STI depend on a high BED, a large single dose, a short treatment period, and delivery of a modest dose to a large lung volume. STI can reduce substantially overall treatment time from

TABLE 5
Comparison of STI Methods and Local Control Rates for Stage I Nonsmall Cell Lung Carcinoma

Author	No. of patients	Total tumor dose (Gy)	Single dose (Gy)	Treatment time (days)	BED (Gy)[a]	Safety Margin (mm)[b]	Breath-hold or respiratory gating	Image-guided repositioning	Median follow-up (mos)	Local disease recurrence (%)
Uematsu et al.[5,27]	50	50–60	5–6	5–12	100–120	0	No	Yes	60	6
Nagata et al.[6,28]	27	48	12	12–13	106	0	No	Yes	19	0
Fukumoto et al.[7]	17	48–60	6–7.5	14	99–137	0	Yes	Yes	24	6
Hof et al.[29]	10	19–26	19–26	1	55–94	5	Yes	No	15	20

Gy: gray; STI: stereotactic irradiation; BED: biological effective dose ($\alpha/\beta = 10$).

[a] BED was recalculated at the isocenter.

[b] Safety margin: subtract the clinical target volume and maximum respiratory motion from the planning target volume.

several weeks of conventional radiotherapy to a few days, offering important advantages to the patient.

In conclusion, hypofractionated high-dose STI with BED < 150 Gy represents a feasible and beneficial method for obtaining curative treatment of patients with Stage I NSCLC. Local control and survival rates were better for BED ≥ 100 Gy than for BED < 100 Gy for all treatment methods and schedules. Survival rates for STI in selected patients (medically operable and BED ≥ 100 Gy) were excellent and reproducible among institutions, irrespective of specific treatment methods, and were potentially equivalent to those of surgery. The current study was a retrospective review, and unknown selection biases for treated and analyzed patients may have been present. Moreover, treatment parameters were very heterogeneous. However, STI may become a standard radical treatment strategy for Stage I NSCLC, at least for compromised patients. More patients and longer follow-up, or a prospective Phase II study based on a single treatment schedule followed by a Phase III trial comparing surgical outcomes with those of STI, are necessary to determine standard treatments for Stage I NSCLC.

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特集

I-III期非小細胞癌の治療
—肺癌診療ガイドラインに基づくコンセンサスと新たな臨床試験の動向—

手術適応外症例の治療方針
—放射線療法—

早川和重*

要　旨

I～III期非小細胞肺癌で根治的放射線療法の適応となるのは，臨床病期Bulky N2IIIA期ならびに悪性胸水・胸膜播種・対側縦隔リンパ節転移を除くIIIB期の局所進行癌と，I/II期であっても高齢などによる心・肺機能の低下や合併症のために医学的に切除不能と判断される症例である。最近の放射線治療技術の進歩により，局所制御率・治療成績は向上しつつあるが，本稿では切除不能非小細胞肺癌に対する放射線療法の現状と治療方針について述べる。

Key words：非小細胞肺癌，放射線治療，化学放射線療法，定位放射線照射，重粒子線治療/non-small cell lung cancer, radiotherapy, chemoradiotherapy, stereotactic irradiation, heavy ion radiotherapy

1 根治的放射線療法の適応と治療方針

I～III期非小細胞肺癌で根治的放射線療法の適応となるのは，臨床病期Bulky N2IIIA期ならびに悪性胸水・胸膜播種・対側縦隔リンパ節転移を除くIIIB期の局所進行癌症例である。I/II期では手術療法が標準治療であるが，高齢などによる心・肺機能の低下や合併症のために医学的に切除不能と判断される症例は放射線治療の適応となる（表1）[1)~3)]。本稿では局所進行III期症例と医学的に切除不能なI/II期症例に対する最近の胸部放射線療法の動向と治療方針について述べる。

2 局所進行III期非小細胞肺癌の放射線療法

局所進行III期症例では，化学放射線療法が標準的治療である。化学放射線療法のよい対象となるのは，全身状態が良好（PS：0，1）な症例であり，高齢やPS不良などの理由で化学療法の適応とならない症例では，無症状であっても放射線単独療法の適応がある[4)5)]。

1）分割照射法と線量

局所制御率を向上させる方法の一つとして時間的線量配分（分割照射法）の最適化があ

Radiation Therapy for Inoperable or Unresectable Non-Small Cell Lung Cancer
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表 1　非小細胞肺癌の放射線治療に関する病期別治療指針案

〔文献 1) 早川和重, III 期非小細胞癌の治療戦略, 末桝恵一, 監, 江口研二, 加藤治文, 西條長宏, ほか, 編. 肺癌の最新医療. 東京：先端医療技術研究所, 2003：160. 2) 早川和重, 北野雅史. 肺癌に対する放射線治療の原則. 2003；49：1265-73. より引用〕

臨床病期分類	実施医療	探索的医療（臨床試験）
I 期	外科切除	切除＋術後補助療法（T2）
	放射線療法（内科的切除不能）	定位放射線照射（T1）
II 期	外科切除	周術期補助療法＋切除[*1]
[*1] Superior sulcus tumor を含む胸壁浸潤 T3N0	放射線療法（内科的切除不能）	化学放射線療法[*1]
IIIA 期		
T3N1	外科切除	周術期補助療法＋切除
T1-3N2（手術ではじめて N2 が判明した病理学的 N2 は除く）		
N2 節外浸潤（−）　単一ステーション	外科切除	周術期補助療法＋切除
複数ステーション	周術期補助療法＋切除	周術期補助療法＋切除
	化学放射線療法[*3]	化学放射線療法
節外浸潤（＋）		放射線療法＋新規抗癌剤
	化学放射線療法[*3]	
BulkyN2（単純 X-P，気管支鏡で所見あり）		化学放射線療法＋分子標的薬剤
IIIB 期		
T4N0-1 同一肺葉内転移	外科切除	周術期補助療法＋切除
左房浸潤，気管分岐部浸潤[*2]	外科切除，	周術期補助療法＋切除
Superior sulcus tumor の 1 部	（含，再建術[*2]）	
	化学放射線療法[*3]	新規抗癌剤，分子標的薬剤
癌性胸膜炎	対症療法（胸膜癒着術）	周術期補助療法＋切除
その他	化学放射線療法[*3]	放射線療法＋新規抗癌剤
T1-4N3		化学放射線療法＋分子標的薬剤

[*1] 実施医療でも術前（化学）放射線療法が行われることがある

[*2] sleeve pneumonectomy，[*3] PS 不良例は除く

る。実際には，1 日 1 回 1.8〜2 Gy で週 5 日照射する通常分割照射法が広く用いられている（図 1）[1)2)6)]。これは，正常組織と腫瘍組織との間で放射線感受性や照射後の回復に差がみられることを利用して確立された照射法である。

最近行われている分割照射法としては 1 日 2 回以上照射を行う多分割照射法（図 1）[1)2)6)] がある。照射間隔は正常組織が照射後の亜致死障害から回復する時間間隔である 4 時間以上あける必要があるが，遅発性有害反応の軽減には最低 6 時間以上あける方がよい。したがって，日常臨床では時間的制約から 1 日 2 回が一般的である。用いられる 1 回線量に応じて，過分割照射法 hyperfractionation（1.2 Gy/回），加速分割照射法 accelerated fractionation（1.8〜2 Gy/回），加速過分割照射法 accelerated hyperfractionation（1.5 Gy/回）に分類される。過分割照射法は遅発性有害反応の増強を抑えて総線量を増加する方法であり，加速（過）分割照射法は，生残腫瘍細胞の再増殖が照射開始後約 4

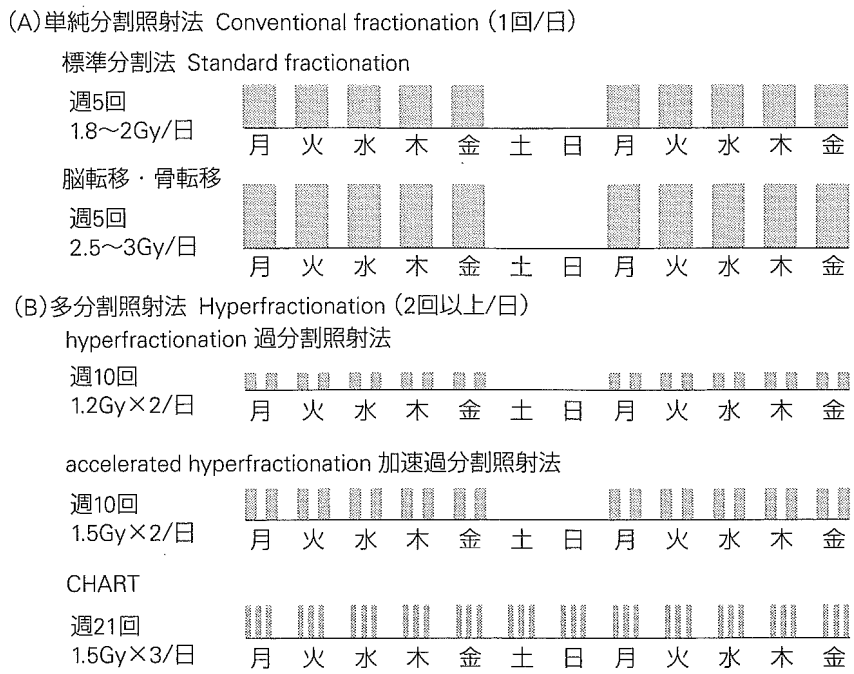

図 1　肺癌に用いられている分割照射法〔文献 2) 早川和重, 北野雅史. 肺癌に対する放射線治療の原則. 2003 ; 49 : 1265-73. より引用〕
CHART はわが国の実地医療では現実的ではないが，照射野の工夫で1日3回照射は可能である。

週以降に加速することから治療期間の短縮を目的とした照射法である。代表的な加速過分割照射法として，1回1.5 Gy を1日3回，12日間連日照射する Continuous, hyperfractionated, accelerated radiotherapy (CHART)[7] の有用性が示されているが，わが国の実地医療の体制では実用的ではない。多分割照射では通常分割照射に比べて急性期の有害事象の増強が問題となり，今後その軽減対策が課題である。

さて，放射線治療では線量に応じて確率的に腫瘍細胞量が減少していくために，放射線治療による腫瘍制御の可能性は腫瘍細胞量に依存する。また，腫瘍サイズが大きくなると放射線感受性の低い低酸素細胞の割合も高くなる。したがって，腫瘍サイズが大きいほど大線量が必要となる[6]。放射線単独療法で線量分割をランダム化比較した英国の4つの臨床試験と米国の RTOG 73-01[8] のメタアナリシス[9] によると，通常分割法に換算して少なくとも線量 60 Gy 以下の領域では治療成績が総線量に依存することが示されており，最低線量として 60 Gy が推奨されている[10]。

一方，通常照射法 60 Gy と約 70 Gy に線量を増加させる過分割照射を比較した3つのランダム化比較試験のメタアナリシス[11] では，過分割照射により死亡のオッズ比が 0.69 (0.51～0.95) と有意に低下した。ただし，これに含まれている通常分割照射法 (60 Gy/30 回，6 週) と過分割照射 (69.6 Gy/

1.2 Gy 1日2回，6週）を比較した大規模なランダム化比較試験（対象458例）[12]では，両群の生存率には有意差は認められていない。また，Coxらが宿主条件のよい（KPS 70-100，体重減少＜5%）T1-3N2III期非小細胞肺癌を対象に行った1回1.2 Gy，1日2回の過分割照射による79.2 Gyまでのランダム化比較試験[13]では，69.6 Gy群がそれ以上線量を増加した74.4 Gy，79.2 Gyの2群よりも有意に生存率が高かった。この理由は不明であるが，局所進行癌では照射野が大きくなるため正常組織への影響が関与した可能性がある。Maguireら[14]は，73.6～80 Gy/4.5～5週の加速過分割照射によって急性障害，晩期障害の程度が高くなり，MSTはIIIA期13カ月，IIIB期10カ月であったと報告している。この成績は通常分割照射による成績[15]と大差がなく，多分割照射による線量増加にも限界があることを示しているものと考えられる。

過分割照射による70 Gyまでは照射の安全性は確認されているが，現時点では通常照射法よりも過分割照射を推奨するにはエビデンスが不十分といわざるをえない。また，70 Gyを超える線量の安全性，有効性は示されていない。現在は，正常組織への影響を考慮した3次元原体照射による線量集中性を高めた照射法による線量増加試験が進められている。

2）照射野

局所進行癌の照射野は原発巣，同側肺門，縦隔を含めるのが標準的である（図2）[6]。上縦隔，鎖骨上窩リンパ節転移例では鎖骨上窩も照射野に含めるが，上葉あるいはS^6原発例では肺門・縦隔さらに鎖骨上窩までを一緒に照射しても照射野が比較的小さくできる。両側肺門部を含む照射は肺機能に大きな影響を及ぼすばかりでなく，重篤な肺臓炎のリスクも高くなるので避けるべきである。照射野辺縁は呼吸性移動などを考慮し，腫瘍辺縁から1.5～2 cm，予防的照射範囲（臨床標的体積PTV）では1 cm前後とする。なお，有害事象としてgrade 2以上の放射線肺臓炎の発症を抑えるためには，20 Gy以上照射される正常肺の体積V_{20}が，放射線単独の場合には正常肺全体の体積の40%を超えないよう（できるだけ35%以下になるよう）[3]に，化学療法併用例では25%を超えないように計画する[16]。原発巣が肺末梢部にある症例では，照射野の縮小時に原発巣と転移リンパ節に照射野を分けて照射する方法も考慮すべきである。

3）化学放射線療法

化学放射線療法では，鎖骨上窩リンパ節転移例も適応になりうると考えられている。順次併用では，70歳以上の高齢者に対する化学療法併用の利益は明らかではない[12]。併用薬剤としては，シスプラチンがkey drugであり[4]，プラチナ製剤を含む化学療法が推奨されている。

化学療法と放射線との併用時期は，順次併用よりも同時併用が推奨されている[4]。また，化学療法を併用しても通常分割照射法での必要な推奨線量は最低60 Gy/6～7週である[4]。化学療法との同時併用では，急性障害の軽減のためにスプリットコース照射法としても，照射休止期期間の生存に対する不利益は明らかではない[17]。

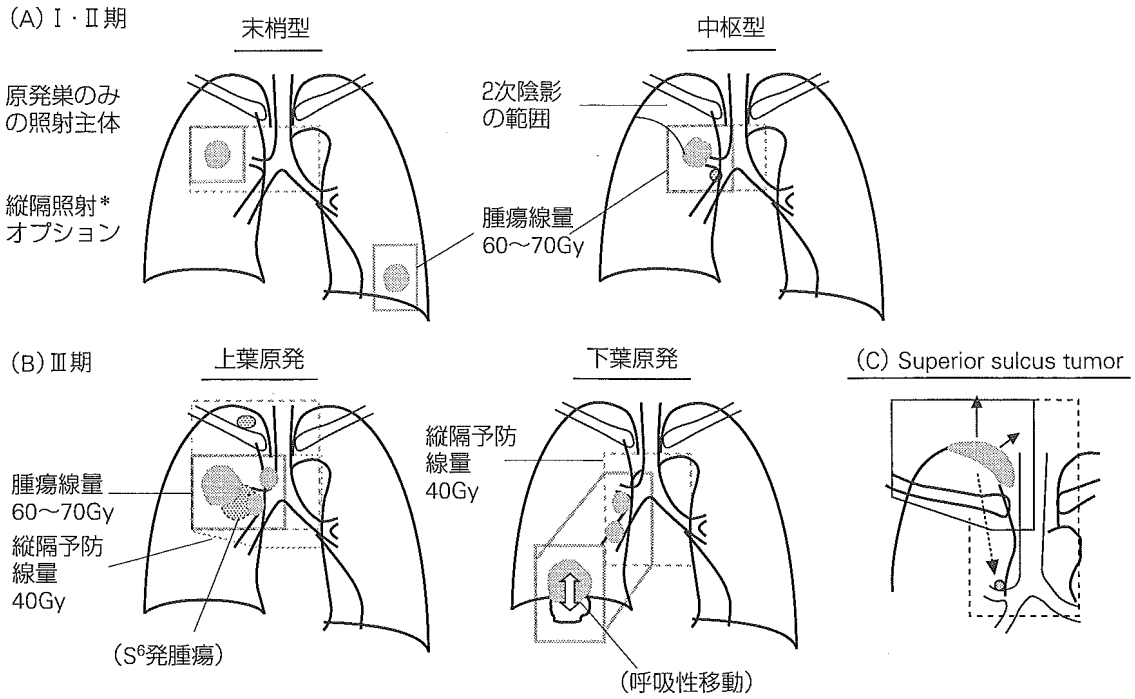

図 2　非小細胞肺癌の根治的放射線治療の照射野〔文献 1）早川和重．III 期非小細胞癌の治療戦略．末舛恵一，監，江口研二，加藤治文，西條長宏，ほか，編．肺癌の最新治療．東京：先端医療技術研究所，2003：160. 2）早川和重，北野雅史．肺癌に対する放射線治療の原則．2003；49：1265-73. 6）早川和重．胸部照射，脳照射．福岡正博，西條長宏，編．プラクティカル内科シリーズ 1：肺癌：患者へのアプローチから治療の最前線まで（改訂第 2 版），東京：南江堂，2003：96. より引用〕

（A）末梢型 N0 例は低肺機能例が対象となることが多く，予防的縦隔照射は必ずしも行わなくてよい。中枢型はリンパ節転移のリスクも高く，所属リンパ節を含めても照射野が大きくならないので，肺門・縦隔への予防照射を行う（*とくに扁平上皮癌）。

（B）上葉あるいは下葉 S^6 原発例では，他部位の原発例と比べて比較的小さな照射野で縦隔の転移リンパ節を含めることができる。また，上葉原発例では，同側鎖骨上窩リンパ節まで照射野に含めても照射野は大きくななならない。一方，下葉原発例では，腫瘍の呼吸性移動により，さらに照射野は大きくなる。

（C）Superior sulcus tumor では鎖骨上窩，椎体方向への浸潤傾向が強く，進行例にもかかわらず肺門リンパ節転移のない症例も少なからず存在する。明らかなリンパ節腫大がみられない場合には，肺尖部と鎖骨上窩を含めた限局した照射野で高線量照射を行う。また，リンパ節転移は重要な予後因子である。

併用薬剤の安全性については，放射線との相性が重要で，シスプラチンあるいはエトポシドは放射線と同時でも比較的安全に使用できる薬剤である。イリノテカンとの同時併用では，肺臓炎や食道炎などの非血液毒性のリスクが高く検討が必要である[1)~4)]。なお，わが国ではゲムシタビンと放射線との同時併用は禁忌である。

化学放射線療法の治療成績を組織型別にみると，順次併用療法は非扁平上皮癌に利益が大きい[2)]が，同時併用療法では組織型による差は明らかではない。

3 医学的に手術不能なI/II期に対する放射線治療

1）放射線治療成績の現状と適応

医学的に手術不能なI/II期非小細胞肺癌の放射線治療に関する大規模なシステマティックレビューとして，Rowellらの26論文2003例の治療成績の分析[18]がある。それによると，全体の生存率は2年33～72%，5年0～42%（平均15～20%）で，他病死が11～43%を占め，原病生存率は2年54～93%，5年13～39%であった。局所再発は6～70%に認められた。さらに，I期症例に限定した根治的放射線治療のレビューでは，Sibley[19]の10論文，Qiaoら[20]の18論文（1988～2000年）の分析がある。Sibleyによると，長期生存例は15%にみられ，全体の死因分析では他病死が25%を占め，遠隔転移死が30%で，局所再発による死亡例は30%であった。治療に伴うGrade 3～5の有害事象は2%未満であった。また，Qiaoらのレビュー[20]では，3年，5年生存率がそれぞれ34±9%，21±8%（平均値±1 SE），死因特異的生存率は3年39±10%，5年25±9%で，生存期間中央値は18～33カ月の範囲であった。一方，再発形式では局所再発率の中央値が40%と大きな問題であったのに対して，所属リンパ節単独の再発は0～3.2%のみであった。

医学的に手術不能なI/II期非小細胞肺癌の治療成績については，手術例と比べると患者背景に大きな差があり，単純に比較することはできない。しかし，Tyldesleyら[5]は，EBMに基づくガイドラインのシステマティックレビューを行い，医学的な理由で手術不能なI/II期非小細胞肺癌に対しては，経過観察よりは根治的放射線療法を行うべきであるとしている。

2）腫瘍線量

I/II期に対する放射線単独療法の治療成績をみると，通常分割照射法による50～65 Gy程度の線量では，5年生存率が15%前後であるのに対して，73.6～80 Gy/4.5～5週の加速過分割照射では生存期間中央値が34カ月[14]，あるいは過分割照射（69.6 Gy/1.2 Gy 1日2回/6週）では5年生存率がI期30%，II期25%という報告[21]がある。また，通常分割照射60 Gyと加速過分割照射の一つであるCHARTによる54 Gyとのランダム化比較試験でのI/II期例のみの分析では，通常分割照射群の2年および4年生存率が24%，12%であったのに対してCHART群ではそれぞれ37%，18%と良好であった[22]。Jeremicら[21]は，医学的切除不能I/II期例の線量-効果関係をレビューし，投与線量として通常分割照射に換算して65～70 Gy相当以上の線量が推奨されるとしている。同様にQiaoらのレビュー[20]でもBEDが高いほど局所制御率が高い傾向があると報告されている（図3）。ただし，肺門部への80 Gy以上の照射は耐容線量を超えていると考えられる[23]。

3）縦隔予防照射の意義

放射線治療の対象となるI/II期症例の多くは高齢者や低肺機能患者であり，可能な限り縦隔・肺門リンパ節への照射は避ける方が望ましい。特に，原発巣が肺野末梢に存在する場合には，肺門・縦隔への予防照射を行う

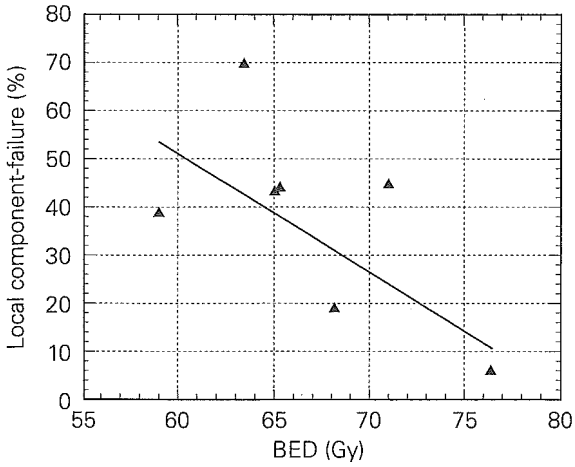

図 3　局所再発率とBED（Biological effective dose）〔文献20）Qiao X, Tullgren O, Lax I, et al. The role of radiotherapy in treatment of stage I non-small cell lung cancer. Lung Cancer 2003；41：1-11. より引用〕

註：local component-failure（局所再発，局所＋リンパ節再発，局所＋遠隔再発をすべて含む）。BED＝nd（1＋d/α/β），n：分割回数，d：1日線量，α/β＝10 Gy（腫瘍）と表される。通常分割照射60 GY/30回（6週）はBD（Gy）＝30×2（1＋2/10）＝72（Gy）となる。

と照射野が大きくなることから，肉眼的腫瘍体積（GTV）に限局した照射が行われることが多い。現在までのところI/II期例に対する縦隔リンパ節への予防照射の有用性に関するランダム化比較試験はないが，Rowellら[18]やQiaoら[20]のレビューでは，I期であれば，原発巣のみの照射でも肺門・縦隔に単独再発する可能性は0～3%である。また，Sibleyの分析[19]でも，I期に対する縦隔予防照射の有効性は確認されていない。したがって，現時点では少なくとも肺野末梢型I期例に対しては原発巣のみへの照射でもよいと考えられる。

しかし一方，肺門部に近い中心型肺癌ではリンパ節転移の頻度は高くなる[2)3)]ことから，扁平上皮癌やII期ではリンパ節への予防照射が予後を改善する可能性がある[20)23)24)]。特に中心型扁平上皮癌では，原発巣のみの照射でも肺門リンパ節は容易に照射野に含まれるうえ，縦隔リンパ節照射を加えても照射野は大きくならない。扁平上皮癌では局所制御がそのまま治癒に結びつく可能性が高く[2)3)25)]，縦隔への予防照射の検討は重要な課題である。

4）定位放射線照射

最近の放射線治療技術の進歩の一つとして，病巣範囲に合わせて立体的に照射を行う3次元原体照射法（3D conformal radiotherapy）がある。特に小腫瘤に対してピンポイントで線量を集中させる定位放射線照射（stereotactic irradiation）が注目されている。定位照射では，照射野が小さいため，分割照射法として1回線量を多くして照射回数を少なくするhypofractionationが用いられる。

末梢小型I期非小細胞肺癌に対するUematsuらの報告[26]では，原発巣のみへの定位放射線治療で3年生存率66%，3年原病生存率88%と良好な治療成績が示されている。Nagataら[27]も16例のT1肺癌に対して中心線量48 Gy/4回の定位照射を行い，観察期間6～36カ月（中央値19カ月）で，すべて局所制御されていると報告している。定位照射による治療成績の向上には大きな期待が寄せられているが，至適分割照射法については今後の重要な検討課題である。

5）重粒子線治療

陽子線や重イオン線を用いた粒子線治療[28]は線量分布が良好なことから3次元照射に適しており，わが国では数施設で治療が進められている。放射線医学総合研究所で行われている肺野末梢型非小細胞癌に対する炭素線治療のI/II相臨床試験では良好な治療結果がえられている[28]。それによると，腫瘍の大きさがT2でも通常の光子に換算して86.4 Gy/18回（6週）あるいは72Gy/9回（3週）以上の照射を行えば90～95%の症例で局所制御可能であり，正常肺組織への影響も軽微であることが分かってきた。これらのデータは今後の陽子線治療や3次元原体照射・定位照射の発展に大いに寄与することが期待されている。

6）気管支腔内小線源治療

肺門部早期扁平上皮癌に対する気管支腔内照射については，わが国から数編の報告[29][30]がみられるのみである。それによると，低～中線量率^{192}Ir密封小線源を用いた気管支腔内照射と外照射の併用で85%前後の局所制御率がえられている[29]。しかし，気管支腔内照射はいまだ探索的治療の範疇に入るものであり，標準治療法としての評価は今後の検討課題である。現時点では，高線量率^{192}Irを用いる場合には，治療法として外照射40 Gy/20回＋気管支腔内照射6 Gy×3回（週1回）が推奨されている[31]。なお，腔内照射にはマレコット型ウイング付アプリケータを用い，線量評価の基準点として気管・主気管支では線源中心から10 mm，葉支以下では5 mmの点を用いることが勧められている[31]。

4 おわりに

最近の放射線治療技術の進歩により，切除不能非小細胞肺癌の局所制御率・治療成績は向上しつつある。しかし，局所進行非小細胞肺癌の治療成績向上のためには分子標的薬剤も含めた化学療法との効果的併用療法に関する研究が非常に重要である。また同時に，わが国における放射線治療技術の品質管理体制の整備も大きな課題である。

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