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CLINICAL INVESTIGATION **Lung**

INTERINSTITUTIONAL VARIATIONS IN PLANNING FOR STEREOTACTIC BODY RADIATION THERAPY FOR LUNG CANCER

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Purpose: The aim of this study was to assess interinstitutional variations in planning for stereotactic body radiation therapy (SBRT) for lung cancer before the start of the Japan Clinical Oncology Group (JCOG) 0403 trial.

Methods and Materials: Eleven institutions created virtual plans for four cases of solitary lung cancer. The created plans should satisfy the target definitions and the dose constraints for the JCOG 0403 protocol.

Results: FOCUS/XiO (CMS) was used in six institutions, Eclipse (Varian) in 3, Cadplan (Varian) in one, and Pinnacle3 (Philips/ADAC) in one. Dose calculation algorithms of Clarkson with effective path length correction and superposition were used in FOCUS/XiO; pencil beam convolution with Batho power law correction was used in Eclipse and Cadplan; and collapsed cone convolution superposition was used in Pinnacle3. For the target volumes, the overall coefficient of variation was 16.6%, and the interinstitutional variations were not significant. For maximal dose, minimal dose, D95, and the homogeneity index of the planning target volume, the interinstitutional variations were significant. The dose calculation algorithm was a significant factor in these variations. No violation of the dose constraints for the protocol was observed.

Conclusion: There can be notable interinstitutional variations in planning for SBRT, including both interobserver variations in the estimate of target volumes as well as dose calculation effects related to the use of different dose calculation algorithms. © 2007 Elsevier Inc.

Stereotactic body radiation therapy, Lung cancer, Treatment planning, Interinstitutional variation.

INTRODUCTION

Promising clinical results of stereotactic body radiation therapy (SBRT) for early-stage lung cancer have been reported by several investigative groups (1–11). However, most of these results were based on data from a single institution, and the treatment protocols differed among institutions. To confirm the clinical value of SBRT for early-stage lung cancer in multi-institutional settings, the Japan Clinical Oncology Group (JCOG) has planned a multi-institutional trial of SBRT for T1N0M0 lung cancer (the JCOG 0403 protocol).

It was recognized that large interinstitutional variations in the trial would damage its credibility and that such variations should be avoided. We conducted a study of planning

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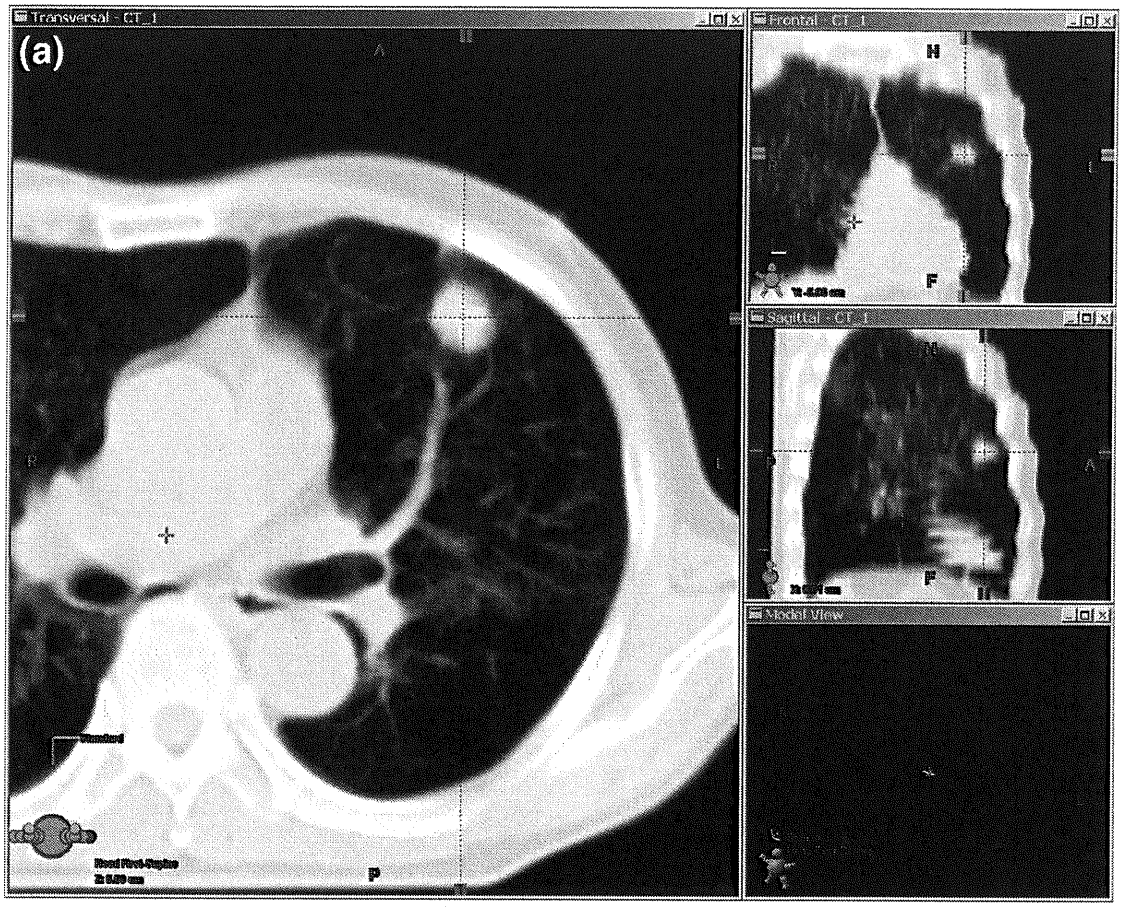

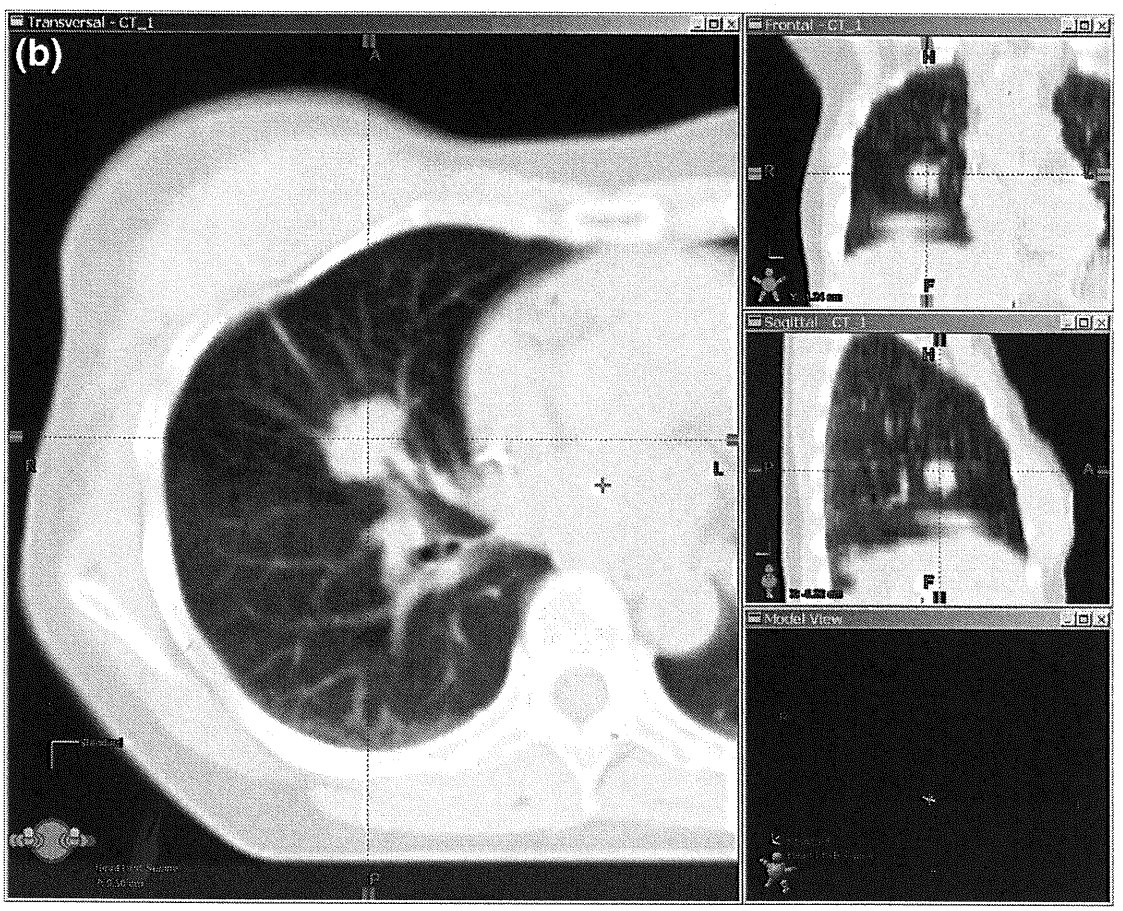

Fig. 1. Images of the cases: (a) Case 1, (b) Case 2, (c) Case 3, and (d) Case 4. Each case is a solitary lung tumor. The tumors were T1 in size (within 3 cm) except for that in Case 4. Figure continues on next page.

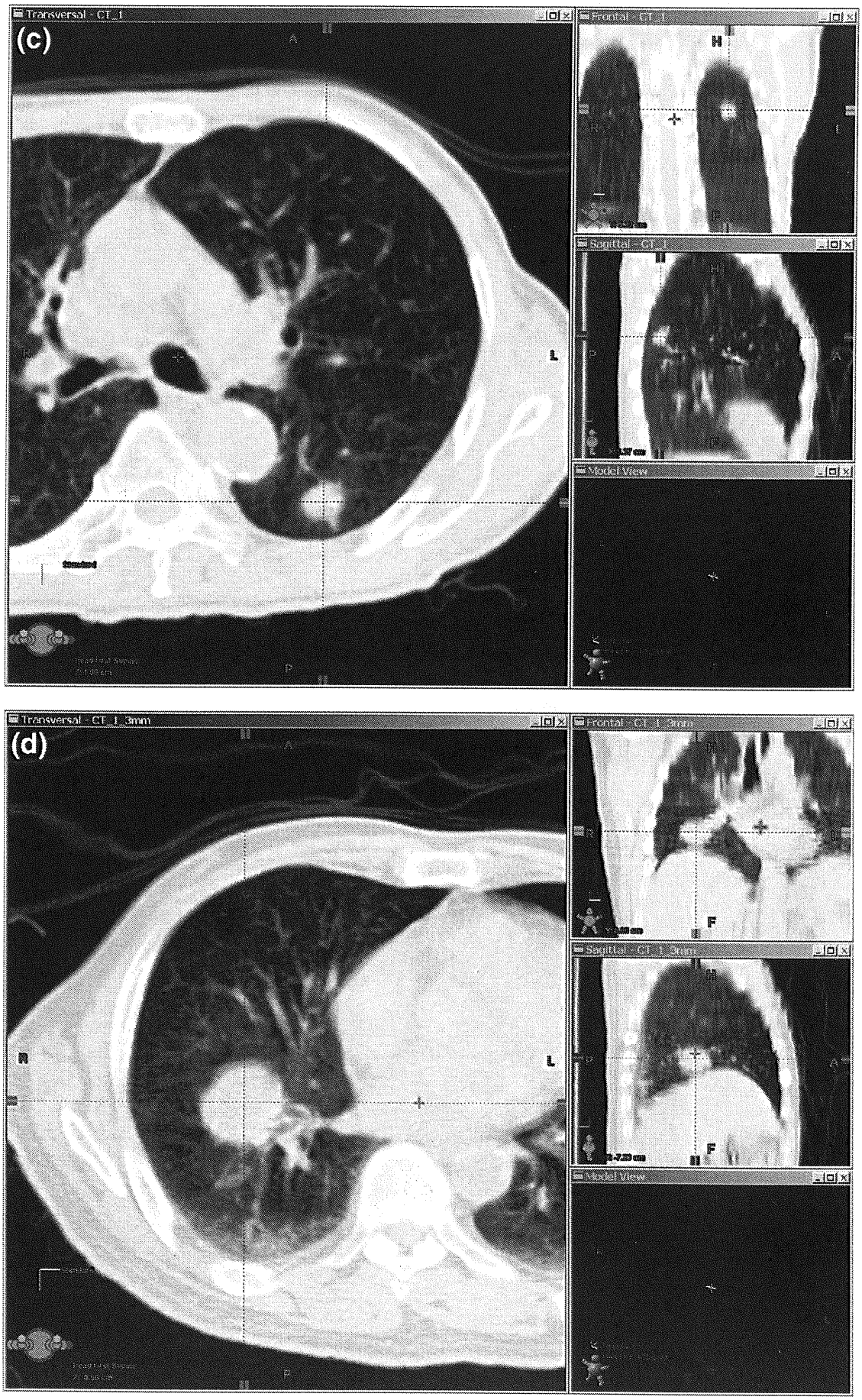

Fig. 1. *(Continued)*

Table 1. Institutional characteristics

Institution	Beam energy	Irradiation technique	TPS	Calculation algorithm
A	6 MV	Static 6 ports	FOCUS/XiO	CL/SP*
B	10 MV	Mixed 9 groups / Static 10 ports†	FOCUS/XiO	CL/SP*
C	6 MV	Static 7 ports	Eclipse	PBC
D	6 MV	Static 3 arcs (total 400 degrees)‡	FOCUS/XiO	SP
E	6 MV	Dynamic 10 arcs (total 1,600 degrees)	FOCUS/XiO	SP
F	6 MV	Static 8 ports	Pinnacle3	CC
G	6 MV	Static 5–10 ports	Eclipse	PBC
H	6, 10 MV	Static 7–8 ports	Eclipse	PBC
I	6 MV	Static 8 ports	Cadplan	PBC
J	4 MV	Static 6 ports	FOCUS/XiO	SP
K	6 MV	Static 10 ports	FOCUS/XiO	CL

Abbreviations: CC = collapsed cone convolution superposition; CL = Clarkson with effective path length correction; PBC = pencil beam convolution with Batho power law correction; SP = superposition; TPS = treatment planning system;

* Institutions A and B changed their algorithm from CL to SP between the series.

† Institution B changed its technique from a mixed style of arcs and static ports to static ports only between the series.

‡ No multileaf collimator was implemented in institution D.

Table 2. Target volumes delineated by 11 institutions on 4 cases

	Target volumes (cc)			
	Case 1	Case 2	Case 3	Case 4
A	9.0	11.0	6.0	34.0
B	4.8	8.2	5.1	36.0
C	5.7	10.7	6.2	35.4
D	8.6	14.1	3.1	28.5
E	7.4	10.7	7.8	33.4
F	6.9	9.5	4.2	28.7
G	7.5	12.8	7.4	29.2
H	6.6	13.1	5.5	34.8
I	7.5	14.2	6.7	38.9
J	8.0	10.0	4.0	30.0
K	9.0	12.0	10.0	38.0
Mean	7.4	11.5	6.0	33.4
SD	1.3	1.9	2.0	3.7
CV	17.9%	16.8%	32.7%	11.2%

Abbreviations: CV = coefficient of variation; SD = standard deviation.

for SBRT for lung cancer before the start of the JCOG 0403 protocol to assess interinstitutional variations in treatment planning.

METHODS AND MATERIALS

This study was performed in two series. In the first series in March 2004, seven institutions (A–G) were asked to create virtual plans for two cases (Cases 1 and 2; Figs. 1a and 1b). In the second series in June 2004, two additional cases (Cases 3 and 4; Figs. 1c and 1d) were added, and institutions A to G made plans for them. At the same time, four institutions (H–K) joined the study and created plans for Cases 1 to 4. In total, the 11 institutions created virtual plans for the four cases.

Cases

Each case was a solitary lung cancer of T1 size (within 3 cm), except for Case 4 (3.6 cm). Computed tomographic (CT) images of Cases 1 and 2 were acquired under breath-holding with 2-mm-thick slices around the tumor and 5-mm-thick slices elsewhere. The CT images of Cases 3 and 4 were acquired under free-breathing with 3-mm-thick slices around the tumor and 5-mm-thick slices elsewhere using the "long-scan-time" technique, which can visualize a major part of the trajectory of tumor movement by scanning each slice for a long time (12). The images were transferred to the participants in a Digital Imaging and Communications in Medicine–formatted CD-ROM.

Treatment planning

Radiation oncologists who were responsible for SBRT planning in each institution planned for the cases in accordance with the JCOG

Table 3. Dose-volumetric data of the planning target volumes (PTVs)

	Case 1	Case 2	Case 3	Case 4
PTVmax (Gy)	49.2 ± 0.7	49.1 ± 0.7	48.9 ± 0.9	49.4 ± 0.9
PTVmin (Gy)	41.4 ± 4.8	42.5 ± 3.5	42.9 ± 2.8	41.0 ± 3.9
D95 (Gy)	44.3 ± 3.3	45.0 ± 2.3	43.9 ± 3.6	43.3 ± 4.3
HI	1.20 ± 0.16	1.16 ± 0.09	1.14 ± 0.06	1.22 ± 0.14
CI	2.04 ± 0.55	1.80 ± 0.32	2.02 ± 0.47	1.75 ± 0.13

Abbreviations: CI = conformity index; HI = homogeneity index.
Data are shown as mean ± SD.

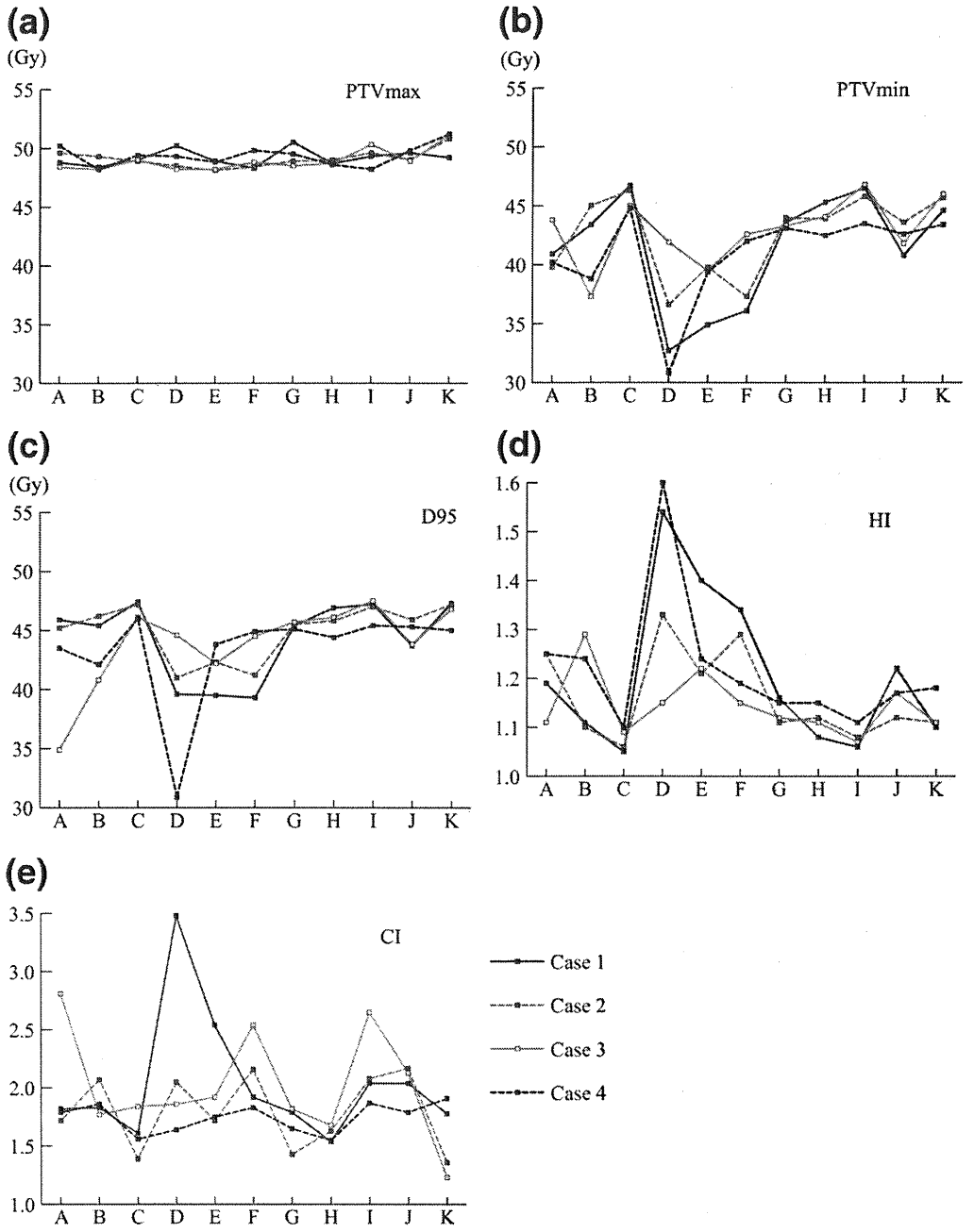

Fig. 2. Variations in the dose–volumetric data of planning target volume (PTV); (a) PTVmax, (b) PTVmin, (c) D95, (d) Homogeneity Index (HI), and (e) conformity index (CI). Lines join points of the same cases. The interinstitutional variations were significant in PTVmax ($p = 0.014$), PTVmin ($p < 0.001$), D95 ($p = 0.007$) and HI ($p < 0.001$). Significant differences were observed between institution K and institutions B, E, F, and H in PTVmax; between institution D and institutions C, G, H, I, J, and K, between institution E and institutions C, I, and K, and between institution F and institutions C and I in PTVmin; between institution D and institutions C, I and K in D95; and between institution D and institutions A, B, C, G, H, I, J, and K in HI. The maximal differences in mean levels of institution were 2.1 Gy in PTVmax (between institutions E and K), 10.2 Gy in PTVmin (between institutions C and D), 7.8 Gy in D95 (between institutions D and K), and 0.33 in HI (between institutions D and I).

0403 protocol (see Appendix). The planning included the following procedures: delineation of targets and organs at risk (OARs); selection of beam energy; arrangement of irradiation beams; and dose calculationculation using their treatment planning systems. In Cases 1 and 2, gross tumor volumes (GTVs) were contoured on the images, and clinical target volumes (CTVs) were set to be identical to the GTVs. Respiratory motion was assumed to be negligible in this virtual planning, so internal target volumes (ITVs) were identical to the GTVs. In Cases 3 and 4, ITVs were directly delineated on the long–scan-time CT images. In all cases, planning target volumes (PTVs) were created by adding 5-mm margins to the ITVs in all directions. Planning OAR volumes (PRVs) were defined for the heart in Case 2, for the aorta in Case 3, and for the spinal cord and the lung in all cases. The margin between PRVs and OARs was 5 mm except

Table 4. Analysis of variance results of the case–institution model (a) and of the case–method model (b)

	PTVmax	PTVmin	D95	HI	CI
(a) Sum of squares					
Model	14.0	445	260	0.410	3.24
Case	1.0 (P = 0.538)	27 (P = 0.205)	16 (P = 0.564)	0.038 (P = 0.134)	0.74 (P = 0.149)
Institution	13.0 (P = 0.015*)	418 (P<0.001*)	244 (P = 0.007*)	0.372 (P<0.001*)	2.50 (P = 0.081)
Error	14.1	166	229	0.192	3.89
R^2	0.499	0.728	0.532	0.681	0.454
(b) Sum of squares					
Model	12.0	451	302	0.421	2.82
Case	1.3 (p = 0.480)	33 (p = 0.117)	4 (p = 0.876)	0.043 (p = 0.080)	0.82 (p = 0.141)
Calculation algorithm	4.9 (p = 0.039*)	96 (p = 0.002*)	117 (p = 0.002*)	0.070 (p = 0.016*)	1.05 (p = 0.077)
Beam energy	2.8 (p = 0.166)	31 (p = 0.132)	42 (p = 0.097)	0.016 (p = 0.446)	0.38 (p = 0.449)
Irradiation technique	1.0 (p = 0.577)	52 (p = 0.032*)	22 (p = 0.323)	0.071 (p = 0.015*)	0.50 (p = 0.326)
Error	16.1	160	188	0.181	4.32
R^2	0.428	0.738	0.617	0.700	0.395

Abbreviation: PTV = planning target volume; HI = homogeneity index; CI = conformity index.

The degrees of freedom were three in case, ten in institution, three in calculation algorithm, three in beam energy, and three in irradiation technique.

The intercase variations were not significant for any of the PTV data. The interinstitutional variations were significant for PTVmax, PTVmin, D95, and HI. The R^2 of the case-method model were similar to those of the case-institution model. In the case-method model, the calculation algorithm was significant for PTVmax, PTVmin, D95, and HI and the irradiation technique was significant for PTVmin and HI.

* Asterisks (*) indicate the statistical significance of the factors.

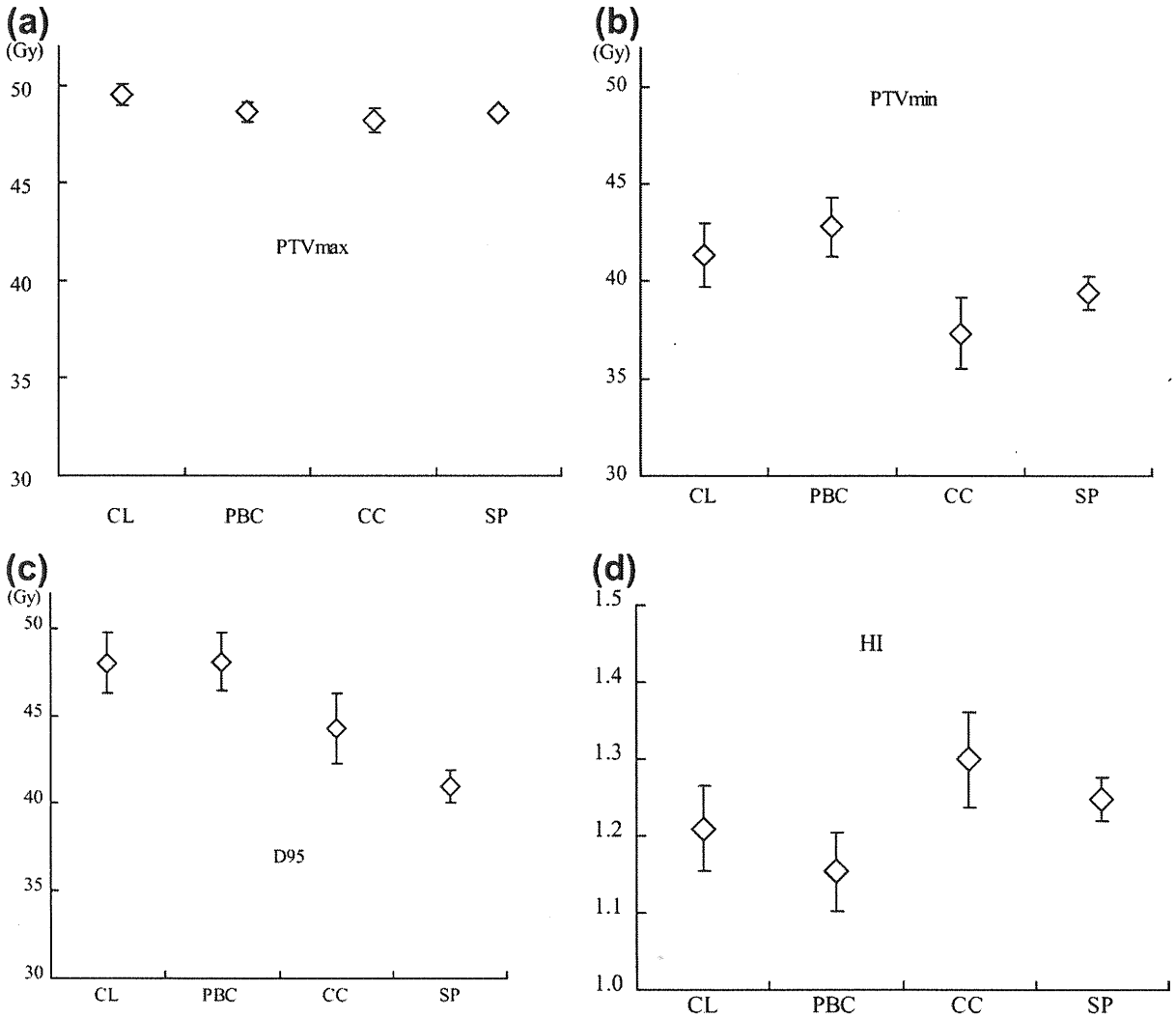

Fig. 3. Dose–volumetric data of planning target volume (PTV) grouped by calculation algorithms; (a) PTVmax, (b) PTVmin, (c) D95, and (d) homogeneity index (HI). Diamonds and bars indicate means and standard errors, respectively. The PTVmax was significantly lower with collapsed cone convolution super position (CC) than with effective path length correction (CL) (p = 0.038). The PTVmin was significantly lower with CC than with CL (p = 0.047) and Batho power law correction (PBC) (p = 0.001). The D95 was significantly lower with superposition (SP) than with CL (p = 0.010) and PBC (p = 0.004). The HI was significantly higher with CC than with PBC (p = 0.012).

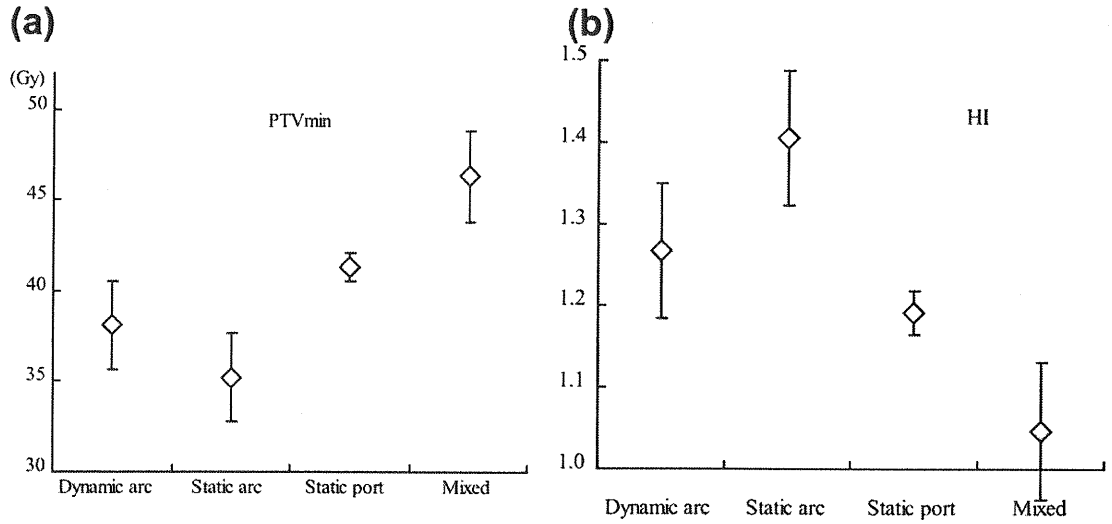

Fig. 4. Dose–volumetric data of planning target volume (PTV) grouped by irradiation method; (a) PTVmin and (b) homogeneity index (HI). Diamonds and bars indicate means and standard errors, respectively. The static-arc method is significantly lower for PTVmin (p = 0.023) and significantly higher for HI (p = 0.017) than the static-port method.

for the spinal cord and the lung. The PRV for the spinal cord was defined as a 3-mm margin with the spinal canal delineated on CT images. The PRV for the lung was defined as the bilateral pulmonary parenchyma outside the PTV. The prescription dose was 48 Gy in 12-Gy fractions at the isocenter. Beam energy, arrangement of irradiation ports, and dose calculationculation were identical to those used clinically at each institution. Created plans should satisfy the dose constraints for the protocol.

Evaluated data

The participating institutions submitted the following data as their planning results: volume of the GTV or ITV; maximal dose (PTVmax), minimal dose (PTVmin), D95 (dose covering 95% volume of PTV), homogeneity index (HI; equal to the maximal dose divided by the minimal dose) and conformity index (CI; equal to the treated volume, which we defined as the volume enclosed by the isodose curve of the PTVmin, divided by PTV volume) of the PTV; mean dose, 40-Gy irradiated volume, V15 (percentage of volume covered by 15-Gy isodose line) and V20 (percentage of volume covered by 20-Gy isodose line) of the PRV for the lung; maximal dose of the PRV for the spinal cord; and 48-Gy– and 40-Gy–irradiated volumes of the PRV for the heart in Case 2 and those of the PRV for the aorta in Case 3. The volumes of GTV and ITV were evaluated as indices of target delineation, and the other dose–volumetric data were evaluated as indices of dose distributions.

Statistical analysis

To assess the significance of the interinstitutional variations, analysis of variance (ANOVA) was performed for a fixed-effect model with the two independent factors of case and institution (case–institution model). All pairwise comparisons were performed using Tukey's Studentized range test, and ANOVA was performed for another fixed effect model with the factors of case, calculation algorithm, beam energy, and irradiation technique (case–method model) to investigate the main cause of the interinstitutional variations. The validity of the case–method model was assessed with comparison of R^2 with that of the case–institution model.

Variations in the target volumes of each case were evaluated

Table 5. Variations in doses to organs at risk (OAR)

PRV	Case 1	Case 2	Case 3	Case 4
Lung				
Mean dose (Gy)	2.5 (2.1–3.3)	5.5 (4.3–7.7)	2.8 (2.0–3.9)	6.9 (6.0–9.0)
40-Gy irradiated volume (cc)	21.8 (1.0–45.1)	39.6 (18.0–79.0)	26.2 (8.0–56.6)	67.0 (39.0–99.6)
V15 (%)	3.9 (2.3–6.0)	12.1 (9.0–17.8)	4.1 (2.5–6.1)	17.2 (14.2–24.0)
V20 (%)	2.5 (1.6–4.0)	7.8 (5.0–12.4)	2.7 (1.8–4.1)	11.8 (8.3–19.0)
Spinal cord				
Maximal dose (Gy)	4.6 (0.2–13.3)	8.8 (2.7–16.9)	7.2 (0.6–14.2)	9.7 (2.3–18.4)
Heart				
48-Gy irradiated volume (cc)		0.0 (0.0–0.0)		
40-Gy irradiated volume (cc)		1.0 (0.0–5.5)		
Aorta				
48-Gy irradiated volume (cc)			0.0 (0.0–0.0)	
40-Gy irradiated volume (cc)			1.0 (0.0–5.3)	

Abbreviation: PRV = planning OAR volume.
Data are shown as mean (range).

with the coefficient of variation (CV), which is equal to the standard deviation (SD) divided by the mean. The overall CV in the study was defined as the mean SD divided by the overall mean of all cases.

RESULTS

Table 1 summarizes the characteristics of the participating institutions. Six institutions performed treatment planning with FOCUS/XiO (CMS, St. Louis, MO), three with Eclipse (Varian, Palo Alto, CA), one with Cadplan (Varian), and one with Pinnacle3 (Philips/ADAC, Milpitas, CA). Dose calculation algorithms of Clarkson with effective path length correction (CL) and superposition (SP) were used in FOCUS/XiO; pencil beam convolution with Batho power law correction (PBC) was used in Eclipse and Cadplan; and collapsed cone convolution superposition (CC) was used in Pinnacle3. Institutions E and F used the algorithm CL in the first series and used SP in the second series. Most institutions used 6-MV x-rays except for institutions B (10 MV), H (6 and 10 MV), and J (4 MV). Institution B used a mixed style of dynamic arcs and static ports in the first series and then used multiple static ports in the second series. Institution D used the multiple static arc technique with fixed rectangular ports, and institution E used the multiple dynamic conformal arc technique. The remaining eight institutions created multiple static port plans.

Variations in the target volumes

Target volumes measured by the 11 institutions in the four cases are shown in Table 2. The CVs were 17.9%, 16.8%, 32.7%, and 11.2% in Cases 1, 2, 3, and 4, respectively. The overall CV was 16.6%. Analysis of variance (ANOVA) of the target volumes in the case–institution model showed that the interinstitutional variations were not significant ($p = 0.089$).

Variations in the dose–volumetric data

The dose–volumetric data of the PTVs are shown in Table 3 and Figure 2. The ANOVA in the case–institution model (Table 4a) showed that the intercase variations were not significant. On the other hand, the interinstitutional variations were significant for PTVmax ($p = 0.014$), PTVmin ($p < 0.001$), D95 ($p = 0.007$), and HI ($p < 0.001$). The maximal differences in mean levels of institution were 2.1 Gy for PTVmax (between institutions E and K), 10.2 Gy for PTVmin (between institutions C and D), 7.8 Gy for D95 (between institutions D and K), and 0.33 for HI (between institutions D and I). For PTVmax, PTVmin, D95, and HI, the R^2 of the case–method models were similar to those of the case–institution models (Table 4b). The ANOVA of the case–method model showed that the dose calculation algorithm was significant for PTVmax ($p = 0.039$), PTVmin ($p = 0.002$), D95 ($p = 0.002$), and HI ($p = 0.016$) and that the irradiation technique was significant for PTVmin ($p = 0.032$) and HI ($p = 0.015$). Comparison of the calculation algorithms (Fig. 3) showed that the PTVmax was significantly lower with CC than with CL ($p = 0.038$). The PTVmin was significantly lower with CC than with CL ($p = 0.047$) and PBC ($p = 0.001$). The D95 was significantly lower with SP than with CL ($p = 0.010$) and PBC ($p = 0.004$). The HI was significantly higher with CC than with PBC ($p = 0.012$). With regard to the irradiation technique (Fig. 4), the differences between the static-arc method and the static-port method were significant for PTVmin ($p = 0.023$) and for HI ($p = 0.017$).

In the OARs, no violation of the dose constraints for the protocol was observed (Table 5).

DISCUSSION

Use of SBRT enables high-dose areas limited to target volume and reduces doses delivered to other areas. Therefore, SBRT planning depends greatly on target delineation. Variations in target delineation of lung cancer have been reported by several investigators (13–15). Bowden *et al.* reported that interclinician variations in measured volumes of lung tumor GTV ranged from 5.0% to 38.6% (mean, 20%) in CV in the first series of their study (13). In a study by Senan *et al.*,the interobserver variations in GTV were 0.60 cc, 4.80 cc, and 12.86 cc in SD for three lung tumors with mean volumes of 4.7 cc, 20.3 cc, and 88.6 cc, respectively (14), and the calculated mean CV in the study was 17.0%. Sakamoto *et al.* reported the mean CV in ITV volumes of 17.6% (15).

Our finding that the overall CV was 16.6% was consistent with these reports and raises questions about whether there should be concern about this level of variation, especially for small lesions. The CV in Case 3, for example, was the largest in this study; there was a difference of more than threefold between the maximum and minimum ITV estimates. The large CV in this case might be caused by the motion blur being relatively large compared with the tumor size, and by small vessels or spiculations being observed around the tumor. It is important to make efforts to reduce the variations in target delineation. In the Bowden *et al.* study, the mean CV decreased to 13% in their second series after a 3-year interval from the first series. They repeated the exercise using a protocol derived from the experience of the first series. Their protocol included contouring issues on slice thickness and window settings of CT images and handling of such CT findings as spiculations, cavitations, and ateclectasis. Although slice thickness (3 mm or less) and window settings for delineation (level −700; width 2,000) were defined in our study, whereas handling of spiculations was not defined; that fact might result in the large CV in Case 3. In the JCOG 0403 protocol, the first case of each institution was reviewed by all participating institutions, and all cases will be reviewed by the study coordinator.

Before this study, the physics group of JCOG 0403 performed a phantom study in all institutions to ensure the accuracy of isocenter dose calculated with the treatment planning systems by a comparison of the measured dose using a phantom specially made for lung SBRT (16). The median differences between calculation and measurement

ranged from 0% to −1% for superposition/convolution algorithms and from 3% to 4% for the other older algorithms. The standard deviations between institutions were the same (2%) for the two groups of algorithms. Thus, it was thought that the calculation accuracy was assured for the isocenter dose in the participating institutions.

The dose distribution of the radiation plan generally depends on multiple factors such as target volume, beam energy, irradiation technique, and calculation algorithm. In this study, the interinstitutional variations were significant in the dose–volumetric data of the PTV. Comparison of the R^2 of the case–method model with those of the case–institution model suggested that the method factors (calculation algorithm, beam energy, and irradiation technique) could account for these interinstitutional variations. Among the method factors, the dose calculationculation algorithm was considered to be the most significant factor.

Task Group No. 65 of the Radiation Therapy Committee of the American Association of Physicists in Medicine categorized inhomogeneity correction algorithms according to the level of anatomy sampled for scatter calculation and the inclusion or exclusion of electron transport (17). The effective path length (EPL) correction performs a ray-trace from the source to the calculation point and scales the depth with the radiologic density along that ray. The EPL correction applies only to primary photons, and lateral electron transports and distribution of scattered photons are ignored (18). The Batho power law (BPL), as well as the EPL, is classified into a simplistic one-dimensional equivalent path correction without consideration of electron transport. The SP and CC are superposition/convolution algorithms that consider three-dimensional scatter calculations with electron transport (19, 20). It is generally accepted that dose distributions with superposition/convolution algorithms are more accurate than those with older inhomogeneity correction algorithms (21–23). The task group recommends that the superposition/convolution algorithm be considered for ascertaining dosage at tumor/lung interfaces in radiation planning for the lung, and that simplistic one-dimensional equivalent path corrections are reasonable only for point dose estimations for lung tumors. In the JCOG 0403 protocol, the dose prescription is defined as a point dose at the isocenter. Most of our clinical experiences, which are the basis for the JCOG 0403, involved the older algorithms, such as the BPL and the EPL. Superposition/convolution algorithms were not available in some institutions (*e.g.*, Eclipse/Cadplan users) at the time when we started the trial. Thus we have agreed that we would not use the superposition/convolution algorithms for the JCOG 0403 protocol to maintain continuing with our treatment experiences and to avoid algorithm-induced interinstitutional variations. We have a plan to use peripheral-dose prescription with superposition/convolution algorithms for an upcoming SBRT study of JCOG. Dose–volumetric data of cases registered for the present trial (JCOG 0403) are recalculated with the superposition/convolution algorithms, if available. These data are collected for the upcoming SBRT study and for a comparison with other studies.

Deviations of institution D in the dose–volumetric data of PTV were marked. The reasons for the marked deviations were thought to be use of the multiple–static-arc technique without a multileaf collimator and use of the SP algorithm. After the study, institution D changed its irradiation technique to multiple static ports and changed the algorithm from SP to CL.

This study was a kind of pretrial "dry run" or dummy run. Dummy runs play an important role in quality assurance (QA) for radiotherapy in clinical trials (24). Through this study, we shared our thoughts concerning treatment planning with other participants and recognized the interinstitutional variations. The importance of QA programs was recognized. The Advanced Technology Consortium (ATC) supports QA of the JCOG 0403. The CT images, structure sets, treatment plans, and dose distributions of all registered cases are sent to the ATC. With the remote review tool provided by the ATC, all plans can be reviewed and their quality can be confirmed.

In conclusion, there can be notable interinstitutional variations in planning for SBRT, including interobserver variations in estimates of target volumes as well as dose calculation effects related to the use of different dose calculation algorithm.

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APPENDIX: SUMMARY OF THE JAPAN CLINICAL ONCOLOGY GROUP (JCOG) 0403 PROTOCOL

TARGET VOLUME DEFINITION

Gross tumor volume (GTV)

The GTV is defined as gross disease determined from imaging modalities. GTV should generally be delineated using the CT pulmonary window (level −700; width 2,000).

Clinical target volume (CTV)

The CTV is identical to GTV in this trial.

Internal target volume (ITV)

The ITV consists of CTV and an internal margin that compensates for internal organ motions. Using long scan-time CT, ITV can be directly delineated on the images.

Planning target volume (PTV)

The PTV consists of ITV and a setup margin. The setup margin is 5 mm.

ORGAN-AT-RISK VOLUME DEFINITION

Planning organ-at-risk volume (PRV)

The PRVs are defined for lung, spinal cord, esophagus, stomach, intestine, trachea, bronchus, and other organs at risk (OARs). The margin between PRV and OAR is 5 mm, except for the spinal cord and the lung. The PRV for the spinal cord is defined as a 3-mm margin with the spinal canal delineated on CT images. The PRV for the lung is the bilateral pulmonary parenchyma outside the PTV.

Dose prescription and calculation

The prescribed dose is 48 Gy in 4 fractions at the isocenter. Noncoplanar static beams (5–10 ports) or multiple-arc beams (total 400 degrees or more) with 4- to 10-MV x-rays are allowed. The margin between the PTV and the field edge is about 5 mm. The dose distribution must be calculated with calculation matrices 2.5 mm or smaller and with inhomogeneity correction enabled.

Dose constraints

The HI of PTV must not exceed 1.6. The dose constraints for the OARs are shown in Table 6.

Table 6. Dose constraints of organs at risk (OARs) for the Japan Clinical Oncology Trial 0403 protocol (as of June 2004)

PRV	Constraint
Lung	Mean dose ≤ 18 Gy
	40-Gy irradiated volume ≤ 100 cc
	V15 ≤ 25%
	V20 ≤ 20%
Spinal cord	Maximal dose ≤ 25 Gy
Esophagus	40-Gy irradiated volume ≤ 1 cc
	35-Gy irradiated volume ≤ 10 cc
Stomach and intestine	36-Gy irradiated volume ≤ 10 cc
	40-Gy irradiated volume ≤ 100 cc
Trachea and main bronchi	40-Gy irradiated volume ≤ 10 cc
Other organs	48-Gy irradiated volume ≤ 1 cc
	40-Gy irradiated volume ≤ 10 cc

Abbreviation: PRV = planning OAR volume.

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Review

Stereotactic body radiation therapy (SBRT) for early-stage lung cancer

Radiothérapie stéréotaxique pour cancer bronchique localisé

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Abstract

Stereotactic body radiation therapy (SBRT) is a new treatment modality for early-stage non-small-cell lung cancer, and has been developed in the United States, the European Union, and Japan. We started a feasibility study of this therapy in July 1998, using a stereotactic body frame. The eligibility criteria for primary lung cancer were: 1) solitary tumor less than 4 cm (T1-3N0M); 2) inoperable, or the patient refused operation; 3) no necessity for oxygen support; 4) performance status equal to or less than 2; 5) the peripheral tumor which dose constraints of mediastinal organs are maintained. A total dose of 48 Gy was delivered in four fractions in 2 weeks in most patients. Lung toxicity was minimal. No grade II toxicities for spinal cord, bronchus, pulmonary artery, or esophagus were observed. The 3 years overall survival for 32 patients with stage IA, and 13 patients with stage IB were 83% and 72%, respectively. Only one local recurrence was observed in a follow-up of 6–71 months. We retrospectively analyzed 241 patients from 13 Japanese institutions. The local recurrence rate was 20% when the biological equivalent dose (BED) was less than 100 Gy, and 6.5% when the BED was over 100 Gy. Overall survival at 3 years was 42% when the BED was less than 100 Gy, and 46% when it was over 100 Gy. In tumors, which received a BED of more than 100 Gy, overall survival at 3 years was 91% for operable patients, and 50% for inoperable patients. Long-term results, in terms of local control, regional recurrence, survival, and complications, are not yet evaluated. However, this treatment modality is highly expected to be a standard treatment for inoperable patients, and it may be an alternative to lobectomy for operative patients. A prospective trial, which is now ongoing, will, answer these questions.

Résumé

La radiothérapie stéréotaxique extracérébrale est une nouvelle modalité thérapeutique du carcinome bronchique non à petites cellules localisé. Cette technique a été développée aux États-Unis, en Europe et au Japon. Nous avons débuté en juillet 1998 une étude de faisabilité de ce traitement avec l'aide d'un cadre stéréotactique corporel. Les critères d'éligibilité pour le cancer bronchique primitif étaient : 1) tumeur isolée de moins de 4 cm (T1-3N0M0) ; 2) tumeur non résécable ou patient refusant la chirurgie ; 3) pas de nécessité d'avoir recours à une oxygénothérapie ; 4) indice de performance égal ou inférieur à 2 ; 5) tumeur périphérique n'entraînant pas une irradiation à dose très importante du médiastin. Une dose totale de 48 Gy a été délivrée en quatre fractions et deux semaines. Chez la plupart des patients, la toxicité pulmonaire a été minimale. Aucune toxicité de grade II n'a été observée pour la moelle épinière, les bronches, les artères pulmonaires ou l'œsophage. Les taux de survie globale à trois ans des 32 patients atteints d'un cancer de stade IA et 13 de stade IB étaient respectivement de 83 et 72 %. Une seule récidive locale a été observée pendant une période de suivi de 6 à 71 mois. Nous avons par ailleurs, rétrospectivement, analysé les résultats obtenus dans une série de 241 patients traités dans 13 institutions japonaises. Le taux de récidive local était de 20 % quand la dose biologique équivalente (BED) était inférieure à 100 Gy, et de 6,5 % quand elle était supérieure à 100 Gy. Le taux de survie à trois ans était de 42 % quand la BED était inférieure à 100 Gy et 46 % quand elle était supérieure. Lorsque la BED était supérieure à 100 Gy, le taux de survie à trois ans était de 91 %, pour les patients atteints d'une tumeur résécable, et 50 % pour les patients inopérables. Les résultats à long terme, en termes de contrôle local, récidive locale, survie et complications ne sont pas encore évalués. Cependant, cette modalité thérapeutique est d'ores et déjà considérée comme le traitement standard pour les patients inopérables et sera une possible alternative à une lobectomie pour les patients opérables. Un essai prospectif en cours permettra de répondre à ces questions.

Keywords: Non-small-cell lung cancer; Stereotactic body radiation therapy

Mots clés : Cancer bronchique non à petites cellules ; Irradiation stéréotactique extracrânienne

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Stereotactic body radiation therapy (SBRT) for early-stage non-small-cell lung cancer (NSCLC) is a new treatment modality, and Japan is one of the leading countries in this three-dimensional radiation therapy. The background of this treatment is the great success of stereotactic irradiation for intracranial tumors, in terms of the technologies used, quality assurance (QA) and quality control (QC), and clinical outcomes. That is, a high local control rate has been shown with minimal toxicities. The success has caused much interest in the application of this treatment for extracranial regions [1,5,13]. Why use stereotactic radiation irradiation (SRI) for lung cancer? The number of patients detected at an early-stage has been increased by screening examinations. Accordingly, the number of older patients with early-stage lung cancer who are not amenable to operation has increased, and the clinical results of conventional radiation therapy are not satisfactory. In regard to technical aspects, the application of this new technique is easier for lung cancer, because it is visible on fluoroscopy and because normal tissue toxicities to radiation are relatively well described compared with other normal tissues.

For the management of stage I NSCLC, surgical resection alone is the standard treatment, and lobectomy is generally accepted as the optimal surgical procedure. Survival outcomes of surgical treatment has recently been reported by the Japanese Association for Chest Surgery. According to these data, the overall survival of patients in clinical stage IA is 81.3% at 3 years, and 71.5% at 5 years, and that of patients in clinical stage IB is 62.9% at 3 years, and 50.1% at 5 years.

What about radiation therapy alone for stage I NSCLC? As is known, radiation therapy has been used primarily for those patients who are not considered to be surgical candidates; that is, those who refuse surgical intervention, and those who are medically inoperable. The reported 5 years survival rate is around 8–27%, and is not satisfactory. Several prognostic factors, such as T stage and total dose, have been reported, and doses higher than 65 Gy did show higher survival rates, which can be a rationale for dose escalation (Table 1).

However, there remain several problems with stereotactic radiation therapy for lung cancer compared to its use in intracranial tumors:

- How should the body be fixed with high accuracy?
- How do we cope with the movement of the tumor caused by respiration?
- What are the optimal treatment regimens?
- Toxicities to normal tissue caused by large-fraction size irradiation have not been examined.
- Fractionated stereotactic radiation therapy is considered to be appropriate for lung cancer, but the optimal fractionation scheme has not yet been decided.

We started a feasibility study of this SBRT for small lung tumors in July 1998 [7,8]. The treatment planning with multiple non-coplanar beams is shown in Fig. 1. The patient was placed in this body frame, and immobilized. We used both X-ray and computed tomography (CT) simulators, with the same table, to improve the accuracy of the setup. The movement of the tumor caused by respiration was estimated using fluoroscopy, and if that movement in the craniocaudal (CC) direction was greater than 8 mm, a diaphragm control was employed to suppress the movement of the chest wall. Then the three-dimensional treatment planning was carried out. We verified the tumor location in each treatment. As regards the movement of the tumor caused by respiration, the largest movement was in the CC direction. It was 0–22 mm, and

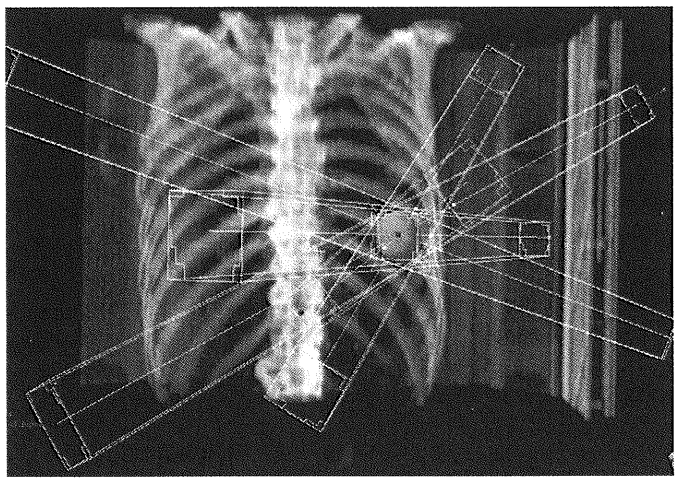

Fig. 1. SBRT for stage I lung cancer.

Table 1
Summary of the results on SBRT for primary lung cancer

Author (Refs.)	Year	Number of patients	Median follow-up (months)	Prescribed dose	Reference point	Isocenter dose (Gy)	BED[a] (Gy)	Overall survival rate (%)	Local control rate (%)
Uematsu et al. [14]	2001	50	36	50–60 Gy/5–10 fr.	Isocenter	50–60	96–100	66 (3 years)	94
Fukumoto et al. [3]	2002	22	24	48–60 Gy/8 fr.	Isocenter	48–60	76.8–105	NA	94
Hof et al. [4]	2003	10	15	19–26 Gy/1 fr.	Isocenter	19–26	55.1–93.6	64	80
Wulf et al. [15]	2004	20	11	30–37.5 Gy/3 fr.	Periphery	45–56.25	113–162	32	92
Onishi et al. [11]	2004	35	13	60 Gy/10 fr.	Periphery	70–75	119–131	58	94
McGarry et al. [6]	2005	47	27 (T1), 19 (T2)	24–72 Gy/3 fr.	Periphery	30–90	60–360	NA	79
Zimmermann et al. [17]	2005	30	18	37.5 Gy/3 fr.	Periphery	62.5	193	75	87
Nagata et al. [7]	2005	45	30	48 Gy/4 fr.	Isocenter	48	106	83 (T1), 72 (T2)	98
Nyman et al. [9]	2006	45	43	45 Gy/3 fr.	Periphery	63	195	71	80
Beitler et al. [2]	2006	75	17	40 Gy/5 fr.	Periphery	47	91.2	45	NA

[a] Biologically effective dose at the isocenter with α/β ratio of 10.

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movement of less than 15 mm occurred in 90% of all tumors. When that movement was over 20 mm, we used the diaphragm control, and, with the use of this device, the movement of the respiration decreased significantly. The set-up error with patients was greater than 3 min in at least one direction. Patient repositioning had to be undertaken in 21.6% of all treatments.

The eligibility criteria for primary lung cancer were as follows: solitary tumor less than 4 cm; inoperable, or the patient refused operation; histologically confirmed malignancy; no necessity for oxygen support; performance status equal to or less than 2; and the tumor was not close to spinal cord.

The eligibility criteria for metastatic lung cancer were as follows: one to two tumors less than 4 cm each, primary tumor controlled, no other metastasis, no necessity for oxygen support, performance status less than 2, and tumors not close to the spinal cord. Between July 1998 and November 2005, a total of 147 patients received this treatment modality. Their ages ranged from 17 to 87 years, with a mean of 74 years. Seventy-nine patients had primary tumors, and 54 patients had secondary tumors. In 115 tumors, a total dose of 48 Gy was delivered, in four fractions in 2 weeks. Twenty-seven tumors were treated with a total dose of up to 60 Gy in five fractions. In the initial three tumors, a total dose of 40 Gy was administered.

Survival curves for 32 patients with stage IA, TINOMO NSCLC are shown in Fig. 2. One local recurrence was observed in a follow-up of 6–71 months (median, 30 months). Intrapulmonary recurrence developed in four patients, regional lymph node recurrence developed in two patients, and bone metastases developed in one patient.

Survival curves for 13 patients with stage IB, T2NOMO NSCLC are shown in Fig. 3. No local recurrence was observed at a follow-up of 6–64 months (median, 22 months). Intrapulmonary recurrence developed in four patients, liver and brain metastases developed in one patient each.

We examined the toxicity by National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2. Lung toxicity was grade II in 4% and grade I in 96%. No grade II toxicities for spinal cord, bronchus, pulmonary artery, or esophagus were observed. The clinical course of one patient who responded well to this treatment is shown in Fig. 4.

We retrospectively analyzed data from 241 patients from 13 Japanese institutes [10]. Their ages ranged from 35 to 92 years, with a median of 76 years. Histology was squamous cell carcinoma in 106 patients, adenocarcinoma in 102 patients, and "others" in 33 patients. As regards clinical stage, 153 patients were stage IA, and 88 patients were stage IB. Tumor diameter ranged from 7 to 58 mm, with a median of 28 mm. One hundred and sixty-one patients were inoperable, and 80 patients were operable. The biological equivalent dose (BED) was 57–180 Gy, with a median of 108 Gy.

Lung toxicities were minimal, with grade II in only 2.2% and no grade III. Local response to the treatment was complete response (CR) in 23%, and partial response (PR) in 62%. The local recurrence rate was 20% when BED was less than 100 Gy, and 6.5% when BED was over 100 Gy, at follow-up periods of 4–72 months (median, 18 months). Overall survival at 3 years was 42% when BED was less than 100 Gy, and 46% when BED was over 100 Gy. For tumors, which received a BED of more than 100 Gy, overall survival at 3 years was 91% for operable patients, and 50% for inoperable patients.

Based upon several good clinical results [2,3,6,12,14–17], we have started a prospective multiinstitutional phase II study with a grant from the Health and Welfare Ministry of Japan. The target is stage IA NSCLC. A total dose of 48 Gy in four fractions will be delivered in 4–8 days. Entry of 165 patients from 16 institutes in 3 years is expected. By the end of May 2006, 85 patients were entried. The primary endpoint is survival. This is the first trial of the Radiation Therapy Study Group (RTSG), which is the newest group in the Japanese Clinical Oncology Group (JCOG). We hope that this trial will provide more conclusive data on stereotactic body irradiation for early-stage NSCLC.

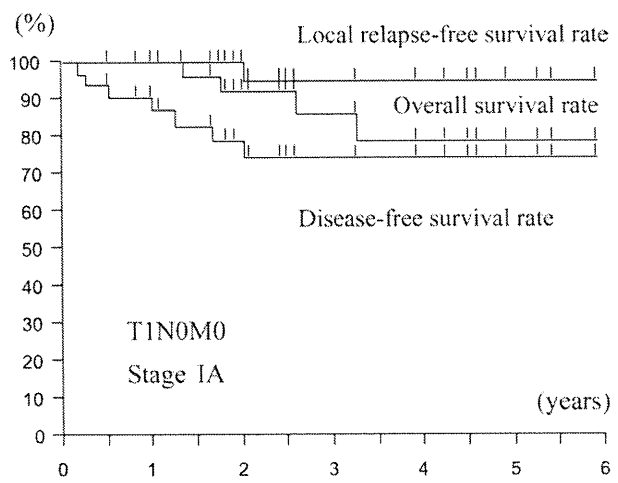

Fig. 2. Survival curves of patients with stage IA: T1N0M0 NSCLC treated with SBRT.

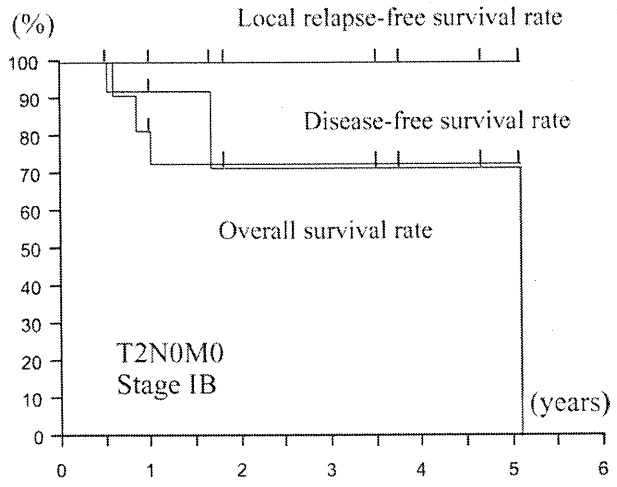

Fig. 3. Survival curves of patients with stage IB: T2N0M0 NSCLC treated with SBRT.

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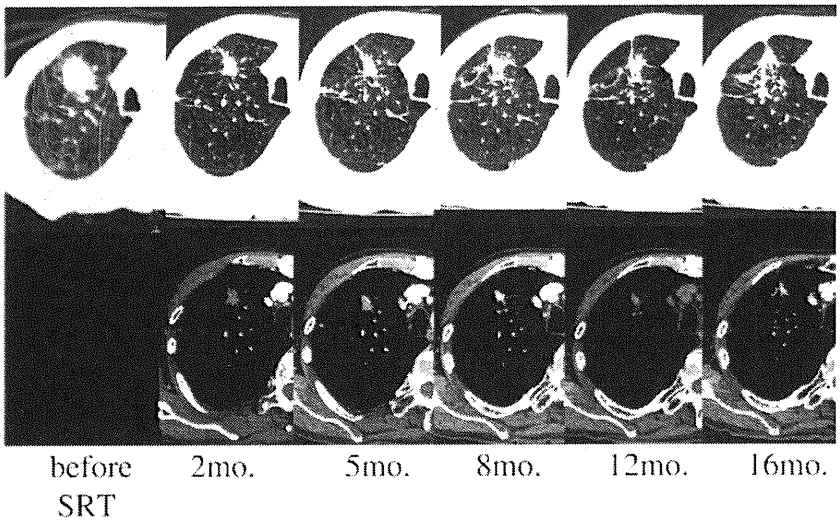

Fig. 4. Clinical course of a patient treated with SBRT. The patient, a 71-year-old man, had primary lung cancer (squamous cell carcinoma; T2N0M0).

In summary, regarding SBRT for early-stage NSCLC:

- long-term results, in terms of local control, regional recurrence, survival, and complications are not yet evaluated;
- technologies to cope with tumor movement, gauging tracking, need to be improved;
- this treatment modality is highly expected to be a standard treatment for inoperable patients, and may be an alternative to lobectomy for operative patients.

A prospective trial ongoing is expected to resolve these matters.

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Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases

A Randomized Controlled Trial

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Context In patients with brain metastases, it is unclear whether adding up-front whole-brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) has beneficial effects on mortality or neurologic function compared with SRS alone.

Objective To determine if WBRT combined with SRS results in improvements in survival, brain tumor control, functional preservation rate, and frequency of neurologic death.

Design, Setting, and Patients Randomized controlled trial of 132 patients with 1 to 4 brain metastases, each less than 3 cm in diameter, enrolled at 11 hospitals in Japan between October 1999 and December 2003.

Interventions Patients were randomly assigned to receive WBRT plus SRS (65 patients) or SRS alone (67 patients).

Main Outcome Measures The primary end point was overall survival; secondary end points were brain tumor recurrence, salvage brain treatment, functional preservation, toxic effects of radiation, and cause of death.

Results The median survival time and the 1-year actuarial survival rate were 7.5 months and 38.5% (95% confidence interval, 26.7%-50.3%) in the WBRT + SRS group and 8.0 months and 28.4% (95% confidence interval, 17.6%-39.2%) for SRS alone ($P=.42$). The 12-month brain tumor recurrence rate was 46.8% in the WBRT + SRS group and 76.4% for SRS alone group ($P<.001$). Salvage brain treatment was less frequently required in the WBRT + SRS group (n = 10) than with SRS alone (n = 29) ($P<.001$). Death was attributed to neurologic causes in 22.8% of patients in the WBRT + SRS group and in 19.3% of those treated with SRS alone ($P=.64$). There were no significant differences in systemic and neurologic functional preservation and toxic effects of radiation.

Conclusions Compared with SRS alone, the use of WBRT plus SRS did not improve survival for patients with 1 to 4 brain metastases, but intracranial relapse occurred considerably more frequently in those who did not receive WBRT. Consequently, salvage treatment is frequently required when up-front WBRT is not used.

Trial Registration umin.ac.jp/ctr Identifier: C000000412

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BRAIN METASTASES OCCUR IN 20% to 40% of all patients with cancer and are generally associated with a poor prognosis.[1,2] The most common route of metastatic dissemination resulting in brain metastases is hematogenous, and it is therefore presumed that the entire brain is "seeded" with micrometastatic disease, even when only a single intracranial lesion is detected. Consequently, whole-brain radiation therapy (WBRT) has been a mainstay of treatment.[1,2]

Recently, the assumption that the entire brain is seeded with micrometastases in all patients with overt brain metastases has been questioned, prompting

For editorial comment see p 2535.

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a contrarian philosophy that in some patients, the intracranial disease is truly limited—the so-called oligometastases situation. For patients who truly have limited intracranial disease, the potential exists that WBRT could be replaced by focal therapeutic options such as resection or stereotactic radiosurgery (SRS), which delivers high-dose, focal radiation.[1-4]

The adverse effects of WBRT require a further examination of its role. Acute adverse effects are generally limited in severity and duration; however, the long-term risks of serious and permanent toxic effects, including cognitive deterioration and cerebellar dysfunction, are poorly understood.[5,6] In the attempt to minimize potential long-term morbidity following WBRT, treatments initially relying on focal therapeutic options are being used with increasing frequency. Although there have been several retrospective reports,[7-14] only 1 prospective randomized study compared the outcome of conventional surgery alone and surgery followed by WBRT.[6] Sneed et al[7] collected raw data on 983 patients from 10 institutions and suggested that there was no survival difference between patients treated with SRS alone and those treated with WBRT plus SRS. Flickinger et al[8] reviewed 116 patients with solitary brain metastases who underwent SRS with or without fractionated large-field radiotherapy and found improved local control, but not improved survival, with the addition of fractionated large-field radiotherapy. Regine et al[9] suggested that SRS alone is associated with an increasingly significant risk of brain tumor recurrence and neurologic deficit with increasing survival time. Pirzkall et al[10] showed a trend for superior local control and survival when SRS was combined with WBRT in 236 patients with 311 brain metastases. Aoyama et al,[11] Chidel et al,[12] and Shirato et al[13] have all shown that omission of WBRT from initial management was not detrimental in terms of overall survival, but brain tumors recurred in more than 50% of patients treated in this manner. Patchell et al[6] have shown that patients with cancer and single metastases to the brain who receive treatment with surgical resection and postoperative WBRT have fewer recurrences of cancer in the brain and are less likely to die of neurologic causes than are similar patients treated with surgical resection alone.

Herein, we report the results of a prospective, multi-institutional, randomized controlled trial comparing WBRT plus SRS vs SRS alone for patients with limited (defined as ≤4) brain metastases. Through a literature search and examination of clinical trial registries, we confirmed that this is the first multi-institutional, prospective, randomized comparison of WBRT plus SRS vs SRS alone.

METHODS

Eligibility Criteria

Patients were eligible who were aged 18 years or older with 1 to 4 brain metastases, each with a maximum diameter of no more than 3 cm on contrast-enhanced magnetic resonance imaging (MRI) scans, derived from a histologically confirmed systemic cancer. Patients with metastases from small cell carcinoma, lymphoma, germinoma, and multiple myeloma were excluded. Eligible patients had a Karnofsky Performance Status (KPS) score of 70 or higher. The protocol was approved by the institutional review boards of Hokkaido University, Sapporo, Japan, and of 10 other institutions that participated in the trial through the Japanese Radiation Oncology Study Group (JROSG 99-1). Written informed consent was obtained from each patient before entry into the study.

Randomization and Treatment

Randomization was performed at the Hokkaido University Hospital Data Center. A permuted-blocks randomization algorithm was used with a block size of 4. A randomization sheet was created for each institution. After written informed consent was obtained, eligible patients were randomly assigned to receive either up-front WBRT combined with SRS or SRS without up-front WBRT. Prior to randomization, the patients were stratified based on number of brain metastases (single vs 2-4), extent of extracranial disease (active vs stable), and primary tumor site (lung vs other sites). Extracranial disease was considered to be stable when the tumor had been clinically controlled for 6 months or longer prior to the detection of brain metastases.

The WBRT dosage schedule was 30 Gy in 10 fractions over 2 to 2.5 weeks. The WBRT treatment visit proceeded to SRS when patients were assigned to the WBRT + SRS group. The SRS dose was prescribed to the tumor margin. Metastases with a maximum diameter of up to 2 cm were treated with doses of 22 to 25 Gy and those larger than 2 cm were treated with doses of 18 to 20 Gy. The dose was reduced by 30% when the treatment was combined with WBRT because the optimal combination of WBRT and SRS had not been studied in well-conducted, prospective, phase 1 dose escalation trials. In the 1990s, the Radiation Therapy Oncology Group (RTOG) initiated a phase 1 dose escalation trial of SRS alone in patients who had previously undergone radiation treatment.[14] This trial was stopped early without reaching the maximum tolerance dose, and tumor size–dependent dose recommendations for SRS alone were described. No phase 1 trial has ever tested the combination of WBRT and SRS doses. Therefore, there is no well-known or scientifically recommended dose for the combination of WBRT and SRS. There are clearly concerns that the combination could be potentially deleterious. Therefore, various studies have adopted different approaches for selection of the dose combinations to be tested. Several retrospective data suggested that the RTOG dose guidelines might be associated with a higher frequency of late radiation toxic effects when used with WBRT.[10,15] Our preexisting experience of SRS with a 30% reduced SRS dose

combined with WBRT indicated that there is not a significant difference in local tumor control (data not shown) compared with SRS with the dose suggested in the RTOG protocol. Therefore, we decided to use a 30% reduced SRS dose in the WBRT + SRS group in this study.

Follow-up Protocol

We performed clinical evaluations and MRI scans 1 and 3 months after treatment and every 3 months thereafter. In cases in which a recurrence was detected, further treatment was administered at the discretion of the attending physician. The size of the treated lesions was measured in 3 dimensions, and this size, the development of new brain metastases, and the development of leukoencephalopathy associated with radiological findings (according to the National Cancer Institute's Common Toxicity Criteria version 2.0[16]) were scored based on serial MRI scans. Local tumor progression was defined as a radiographic increase of 25% or more in the size of a metastatic lesion (bidimensional product). If an MRI result showed central or heterogeneous low intensity and if the lesion size decreased on serial studies, brain necrosis was scored; positron emission tomography or surgical resection was encouraged as appropriate to confirm MRI findings.

At each visit, functional status and neurologic toxic effects were scored. Systemic functional status was evaluated by using the KPS score. Neurologic function was evaluated according to the criteria listed in TABLE 1.[17] Neurosurgeons or radiation oncologists specializing in neuro-oncology measured the neurologic status as well as the KPS score at the clinic. We did not attempt to blind the investigators with regard to patients' treatment assignments. Systematic functional status and neurologic function were scored by the physicians who treated the patients. An acute toxic effect was identified as an event that arose within 90 days of the initiation of radiotherapy and a late toxic effect was considered as an event that occurred thereafter, according to the central nervous system toxicity criteria listed among the RTOG Late Radiation Morbidity Scoring Criteria.[18] For all patients who died, the cause of death was determined. The cause of death was determined by autopsy in 1 patient and by clinical evaluation based on the definition proposed by Patchell et al[6] in all other patients. Patients were considered to have died of neurologic causes if they had stable systemic disease and

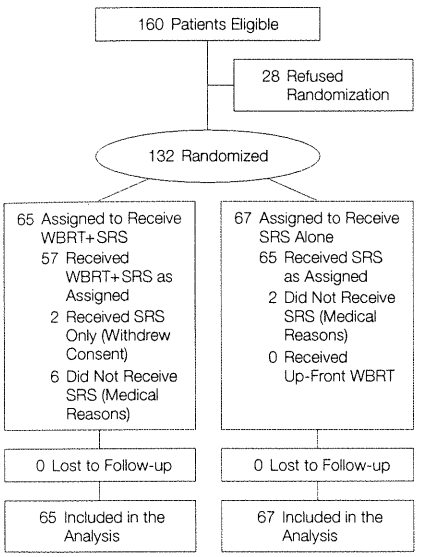
Table 1. Baseline Characteristics*

Characteristics	WBRT + SRS (n = 65)	SRS Alone (n = 67)
Age at diagnosis, mean (range), y	62.5 (36-78)	62.1 (33-86)
<65	32 (49)	34 (51)
≥65	33 (51)	33 (49)
Men	46 (71)	53 (79)
No. of brain metastases		
1	31 (48)	33 (49)
2-4	34 (52)	34 (51)
Primary tumor site		
Breast	6 (9)	3 (4)
Lung	43 (66)	45 (67)
Colorectal	5 (8)	6 (9)
Kidney	5 (8)	5 (7)
Other	6 (9)	8 (12)
Primary tumor status		
Stable	30 (46)	33 (49)
Active	35 (54)	34 (51)
Extracranial metastases		
Stable	41 (63)	38 (57)
Active	24 (37)	29 (43)
RPA		
Class 1 (aged <65 years; no active extracranial disease)	11 (17)	8 (12)
Class 2 (aged ≥65 years; active extracranial disease)	54 (83)	59 (88)
Histological status		
Squamous cell	11 (17)	11 (16)
Adenocarcinoma	43 (66)	43 (64)
Large cell	2 (3)	4 (6)
Other	9 (14)	9 (13)
KPS score†		
70-80	31 (48)	23 (34)
90-100	34 (52)	44 (66)
Neurologic function		
No symptoms (grade 0)	38 (59)	47 (70)
Minor symptoms, fully active without assistance (grade 1)	12 (18)	13 (19)
Moderate symptoms; fully active but requires assistance (grade 2)	8 (12)	4 (6)
Moderate symptoms; less than fully active, requires assistance (grade 3)	7 (11)	3 (5)
Severe symptoms; totally inactive (grade 4)	0	0
Chemotherapy after brain treatment	18 (38)	19 (40)
Maximum diameter of brain metastases, cm		
Mean (SD)	1.53 (0.78)	1.42 (0.79)
Median (range)	1.40 (0.2-3.0)	1.30 (0.2-3.0)
SRS dose at the tumor margin, mean (SD), Gy	16.6 (3.6)	21.9 (2.7)

Abbreviations: KPS, Karnofsky Performance Status; RPA, recursive partition analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*Data are expressed as No. (%) of participants unless otherwise noted.
†A higher score indicates better performance.

progressive neurologic dysfunction. Patients with severe neurologic disability who died of intercurrent illness were also included among neurologic deaths, as were patients with both rapidly progressive systemic disease and advancing neurologic dysfunction, because these patients also represent brain treatment failures.

Figure 1. Flow of Study Participants



SRS indicates stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

End Points and Statistical Analysis

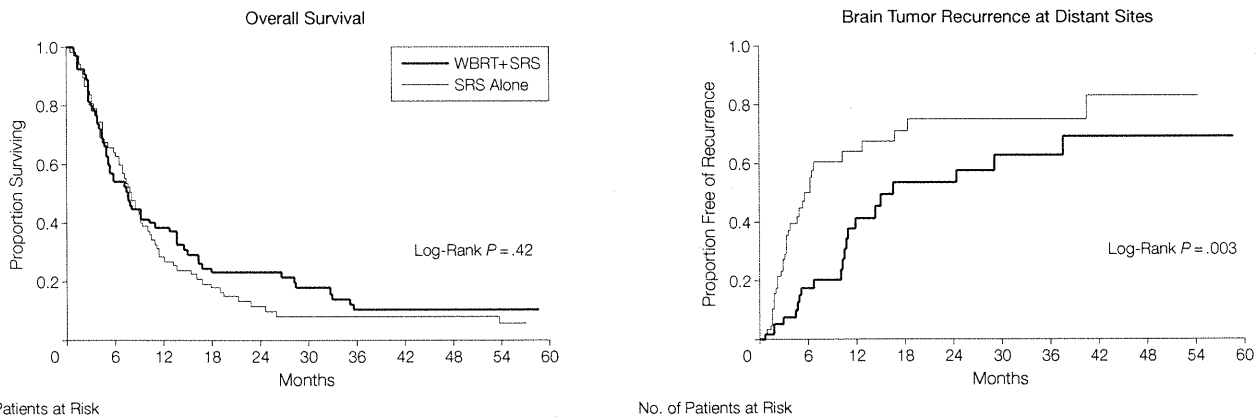
The primary end point of the study was overall survival. Secondary end points were cause of death, functional preservation, brain tumor recurrence, salvage treatment, and toxic effects of radiation. All analyses were conducted on an intention-to-treat basis. The study was designed to have 80% power to detect an absolute difference of 30% in the median survival time, with a 2-sided α level of .05. Using an estimated median survival time of 8.7 months for the group receiving SRS alone[11] and a follow-up time of 15 months, the sample size required to detect this difference was 89 patients per group. An interim analysis was planned wherein 50 patients would be assigned to each group to determine whether the sample size was large enough to show a significant difference with a 2-sided α level of .05. End points were measured beginning at the date of randomization. Univariate analyses were carried out by the Kaplan-Meier method.[19] We assumed that the survival rate was always higher in the WBRT + SRS group than in the SRS-alone group based on the suggestions in a retrospective study, and we used the log-rank test to compare differences between the groups. The χ^2 test was used to determine the relationship between 2 categorical variables, and the Fisher exact test was used when small cell sizes were encountered in 2×2 contingency tables. A 2-tailed t test was used to compare the means of continuous variables between the treatment groups. Multivariate analyses were performed to evaluate the factors selected via the univariate analyses ($P<.10$). Stratification in the randomization was taken into account in the statistical analysis. The Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals (CIs).[20] A 2-sided P value of .05 or less was considered to reflect statistical significance. Additional covariates were examined as appropriate and are noted in the "Results" section. All statistical analyses were initially performed by a physician (H.A.) using a commercial statistical software package (StatView version 5.0J, SAS Institute Inc, Cary, NC), and all results were verified by a statistician (G.K.) using a different software package (SAS, version 9.1, SAS Institute Japan Ltd, Tokyo, Japan).

RESULTS

Patients and Treatment

The recruitment period was from October 1999 to December 2003. There were

Figure 2. Overall Survival and Brain Tumor Recurrence at Distant Sites



The mean survival time was 7.5 months for patients receiving whole-brain radiation therapy (WBRT) plus stereotactic radiosurgery (SRS) and 8.0 months for patients receiving SRS alone. This difference was not significant ($P=.42$). There was a statistically significant decrease in brain tumor recurrence in the WBRT+SRS group ($P=.003$).

160 eligible patients, of whom 132 (83%) were randomized (65 to WBRT + SRS and 67 to SRS alone) (FIGURE 1). The date of last follow-up was April 2005. The interim analysis was performed with 122 patients (about 60 in each group), which takes into account the possible number of patients with protocol violations. Patient accrual was terminated before the planned final accrual number had been reached because the results of the interim analyses indicated that at least 805 patients were necessary to detect a significant difference in the primary end points. In addition, the numbers of patients appeared sufficient to detect a significant difference in brain tumor recurrence rates: 31 patients in each group were shown to be enough to detect a 30% difference in the median month of 50% brain tumor recurrence (16.2 months with WBRT + SRS vs 5.5 months with SRS alone).

There was no statistical difference between the groups in the baseline characteristics of the patients (Table 1). The median follow-up time was 7.8 months (range, 0.5-58.7 months) for the entire study and 49.2 months (range, 19.6-58.7 months) for survivors. Ninety-two percent of the patients included in the study completed the assigned treatment (Figure 1).

Survival and Cause of Death

By the time of the last follow-up visit in April 2005, 57 patients in the WBRT + SRS group and 62 patients in the SRS-alone group had died. Death was attributed to neurologic causes in 13 patients (22.8%) in the WBRT + SRS group and in 12 patients (19.3%) in the SRS-alone group ($\chi^2 = 0.21$; $P = .64$). The median survival time was 7.5 months with WBRT + SRS and 8.0 months with SRS alone. The higher median survival time with SRS alone was discordant with the 1-year actuarial survival rates of 38.5% (95% CI, 26.7%-50.3%) for the WBRT + SRS group and 28.4% (95% CI, 17.6%-39.2%) for the SRS-alone group ($P = .42$). FIGURE 2A shows that this discordance was due to the crossing of the 2 survival curves. The results of the univariate and multivariate analyses are shown in TABLE 2 and TABLE 3. The number of patients in each institution was too small to allow for a meaningful comparison among institutions. Recursive partition analysis was not included in the multivariate analysis because it is not independent of age and extracranial metastases. Treatment group was not found to be significant in either analysis.

Posttreatment Neurologic Toxicity

A summary of posttreatment neurologic toxicity is given in TABLE 4. Symptomatic acute neurologic toxicity was observed in 4 patients receiving WBRT + SRS and in 8 patients receiv-

Table 2. Univariate Survival Analysis

	No. of Participants	Survival Time, Median (Range), mo	*P* Value
Treatment group			
WBRT + SRS	65	7.5 (0.8-58.7)	.42
SRS alone	67	8.0 (0.5-57.0)	
Age, y			
<65	66	8.9 (0.9-58.7)	.07
≥65	66	6.5 (0.5-55.6)	
Sex			
Male	99	7.1 (0.5-58.7)	.20
Female	33	10.5 (0.8-57.0)	
No. of brain metastases			
1	68	8.6 (1.4-58.7)	.02
2-4	64	7.3 (0.5-55.6)	
Primary tumor site			
Lung	88	8.1 (0.5-58.7)	.33
Other	44	7.1 (0.9-57.0)	
Primary tumor status			
Stable	69	9.2 (0.9-58.7)	<.001
Active	63	6.5 (0.5-53.8)	
Extracranial metastases			
Stable	79	13.3 (1.1-58.7)	<.001
Active	53	6.1 (0.5-55.6)	
RPA			
Class 1	19	16.0 (0.9-58.7)	<.001
Class 2	113	7.5 (0.5-55.6)	
KPS score			
70-80	54	5.0 (0.5-58.7)	<.001
90-100	78	9.2 (0.8-57.0)	
Chemotherapy after brain treatment			
Yes	37	10.1 (1.3-53.8)	.34
No	95	6.8 (0.5-58.7)	

Abbreviations: KPS, Karnofsky Performance Status; RPA, recursive partition analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

Table 3. Multivariate Survival Analysis

Variables*	Hazard Ratio (95% CI)	*P* Value
Treatment group (WBRT + SRS)	1.37 (0.93-1.98)	.11
Age (<65 y)	1.48 (1.01-2.16)	.04
No. of brain metastases (1)	1.36 (0.94-1.97)	.10
Primary tumor status (stable)	1.62 (1.11-2.36)	.01
Extracranial metastases (stable)	2.35 (1.55-3.55)	<.001
KPS score (90-100)	1.69 (1.16-2.47)	.007

Abbreviations: CI, confidence interval; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*Referents appear in parentheses.

Table 4. Treatment-Related Neurotoxic Effects*

	No. in WBRT + SRS Group (n = 65)				No. in SRS-Alone Group (n = 67)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Acute toxic effects	2	1	1	0	3	3	2	0
Seizure	0	0	1	0	1	2	1	0
Other	2	1	0	0	2	1	1	0
Late toxic effects	3	0	2	2	1	0	0	2
Radiation necrosis	1	0	0	2	0	0	0	1
Leukoencephalopathy	1	0	2	0	0	0	0	0
Other†	1	0	0	0	1	0	0	1
Radiological leukoencephalopathy	2	3	2	0	1	1	0	0

Abbreviations: SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*From the National Cancer Institute's Common Toxicity Criteria version 2.0.[16]
†Other effects included 1 case of slight lethargy (grade 1) in the WBRT + SRS group and 1 case each of seizure (grade 4) and headache (grade 1) in the SRS-alone group.

Table 5. Univariate Analysis of Development of New Metastases at Distant Brain Sites

	Actuarial Rate, %		Log-Rank *P* Value
	6 mo	12 mo	
Treatment group			
WBRT + SRS	17.5	41.5	.003
SRS alone	49.9	63.7	
Age, y			
<65	34.5	55.9	.65
≥65	33.9	49.0	
Sex			
Male	32.7	51.5	.39
Female	36.3	55.9	
No. of brain metastases			
1	27.3	39.2	.03
2-4	42.4	69.9	
Primary tumor site			
Lung	29.5	52.0	.40
Other	43.1	55.9	
Primary tumor status			
Stable	32.8	44.8	.20
Active	37.1	69.6	
Extracranial metastases			
Stable	29.5	38.4	.02
Active	37.3	69.3	
KPS score			
70-80	43.2	57.4	.05
90-100	29.9	50.8	
Chemotherapy after brain treatment			
Yes	37.1	59.0	.33
No	32.9	50.0	

Abbreviations: KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

ing SRS alone ($P=.36$), including 1 and 2 patients with grade 3 toxicity, respectively, in each group. The symptoms developed a median of 6 days after initiation of treatment (range, 1-64 days) in the WBRT + SRS group and 10 days (range, 1-86 days) in the SRS-alone group. Symptomatic late neurologic radiation toxic effects were observed in 7 patients in the WBRT + SRS group and in 3 patients in the SRS-alone group ($P=.20$). Toxic effects were experienced for a median of 15.6 months (range, 6.7-59.4 months) in the WBRT + SRS group and 6.2 months (range, 5.8-8.1 months) in the SRS-alone group. There were 3 cases of radiation necrosis (grade 1, n = 1; grade 4, n = 2), 3 cases of leukoencephalopathy (grade 1, n = 1; grade 3, n = 2), and 1 case of slight lethargy (grade 1) in the WBRT + SRS group. In patients receiving SRS alone, the following effects were observed: 1 case of radiation necrosis (grade 4), 1 of seizure (grade 4), and 1 of headache (grade 1). Radiation necrosis was diagnosed using positron emission tomography or surgical resection in all cases. Radiological findings consistent with leukoencephalopathy were observed in 7 patients in the WBRT + SRS group and in 2 patients in the SRS-alone group ($P=.09$). Three of these 9 patients also experienced symptomatic leukoencephalopathy; the other 6 patients were asymptomatic.

Brain Tumor Recurrence

Brain tumor recurrence at either distant or local sites in the brain was observed in 63 patients (23 in the WBRT + SRS group and 40 in the SRS-alone group). The 12-month actuarial brain tumor recurrence rate was 46.8% (95% CI, 29.7%-63.9%) in the WBRT + SRS group and 76.4% (95% CI, 63.3%-89.5%) in the SRS-alone group ($P<.001$).

Fifty-five patients had new brain metastases at distant sites (21 in the WBRT + SRS group and 34 in the SRS-alone group). The 12-month actuarial rate of developing new brain metastases was 41.5% (95% CI, 24.4%-58.6%) in the WBRT + SRS group and 63.7% (95% CI, 49.0%-78.4%) in the SRS-alone group ($P=.003$) (Figure 2B).