tumor movement during free breathing using fluoroscopy. When the tumor moved more than 10 mm in the craniocaudal (C-C) direction, a small abdominal pressing plate called a "diaphragm control" was applied before computed tomography (CT) scanning, which suppresses the movement of the diaphragm and reduces tumor movement during respiration. CT images were then sequentially scanned from the neck to the upper abdomen with a CT simulator. The CT slice thickness and pitch were 1 to 3 mm each in the area of the tumor and 10 mm each in the other areas. Each CT slice was scanned with an acquisition time of 4 s to include the whole phase of one respiratory cycle. A series of CT images, therefore, included the tumor and its respiratory motion. The isocenter coordinate was defined using a three-dimensional radiation treatment planning system (3D RTPS) (CADPLAN R.6.0.8, Varian Associates, Palo Alto, CA). Anteroposterior (A-P) and lateral films for verification were then obtained using the X-ray simulator at a designated isocenter. Because the CT simulator and the X-ray simulator employed the same couch in our integrated system, the patient's position on verification films was the same as that on CT images in relation to SBF (10).

The outlines of the target were delineated on 3D RTPS using lung CT window settings (window width 2000 Hounsfield units (HU) and window level −700 HU, typically). A physician delineated both the solid area (tumor itself), which could be seen even using mediastinal CT window settings (window width 350 HU and window level 40 HU, typically), and the surrounding obscure area, which could be seen only under lung CT settings. The obscure area is important because it indicates either tumor microscopic invasion or respiratory tumor motion. This target volume corresponded to the ITV in International Commission on Radiation Units and Measurements Report 62. The outlines of gross tumor volume and clinical target volume were included in the ITV, and gross tumor volume and clinical target volume could not be delineated on the planning CT in our system because the CT images already included the internal motion. Spiculation and pleural indentation were included within the ITV. Neither mediastinal nor hilar lymph nodes were included within the ITV.

The physician also delineated the outline of the following OARs: lung, spinal cord (canal), pulmonary artery, heart, and esophagus. The outline of the lung included that of the target. The pulmonary artery, heart, and esophagus were delineated with each outer contour and included both the wall and content of each organ. The pulmonary artery was delineated from its origin to the pulmonary hila. The esophagus was delineated from the level of the sternal notch to the esophagocardial junction.

Treatment planning was performed using the 3D RTPS, and 5–10 noncoplanar static ports were selected. Edges of the multileaf collimator (MLC) were located 8–10 mm outside of the ITV in the C-C direction and 5 mm in the A-P and lateral directions. The distance in the C-C direction was larger than that in the other directions, because the former was set to compensate for an irregular respiratory motion which could not be included in the ITV using the CT scan with the acquisition time of 4 s. The prescribed dose was 12 Gy per fraction at the isocenter, and the total dose was 48 Gy with four fractions. The dose was delivered by a linear accelerator (CLINAC 2300 C/D, Varian medical systems) with 6-MV photons. Each MLC had a 1-cm leaf width at the isocenter. One of the planning goals was to maintain a dose homogeneity of ITV within 10%, which meant a dose to ITV ranging from 90% to 110% of the isocenter dose. Another goal was to maintain V_{20} (the volume irradiated with 20 Gy or more) of the bilateral lung at less than 25%. Beam arrangement was also selected to minimize doses to OARs. The use of the beam that passed directly through the spinal cord was avoided.

Beam arrangement

The applicable area of noncoplanar beam directions is more limited in SRT for extracranial tumors compared with intracranial tumors. There are three main causes: *(1)* risk of collision of the couch and the gantry; *(2)* blockade of the contralateral posterior beams by the supporting metal bar at the couch center; and *(3)* usage of the SBF that might cause the additional collision with the gantry. Figure 1 shows examples of the applicable gantry angle range that varies depending on the couch angle. We usually shift the position of the supporting couch and SBF in the lateral direction to avoid the metal bar on the center of the couch for a posterior beam, as shown in Fig. 2a. The figure shows the scheme of the couch and SBF shift from the foot-side view, in which the couch is shifted to the left side by 16.5 cm, and the SBF is shifted to the right side by 6.5 cm to put the center of the right-sided target on the isocenter. To find the applicable beam directions on the 3D RTPS more easily, we made diagrams that indicated applicable combinations of couch and gantry angles (11). Fig. 2b shows the diagram for the right-sided tumor. The area between an upper line and a lower line presents the applicable combination of the gantry and couch angles in each different isocenter height from the SBF base that determines the couch height. The diagrams were very useful in finding applicable beam directions at the time of treatment planning.

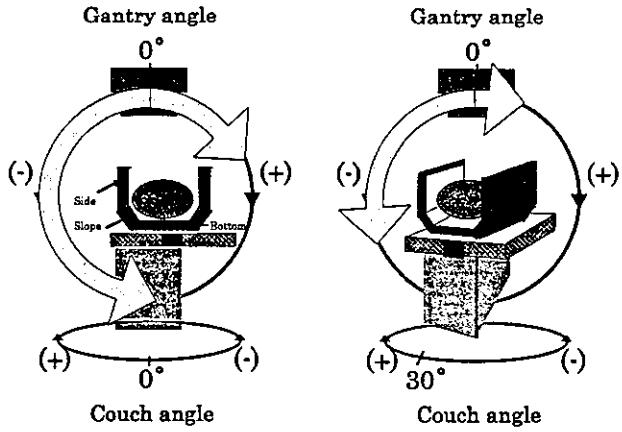

Fig. 1. Limitation of the couch and gantry angles. The left figure shows the applicable gantry position when the couch is set to the standard position (0° of the couch angle) and the tumor is in the right lung. The beam from the left direction cannot be used either because of the collision of the gantry and the couch or SBF. The beam from the posterior direction cannot be used either because of the interference of the supporting bar that lies in the center of the couch. Therefore, the applicable gantry angles are limited in the range of the thick arrow. Larger we set the couch rotation angle (e.g., 30° as shown in the right figure of Fig. 1), wider gets the zone in which the gantry and either the couch or stereotactic body frame mutually interfere. The range of the applicable gantry angle, therefore, is limited further as the thick arrow shows in the right figure. The supporting bar at the couch center is shown as a black square. The outer stiff frame of the stereotactic body frame consists of bilateral "side" walls, a "bottom" wall, and "slope" walls between the side and the bottom.

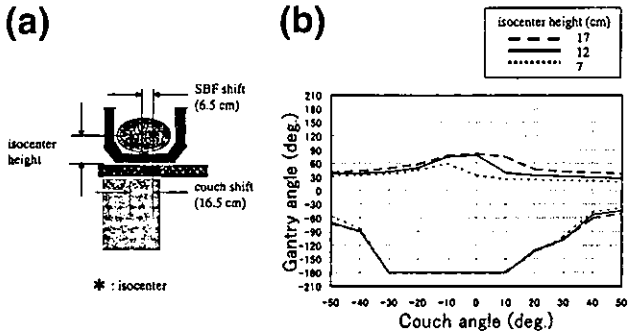

Fig. 2. Diagrams of beam arrangements. (a) Scheme of the couch and stereotactic body frame shift, which is necessary to avoid the metal bar on the center of the couch for a posterior beam. Isocenter height from the stereotactic body frame base is the parameter determining the couch height. (b) The applicable area of beam arrangement at the different isocenter heights. The area between each sequential line presents the applicable combination of the gantry and couch angles.

The procedure for choosing the optimal beam arrangement was forward planning based on our experiences. The beam arrangement used in our planning consisted of 5–10 beams, which included 1–4 coplanar beams and 2–6 noncoplanar beams. The alignment of the beams was chosen to be geometrically homogeneous wherever possible within the limitation. The use of opposing beams was avoided. The use of the beam that passed directly through the spinal cord was also avoided, although just one of the beams is allowed to pass directly through the spinal cord in recent planning. After checking the dose distribution by means of both DVH and dose distribution on axial images, modification of the beam alignment, number of beams, and weight of each beam was made to create an optimal dose distribution, which showed homogenous distribution to the target and low dose distribution to the normal tissues. A typical beam arrangement and the dose distribution are shown in Fig. 3 and Table 1.

Dose correction

There are two important issues for dose correction in SRT for lung tumors. One is lung inhomogeneity correction; the other is correction for dose attenuation caused by SBF.

We use the generalized Batho method to calculate the dose distribution with lung inhomogeneity correction. The center dose of lung tumors calculated by 3D RTPS without lung inhomogeneity correction were higher than the dose calculated with a house-made Monte Carlo simulation by 6% as an average (range 1–14%) in our institutional experiment. In contrast, the dose calculated with the generalized Batho method almost corresponded to the dose calculated with the Monte Carlo simulation. When the radiation field became too small, the dose calculated with the generalized Batho method did not correspond to the actual dose. Therefore, we did not use a radiation field smaller than 3 cm × 3 cm.

Another experiment revealed that the beams passing through the SBF showed a considerable dose reduction, although the frame, which has a honeycomb structure with a center of paper and surrounding glass fiber surface with edgings of pure birch, absorbs fewer X-rays compared with other materials. The outer stiff frame of the SBF consists of bilateral side walls, a bottom wall, and sloped walls between the side and bottom, as shown

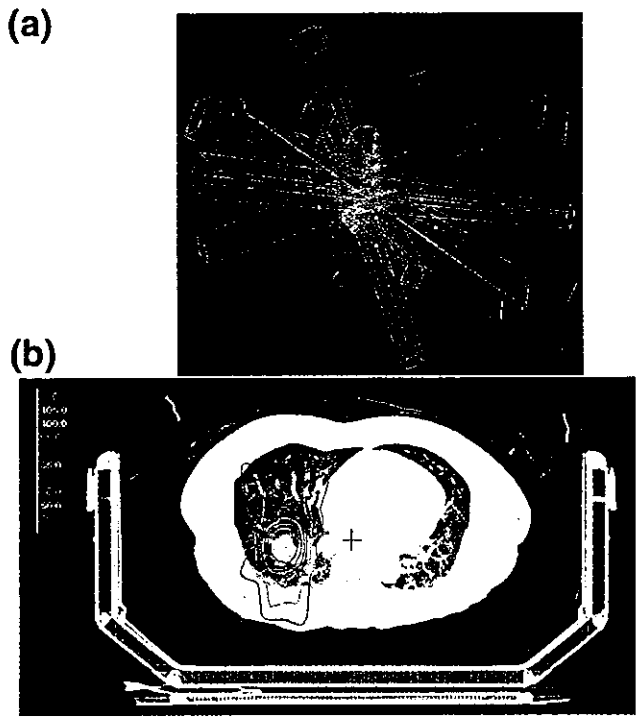

Fig. 3. A typical beam arrangement and the dose distribution. (a) A three-dimensional figure of a typical beam arrangement consisting of two coplanar beams and four noncoplanar beams. The detail of the gantry and the couch angles are shown in Table 1. (b) The two-dimensional dose distribution using this beam arrangement.

in Fig. 1. In the experiment, the mean dose attenuation ratio through each part of the frame was 7.5% for the side wall, 10.6% for the sloped wall, 9.5% for the bottom wall, 11.9% for transitional part between the side and sloped wall, and 11.8% for the transitional part between the sloped and bottom wall. The dose attenuation ratio ranged from 6.0 to 15.4%, and the mean value was 9.3%. Therefore, we used a uniform dose correction of 9.3% for beams passing through SBF in clinical use. According to another experiment using a phantom, the uniform dose correction of 9.3% minimized the dose difference from the actual dose by less than 3% (11).

Analysis of treatment planning

We analyzed the plans of 37 consecutive patients who underwent hypofractionated single high-dose SRT for small lung tumors at our institute between October 1998 and December 2000. All tumors were located at periphery of the lung and were of sizes smaller than 4 cm in the largest diameter on a diag-

Table 1. A typical beam arrangement

Port no.	Gantry angle	Couch angle (degrees)
1	180	0
2	260	0
3	340	40
4	30	40
5	35	320
6	295	320

nostic CT image or radiograph. In the analysis of target dose, we evaluated maximum dose, minimum dose, 90% coverage volumes, and homogeneity index. Homogeneity index was defined as the ratio of maximum dose to minimum dose. In the analysis of dose to the lung, we evaluated the V_{20} as an index related to the risk of radiation pneumonitis. In the analysis of dose to the other normal tissues, we evaluated maximum dose and mean dose to the spinal cord, heart, esophagus, and pulmonary artery. The median (range) clinical follow-up was 32 (3–63) months.

RESULTS

Target dose

The ITV ranged from 0.3 to 41.3 mL (mean, 13.4 mL). The ITV maximum dose ranged from 100.0 to 107.5% (mean, 102.6%), and the ITV minimum dose ranged from 82.5 to 99.2% (mean, 92.0%). The homogeneity index ranged from 1.03 to 1.25 (mean, 1.12). Figure 4 shows the relationship of the target volume with minimum dose, maximum dose, and homogeneity index for all patients. The minimum dose generally decreased as the target volume increased (coefficient of determination: $r^2 = 0.53$). On the other hand, the homogeneity index increased as well, because the index nearly equaled to the inverse number of the minimum dose ($r^2 = 0.59$). When the ITV exceeded 30 mL, the minimum dose was less than 90% and the homogeneity index was more than 1.2 in all cases. The percentage of the target volume irradiated with a dose of 90% or more of the isocenter dose (90% coverage volumes) exceeded 99.5% in all patients but one, whose ITV exceeded 40 mL.

Dose to the normal tissues

Doses to the normal tissues were analyzed for the lung, spinal cord, esophagus, heart, pulmonary artery, and bronchus. The results are summarized in Table 2, except for the dose to the lung.

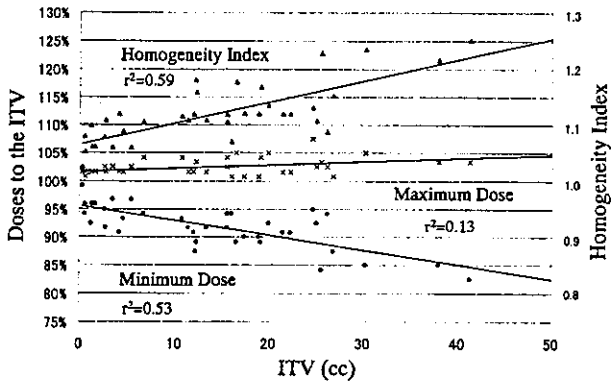

Fig. 4. Correlation with the internal target volume (ITV) and the dose to the ITV. Minimum and maximum doses to the ITV and homogeneity indices in each patient are presented in association with the value of ITV. Minimum dose had the tendency to decrease as the target volume increased ($r^2 = 0.53$). Homogeneity index had also a tendency to increase ($r^2 = 0.59$).

Table 2. Dose to the normal tissues

	Mean dose	Max dose
	Mean (range) Gy/fraction	
Esophagus	0.5 (0.0–1.3)	1.9 (0.1–5.2)
Bronchus	0.8 (0.0–5.0)	1.8 (0.1–7.9)
Pulmonary artery	0.8 (0.1–1.5)	2.6 (0.1–11.8)
Heart	0.3 (0.0–1.5)	2.7 (0.1–10.6)
Spinal cord	0.1 (0.0–0.2)	0.5 (0.0–2.2)

Mean and maximum doses of the normal tissues in each plan are summarized in this table. The values outside and between parentheses represent the average and the range for all patients, respectively.

Lung. V_{20} of the whole lung ranged from 0.3% to 11.6% with a mean value of 4.3%. There were 3 patients whose V_{20} exceeded 10%. One of them had only one lung because of tuberculosis. The other 2 patients had larger tumors than all other patients. Figure 5 shows the relationship of the target volume with V_{20} of the whole lung in all patients. In most of the patients, V_{20} increased in proportion to the target volume. Some patients, however, showed much larger V_{20} than patients with the same target volume when the tumor was located near the center of the lung. On the other hand, some patients showed smaller V_{20} when the tumor was located near the chest wall. Regarding pulmonary toxicity, only 2 patients (5%) had Grade 2 radiation pneumonitis in the National Cancer Institute - Common Toxicity Criteria (NCI-CTC), and no patients had more than Grade 2 pneumonitis. Thirty-four patients (92%) showed Grade 1 radiation pneumonitis, and most of them were asymptomatic and had only pneumonitis changes on CT images.

Spinal cord. A low dose to the spinal cord was maintained, because the use of beams that pass through the cord directly was intentionally avoided. The maximum dose in all patients was only 2.2 Gy per fraction. No patients showed cord toxicity.

Esophagus. The maximum dose to the esophagus in all patients was 5.2 Gy per fraction. The dose to the esophagus exceeded 5 Gy per fraction (20 Gy in total dose) only for the patient who showed the maximum dose. No severe esophageal toxicity greater than NCI-CTC Grade 2 was encountered.

Heart. The maximum dose to the heart in all patients was 10.6 Gy per fraction. The maximum volume of the heart irradiated over 5 Gy per fraction was 7.2 mL in the same patient. There were 5 patients whose maximum dose to the heart exceeded 5 Gy per fraction. In 3 of the 5 patients, more than 1 mL was irradiated with 5 Gy per fraction, and DVHs are shown in Fig. 6a. No severe cardiovascular toxicity greater than NCI-CTC Grade 2 was encountered.

Pulmonary artery. The maximum dose to the pulmonary artery in all patients was 11.2 Gy per fraction. The patient who showed the maximum dose to the pulmonary artery had a tumor near the pulmonary hilum. The volume irradiated

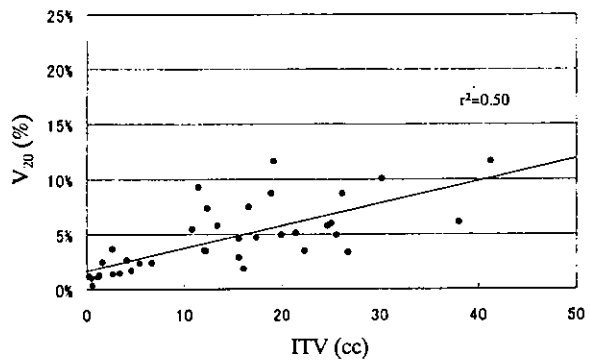

Fig. 5. Correlation with the internal target volume (ITV) and the volume irradiated with 20 Gy or more (V_{20}) of the lung. V_{20} had a tendency to increase as ITV increased ($r^2 = 0.50$). However, V_{20} also depended on the total lung volume and tumor position.

with 5 Gy or more was 5.13 mL, and the volume irradiated with 10 Gy or more was 0.86 mL in this patient. Dose to the pulmonary artery exceeded 5 Gy in 14 patients, the volume irradiated with 5 Gy or more exceeded 1 mL in 7 patients, whose DVH are shown in Fig. 6c. No clinical toxicity such as pulmonary bleeding or pulmonary artery obstruction was encountered.

Bronchus. Maximum dose to the bronchus in all patients was 7.9 Gy, and the maximum volume irradiated with 5 Gy or more was 2.92 mL. Figure 6b shows the DVH of the patient who was irradiated with the maximum dose to the bronchus. Though dose to the bronchus exceeded 5 Gy in 5 patients, the volume irradiated with 5 Gy or more did not exceed 1 mL except in the patient previously mentioned. No clinical toxicity such as symptomatic bronchitis or bronchial stenosis was encountered.

DISCUSSION

Stereotactic body frame was originally developed by Blomgren and Lax at Karolinska Hospital in Sweden (12, 13). It gives the following advantages: *(1)* Effective patient immobilization during treatment; *(2)* greater daily setup accuracy; *(3)* easy setup correction because of measuring scales on the frame; and *(4)* successful reduction of the respiratory tumor movement with a small abdominal pressing plate. Daily setup accuracy is much more important for SRT than for conventional radiotherapy, because a setup error in single treatment causes a larger error in total dose distribution. Its accuracy has been proven to be high enough in many articles, although verification and repositioning at every treatment are recommended (10, 12, 14). Its effectiveness on the reduction of respiratory tumor movement has also been proven in some articles (10, 14). On the other hand, this frame has the following disadvantages: excessive time required to arrange stereotactic coordinates; inappropriate application for obese patients; or limited availability of beam arrangement. The last disadvantage was considered an issue that should be solved before starting the practice of SRT with SBF. Therefore, we made the diagrams for available combinations of couch and gantry angles to use in routine clinics (11). We configured 5–10 noncoplanar beams using the diagrams, aiming for a practicable and balanced arrangement under the limitation. The diagrams were helpful in avoiding the selection of unusable beams in actual treatment.

We routinely use noncoplanar multiple static ports. The number of ports depends on the tumor size and location and is selected from 5 to 10 in our plan. Although a large number of ports makes dose distribution more conformal compared with a small number in general, our simulation revealed that it has made little difference in the increase of the number of ports more than 10 under the limitation of the couch and gantry arrangement. Moreover, because radiotherapy staff member enter the treatment room for checking that there is no collision when the gantry or the couch are moved, the large number of ports increases both treatment time and workload of the staff. These are the reasons why we use 5–10 static ports. Despite the limitation of the beam arrangement because of usage of the body frame and the supporting metal bar in the center of the couch, appropriate dose distributions were successfully achieved. Dose homogeneity indices for ITV were very small, and 90% dose coverage volumes were more than 99.5% in all cases except one.

The multiple arc technique is applied to SRT for extracranial tumors in a few institutes (15). However, there were some problems using this technique in our institute. Because the available beam range was limited by the SBF and couch structure, sufficient gantry rotational angles were not available. Also, the dose attenuation correction was practically impossible for an arc that contained both beams that passed and those that did not pass through the SBF. In our fundamental experiment for comparing the dose distribution between multiple static ports (6, 8, or 10 ports) and multiple arcs (3, 5, or 7 arcs, 300°), few differences were observed

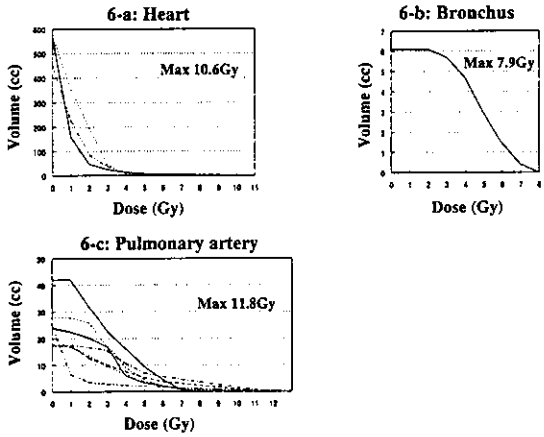

Fig. 6. Dose–volume histogram of the normal tissues. The dose–volume histogram of patients irradiated with more than 5 Gy to 1 mL or more of each normal tissue. (a) Heart. (b) Bronchus. (c) Pulmonary artery.

between both techniques in SRT for extracranial tumors under the constraints mentioned here. Therefore, we routinely use noncoplanar multiple static ports.

In regard to normal tissues, Emami *et al.* reported tolerance doses at a 5% complication rate in 5 years (TD 5/5) when irradiated with 2 Gy per fraction (16). This result, however, may not be applicable to hypofractionated, single, high-dose radiotherapy. Some recent articles reported on normal tissue complications in SRT for lung tumors. Severe toxicities are summarized in Table 3 (3, 4, 6, 13, 17). There are, however, few articles that have reported on the relationship between doses to normal tissues and their complications.

For lung doses, Graham *et al.* compared the total lung DVH parameters with the incidence and grade of pneumonitis after treatment for non–small-cell lung cancer. They concluded that V_{20} might be useful in comparing competing treatment plans to evaluate the risk of pneumonitis (18). We have used V_{20} of the total lung volume as a dose constraint for the lung. V_{20} was sufficiently lower than the dose constraint (25%) in our planning. We have encountered only 2 patients who showed radiation pneumonitis of Grade 2 in the NCI-CTC version 2.0, and no patients who showed Grade 3 or more. It is, however, controversial whether V_{20} can be applied to SRT in the same way as it is applied to conventional radiotherapy. We must follow this up carefully and analyze other parameters when severe toxicity occurs in the future.

A low dose to the esophagus was maintained in our planning, and no toxicity has yet been seen. Onimaru *et al.* have reported a patient who died because of a radiation-induced esophageal ulcer after receiving 48 Gy in eight fractions (6). The review of the planning revealed that 1 mL of the esophagus might have received 42.5 Gy with a maximum dose of 50.5 Gy. Though the case of this patient may have indicated the tolerance dose, they could not determine the essential maximum tolerance dose of the esophagus because of uncertainty in the contouring.

Wulf *et al.* reported fatal bleeding from the pulmonary artery 9 months after stereotactic irradiation (Grade 5) in a patient who received a previous conventional irradiation with a total dose of 60 Gy and stereotactic irradiation with a total dose of 30 Gy per 10 fractions. In our study, dose to the pulmonary artery was relatively higher when the tumor was located near the pulmonary hilum. Five Gy per fraction in more than 1 mL was irradiated in 5 of 7 patients. Severe toxicity has not yet been presented. The true volume of a pulmonary arterial wall irradiated with 5 Gy in the patients was smaller than the volume containing arterial blood used in our analysis. This might be one of the reasons why there has been no severe toxicity. However, the true tolerance dose to the pulmonary artery is still unknown.

Dose to the bronchus using brachytherapy has been reported to be from 4 to 6 Gy at a reference point per fraction with four fractionations in some typical protocols in other institutes. The reference point was typically located at a 5-mm depth from the mucosal surface, and more doses were irradiated at the mucosal surface. Our dose to the bronchus was considered to be much safer in comparison with these reports.

A low dose to the spinal cord was maintained in our planning because the use of the beam that included the spinal cord in the beam pathway was avoided. No patient with radiation myelitis has been reported after SRT. We changed the strategy of the beam arrangement and allowed just one of the beams to pass directly through the spinal cord in recent planning to improve the dose distribution for the target. One beam delivered a dose of about 2 Gy or less per fraction to the cord, when the fractional dose of 12 Gy was evenly delivered by six ports.

There is no report to be referred to regarding severe toxicity of the heart after stereotactic single high dose radiotherapy. In our study, although part of the heart was irradiated with a high dose in some patients, no severe complication has been encountered. However, the effect of high-dose irradiation to the coronary artery remains unclear, and the risk of severe toxicity may increase when a patient suffers from arterial atherosclerosis. Therefore, we must follow patients carefully over a long period. In regard to skin reaction, 7 patients (19%) showed erythema or pigmentation denoting Grade 1 acute toxicity at the entrance of a beam. No patient showed skin toxicity with Grade 2 or more.

Tolerance dose to OARs in SRT is a great concern for

Table 3. Severe toxicities (Grade 3 or more)

Authors	No. of targets (patients)	Dose/fraction at isocenter	Severe toxicities
Blomgren *et al.*	17 (13)	23–68 Gy/1–3 Fr.	Grade 3: Chronic cough (6%)
Hara *et al.*	23 (19)	20–30 Gy/1 Fr. (minimum to GTV)	Grade 3: Respiratory symptom (O_2 supply) (4%)
Onimaru *et al.*	57 (45)	48–60 Gy/8 Fr.	Grade 5: Esophageal ulcer (2%)
Wulf *et al.*	27	45 Gy/3 Fr.	Grade 3: Esophageal ulcer (4%) Grade 5: Pulmonary artery bleeding (4%)
Gomi *et al.*	38 (35)	40–62.5 Gy/4–5 Fr.	Grade 4: Pneumonitis (3%) Grade 4: Dermatitis (3%) Grade 3: Esophagitis (3%)

Abbreviations: Fr. = fraction; NCI-CTC = National Cancer Institute - Common Toxicity Criteria.

Severe toxicities of Grade 3 or more in NCI-CTC are summarized in this table. All of the authors in the table used three-dimensional conformal radiotherapy for lung tumors using hypofractionation or single fractionation shown in the table.

radiation oncologists. However, it could not be determined in our study, because we did not encounter any severe toxicity.

Verification is a very important process, especially in hypofractionated stereotactic radiotherapy. Negoro *et al.* previously reported the details of our verification method and the results of setup error (10). We used A-P and lateral verification films obtained by a X-ray simulator after CT scan, to compare linacography (A-P and lateral port films) immediately before irradiation. X-ray simulation films have a higher resolution than digital reconstructed radiography, especially in the C-C direction. X-ray simulation films can be easily taken using our integrated system, in which the CT simulator and the X-ray simulator are employed on the same couch. Therefore, we used X-ray simulation films to verify patient setup.

Dose correction for lung inhomogeneity is still a controversial issue. The application of the Monte Carlo calculation method to routine clinics in the future is one of the solutions. In the present situation, we consider that dose correction using a method such as the generalized Batho method should be performed to deliver the true prescribed dose.

Target delineation and definition are other important issues in SRT for lung tumors. Interobserver variation in target delineation is not negligible in some cases. There has been no universal target definition for small solitary lung tumor in SRT. Although the only concept is proposed by International Commission on Radiation Units and Measurements Report 62, details of target definition depend on the treatment methods, such as the way to scan the CT of the tumor and the verification method. Further discussions on these issues are necessary.

In conclusion, the use of multiple noncoplanar static ports achieved homogeneous target dose distribution and avoided high dose to normal tissues, despite the limitation of the beam arrangement from the use of the body frame and couch structure. Tolerance doses to the normal tissues are yet unknown when using single high-dose irradiation. Therefore, we should continue to make treatment plans carefully. In addition, further follow-ups of clinical cases are required to know the tolerance dose to the normal tissues in stereotactic radiotherapy.

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Int J Clin Oncol (2004) 9:352–355
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FROM THE ASCO-JSCO JOINT SYMPOSIUM

Masahiro Hiraoka · Yasushi Nagata

Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the Japanese experience

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Abstract Stereotactic body radiation therapy is a new treatment modality for early-stage non-small-cell lung cancer, and is being intensively investigated 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; (2) inoperable, or the patient refused operation; (3) histologically confirmed malignancy; (4) no necessity for oxygen support; (5) performance status equal to or less than 2, and (6) the tumor was not close to the spinal cord. 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. Overall survival for 29 patients with stage IA, and 14 patients with stage IB disease was 87 % and 80 %, respectively. No local recurrence was observed in a follow-up of 3–50 months. Regional lymph node recurrence developed in 1 patient, and distant metastases developed in 4 patients. 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.

Key words Non-small-cell lung cancer · Stereotactic radiation therapy

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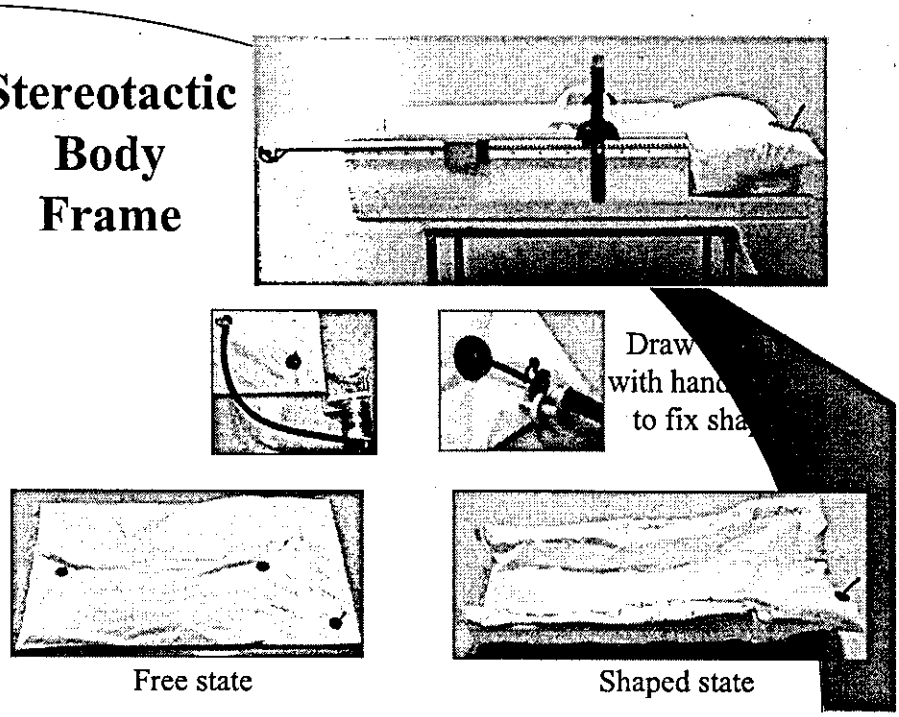
Stereotactic body radiation therapy for early-stage non-small-cell lung cancer (NSCLC) is a new treatment modality, and Japan is one of the leading countries in using three-dimensional radiation therapy. The background of this treatment is the great success of stereotactic irradiation for intracranial 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. 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 have 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

Fig. 1. Stereotactic body frame



candidates; that is, those who refuse surgical intervention, and those who are medically inoperable. The reported 5-year 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.

However, there remain several problems with stereotactic radiation therapy for lung cancer compared to its use in intracranial tumors. (1) How should the body be fixed with high accuracy? (2) How do we cope with the movement of the tumor caused by respiration? (3) What are the optimal treatment regimens? (4) Toxicities to normal tissue caused by large-fraction size irradiation have not been examined. (5) 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 stereotactic body radiation therapy for small lung tumors in July 1998. The stereotactic body frame shown in Fig. 1 was used. 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 set-up. 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 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 mm 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 September 2002, a total of 70 patients received this treatment modality. Their ages ranged from 70 to 87 years, with a mean of 71 years. Fifty patients had primary tumors, and 20 patients had secondary tumors. Seven of the 20 secondary tumors were solitary. In 57 tumors, a total dose of 48 Gy was delivered, in four fractions in 2 weeks. Ten tumors were treated with a total dose of up to 60 Gy. In the initial three tumors, a total dose of 40 Gy was administered.

We examined the toxicity by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2. Lung toxicity was grade II in 4%, grade I in 92 %, and grade 0 in 4 %. No grade II toxicities for spinal cord, bronchus, pulmonary artery, or esophagus were observed. The clinical course of 1 patient who responded well to this treatment is shown in Fig. 2.

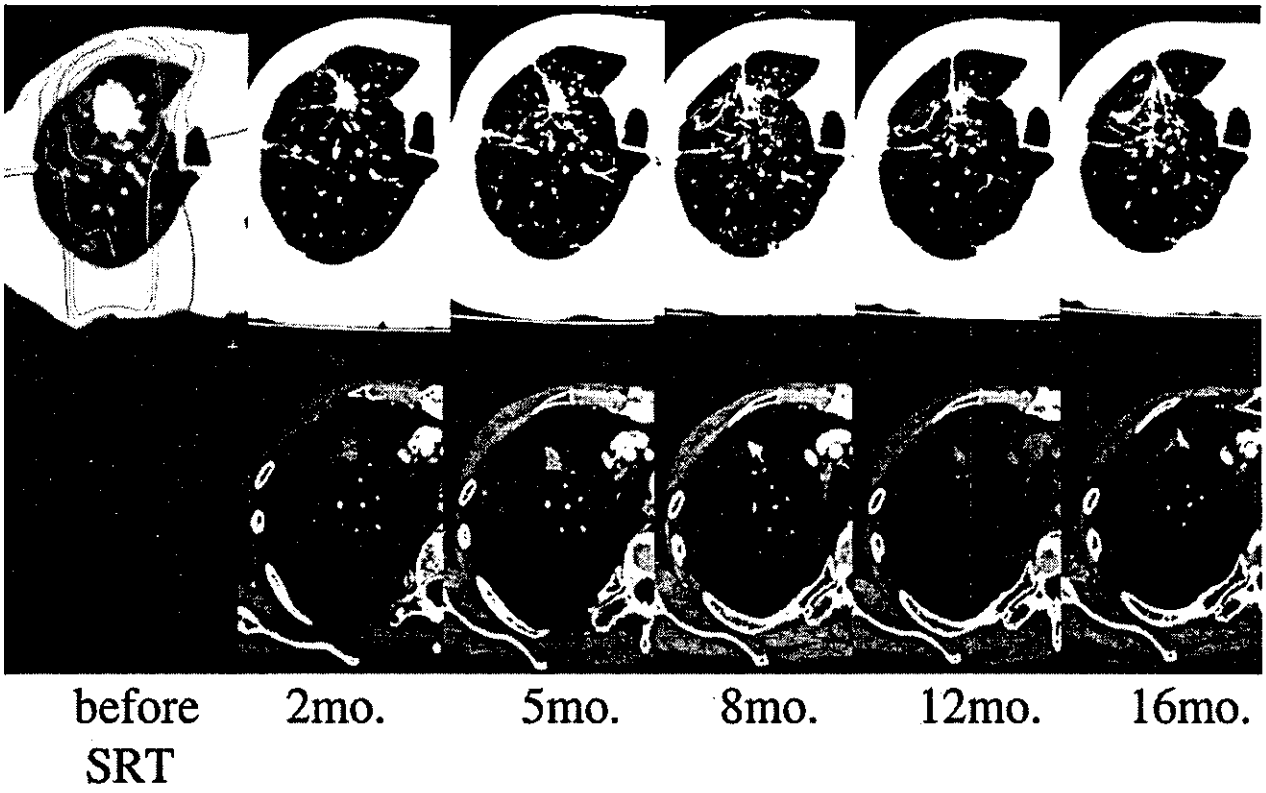


Fig. 2. Clinical course of a patient treated with stereotactic radiation therapy (*SRT*). The patient, a 71-year-old man, had primary lung cancer (squamous cell carcinoma; T2N0M0). *mo.*, months

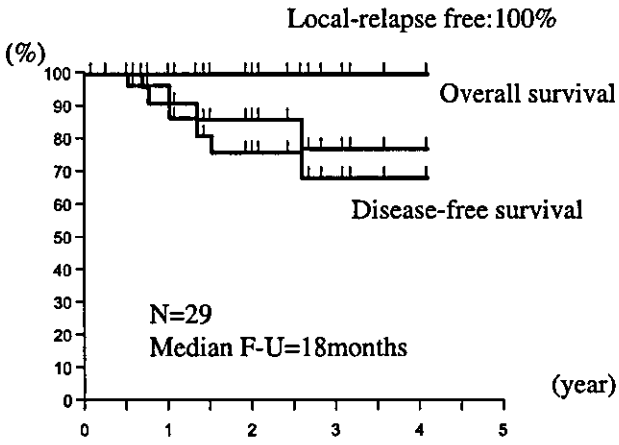


Fig. 3. Survival curves of patients with stage IA: T1N0M0 non-small-cell lung cancer (NSCLC) treated with SRT. *F-U*, follow-up

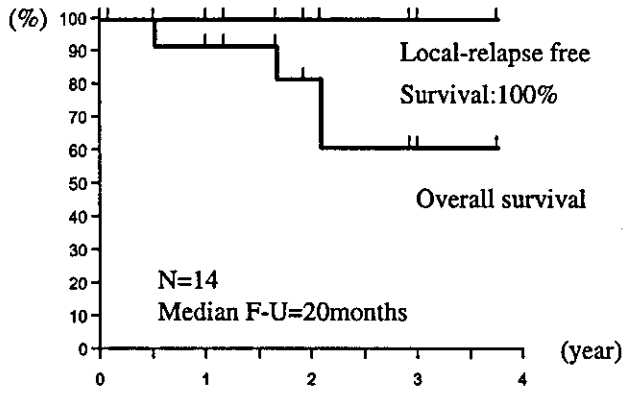


Fig. 4. Survival curves of patients with stage IB: T2N0M0 NSCLC treated with SRT

Survival curves for 29 patients with stage IA, T1N0M0 NSCLC are shown in Fig. 3. No local recurrence was observed in a follow-up of 6–50 months (median, 18 months). Regional lymph node recurrence developed in 1 patient, and bone metastases developed in 2 patients.

Survival curves for 14 patients with stage IB, T2N0M0 NSCLC are shown in Fig. 4. No local recurrence was observed at a follow-up of 3–45 months (median, 20 months). Liver and bone metastases developed in 1 patient each.

We retrospectively analyzed data from 241 patients from 13 Japanese institutes. Their ages ranged from 35 to 92 years, with a median of 76 years. Histology was sqnamous 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 58mm, with a median of 28mm. 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.

We are going to start 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 to 8 days. Entry of 150 patients from 15 institutes in 3 years is expected. 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.

In summary, regarding stereotactic body radiation therapy for early-stage NSCLC, (1) long-term results, in terms of local control, regional recurrence, survival, and complications are not yet evaluated. (2) Technologies to cope with tumor movement, gauging tracking, need to be improved. (3) 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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ORIGINAL ARTICLE

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Concurrent chemoradiotherapy for esophageal cancer: comparison between intermittent standard-dose cisplatin with 5-fluorouracil and daily low-dose cisplatin with continuous infusion of 5-fluorouracil

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Abstract
Background. Although current standard treatment for advanced esophageal cancer is intermittent standard-dose cisplatin with 5-fluorouracil (5-FU) (ISD-FP), daily low-dose cisplatin with continuous infusion of 5-FU (CLD-FP) is advocated for equivalent effectiveness and lower toxicity. The feasibility of these two concurrent chemoradiotherapeutic protocols was retrospectively reviewed for local control rate, overall survival, toxicity, and compliance in a single institutional situation.
Methods. Concurrent chemoradiotherapy, using 60 Gy of radiation and ISD-FP or CLD-FP was non-randomly scheduled for 29 patients between June 1994 and March 2001.
Results. Complete response in the irradiated volume at the end of primary treatment was shown by 8 of 15 and 9 of 14 patients in the ISD-FP and CLD-FP groups, respectively. The projected overall survival rate at 2 years was 55% for stage III patients and 13% for stage IV. Median survival times were 14 months versus 15 months in the ISD-FP and CLD-FP groups, with no significant difference. Toxicities were similar, including two treatment-related deaths in each group. Chemotherapy was completed for 10 of 15 and 11 of 14 patients in the ISD-FP and CLD-FP groups, respectively. Modification of the planned regimen was more often required for the CLD-FP group.
Conclusion. CLD-FP therapy has no apparent advantage over ISD-FP therapy from the perspective of compliance and safety. A randomized phase II clinical trial comparing ISD-FP and CLD-FP, currently being performed, is expected to provide further information.

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Key words Esophageal cancer · Concurrent chemoradiotherapy · Pilot study

Introduction

The incidence of esophageal cancer in Japan is relatively high compared to that throughout the world.[1] There were 9991 deaths from esophageal cancer registered in Japan in 1999 and it was the eighth leading cause of death from malignant tumors in 1999.[2] The age-adjusted incidence of esophageal cancer was 14.2 per 100000 in 1996.[2] Primary treatment modalities include surgery alone or chemotherapy with radiation therapy. Esophageal cancer is commonly found in an advanced stage in elderly patients and, hence, curative surgery is not always possible. An intergroup randomized trial[3–5] showed that the results of chemoradiotherapy for esophageal cancer matched those of surgery. To decrease the adverse effects of concurrent chemoradiotherapy, protracted low-dose continuous infusion of 5-fluorouracil (5-FU)[6] and 5-FU plus cisplatin[7] were proposed. The present study retrospectively assessed the clinical feasibility and initial results of the two methods of concurrent chemoradiotherapy, low-dose cisplatin with continuous infusion of 5-FU (CLD-FP) and intermittent standard-dose cisplatin with 5-FU (ISD-FP) used by a single radiotherapy team.

Patients and methods

Patient recruitment criteria

Selected patients should have: (1) pathologically proven esophageal carcinoma (either squamous cell carcinoma or adenocarcinoma); (2) Karnofsky performance scale of ≧60%; (3) normal hemogram and adequate liver and renal function (GOT/GPT <2 times upper limit of reference values; total bilirubin, <1.5 mg/dl; creatinine, ≦1.5 mg/dl;

creatinine clearance ≧60ml/min); (4) signed informed consent; and (5) no concomitant advanced cancer in other organs. Patients in stage IVB were eligible as long as their primary treatment was chemoradiotherapy. Patients with prior chemotherapy were not excluded from this study. All patients were referred to our department due to inoperable condition or the patient's preference.

Patient characteristics

Between June 1994 and March 2001, a total of 29 patients with esophageal cancer were treated with concurrent chemoradiotherapy. Before June 1998, all 11 patients were treated with ISD-FP. Thereafter, CLD-FP was preferred. Fourteen of 18 patients were treated with CLD-FP after July 1998. Consequently, 15 and 14 patients were treated with ISD-FP and CLD-FP, respectively.

The median patient age was 67 years (range, 48–80 years). The Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 12 patients, 1 in 11, and 2 in 6 patients. Squamous cell carcinoma was the predominant histological type. Endoscopic ultrasonography (EUS) was mainly used for determination of the T-stage. If EUS could not be performed due to stenosis, computed tomography (CT) was used for T-staging. Invasion of the aorta was determined using criteria proposed by Picus et al.[8] Bronchoscopy was performed if tracheobronchial invasion was suspected. Lymph nodes were regarded as positive if the short-axis diameter was equal to or larger than 5mm.[9] Patient characteristics in each treatment group are summarized in Table 1.

Table 1. Clinicopathological features

	Total	ISD-FP	CLD-FP
Sex (M:F)	28:1	14:1	14:0
Age, years; median (range)	67 (48–80)	64 (48–80)	69 (52–72)
Pathology			
Squamous cell carcinoma	26	13	13
Adenocarcinoma	3	2	1
Performance status (ECOG)			
0	12	4	8
1	11	7	4
2	6	4	2
Clinical stage (UICC 1997)			
II	4	2	2
III	11	4	7
IVa	5	3	2
IVb	9	6	3
Location			
Ce	2	1	1
Ut	5	3	2
Mt	15	7	8
Lt	7	4	3
Prior chemotherapy	5	4	1
Length of involvement (cm)	6.7 ± 3.0	7.0 ± 2.4	6.4 ± 3.6

ISD-FP, intermittent standard-dose cisplatin with 5-fluorouracil (5-FU); CLD-FP, daily low-dose cisplatin with continuous 5-FU infusion; ECOG, Eastern Cooperative Oncology Group; UICC, International Union Against Cancer; Ce, cervical esophoagus; Ut, upper intrathoracic espophagus; Mt, middle intrathoracic esophagus; Lt, lower intrathoracic esophagus

Radiation therapy

Radiation therapy was given with either 6- or 15-MV X-rays. Initial clinical treatment volumes were designed as follows: mediastinum 4cm beyond the first carina and cervical lymph nodes for upper-thoracic tumor; the whole mediastinum for middle-thoracic tumor; and involved mediastinum with left gastric artery lymph nodes for lower-thoracic tumors. Forty Gy of irradiation, in 20 fractions, was delivered for the initial treatment volume at the anterior and posterior opposed fields. After 40-Gy irradiation, boost irradiation of 20Gy, in 10 fractions, was given to a cone down field which encompassed the initial gross target volume. Radiation portals were arranged so that the dose to the spinal cord was kept below 40Gy. For the ISD-FP group, a split-course irradiation schedule consisted of two courses of 30Gy, in 15 fractions of 2Gy, separated by a 1-week interval. There was no planned interruption for the CLD-FP group.

Concurrent chemotherapy

In the ISD-FP group, the regimen consisted of 70mg/m^2 of cisplatin, given intravenously, on the first days of weeks 1 and 5. The patients were also given a continuous infusion of 5-FU, 700mg/m^2 per day, for the first 4 days of weeks 1 and 5 (Fig. 1a). If creatinine clearance deteriorated to below 60ml/min, carboplatin, 350mg/m^2 per day was delivered instead of cisplatin. In the case of severe hematologic toxicities, where grade 3 or 4 of the National Cancer Institute common toxicity criteria (NCI-CTC) occurred in the first 4 weeks, the dose of cisplatin and 5-FU was reduced by 20%.

In the CLD-FP group, 5mg/m^2 of cisplatin was intravenously delivered 1h before irradiation on the first 5 days of each week. The patients were also given a continuous infusion of 5-FU, 200mg/m^2 per 24h for the first 5 days of each week (Fig. 1b). If creatinine clearance deteriorated to below

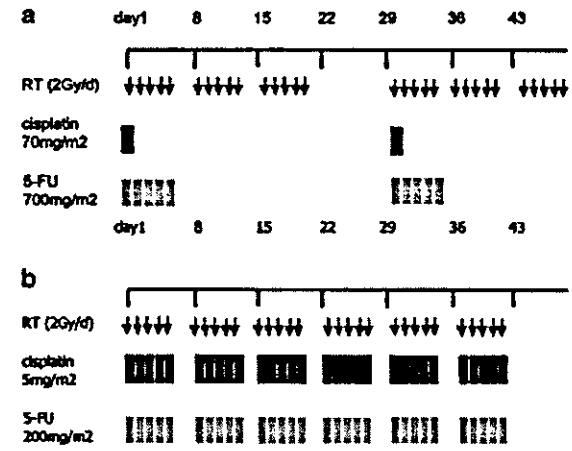

Fig. 1a,b. Schematic diagram of the regimens. **a** Intermittent standard-dose cisplatin with 5-FU (ISD-FP) and **b** daily low-dose cisplatin with continuous infusion of 5-FU (CLD-FP)

60 ml/min, carboplatin, 25 mg/m^2 per day was delivered instead of cisplatin. If grade 3–4 hematologic toxicities occurred, the dose of cisplatin and 5-FU was reduced by 20% or stopped. If there was still no improvement in the clinical condition, radiotherapy was interrupted or terminated.

All patients were hospitalized throughout the entire treatment course because of the continuous infusion of chemotherapy and the parenteral nutrition that was administered when indicated. Concurrent chemotherapy was considered to have been completed when 80% of the planned chemotherapy doses were delivered during radiotherapy. There was no adjuvant chemotherapy.

Evaluation of response and toxicity

During the treatment, hemograms, blood chemistry, and renal function were checked at least once a week. Treatment-related acute toxicities were evaluated according to the NCI-CTC. We performed a post-treatment workup of barium swallow, endoscopy, and CT scan at intervals of 3 to 4 months. Complete response (CR) in the irradiated volume was defined as a condition where no apparent tumor was observed during endoscopy and no lymphadenopathy was observed on the CT scan within the irradiated volume 1 to 3 months after completion of chemoradiotherapy.

Statistical analyses

All follow-up data were updated at the end of June 2002. Survival calculations were based on the first day of chemoradiotherapy, using the Kaplan-Meier method, and comparisons between groups were made using the log-rank test. The χ^2 test (Fisher's exact probability test) was used to determine whether the difference in efficacy was significant between the ISD-FP and CLD-FP groups. A P value of less than 0.05 was considered significant.

Results

Local response and survival

No patient was lost to follow-up. Among the 15 patients who received ISD-FP, 8 patients (53%) had a CR in the irradiated volume at the end of primary treatment, while 9 patients (64%) among the 14 patients who received CLD-FP had a CR. Complete response (CR) in the irradiated volume was observed in 3 of 4, 6 of 11, and 9 of 14 patients in stages II, III, and IV, respectively. The median survival times were 14 months for ISD-FP and 15 months for CLD-FP, with no apparent significant difference (P = 0.89; Fig. 2). For all patients, the overall survival rate at 2 years was 55% for stage III and 13% for stage IV (Fig. 3). Median survival time was 21 months for stage III and 10 months for stage IV. Three of the 15 patients who received ISD-FP and 7 of the 14 who received CLD-FP were treated with carboplatin due to renal dysfunction. There was no significant difference between the cisplatin regimen and the carboplatin regimen with respect to survival rate (P = 0.76; Fig. 4). Three patients were alive with disease and 6 patients were alive without evidence of disease at the time of analysis.

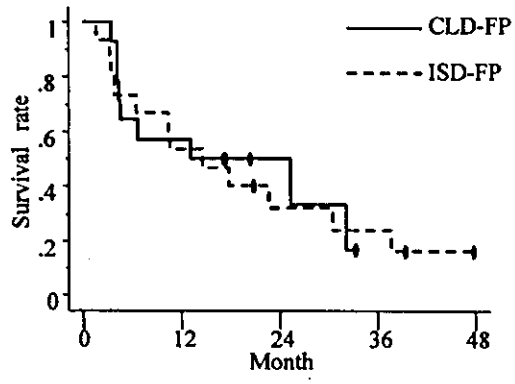

Fig. 2. Kaplan-Meier actuarial overall survival for patients with esophageal cancer treated with CLD-FP or ISD-FP. The difference in overall survival between the two groups was not significant (P = 0.89)

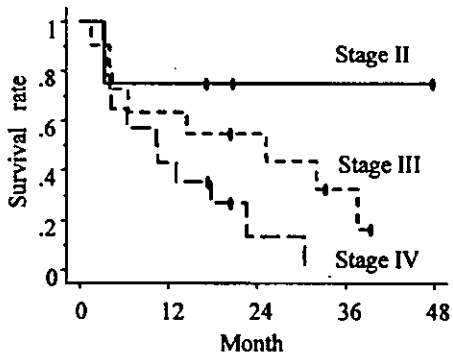

Fig. 3. Kaplan-Meier actuarial overall survival for patients with esophageal cancer in relation to clinical stage

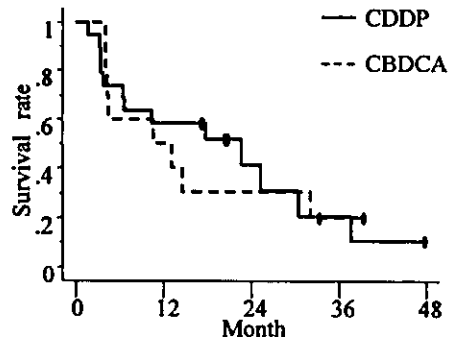

Fig. 4. Kaplan-Meier actuarial overall survival for patients with esophageal cancer in relation to chemotherapy modification. The difference in overall survival between the two groups was not statistically significant (P = 0.76). *CDDP*, cisplatin; *CBDCA*, carboplatin

Table 2. Summary of results

	Total	ISD-FP	CLD-FP
Initial response[a]	17/29 (58)	8/15 (53%)	9/14 (64%)
Median survival time; months (range)	14 (2–44)	14 (2–44)	13 (3–31)
Overall survival (2-year)	42%	39%	50%
Toxicity (NCI-CTC grade 3–4)			
Leukocytopenia	12 (41%)	5 (33%)	7 (50%)
Thrombocytopenia	2 (7%)	1 (7%)	1 (7%)
Esophagitis	4 (14%)	1 (7%)	3 (21%)
Nephrologic	0 (0%)	0 (0%)	0 (0%)
Decrease in creatinine clearance		38 ± 23%	54 ± 21%
Treatment-related death	4 (14%)	2 (13%)[b]	2 (14%)[c]
Completion of planned CRT[d]	21 (72%)	10 (67%)	11 (79%)
Modification of chemotherapy		2/10	6/11

NCI-CTC, National Cancer Institute common toxicity criteria; CRT, chemoradiotherapy
[a]The rate of complete response in the irradiated volume at the end of primary treatment
[b]Esophagobronchial fistula (n = 2)
[c]Hepatic dysfunction (n = 1), radiation pneumonitis (n = 1)
[d]Completion of planned CRT was considered to have taken place when 80% of the planned chemotherapy doses were completed during radiotherapy

Acute toxicity

Grade 3–4 leukocytopenia was observed in 5 of the 15 patients treated with ISD-FP and 7 of the 14 patients treated with CLD-FP. Grade 3–4 thrombocytopenia was observed in 1 of the 15 patients treated with ISD-FP and 1 of the 14 patients treated with CLD-FP. Grade 3–4 esophagitis was observed in 1 and 3 of the patients treated with ISD-FP and CLD-FP, respectively.

There were four treatment-related deaths, two in each group. Two patients with T4 disease were revealed to have esophagobronchial fistula in the middle of the course or early after completion of ISD-FP; hence, we considered them to be treatment-related deaths, though progressive disease may have been the main cause of death. A patient with stage III disease complained of dyspnea 3 months after completion of CLD-FP and died 10 days after this symptom was shown, due to radiation pneumonitis. Another patient, with stage IIB disease, who had had mild hepatitis C showed gradual exacerbation of liver dysfunction and died of hepatic failure 2 months after completion of CLD-FP.

The interval between the start of treatment and the nadir of leukocytopenia and thrombocytopenia for CLD-FP appeared to be longer than that for ISD-FP. As shown in Table 2, creatinine clearance decreased to 54.0 ± 21.4% of the initial value for CLD-FP and to 38.3 ± 22.8% for ISD-FP (P = 0.078), while the onset of the nadir of renal toxicity was similar in the two groups (34.1 ± 13.5 vs 32.8 ± 19.9 days after a start in chemoradiotherapy; P = 0.85). Renal dysfunction was reversible; there was no grade 3–4 renal toxicity observed in either treatment arm.

Compliance for the two concurrent chemoradiotherapy regimens

Ten (67%) of the 15 patients treated with ISD-FP and 11 (79%) of the 14 patients treated with CLD-FP completed the concurrent chemoradiotherapy without modification. Among the patients who had completed the chemoradiotherapy, modification or reduction of the regimen was necessary due to leukocytopenia or decreased creatinine clearance in 2 of 10 patients treated with ISD-FP and in 6 of 11 patients treated with CLD-FP.

Discussion

Since the Radiation Therapy Oncology Group (RTOG) phase III trial RTOG 85-01, concurrent chemoradiotherapy using 5-fluorouracil (5-FU) and cisplatin has been considered the standard treatment for locally advanced esophageal cancer.[3–5] The result of RTOG 85-01 for concurrent chemoradiotherapy appears to match that of surgery in Japan.[10] In RTOG 85-01, severe acute toxic effects were greater in the concurrent chemoradiation group. Ten percent of the patients had life-threatening toxic effects with concurrent chemoradiotherapy, in contrast to 2% in the radiotherapy-only group. Despite the high intensity of combined therapy, persistence of disease was still the most common mode of treatment failure.

Intermittent standard-dose cisplatin with 5-FU seemed to be preferable for patients with stage IV disease in our study, partly because standard-dose chemotherapy was considered to be more effective on distant lesions than continuous low-dose chemotherapy. Because patients with distant metastasis had poor prognoses, we did not find an apparent benefit. Against our expectations, we did not find an apparent benefit in delaying or suppressing the development of distant metastasis in the ISD-FP arm.

To improve the local control rate without severe systemic toxic effects, protracted low-dose concurrent chemotherapy was proposed,[6,7,11] because cisplatin is not only a cytotoxic agent, but also a chemical modulator, enhancing the chemotherapeutic effects of 5-FU on tumor cells,[12,13] and it is also a radiosensitizer.[14–16] Daily low-dose 5-FU (250–

300 mg/m^2 per 24 h) and concurrent external beam irradiation was also safely delivered to 28 patients with inoperable esophageal squamous cell carcinoma; 25 of the 28 patients (89%) completed the planned course of chemoradiotherapy.[6] Hsu et al.[7] used daily low-dose cisplatin (6 mg/m^2 per day) and continuous infusion of 5-FU (225 mg/m^2 per day) and suggested that lower hematological and mucosal side effects were obtained. In their study, grade 3–4 leukocytopenia, thrombocytopenia, and non-hematologic toxicity developed in 14 (56%), 7 (28%), and 4 (16%) patients, respectively. Eighteen of 25 patients (72%) completed chemotherapy, but 40%–60% of patients required a dose reduction of chemotherapy.

There are accumulated reports that platinum-based chemotherapy seemed to be effective when used concurrently with radiotherapy. Jefford et al.[17] reported that concurrent chemoradiation using carboplatin with 5-FU was also effective for localized esophageal cancer. Carboplatin was also used as an agent in concurrent chemoradiotherapy for squamous cell lung carcinoma, cervical cancer, and head and neck cancer.

In the present pilot study, daily low-dose cisplatin with a continuous infusion of 5-FU had no apparent advantage over intermittent standard-dose cisplatin with 5-FU with respect to survival, local control, and toxicities, though CLD-FP was expected to show advantages of reduced systemic toxicity and appropriate cessation of concurrent chemotherapy. Hematological toxicities were similar with both treatment regimens. Transient renal toxicities were also similar. Modification of the planned regimen was more frequently necessary for the CLD-FP group.

We had four treatment-related deaths in this study. This result seemed to be higher than those in other groups. But due to the small number of patients and a recruitment bias, no significant results were concluded from this study as to the rate of treatment-related deaths. There is a potential risk of severe liver dysfunction in the course of chemoradiation using cisplatin/carboplatin and 5-FU for patients with viral hepatitis.

Because of the limitation of this study design and the relatively small number of enrolled patients, it remains unclear whether low-dose cisplatin and continuous infusion of 5-FU is an alternative treatment to the conventional or modified RTOG 85-01 regimen using intermittent standard-dose cisplatin and 5-FU. There seemed to be non-negligible differences in our patients' backgrounds, in terms of performance status and prior chemotherapy, between the two groups. The CLD-FP group had more patients without symptoms such as dysphagia, which seemed to favor a better survival rate. The ISD-FP group had more patients after neoadjuvant chemotherapy. Because responders to chemotherapy were candidates for esophagectomy, the impact of neoadjuvant chemotherapy on survival rate was unclear in this study.

Although concurrent chemoradiotherapy using continuous low-dose cisplatin with 5-FU prevails in Japan, there seems to be little evidence to support its effectiveness. We began a phase-II randomized study in 2001, which will explain the characteristics of CLD-FP in more detail.

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CLINICAL INVESTIGATION **Breast**

FEASIBILITY OF BREAST-CONSERVING THERAPY FOR MACROSCOPICALLY MULTIPLE IPSILATERAL BREAST CANCER

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Purpose: Macroscopically multiple ipsilateral breast cancer (MMIBC) is generally considered a contraindication for breast-conserving therapy (BCT). The result of BCT for MMIBC is reported and the feasibility discussed.
Methods and Materials: Between July 1993 and February 1999, 34 patients with MMIBC underwent BCT at our clinic. The local control, disease-free survival, and cosmetic results in these patients were compared with those of patients with single disease.
Results: After wide excision, 21 (62%) of 34 patients with MMIBC had a close surgical margin and the rate was significantly greater than that of patients with a single lesion. However, the size of the boost irradiation field was not significantly increased. At a median follow-up of 98 months, no statistically significant difference was noted in local control, disease-free survival, or cosmetic result compared with patients with a single lesion.
Conclusion: Although patients with MMIBC frequently had close surgical margins after BCT, it can be a treatment option for these patients as long as the close surgical margin is accurately detected and treated with an appropriate radiation technique. © 2004 Elsevier Inc.

Macroscopically multiple ipsilateral breast cancer, Breast-conserving therapy, Surgical margin, Boost irradiation.

INTRODUCTION

Breast-conserving therapy (BCT) was developed to achieve survival equivalent to that after mastectomy, while providing a better quality of life, and this goal has been accomplished in many trials (1–4). However, macroscopically multiple ipsilateral breast cancer (MMIBC) is generally considered a contraindication for BCT (5–8). According to some reports, the local recurrence rate in MMIBC after BCT was significantly greater than that after BCT for a single tumor (9–11). However, other reports have demonstrated good local control for MMIBC treated by BCT, equal to that for single lesions, and concluded that BCT can be considered for MMIBC, as long as negative margins and negative extensive intraductal component was ensured (12, 13).

Since 1993, we have been offering BCT to patients with MMIBC as long as each of the tumors individually meets the criterion for breast-conserving surgery. In this study, we retrospectively compared local control, disease-free survival, and the cosmetic result between the patients with MMIBC and those with single lesions and assessed whether MMIBC can be a candidate for BCT.

METHODS AND MATERIALS

Between July 1993 and February 1999, 34 patients with MMIBC underwent BCT in the Kodama Breast Clinic and Kyoto University Hospital. This corresponded to 5.4% of all patients who underwent BCT (34 of 628) and 49.3% (34 of 69) of all patients with MMIBC in the same period. Their median age was 45 years (range, 29–81 years). The condition of the tumor, as well as patient preference, was considered in making the decision about the extent of surgery. These 34 patients wished to be treated with BCT, did not have absolute contraindications for radiotherapy (RT), such as pregnancy or previous RT to the affected breast, or relative contraindications, such as active collagen disease, and each of their tumors met the criteria for breast-conserving surgery (i.e., neither extensive microcalcification nor nipple invasion was present). The size of the individual

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Table 1. Background of patients with multiple tumors

Median follow-up (mo)	58 (38–105)
Median age (y)	48 (27–81)
Tumor number (*n*)	
2	30
3	4
Tumor location (*n*)	
Same quadrant	22
Next quadrant	10
Opposite quadrant	2
Diagnosis of multiple lesions (*n*)	
Preoperative	26
Intraoperative	8

tumors was not larger than those of the 35 patients with MMIBC treated by mastectomy (21.2 ± 7.0 mm in the BCT group vs. 24.8 ± 9.1 mm in the mastectomy group, $p = 0.07$) Microcalcification was observed in 12 (34%) of the 35 patients in the mastectomy group.

In the patients with MMIBC treated by BCT, tumor multiplicity was detected before surgery in 26 patients and during surgery in 8 patients. The patient characteristics, such as age, number of tumors, and tumor distribution, are shown in Table 1. The distance between each tumor was recorded in only 5 cases and therefore could not be presented as a reliable average or median value. Mammography and ultrasonography are presented for representative cases of multicentric/multifocal disease (Fig. 1).

Breast-conserving therapy at our institute basically consists of wide excision of the primary tumor followed by postoperative breast RT. All patients underwent wide excision and axillary dissection. Surgical clips were placed at the surgical margins during surgery for later use as a landmark to determine the boost irradiation field. RT was initiated within 8 weeks after surgery. A total of 50 Gy was delivered to the whole breast in 2-Gy fractions during a 5-week period by opposing tangential fields. Conserved breasts were treated with either ^{60}Co γ-rays or 6-MV X-rays, which was adequate for the breast size. CT simulation was used for treatment planning. For patients with close or positive resection margins, defined as cancer cells observed within 5 mm of the resection margin, boost RT was delivered. The dose of boost RT was fixed to 10 Gy regardless of the shortest distance from the resection margin. The boost RT covered the breast tissue within 3 cm from the clips with positive or close margins. Electron beam RT was usually used. The depth of the anterior chest wall was measured on CT simulation, and the energy was chosen so that the anterior chest wall received 80% of the prescribed dose. If the required energy exceeded 13 MeV, tangential photon

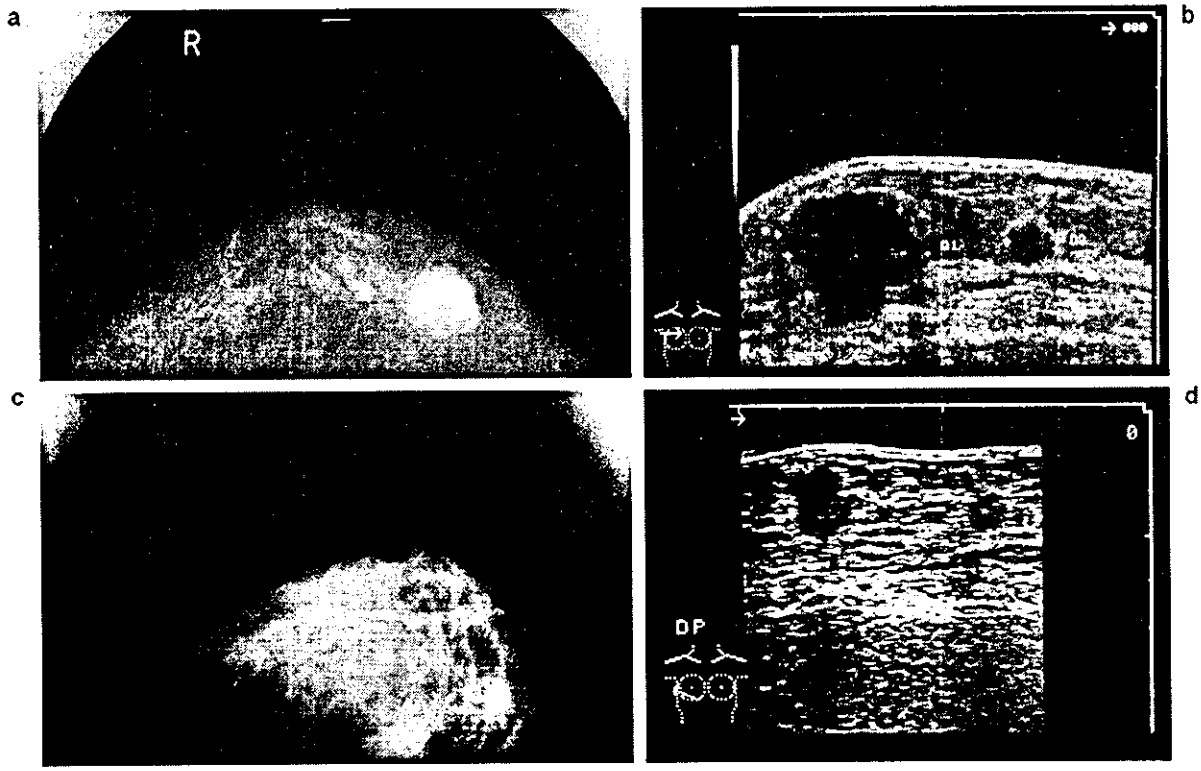

Fig. 1. (a) Mammogram and (b) ultrasound scan of 71-year-old patient who presented with two tumors in right upper-outer quadrant. Diameter of larger and smaller tumors and distance between the two was 20.8 mm, 7.5 mm, and 11.7 mm, respectively. Continuity was found on histologic examination. (c) Mammogram and (d) ultrasound scan of 50-year-old patient who presented with two tumors in right upper-inner quadrant. Diameter of larger and smaller tumors and distance between the two was 21 mm, 10 mm, and 37 mm, respectively. No continuity was found on histologic examination.

beams were used. The same policy and method were applied to both MMIBC and single lesions. The RT method was presented in detail in our previous publication (14, 15). Of 21 MMIBC patients with close or positive margins, 19 received electron boost with energy of 7–13 MeV. One patient with extensive margin involvement received 62 Gy to the whole breast RT using ^{60}Co γ-rays. The remaining 1 patient with close margins (5 mm) did not receive boost RT.

All patients underwent systemic chemotherapy in the form of tamoxifen and 5-fluorouracil for 2 years after surgery. This was initiated after surgery and before RT. No additional systemic therapy was given until breast cancer recurrence was confirmed.

Local control and disease-free survival was estimated by the Kaplan-Meier method. Statistical analysis was performed using the Stat-View program. The cosmetic result was evaluated using the global cosmetic score (8, 16). Patients were divided into two groups according to the cosmetic result: excellent to good and fair to poor. Cosmesis was also analyzed by the chi-square test. $p < 0.05$ was defined as statistically significant.

RESULTS

After wide excision, 21 (62%) of the 34 patients with MMIBC and 167 (28%) of the 594 patients with single lesions had a close surgical margin. The difference was statistically significant ($p < 0.001$). However, the boost irradiation field size was not significantly different between the two groups (71 ± 54.6 cm^2 for multiple disease and 64 ± 30.7 cm^2 for single disease, $p = 0.42$). Patient age, estrogen receptor status, pathologic T and N stage, and tumor pathologic findings were not significantly different between the two groups (Table 2). Of the 34 MMIBC patients and 564 single-lesion patients, 6 (18%) and 126 (21%), respectively, had extensive intraductal component-positive tumors. The difference was not statistically significant.

Pathologic examination demonstrated microscopic continuity between individual tumors in 20 patients (multifocal) and no continuity in 12 patients (multicentric). The information was insufficient for the remaining 2 patients (Table 3).

The median follow-up period for the patients with MMIBC was 58 months (range, 38–105 months). One patient (2.9%) with MMIBC had local recurrence 98 months after BCT. The patient was 41 years old at diagnosis, and the tumors were pathologically Stage IIB (pT2N1M0), extensive intraductal component negative, and margin positive. The recurrence occurred as a solitary nodule near one of the primary lesions. The patient was salvaged by simple mastectomy and was disease free at the latest follow-up visit. Two of the patients with MMIBC (6.5%) developed distant metastases. One patient had bone metastasis 27 months after BCT, the other patient had lung metastasis 39 months after BCT. Of the 564 patients with single lesions, 15 (2.4%) had local recurrence. Consequently, the 5-year local control rate was 100% for patients with MMIBC and 97% for patients with a single lesion. The difference in local control was not statistically significant between the two groups (Fig. 2). The 5-year disease-free survival rate was 93% for patients with MMIBC and 90% for patients with a single lesion, also not a statistically significant difference (Fig. 3).

Regarding the cosmetic results, we compared the ratio of patients with an excellent to good cosmetic score at 2 years of follow-up between the two groups. Twenty-six (79%) of 33 patients with MMIBC and 444 (81%) of 545 with single lesions had an excellent to good score. Again, the difference was not statistically significant ($p = 0.70$).

Table 2. Patient characteristics

Characteristic	MMIBC	Single lesions	p
Median age (y)	48 ± 12	50 ± 10	0.26
Pathologic T stage (n)			
pT1	14 (41)	322 (54)	
pT2	20 (59)	270 (45)	0.30
Pathologic N stage (n) (UICC)			
N0	21 (62)	434 (73)	
N1	13 (38)	144 (24)	0.14
N2	0	16 (2)	
Histologic type (n)			
Invasive ductal carcinoma	29 (85)	511 (86)	
DCIS	0	22 (4)	0.60
Invasive lobular carcinoma	3 (9)	27 (5)	
Other	2 (6)	34 (6)	
ER positive (n)	22/34 (65)	306/594 (52)	0.52
EIC positive (n)	5/34 (15)	126/594 (21)	0.86
Close/positive margin (mm)	21/34 (62)	160/594 (27)	<0.01
≥2 to ≤5	8/34 (24)	50/594 (8)	<0.01
>0 to ≤2	7/34 (21)	53/594 (9)	0.02
0	6/34 (18)	57/594 (10)	0.13
Mean boost field size (cm^2)	71 ± 55	65 ± 31	0.46

Abbreviations: UICC = International Union Against Cancer; DCIS = ductal carcinoma in situ; ER = estrogen receptor; EIC = extensive intraductal component, MMIBC = Macroscopically multiple ipsilateral breast cancer; Numbers in parentheses are percentages.

DISCUSSION

Macroscopically multiple ipsilateral breast cancer includes both multicentric disease and multifocal disease.

Table 3. Location of multiple tumors and continuity on histologic examination

Location	Continuity		
	Yes	No	Unknown
Same quadrant (n = 22)	14	8	0
Next quadrant (n = 10)	6	3	1
Opposite quadrant (n = 2)	0	1	1

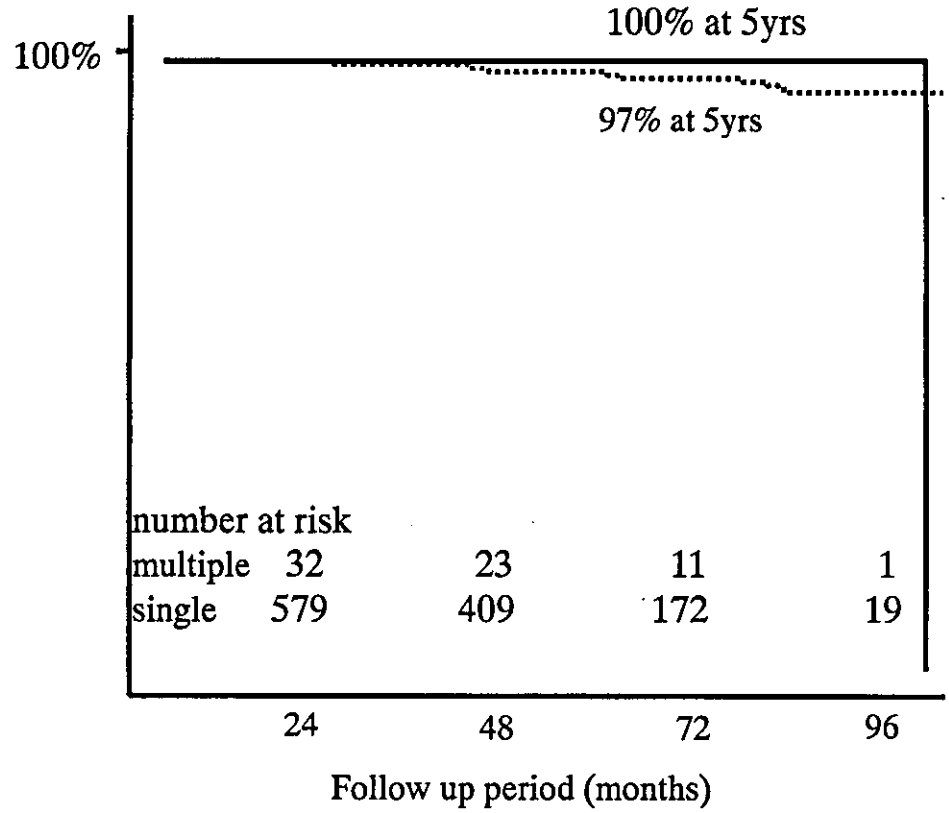

Fig. 2. Local control for macroscopically multiple ipsilateral breast cancer (solid line) and single disease (dashed line). No statistically significant differences were found ($p = 0.8$).

Multifocality and multicentricity were originally pathologic terms and should be discussed from a pathologic point of view. In the currently accepted terminology, multifocality represents the presence of multiple foci of the same tumor, and multicentricity suggests different primary tumors in the same breast (17). Although some researchers have tried to identify such continuity preoperatively using helical CT and/or MRI, these diagnostic imaging modalities are not sufficiently reliable. From a practical point of view, it is generally considered that multifocal tumors are those within the same quadrant and multicentric tumors are those in different quadrants. However, our results indicate that this approximation is not always accurate, because 8 (36%) of 22 tumors that were located in the same quadrant had no apparent continuity on histologic examination.

According to the guidelines for BCT, such as the National Institutes of Health consensus statement, MMIBC is excluded from the indications for BCT (7). A high incidence of local recurrence in early series and a deterioration in the cosmetic result caused by removal of a large amount of the breast tissue were the main reasons for this recommendation. A study by Fowble *et al.* (18), in which the pathologic review of the mastectomy specimens revealed extensive residual disease in three or four quadrants of the breast after excisional biopsy in 50% of the patients with MMIBC, supports this recommendation further.

Some previous reports regarding BCT for MMIBC have been published (Table 4). Kurtz *et al.* (9), Leopold *et al.* (10), and Wilson *et al.* (11) reported a high local recurrence rate for patients with MMIBC who underwent BCT (23–40%). In their studies, the surgical margin status was insufficient or not fully examined (9–11). Kurtz *et al.* (9) reported that the local recurrence rate in 22 patients with clearly adequate margins was low (1 of 22 or 4.5%) and in 39 patients with unknown or positive margins it was very high (14 of 39 or 36%). Hartsell *et al.* (12) reported a good local control rate (local recurrence rate 3.7%), and in their study, the close (<1 mm) or positive margin rate was only 22% (6 of 27). In a recent study by Cho *et al.* (13), BCT was offered to 15 patients in whom microscopically negative margins were obtained, and none of them had local recurrence at a median follow-up of 77 months. A positive surgical margin is one of the major risk factors for local recurrence (19–21). However, a large surgical margin will reduce the residual breast volume and deteriorate cosmesis, one of the most important goals of BCT (22).

The effectiveness of boost RT to decrease local recurrence has been established in a randomized trial (23). To increase the accuracy of postoperative RT, including boost RT, we placed different-size radiopaque clips at the surgical margin together with radial sectioning of the pathologic specimen. This facilitated identification of a close or positive margin on CT simulation and was useful for determining an adequate boost field (14).

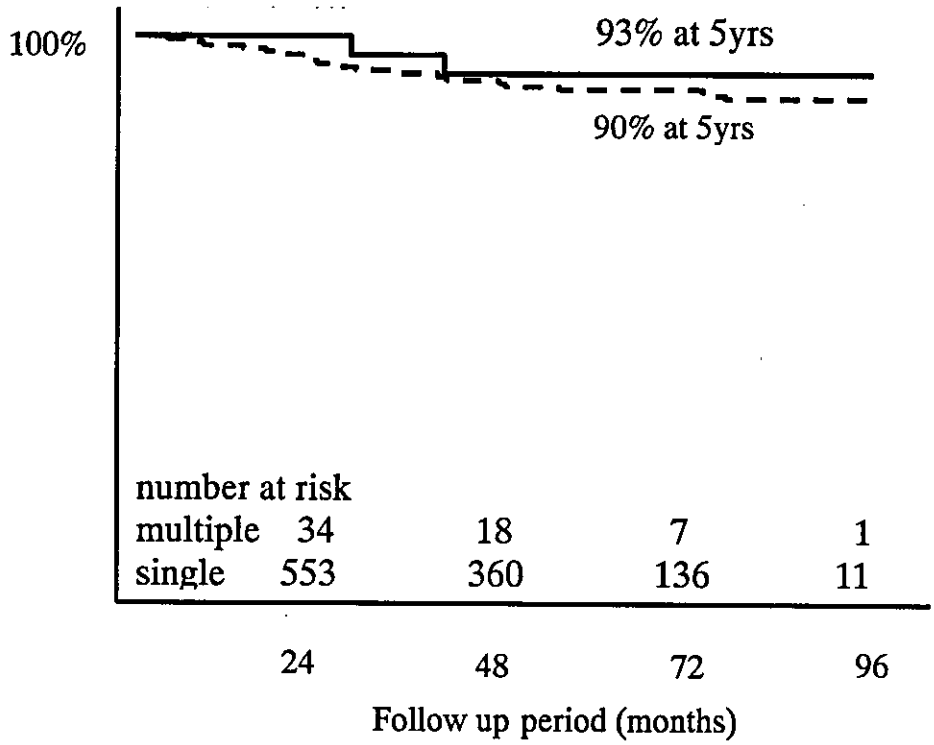

Fig. 3. Disease-free survival between macroscopically multiple ipsilateral breast cancer (solid line) and single disease (dashed line). No statistically significant differences were found ($p = 0.63$).

In our study, 62% of the patients with MMIBC had close surgical margins, significantly greater than that in the patients with single disease, but the local control rate was not significantly different. We believe that meticulous treatment planning using surgical clips and CT simulation ameliorated the local control rate. Moreover, this also facilitated control of the size of the boost field for multiple lesions by avoiding inclusion of "safe" parts of the resection margin. Thus, we believe our boost irradiation technique contributed to the favorable cosmetic result; a large boost dose and volume may deteriorate the cosmetic result (24). The excellent to good cosmetic score rate did not differ significantly between those with multiple and single lesions.

When interpreting these observations, possible ethnic differences between Japan and Western countries, in both the natural history and the patterns of care of breast cancer, should be taken into account. As several researchers have pointed out, Japanese women with breast cancer seem to have a substantially more favorable prognosis than patients in Western countries (25, 26). In our series, the 5-year disease-free survival rate for patients without pathologically positive axillary lymph nodes, with one to three positive nodes, four to nine nodes, and more than nine positive nodes was 95.2%, 94.5%, 76.5%, and 38.9%, respectively (27). In such situations, intensive chemotherapy with significant toxicity is difficult to jus-

Table 4. Results of other trials

	Leopold (1989)	Kurtz (1990)	Wilson (1993)	Hartsell (1994)	Cho (2002)	Our study
Local recurrence (%)	4/10 (40)	15/61 (25)	3/13 (23)	1/27 (3.7)	0/15	1/34 (2.9)
Median follow-up (mo)	64	71	71	53	77	98
Radiotherapy (6y)	45–52 ± boost	50 + boost	50 + boost	45–54 ± boost	45–50 + boost	50 ± boost
Close/positive margin	Not fully examined	Positive 12/61 Unknown 34/61	Not fully examined	6/27 (22)	0/15	21/34 (62)
Chemotherapy	Not done	For some cases	CMF for 6 patients	AC or CMF TAM	AC, CMF or other	TAM, 5-FU

Abbreviations: CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; AC = doxorubicin and cyclophosphamide; TAM = tamoxifen; 5-Fu = 5-fluorouracil.