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SPECIAL FEATURE: ORIGINAL ARTICLE

New trends in radiation therapy as a component of breast conserving therapy

Feasibility of accelerated partial breast irradiation using three-dimensional conformal radiation therapy for Japanese women: a theoretical plan using six patients' CT data

Yasuhiro Kosaka · Michihide Mitsumori · Chikako Yamauchi · Yuichiro Narita · Masahiro Hiraoka

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Abstract
Background Several methods have been reported for accelerated partial breast irradiation (APBI), but in Japan, there are few facilities where brachytherapy or intra-operative radiotherapy is available. Japanese women have smaller physiques than American women in general. Thus, we developed external beam plans for APBI using computed tomography (CT) data of Japanese patients, to investigate whether APBI using three-dimensional conformal radiation therapy is safely applicable for Japanese women, while verifying the dose distributions.
Methods We used CT data from six Japanese patients with early breast cancer, which were obtained in routine clinical practice during whole breast irradiation (WBI) after wide excision, and made 32 APBI plans according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39 and the Radiation Therapy Oncology Group (RTOG) 0413 protocol, which compared APBI with WBI. We then investigated the compliance to the dose constraints of the protocol.
Results None of 16 plans for the medial regions met the dose constraints regardless of laterality of the breast. The major reason was overdosage to the contralateral breast. Thirteen of 16 plans (81%) for the lateral regions met the dose constraints. The remaining three plans (19%) did not meet the dose limitation of the uninvolved normal breast, suggesting that a large ratio of the target to the breast was problematic.
Conclusions In Japanese women, patients with a laterally located small tumor can be candidates for APBI using three-dimensional conformal radiation therapy.

Keywords Breast cancer · Breast-conserving therapy · Accelerated partial breast irradiation (APBI) · Three-dimensional conformal radiation therapy

Abbreviations

APBI	Accelerated partial breast irradiation
WBI	Whole breast irradiation
NSABP	National Surgical Adjuvant Breast and Bowel Project
RTOG	Radiation Therapy Oncology Group
CT	Computed tomography
CTV	Clinical target volume
PTV	Planning target volume
DVH	Dose–volume histogram
IDL	Isodose line

Introduction

Breast-conserving therapy including breast-conserving surgery and subsequent radiation therapy is now the standard treatment for early-stage breast cancer. Moreover, many patients for whom the initial surgery would be mastectomy can undergo breast-conserving therapy following neoadjuvant chemotherapy [1, 2].

However, some patients choose to avoid whole breast irradiation (WBI) because of the long-term treatment of

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5–7 weeks, and some physicians either delay or omit WBI to start chemotherapy early. There are also other problems with late adverse effects of WBI including symptomatic radiation pneumonitis [3], ipsilateral arm edema [4] and breast edema or fibrosis with poor cosmesis [5].

Prospective randomized trials have shown that the majority of recurrences in the ipsilateral breasts of patients who did not receive WBI occurred in the vicinity of the tumor bed [6, 7]. It has also been shown that the recurrence rate in remote regions of the ipsilateral breast after breast-conserving therapy is similar to the incidence rate of contralateral breast cancer [6]. Consequently, clinical trials of accelerated partial breast irradiation (APBI), which is a method of irradiating the target volume around the tumor bed in a short period, were begun to investigate whether APBI can be an alternative to WBI. Several different techniques have been developed for APBI, including multicatheter interstitial brachytherapy [8, 9], the MammoSite™ balloon apparatus [10, 11], three-dimensional conformal external beam irradiation [12, 13], and intra-operative radiation therapy using low energy photons [14] or electrons [15]. The target volume for APBI is much smaller than that for WBI, so it is possible to increase the fraction dose to the target volume and shorten the treatment time to less than 1 week while decreasing the dose to the surrounding normal tissues regardless of the technique.

Both adverse events and local control rates have been reported to be satisfactory in early trials [16, 17]; therefore, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG) began a randomized phase III trial comparing APBI to conventional WBI for women with Stage 0, I, or II breast cancer (NSABP B-39/RTOG 0413) [18].

In Japan, the demand for APBI is expected to increase. Nose et al. [19] presented the first report on APBI with high-dose-rate interstitial brachytherapy applied to Japanese women in 2006. However, there are few facilities where brachytherapy or intra-operative radiotherapy is available. Thus, we developed external beam APBI plans using computed tomography (CT) data from Japanese patients, obtained during routine WBI clinical practice at Kyoto University Hospital, and investigated whether APBI using three-dimensional conformal radiation therapy is safely applicable for Japanese women, while verifying that the dose distributions meet the dose constraints of the NSABP B-39/RTOG 0413 protocol.

Materials and methods

We used CT data from six Japanese women with early breast cancer, which were obtained for WBI after breast-conserving surgery at Kyoto University Hospital, and made three-dimensional conformal external beam plans. For every patient, we made virtual plans for the other three quadrants as well as for the true primary quadrant in the following way. Additionally, we made four virtual plans for the contralateral breast for two patients. So we made 32 plans in total (16 plans for each side).

We regarded the excision cavity as the target volume according to the NSABP B-39/RTOG 0413 protocol [18]. If the excision cavity cannot be identified on computed tomography, we assumed the excision cavity to include all clips, which were placed to mark the resection margin during the breast-conserving surgery. For contouring in quadrants other than the original, we assumed a virtual excision cavity of approximately the same size near the center of the quadrant. We then added the prescribed margin to the aforesaid excision cavity to define the clinical target volume (CTV) and planning target volume (PTV), and to define the structure "PTV_EVAL", which is only used for dosimetric analysis. According to the protocol, the details of the contouring target volumes are as follows.

CTV

CTV is defined by uniformly expanding the excision cavity volume by 15 mm, but limited to 5 mm from the skin surface and by the posterior breast tissue extent (pectoralis muscles are not to be included).

PTV

PTV is defined by uniformly expanding the CTV by 10 mm.

PTV_EVAL

PTV_EVAL is defined by limiting the PTV to 5 mm from the skin surface and by the posterior breast tissue extent.

For planning, we also conformed to the NSABP B-39/RTOG 0413 protocol. In simplest terms, the beam arrangements included non-coplanar 3-, 4-, and 5-field beams using 6-MV photons. The 4-field technique consists of left anterior superior-to-inferior oblique, left anterior inferior-to-superior oblique, right anterior inferior-to-superior oblique, and right posterior superior-to-inferior oblique for a right breast lesion (Fig. 1). We did not use the 3-, or 5-field technique for simplicity and to compare the plans. We did not use intensity-modulated radiotherapy because not all facilities can use this. For complete information on contouring and beam arrangement, refer to the NSABP B-39/RTOG 0413 protocol.

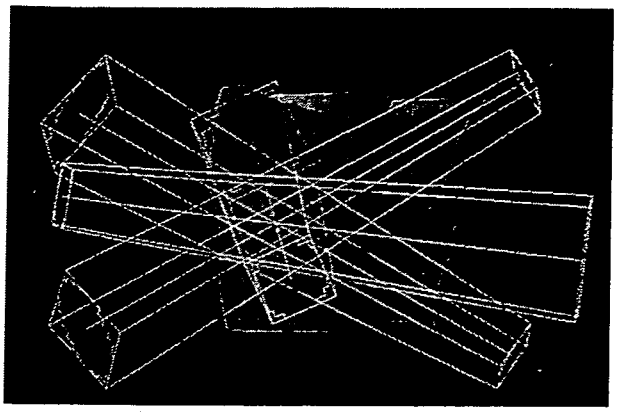

Fig. 1 Four-field beam arrangement of three-dimensional conformal beam radiotherapy

The dose was prescribed to the isocenter of the treatment fields and a total of 38.5 Gy was assumed to be given in 10 fractions in 5 days. In all plans we calculated a dose–volume histogram (DVH) and investigated the compliance with dose constraints described in the NSABP B-39/RTOG 0413 protocol. Dose constraints are listed in Table 1.

We did not evaluate the DVH of the thyroid because some computed tomography did not include the thyroid structure in the imaging area.

After we investigated the compliance with dose constraints, we determined why the plans did not comply with dose constraints.

Results

The mean and median sizes of the excision cavity, including the virtual cavity, were 19 and 16 cc, respectively (range 6–72 cc) (Table 2). The mean and median sizes of the CTV were 85 and 71 cc, respectively (range 43–232 cc). The mean and median sizes of the PTV_EVAL were 139 and 113 cc, respectively (range 77–370 cc). The mean and median sizes of the uninvolved normal breast were 486 and 426 cc, respectively (range 326–1087 cc). The mean and median ratios of the PTV_EVAL to the uninvolved normal breast were both 0.30 (range 0.16–0.50).

The mean and median coverage of the CTV by the 100% isodose line (IDL) were 40 and 43%, respectively (Table 3). The mean and median coverage of the CTV by 95% IDL were both 91%. The mean and median coverage of the PTV_EVAL by 100% IDL were 37 and 39%, respectively. The mean and median coverage of the PTV_EVAL by 95% IDL were 86 and 85%, respectively.

Thirteen of 32 plans (41%) met all dose constraints described in the NSABP B-39/RTOG 0413 protocol, whereas the other 19 plans (59%) did not. Categorized by medial and lateral quadrants, the details of the dose constraints of the unsuccessful plans are shown in Table 4.

None of the 16 plans for the medial quadrants met the dose constraints regardless of the laterality of the breast. The major reason was overdosage to the contralateral breast (14 plans). Overdosage to the ipsilateral lung was seen in four plans in right-sided lesions and in five plans in left-sided lesions. Overdosage to the heart was seen in four plans in right-sided lesions and in six plans in left-sided lesions, and overdosage to the uninvolved normal breast was seen in four plans only in left-sided lesions.

For the lateral quadrants, 13 of 16 plans (81%) met the dose constraints. The remaining three plans (19%) did not meet the dose constraint of the uninvolved normal breast. No overdosage to the contralateral breast, ipsilateral lung or heart was seen.

An example of a plan which met the dose constraints is shown in Fig. 2a. The WBI plan for the same breast is also shown for comparison (Fig. 2b). Additionally, DVHs of the ipsilateral lung and the heart in both plans are shown in Fig. 2c, d. Note that the fraction dose and the total dose are different between the two plans, however, we can decrease the ipsilateral lung dose and the heart dose in the APBI plan.

Discussion

For WBI there are problems regarding the time needed for treatment, sequencing with chemotherapy and adverse

Table 1 Dose constraints described in NSABP B-39/RTOG 0413 protocol

Uninvolved normal breast	Ideally, <60% of the whole breast volume should receive ≥50% of the prescribed dose and <35% of the whole breast volume should receive the prescribed dose
Contralateral breast	The contralateral breast volume should receive <3% of the prescribed dose to any point
Ipsilateral lung	≤15% of the lung can receive 30% of the prescribed dose
Heart (right-sided lesions)	<5% of the heart should receive 5% of the prescribed dose
Heart (left-sided lesions)	The volume of the heart receiving 5% of the prescribed dose should be less than 40%
Thyroid	Maximum point dose of 3% of the prescribed dose

effects. APBI is expected to be an alternative to solve these problems.

Among APBI techniques three-dimensional conformal external beam irradiation is a non-invasive technique and can be done with sufficient pathologic information including the margin of resection, although it is affected by setup errors and respiratory movement and the dose to the surrounding normal tissues is higher than in other methods.

In the US many early trials have been investigated. It has been reported that acute adverse effects are tolerable and the ipsilateral breast control rate and cosmetic outcomes are satisfactory in all methods [16, 17].

As in the US, in Japan, the demand for APBI will likely increase in the near future, but there will be many problems other than efficacy when APBI is introduced into Japan. First, there are very few facilities where brachytherapy or intra-operative radiotherapy is possible compared to the number of patients who undergo breast-conserving therapy. External beam irradiation, however, can be done in almost all facilities where radiation therapy is available. Second, there is difference of physique, including the shape and size of breasts between Japanese and American women. Generally speaking, Japanese women have smaller breasts than American women; thus the ratio of breast cancer to breast is different when the size of the breast cancer is the same. So it is uncertain whether we can decrease the dose to the surrounding normal breast.

As a result of our feasibility study of APBI for Japanese women, the median size of the excision cavity was 16 cc, which was almost equivalent to the results of American reports (12–24 cc) [12, 13, 20]. The median size of the PTV_EVAL was 113 cc, which was smaller than the results of American reports (155–240 cc) as was the median size of the CTV (71 vs 112 cc), although these American reports included cases of smaller CTV or PTV margin compared to the NSABP B-39/RTOG 0413 protocol. The smaller size of the PTV_EVAL in our result was due to the small breasts of Japanese women, which excluded many volumes of PTV_EVAL outside the ipsilateral breast and the first 5 mm of tissue under the skin. The median ratio of the PTV_EVAL to the uninvolved normal breast was 0.30. This was larger than in American reports (0.17–0.23). These findings suggest that the

Table 2 Sizes: excision cavity, CTV, PTV_EVAL, and uninvolved normal breast

Structure	Mean	Median	Range
Excision cavity	19 cc	16 cc	6–72 cc
CTV	85 cc	71 cc	43–232 cc
PTV_EVAL	139 cc	113 cc	77–370 cc
Uninvolved normal breast	486 cc	426 cc	326–1,087 cc
PTV_EVAL/uninvolved normal breast	0.30	0.30	0.16–0.50

CTV clinical target volume, *PTV* planning target volume
PTV_EVAL is defined for dosimetric analysis

Table 3 Dosimetric findings: CTV, PTV_EVAL, and uninvolved normal breast

Dosimetric characteristics	Mean (%)	Median (%)	Range (%)
Maximum dose (% of prescribed dose)	106	105	101–114
CTV coverage			
100% IDL	40	43	1–72
95% IDL	91	91	80–100
PTV_EVAL coverage			
100% IDL	37	39	1–70
95% IDL	86	85	70–99
Uninvolved normal breast			
100% IDL	13	12	2–31
50% IDL	57	56	42–79

CTV clinical target volume, *PTV* planning target volume, *IDL* isodose line
PTV_EVAL is defined for dosimetric analysis

Table 4 Compliance with dose constraints

Quadrant	Side	Number of plans	Number of successful plans	Reasons for unsuccessful plans	
				Overdosage to	
Medial	Right	8	0	Contralateral breast	7 plans
				Ipsilateral lung	4
				Heart	4
	Left	8	0	Contralateral breast	7
				Uninvolved normal breast	4
				Ipsilateral lung	5
				Heart	6
Lateral	Right	8	7	Uninvolved normal breast	1
	Left	8	6	Uninvolved normal breast	2

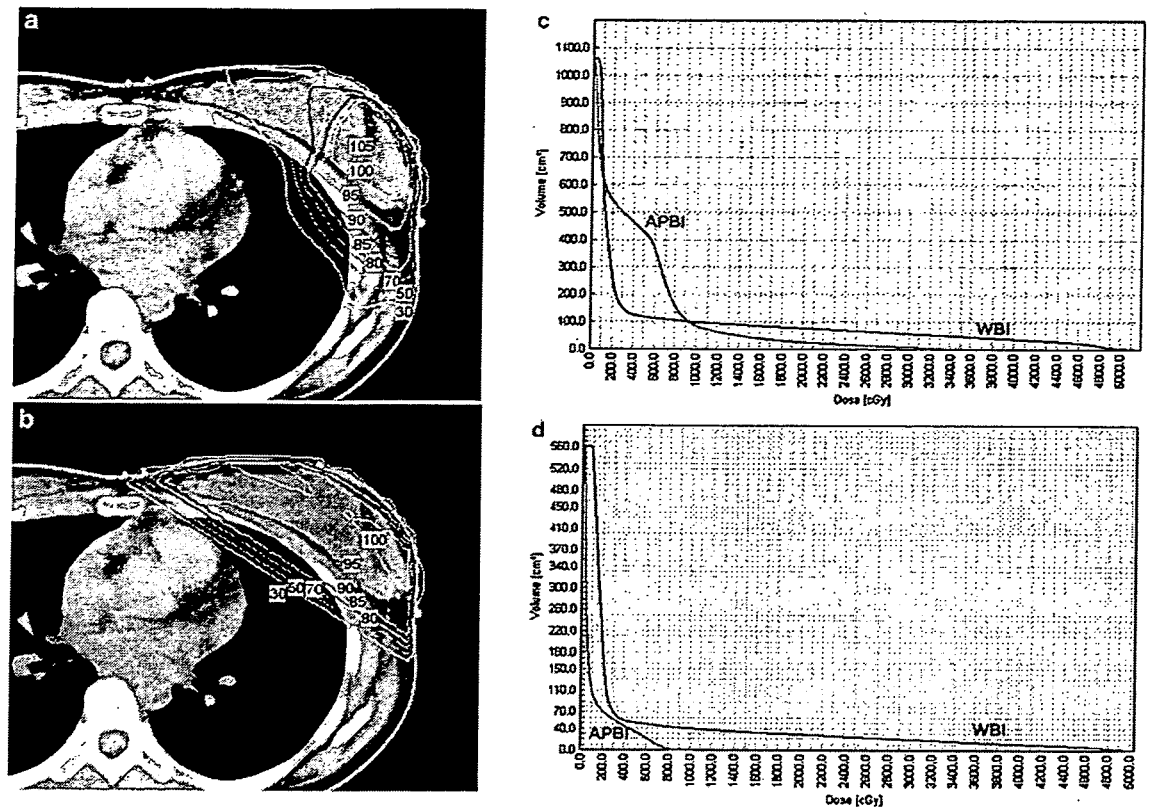

Fig. 2 Comparison of dose distribution between APBI **a** and WBI **b**. *Lines* are isodose lines and *digits* are percentage of the prescribed dose (APBI: 38.5 Gy, WBI: 50 Gy). **c** is a dose-volume histogram (DVH) of the ipsilateral lung in both plans, and **d** is the DVH of the heart. After considering the difference of the prescribed dose between two plans, the irradiation dose of the surrounding normal tissue is lower in the APBI plan, as is the irradiated volume

Japanese women in our study had smaller breasts than American women (the breast sizes of the American women were not clear).

The coverage of the PTV_EVAL by 95% IDL was lower than those in American reports (85 vs 100%) [13]. This was due to the larger ratio of PTV_EVAL to the uninvolved normal breast.

For the medial quadrants, no plans complying with dose constraints can be made. In the beam arrangement to the medial quadrants, the medial beam usually crossed the center line, which resulted in overdosage to the contralateral breast, and if the medial beam is steeper to avoid overdosage of the contralateral breast, it often causes overdosage to the ipsilateral lung or the heart. Consequently, plans for the medial quadrants are difficult regardless of the laterality of the breast if we comply strictly with the dose constraints of the protocol.

For the lateral quadrants, 13 of 16 plans (81%) met the dose constraints, but the remaining three plans (19%) did not meet the dose limitation of the uninvolved normal breast. It appears that the dosage of the uninvolved normal breast correlates with the ratio of the target to the uninvolved normal breast (Fig. 3); thus, it is difficult for patients with large primary tumor, a small build or small breasts (the ratio of the PTV_EVAL to the uninvolved normal breast is >0.3) to meet the dose constraints. Although the breast cancer had to be less than 3 cm to be eligible for the NSABP B-39/RTOG 0413 protocol, we need to have more strict criteria for the size of the tumor in women with a small build.

Recently, a new beam arrangement using a combination of photons and electrons was proposed by Massachusetts General Hospital [20]. This beam arrangement seems to be more suited to Japanese women than that of the NSABP B-39/RTOG 0413 protocol. With this technique, more cases are expected to comply with the dose constraints, and we will investigate whether this technique is feasible for Japanese women. Furthermore, we need more consideration of CTV, which is a region regarded to be at risk for microscopic tumor extension. In the NSABP B-39/RTOG 0413 protocol, the CTV margin around the excision cavity is 15 mm, but Vicini et al. [21] showed that a margin of 10 mm is adequate in >90% of patients treated with PBI. Additionally, taking into account differences in the extent

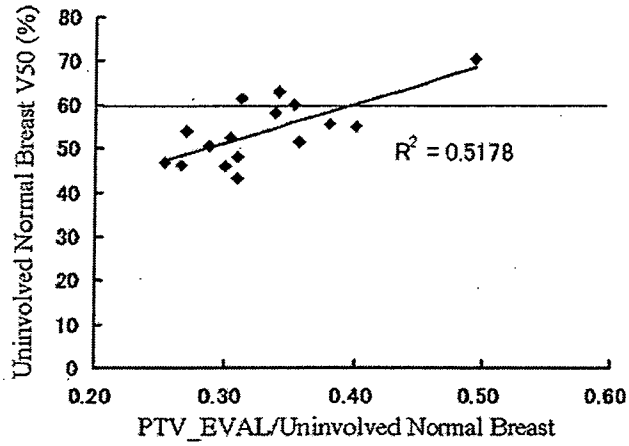

Fig. 3 Correlation between the dosage of the uninvolved normal breast and the ratio of PTV_EVAL to the uninvolved normal breast in APBI plans for lateral regions. Dose constraint of the uninvolved normal breast is lined (<60% of the whole breast volume should receive ≥50% of the prescribed dose). The higher ratio probably leads to non-compliance with the dose constraint. In other words, patients with a laterally located small tumor can be good candidates for APBI

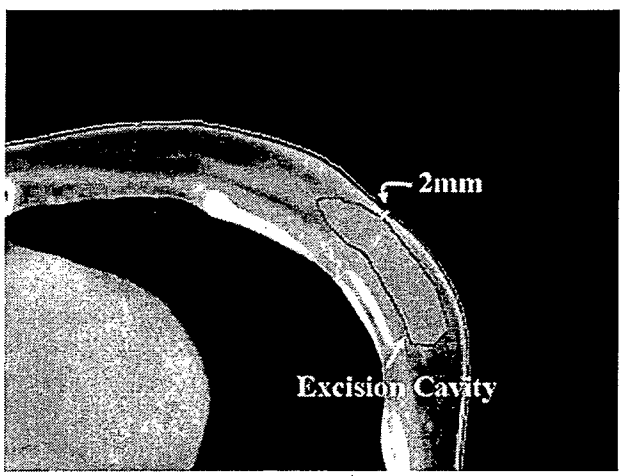

Fig. 4 Some patients have a mammary gland or excision cavity in the first 5 mm of tissue under the skin. For these patients we may need to expand CTV to include the mammary gland or the excision cavity

of surgery between the US and Japan, we may be able to set the CTV margin smaller than that of the NSABP B-39/ RTOG 0413 protocol.

There is another problem with CTV. The first 5 mm of tissue under the skin is excluded from CTV in the protocol, probably because a hypothesis exists that there is no mammary gland in this region. For some Japanese patients this CTV is insufficient because it appears on CT that they have a mammary gland or excision cavity in this region (Fig. 4). We may need to expand CTV for them, but this increases the dose to the skin so adverse effects may be worse. We must define CTV for the treatment of Japanese women instead of using the CTV in the NSABP B-39/ RTOG 0413 protocol.

In this context, there is the problem of "the excision cavity". In most cases, the excision cavity cannot be identified because many Japanese surgeons close the excisional cavity to maintain good cosmesis. This causes difficulty with the contouring target volume. Therefore, when we perform APBI, we must ask surgeons to show the stumps clearly, for example, clipping the excision margin or changing their surgical techniques if necessary.

In conclusion, in Japanese women, patients with a laterally located small tumor can be candidates for APBI using three-dimensional conformal radiation therapy at this time, although patients with a medially located tumor can not. We must consider the dose constraints or the CTV margin, and must try other beam arrangements such as a combination of photons and electrons so that more patients can be candidates for APBI with external beam irradiation.

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REVIEW ARTICLE

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Current status of stereotactic body radiotherapy for lung cancer

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Abstract Stereotactic radiotherapy (SRT) for extracranial tumors has been recently performed to treat lung and liver cancers, and has subsequently been named stereotactic body radiotherapy (SBRT). The advantages of hypofractionated radiotherapy for treating lung tumors are a shortened treatment course that requires fewer trips to the clinic than a conventional program, and the adoption of a smaller irradiated volume allowed by greater setup precision. This treatment is possible because the lung and liver are considered parallel organs at risk. The preliminary clinical results, mostly reported on lung cancer, have been very promising, including a local control rate of more than 90%, and a relatively low complication rate. The final results of a few clinical trials are awaited. SBRT may be useful for the treatment of stage I lung tumors.

Key words Stereotactic body radiotherapy · Conformal radiotherapy · Lung cancer · Stereotactic body frame · Stereotactic radiotherapy · Extracranial tumors

Introduction

Stereotactic radiotherapy (SRT) for extracranial tumors has been recently performed to treat extracranial tumors, mainly lung and liver cancers, and has subsequently been named stereotactic body radiotherapy (SBRT) or extracranial stereotactic radiotherapy (ESRT). The advantages of hypofractionated radiotherapy for treating lung tumors are a shortened treatment course that requires fewer trips to the clinic than a conventional program, and the adoption of a smaller irradiated volume allowed by greater setup precision. This treatment is possible because the lung and liver are considered parallel organs at risk (OAR). The disadvantages of SBRT are the uncertain effects of altered fractionation and the theoretical risk of worsening the ratio of normal tissue to tumor tissue through the use of a high dose per fraction. In this article, the technical procedures and clinical results of SBRT, especially in lung cancer, are reviewed.

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Biology

The biological background of SBRT is important. There is no past clinical evidence for this kind of hypofractionated regimen to extracranial tumors; therefore, most clinical regimens should be based on biological estimations.

The two great issues in hypofractionated regimens are dose response for tumor control and toxicity to normal tissue. Can the conventional linear-quadratic (LQ) model be applied in the SBRT dose range? Can repopulation be avoided in the SBRT regimen? How great is the effect of hypoxia in SBRT?

Fowler et al.[1] answered these questions, which are mostly applicable to SBRT; however, they recommended that SBRT be performed three to five fractionated schedule rather than using single SRS. These biological speculations should be reconfirmed in the clinical setting.

Body fixation

The first body fixation device was introduced in clinical practice as a stereotactic body frame by Bromgren et al.[2] and Lax et al.[3] Patients were fixed in the stereotactic frame, using a vacuum pillow. The concept of this frame is to utilize the cranial SRT coordinates for extracranial SBRT. The difference between cranial SRT and extracranial SBRT is the accuracy of the setup. The Japanese national guidelines for SRT state that the allowance of setup error is 2 mm for cranial tumors and 5 mm for extracranial tumors.

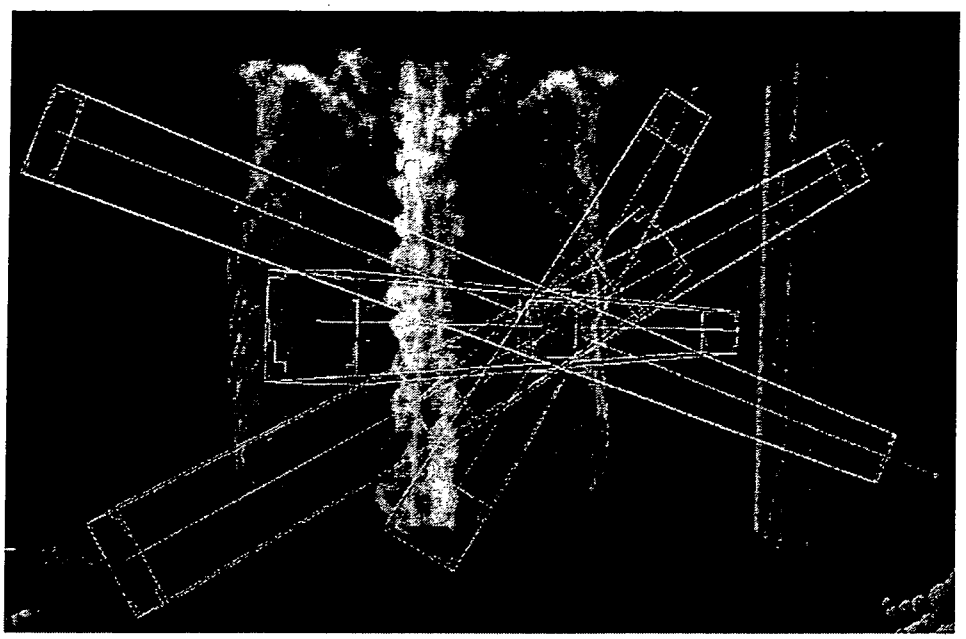

Fig. 1. Stereotactic body radiotherapy (SBRT) for lung cancer. In this image for treatment planning for left lung cancer, five beams are focused on the target

Some other fixing apparatuses using a vacuum sheet or thermoplastic shell are clinically available.

Respiratory monitoring

In the clinical practice of SBRT, the regulation of respiratory movement is essential. There are three ways to regulate the respiration of patients: respiratory holding, respiratory regulation, and respiratory gating.

The respiratory holding method is to ask patients to hold their breath for about 10s during radiation; therefore, radiation is performed intermittently four to ten times. Theoretically, this method can reduce the internal target volume (ITV). Holding can be done either voluntarily by patients or by using devices such as an active breathing control (ABC).

Respiratory regulation can be performed by exerting pressure on the abdomen using a plate like our diaphragm control or an abdominal belt.[4]

The respiratory gating method was originally developed in Japan. The gating sensors are a respiratory flow monitor, abdominal wall fiducials, and implanted gold fiducials.

Target definition

In computed tomography (CT) images taken under free-breathing long-scan (4–8s) conditions, the target outlines of the ITV are delineated. These CT images include the respiratory movement of the target. ITVs and Clinical Target Volume (CTV)s were not edited for anatomy.

If patients are irradiated with gated radiotherapy, the target outlines of CTV could be delineated under gating conditions.

The setup margins between the ITV and the planning target volume (PTV) must be determined at each institution. Our margins are 5mm for the anteroposterior (AP), 5mm for the lateral, and 8–10mm for the craniocaudal directions. Overlapping the outlines under inhale and exhale conditions is an alternative choice.

Treatment planning

There are two different concepts of Radiotherapy Treatment Planning (RTP) for SBRT. One concept, mainly used in Japan, is to maintain dose homogeneity within the target. In this case, the dose is usually prescribed at the isocenter. The other concept, mainly used in the United States, is not to maintain dose homogeneity. In this case, the dose is prescribed at the PTV margin. Our method adheres to the former concept, with selection of the optimal direction of noncoplanar beams, with the goal of the RTP being 6–10 portals for noncoplanar static beams, as shown in Fig. 1. The beam energy used was 6 MV and the isocenter was single for all beams. Four single treatments with 12 Gy of radiation were prescribed at the isocenter. Using an LQ model,[5] the Biological Effective Dose (BED) was here defined to be nd (1 + d / alpha-beta) Gy, where n is the fractionation number, d is the daily dose, and the alpha-beta ratio for tumors was assumed to be 10. The value was 105.6 Gy-BED for 48 Gy in four fractions. The most important issue for RTP in SBRT is to maintain the dose constraints of OAR to avoid serious complications. The dose constraints of the OAR, including the spinal cord, pulmonary artery, bronchus, and heart, under the Japan Clinical Oncology Group (JCOG) 0403 protocol, are shown in Table 1.

Verification before radiation

In the clinical practice of SBRT for lung cancer, verification before each treatment is mandatory. In our institute, before each treatment, AP and lateral portal films are taken for verification. The position of each patient is verified by three experienced oncologists and technologists for each treatment. When the setup errors are larger than 2 mm between the X-ray simulation film and portal film in any direction, the patient is repositioned and portal films are taken and verified again. CT on rails and FOCAL units are also useful materials for verification before each treatment.

Clinical indications for SBRT

Currently, the eligibility criteria for patients with primary lung cancer are: (1) tumor size less than 5 cm in diameter without nodal and distant metastases (T14N0M0); (2) surgery was contraindicated or refused; (3) the patient could remain stable in the body frame for longer than 30 min (WHO performance status <=2); (4) no active interstitial pneumonitis; and (5) written informed consent was obtained. The criteria for patients with secondary lung cancer are: (1) tumor size less than 5 cm in diameter; (2) tumor number three or less; (3) no other metastases, and (4) local tumor is controlled.

Tumor size is an important factor when dose homogeneity within the target should be maintained. The dose constraints of mediastinal organs should be maintained; therefore, a central tumor could be less suitable for SBRT indications than a peripheral tumor.

Table 1. Dose constraints of various organs at risk, according to the JCOG 0403 protocol

Organ	Dose	Volume	Dose	Volume
Lung	40 Gy	<=100 cc	MLD	<=18 cc
	V15	<=25%	V20	<=20%
Spinal cord	25 Gy	Max		
Esophagus	40 Gy	<=1 cc	35 Gy	<=10 cc
Pulmonary artery	40 Gy	<=1 cc	35 Gy	<=10 cc
Stomach	36 Gy	<=10 cc	30 Gy	<=100 cc
Intestine	36 Gy	<=10 cc	30 Gy	<=100 cc
Trachea, main bronchus	40 Gy	<=10 cc		
Other organs (heart, etc)	48 Gy	<=1 cc	40 Gy	<=10 cc

18-Fluoro-deoxy-glucose (FDG)-positron emission tomography (PET)

18-Fluoro-deoxy-glucose (FDG)-PET scanning is an important examination both for the staging and the follow-up of lung cancer. For lung cancer staging, occult mediastinal and hilar lymph nodes, and distant metastases, are frequently found by FDG-PET.

In the follow-up of lung cancer after SBRT, radiation fibrotic change cannot be distinguished from residual tumor. FDG-PET is also useful in this situation.[6]

Clinical results

Local tumor response

The local control rates of primary lung cancer with SBRT have been previously reported by several authors, as shown in Table 2: 94 % (47/50) for 50–60 Gy in five fractions with a median follow-up of 36 months,[7] 92 % (22/24) for 60 Gy in 8 fractions with a median follow-up of 24 months,[8] 81% (30/37) for 60 Gy in three fractions with a median follow-up of 15 months,[9] 80% for 48–60 Gy in eight fractions with a median follow-up of 17 months,[10] 95% for 45–56.2 Gy in three fractions with a median follow-up of 10 months,[11] 90% for 30–40 Gy in four fractions with a median follow-up of 21 months,[12] and 98% (44/45) for 48 Gy in four fractions with a median follow-up of 30 months.[13] However, the definition of local control after radiotherapy is difficult because local tumor failure and Radiation Induced Lung Damage (RILD) cannot be clearly delineated. Even though the definition of local control is different in various trials, a BED larger than 100 Gy may be effective for the SRT of solitary lung cancer with a local control rate of above 85%.

Survival

The survival rates of stage IA (T1N0M0) lung cancer and stage IB (T2N0M0) lung cancer have not been separately reported by several authors. In our stage IA series, the 1-year and 5-year local relapse-free survival rates were 100% and 95%. The isease-free survival rates after 1, 3, and 5 years were 80%, 72%, and 72%, respectively, and the overall survival rates were 93%, 83%, and 83%, respectively. In our stage IB series, the 1-year local relapse-free survival

Table 2. Local control rates of stereotactic radiotherapy for primary lung cancer

Author (year)	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control	Median follow-up (months)
Uematsu[7] (2001)	50–60	10	80% Margin	94% (47/50)	36
Arimoto[8] (1998)	60	7.5	Isocenter	92% (22/24)	24
Timmerman[9] (2003)	60	20	80% Margin	81% (30/37)	15
Onimaru[10] (2003)	48–60	6–7.5	Isocenter	80% (20/25)	17
Wulf[11] (2004)	45–56.2	15–15.4	80% Margin	95% (19/20)	10
Nagata[13] (2005)	48	12	Isocenter	98% (44/45)	30
Lee[12] (2003)	30–40	10	90% Margin	90% (8/9)	21

Table 3. Clinical toxicities after stereotactic radiotherapy for primary lung cancer

Author (year)	Number of cases	Lung >=grade 3	Lung grade 5	Other grade 5
Uematsu[7] (2001)	50	0%	0	
Arimoto[8] (1998)	24	NA	0	
Lee[12] (2003)	28	0	0%	
Onimaru[10] (2003)	45	2%	0%	Esophagus
Wulf[11] (2004)	61	0	0%	
Nagata[13] (2005)	45	0	0	
Timmerman[16] (2006)	70	20%	9%	Hemoptysis, pericarditis
J-CERG[5] (2006)	2106	NA	0.50%	Esophagus, hemoptysis

NA, not available

rate was 100%. The disease-free survivals after 1, 3, and 5-years were 92%, 71%, and 71%, respectively, and the overall survival rates were 82%, 72%, and 72%, respectively.[13] Onishi et al.[14] recently reported the results for 13 institutions in Japan, which summarized findings for 245 patients: 155 with stage IA lung cancer and 90 with stage IB lung cancer. There were 87 operable and 158 inoperable patients, and their results showed that the intercurrent death rate was especially high in the inoperable patient group. Moreover, the 5-year survival rates of operable patients irradiated with more than BED=100 Gy was 90% for stage IA and 84% for stage IB, and their clinical results were as good as those for surgery.

These survival rates should be compared with the results of surgery; however, the results of SBRT may differ depending on how many of the group are operable and how many are inoperable, and how many of the tumors are central and how many, peripheral.

Toxicities

The great concern of pulmonary toxicity with this SBRT treatment was relieved by the very low rates of complications in early studies. Most pulmonary complications were less than National Cancer Institute common toxicity criteria (NCI-CTC) version 2.0 grade 2. No other serious complications were reported, except for rib fracture, intercostals neuralgia, and mild dermatitis. However, recently, a few serious complications have been reported by several institutions in Japan.[15] These complications include grade 5 pulmonary complications, radiation pneumonitis, hemoptysis, and radiation esophagitis. Most cases of grade 5 radiation pneumonitis were associated with interstitial pneumonitis. Cases of interstitial pneumonitis should be carefully considered. Thoraco-cutaneous fistula was reported in a patient with previous tuberculosis history. Acute cholecystitis was reported in a patient with gallstones who had been pressed with an abdominal press board at the time of SBRT.

Another toxicity concern was the effect on the central bronchus, pulmonary artery, esophagus, heart, and spinal cord. The effects of a hypofractionated dose on the main bronchus, pulmonary artery, heart, and esophagus have not been followed up for a sufficiently long time. Lethal pulmonary bleeding and esophageal ulcer have been reported previously by several authors. Timmerman et al.[16] recently reported a series of complications with SBRT. Central hilar tumors adjacent to mediastinal organs should be carefully considered.[17] Table 3 shows the toxicities reported by various groups.

Ongoing clinical trials

Recently, a multi-institutional phase II study of SBRT for T1N0M0 non-small cell lung cancer under JCOG (http://www.jcog.jp/) protocol 0403 was started in Japan. Sixteen institutions entered together and started the same 48-Gy SBRT dose at the isocenter in four fractions for T1N0M0 lung cancer. One hundred patients have been registered. The results of SBRT for both inoperable and operable stage I lung cancer patients are awaited.

A new dose-escalation study of SBRT for T2N0M0 lung cancer is also planned, under the JCOG.

Timmerman et al.[9] concluded that a 60-Gy marginal dose in three fractions was the limiting dose, and the Radiation Therapy Oncology Group (RTOG) study 0239 for inoperable patients is already closed. There are a few other reports so far.[18–23] The coming RTOG protocols for operable patients, central tumors, and lung metastases are awaited.

Future directions

Both a new IGRT technique and four-dimensional RTP are future directions of SBRT. Systemic chemotherapy may be considered when the local tumor is well controlled and regional/distant metastases are frequent.

The primary indication for stereotactic radiotherapy in lung cancer could be a stage 1A (T1N0M0) patient. Very early-stage lung cancer can now be detected by screening CT examination, and these cases are also good indications for SRT; however, the issue in these cases is histological confirmation. In our clinical experience, 7 of a total of 95 SRT cases could not be finally confirmed histologically. Of course, these 7 cases were not included in our study.[13] They could not be histologically confirmed because of failure or difficulty in CT-guided biopsy or transbronchoscopic lung biopsy (TBLB). Currently, CT screening has revealed very early-stage lung cancer with ground glass opacity (GGO) and some patients with severe emphysema could be contraindicated for biopsy. Therefore, the indication for SRT for

these cases without histological confirmation should be discussed in the future. When the tumor is larger than 3 cm in diameter, which corresponds to stage 1B (T2N0M0), SRT is possible; however, the intratumor dose becomes less homogeneous, and the rate of occult distant metastases may increase. Therefore, extension of the indication of this technique for T2 tumors requires more consideration for dose escalation or adjuvant chemotherapy.

The current standard choice for stage IA lung cancer treatment is lobectomy;[24] however, for many patients this is not indicated because of accompanying diseases, such as chronic obstructive pulmonary disease (COPD), cardiac disease, and diabetes. For such patients, various minimal surgical techniques are indicated, including wedge resection and video-assisted thoracoscopic surgery (VATS), as well as ablation. The local control rates of various other modalities for primary stage I lung cancer previously reported were 93% for wedge resection and 83%-95% for VATS, and the 5-year survival rates were 82% and 50%-70%, respectively. A further randomized trial comparing SBRT with surgery should be considered.

Conclusion

SBRT is a safe and effective treatment method for stage I lung tumors. Further clinical studies are therefore warranted.

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Patterns of Care Study of Breast-conserving Therapy in Japan: Comparison of the Treatment Process between 1995–1997 and 1999–2001 Surveys

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Background: The Japan Patterns of Care Study (JPCS) conducted two national surveys to identify changes associated with the treatment process of care for patients undergoing breast-conserving therapy (BCT). Between the two national surveys, the Japanese Breast Cancer Society published its treatment guideline for BCT.
Method: The first survey collected data on 865 patients treated between 1995 and 1997 (JPCS-1), and the second on 746 patients treated between1999 and 2001 (JPCS-2) by extramural audits.
Results: There was a shift to an older age distribution in JPCS-2 compared with JPCS-1. In JPCS-2, the average patient age was 53.9 compared with 51.5 in JPCS-1 ($P < 0.001$). There was a reduction in the extent of breast surgery and the proportion of the patients who received quadrantectomy was 57.0% in JPCS-1 and 30.3% in JPCS-2 ($P < 0.001$). In JPCS-2, a cast or shell for immobilization was used at a significantly higher rate of 52.9% compared with 32.6% for JPCS-1 ($P < 0.001$). The rate of boost irradiation was increased in JPCS-2, especially for patients with a positive surgical margin; it was significantly increased to 83.5% in JPCS-2 compared with 53.9% in JPCS-1 ($P < 0.001$).
Conclusions: The second survey revealed a rapid change in the trend of the treatment of BCT in Japan and represented high compliance of the treatment guideline for BCT published by the Japanese Breast Cancer Society (JBCS) in 1999.

Key words: patterns of care study – breast cancer – breast conserving-therapy – radiation therapy

INTRODUCTION

Breast-conserving therapy (BCT) was incorporated into practice in the mid 1980s in Japan. Since then, the number of patients with breast cancer undergoing BCT has been rapidly increasing, and BCT is now the treatment of choice for early breast cancers in Japan. According to a national survey by the Japanese Breast Cancer Society (JBCS) in the year 2003 (1), 48.4% of patients received BCT. The Patterns of Care Study (USPCS) by the American College of Radiology has made significant contributions to improvements in care of patients with breast cancer in the United States (2,3). The Japan Patterns of Care Study Group (JPCS) started its national survey for breast cancer in 1998. The first survey (JPCS-1) collected data on 865 patients who underwent BCT between 1995 and 1997, and revealed considerable variation and some inappropriate implementation of the BCT treatment process in Japan at that time (4). On the other hand, the Japanese Breast Cancer Society published its treatment guideline for BCT in 1999. The purpose of this study is to compare the results of the two national surveys and to

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evaluate the impact of the JBCS guideline at the same time since the cases of JPCS-2 were treated after the publication of the guidelines.

MATERIALS AND METHODS

The JPCS conducted two national surveys. From September 1998 to December 1999, JPCS-1 collected the data on patients treated between1995 and 1997, and from July 2002 to June 2004, JPCS-2 collected data on patients treated between 1999 and 2001. The institutions and patients were selected by two-stage cluster sampling (5). For JPCS-1, 556 institutions nationwide were stratified into four classifications based on the Japanese facility master list in 1995, and for JPCS-2 640 institutions were stratified into four classifications in 2001. The JPCS-1 randomly selected 72 institutions and collected data on 865 BCT cases which were randomly sampled from lists of eligible patients that were supplied by the institutions. The JPCS-2 also selected 76 institutions and collected data on 746 cases. (Table 1).

Table 1. Difinition of facility categories and the number of patients registered in each category

	JPCS-1		JPCS-2	
	No. of facilities	No. of patients	No. of facilities	No. of patients
A facilities: university hospitals and cancer centers				
A1 facility				
JPCS-1: ≥300 patients per year	20	296	20	196
JPCS-2: ≥430 patients per year				
A2 facility				
JPCS-1: <300 patients per year	19	193	18	203
JPCS-2: <430 patients per year				
B facilities: commmunity-based hospitals				
B1 facility				
JPCS-1: ≥120 patients per year	18	256	20	210
JPCS-2: ≥130 patients per year				
B2 facility				
JPCS-1: <120 patients per year	15	121	18	137
JPCS-2: <130 patients per year				
Total	72	865	76	746

JPCS, Japan Patterns of Care Study Group.

The data was collected by extramural audits of institutions and the auditors were member physicians of the Japanese PCS Working Group. For JPCS-1, we used a data format that was developed on the basis on the USPCS data format and a computer file in FileMaker Pro® version 4.0 database (FileMaker Inc., Santa Clara, CA, USA). For JPCS-2, we developed a new data format on the Access® 2000 database (Microsoft) according to the revised best current management drafted by JPCS Working Subgroup of Breast Cancer. They consist of 316 and 362 items on the BCT process, respectively. The data was collected from all available resources at the location, not only from charts of the radiation oncology department. The eligibility criteria for these analyses were as follows: (1) female; (2) absence of gross multiple tumors; (3) absence of diffuse micro-calcification on pre-treatment mammography; (4) absence of distant metastases; (5) no bilateral lesions; (6) no prior or concurrent malignancies; (7) no prior history of the irradiation of the breast; and (8) no collagen vascular disease other than rheumatoid arthritis. The extent of surgery, prescription and technique of radiation therapy, and the regimen of systemic chemo-endocrine therapy were compared between the two surveys. In the tables below, 'unknown' indicates that the item in the format was filled with data labeled as 'unknown', whereas 'missing' means that the item in the format was left empty. We combined 'unknown' and 'missing' in the tables because their meanings were the same in most cases: no valid data was found in the given resources. 'Unknown/missing' data for categorical data were included in the ratio calculation, whereas the data for the continuous variables was excluded from the ratio calculation, as seen in a corresponding report from the USPCS (6). Paired and unpaired t-tests and chi-square tests were used for statistical analyses where appropriate. A P value of less than 0.05 was regarded as significant.

RESULTS

Patient Characteristics

The patient characteristics are shown in Table 2. Compared with JPCS-1, patients in JPCS-2 had an older age distribution. In JPCS-2, the average patient age was significantly increased from 51.5 in JPCS-1 to 53.9 ($P < 0.001$), and 60% of the patients were ≥ 50 years of age, compared with 47% in JPCS-1 ($P < 0.001$).

Evaluation and Staging

The evaluation and staging of the tumors are shown in Table 3. In JPCS-1, mammography was performed on 79.4% of the patients during their evaluation compared with 65.5% in JPCS-1, although the number of missing/unknown is large. In JPCS-1, the proportions of patients with tumors of <2 and 2–5 cm were 70.3 and 28.9%, respectively, although it was frequently unknown. In JPCS-2, 52.5% of the patients had tumors of <2 cm and 46.3% had 2–5 cm tumors.

Table 2. Patient characteristics

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Age	51.5 ± 11.2[a]	53.9 ± 11.6[a]
20–29	19 (2.2%)	12 (1.6%)
30–39	94 (10.9%)	51 (6.9%)
40–49	347 (40.1%)	236 (31.7%)
50–59	215 (24.8%)	221 (29.7%)
60–69	129 (14.9%)	154 (20.7%)
70+	62 (7.2%)	71 (9.5%)
Missing	9	1
Menstrual status		
Premenopausal	312 (36.1%)	265 (35.5%)
Perimenopusal	86 (9.9%)	33 (4.4%)
Postmenopousal	313 (36.2%)	372 (49.9%)
Unknown/Missing	154 (17.8%)	76 (10.2%)

[a]Mean ± SD.

Surgical Procedures

The results of the surgical procedures are shown in Table 4. There was a reduction in the extent of breast surgery, and the ratio of the patients who received quadrantectomy was 57.0% in JPCS-1 and 30.3% in JPCS-2 ($P < 0.001$).

Table 3. Evaluation and staging of the primary tumor

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Mammography performed		
Not performed	11 (1.3%)	10 (1.3%)
≤3 months before excision	539 (62.3%)	582 (78.0%)
After excision	8 (0.9%)	6 (0.8%)
Before and after initial excision	20 (2.3%)	4 (0.5%)
Unknown	287 (33.2%)	144 (19.3%)
Clinical size of the primary tumor	1.9 ± 0.9[a]	2.1 ± 1.8[a]
≤1.0 cm	140/713(19.6%)	49/667 (7.3%)
1.1–2.0 cm	361/713 (50.6%)	301/667 (45.1%)
2.1–3.0 cm	171/713 (24.0%)	232/667 (34.8%)
3.1–4.0 cm	28/713 (3.9%)	72/667 (10.8%)
4.1–5.0 cm	7/713 (1.0%)	5/667 (0.7%)
≥5.1 cm	6/713 (0.8%)	8/667(1.2%)
Missing	152	79
Clinical N stage (UICC 97)		
N0	741/831 (89.2%)	625/714 (87.5%)
N1	87/831 (10.5%)	85/714 (11.9%)
N2	3/831 (0.4%)	4/714 (0.6%)
Missing	34	32

[a]Mean ± SD.

Table 4. Surgery

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Extent of final breast surgery		
≤Tumorectomy[a]	47 (5.4%)	60 (8.0%)
Wide excision[b]	325 (37.5%)	460 (61.7%)
Quadrantectomy[c]	493 (57.0%)	226 (30.3%)
Missing	0	0
Axillary LN dissection		
Performed	816 (94.3%)	678 (90.9%)
Not performed	49 (5.7%)	68 (9.1%)
Extent of axillary dissection		
Level I	176/816 (21.6%)	175/678 (25.8%)
Level II	509/816 (62.4%)	319/678 (47.1%)
Level III	74/816 (9.1%)	151/678 (22.3%)
Unknown/missing	57/816 (7.0%)	33/678 (4.9%)
Sentinel lymph node biopsy performed		90/741 (12.1%)

LN, lymph node.
[a] Includes incisional biopsy, excisional biopsy, microdochectomy (single duct excision), and tumorectomy.
[b] Includes wide excision and partial mastectomy.
[c] Includes segmental resection and quadrantectomy.

Axillary LN dissection was performed on 94.3% of the patients in JPCS-1 and 90.9% in JPCS-2 ($P = 0.008$). On the other hand, 12.2% of the patients underwent sentinel lymph node biopsy (SLNB) in JPCS-2, although the data about SLNB was not collected in JPCS-1.

Histopathological Assessment

The results of the histopathological assessment are shown in Table 5. In JPCS-2, 79.6% of the pathology reports were shown on the charts and the rate was significantly higher than in the prior study ($P < 0.001$). The final microscopic margin was stated for 96.2% of the patients in JPCS-2 and for 88.8% in JPCS1 ($P < 0.001$). The surgical margin was defined as 'positive margin' in this study, when there were malignant cells at the surgical margin. The final microscopic margin was positive in 7.5 and 13.0% of the patients in JPCS-1 and JPCS-2, respectively. In JPCS-1, estrogen receptor evaluation was performed for 54.9% of the patients, and in JPCS-2 it increased to 78.0% ($P < 0.001$). In JPCS-1, 49.6% of the patients underwent progesterone receptor evaluation, and in JPCS-2 this increased to 75.0% ($P < 0.001$). In JPCS-1 and JPCS-2, axillary lymph node was pathologically positive in 21.9 and 26.0% of the patients, respectively ($P = 0.078$).

Systemic Therapy

Tamoxifen was given to 60.4% of the patients in JPCS-1 and 68.8% in JPCS-2 ($P < 0.001$). The administration of

Table 5. Results of histopathological assessment

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Pathology report on the chart		
Yes	564 (65.2%)	594 (79.6%)
No	260 (30.1%)	129 (17.3%)
Unknown/missing	41 (4.7%)	23 (3.1%)
Final microscopic margin		
Positive	65 (7.5%)	97 (13.0%)
Close (2 mm or less)	40 (4.6%)	39 (5.2%)
Negative	663 (76.7%)	582 (78.0%)
Unknown or not stated/missing	97 (11.2%)	28 (3.8%)
Estrogen receptor status		
Not performed	96 (11.1%)	27 (3.6%)
Positive	269 (31.1%)	373 (50%)
Negative	199 (23.0%)	201 (26.9%)
Insufficient tissue	7 (0.8%)	8 (1.1%)
Unknown/missing	294 (34.1%)	137 (18.4%)
Progesterone receptor status		
Not performed	114 (13.2%)	33 (4.4%)
Positive	252 (29.1%)	348(46.6%)
Negative	170 (19.7%)	203 (27.2%)
Insufficient tissue	7 (0.8%)	8 (1.1%)
Unknown/missing	322 (37.2%)	154 (20.6%)
Number of pathologically positive axillary lymph nodes		
0	569/729 (78.1%)	502/678 (74.0%)
1–3	126/729 (17.3%)	142/678 (21.0%)
≥4	34/729 (4.7%)	34/678 (5.0%)
Missing	136	68
Max	37	30

tamoxifen according to the hormone receptor is shown in Table 6. In JPCS-1 and JPCS-2, tamoxifen was administered to 72.5 and 85.3% of the receptor-positive patients, respectively ($P < 0.001$). Also, tamoxifen was given to 52.3% of the receptor-negative patients in JPCS-1, and 39.5% in JPCS-2 ($P = 0.03$). Chemotherapy, defined as all kinds of chemotherapy including single-agent oral administration of 5-FU or its derivatives, was administered to 38.7% of the patients in JPCS-1 and 35.0% in JPCS-2 ($P = 0.001$). The administration of chemotherapy according to pathological lymph nodes is shown in Table 7. For 64.4 and 73.9% of the patients who had pathologically positive lymph nodes, respectively, chemotherapy was administered in JPCS-1 and JPCS-2 ($P = 0.06$). In addition, the use of chemotherapy that incorporated at least one out of doxorubicin, cyclophosphamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, vinblastine, and vincristine increased

Table 6. Tamoxifen according to the hormone receptor

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Tamoxifen was given to:		
ER (+) or PgR (+)	234/323 (72.5%) Missing: 7/323 (2.2%)	365/439 (85.3%) Missing: 11/439 (2.5%)
ER (−) and PgR (−)	68/130 (52.3%) Missing: 6/130 (4.6%)	51/129 (39.5%) Missing: 5/129 (0.4%)
Receptor status unknown/ missing	220/412 (53.4%) Missing: 21/412 (5.1%)	97/178 (54.5%) Missing: 12/178 (6.7%)

ER, estrogen receptor; PgR, progesterone receptor.
[a]Mean ± SD.

significantly during the two survey periods, with 36.9% in JPCS-1 and 52.3% in JPCS-2 ($P = 0.02$).

Radiation Therapy

Table 8 presents details of the radiation planning. In JPCS-2, a cast or shell for immobilization was used on only 52.9% of the patients, although the rate was significantly higher than in JPCS-1 ($P < 0.001$). The clinical set-up of the radiation treatment was planned without the aid of computed tomography (CT) or X-ray simulation for 5.8% of JPCS-2 cases compared with 10.1% in JPCS-1 ($P = 0.002$). On the other hand, CT simulation was used for 26.7% of JPCS-2 cases compared with 22.2% of JPCS-1 cases ($P = 0.037$). Whole breast irradiation was performed on almost all cases in both surveys (Table 9). Additionally, 49.7% of JPCS-2 cases also had the regional nodes treated, compared with 53.7% in JPCS-1. Breast irradiation was given predominantly with photons of 6 MV (91.3%) in JPCS-2 compared with JPCS-1 (73.3%; $P < 0.001$). Photons of 10 MV without bolus, which is inappropriate for small breasts, was used on up to 4.4% of the patients in JPCS-1 and 2.0% in JPCS-2. Matching of the dorsal margin of tangential fields was not performed for 17.3% of JPCS 1 cases and 14.4% of JPCS-2 cases ($P = 0.069$). The median total dose to the whole breast was

Table 7. Chemotherapy for node-positive patients

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Chemotherapy[a] was given	103/160 (64.4%)	130/176 (73.9%)
Non-intensive[b]	54/103 (52.4%)	6/130 (4.7%)
Intensive[c]	38/103 (36.9%)	68/130 (52.3%)
Unknown/missing	11/103 (10.7%)	56/130 (43.1%)

[a]Includes all kinds of chemotherapy.
[b]Includes single-agent, oral administration of 5-FU or its derivative.
[c]Includes chemotherapy that incorporated at least one of the following: doxorubicin, cyclophosphamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, vinblastine, and vincristine.

Table 8. Radiotherapy planning

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Cast or shell was used		
Yes	282 (32.6%)	395 (52.9%)
No	578 (66.8%)	342 (45.8%)
Unknown/N/A/missing	5 (0.6%)	9 (1.2%)
Simulation		
Clinical set-up only	87 (10.1%)	43 (5.8%)
X-ray simulation without diagnostic CT	257 (29.7%)	233 (31.2%)
X-ray simulation with diagnostic CT	327 (37.8%)	270 (36.2%)
CT simulation	192 (22.2%)	199 (26.7%)
Missing	2 (0.2%)	1 (0.1%)

CT, computed tomography.

50 Gy in JPCS-1 and JPCS-2. Boost irradiation was administered to 16.9% of JPCS-1 patients and 27.4% of JPCS-2 patients ($P < 0.001$) (Table 10). In particular, for the patients with a positive surgical margin, the rate of boost irradiation was significantly increased to 83.5% in JPCS-2 compared with 53.9% in JPCS-1 ($P < 0.001$). The median boost dose was 10 Gy in both surveys.

DISCUSSION

The Patterns of Care Study was originally developed in the United States and assesses the evaluation and treatment patterns of malignancies. The Japan Patterns of Care Study Group started its national survey in 1998 and carried out two national surveys. This report documents the evaluation process and management of BCT in Japan.

BCT for breast cancer was introduced in Japan in the late 1980s, although it was started in the early 1970s in North America and Europe. At that time, it tended toward attaching great importance to surgery and the extent of breast surgery was large, although the feasibility of BCT had been recognized in the Western countries. Moreover, breast-conserving surgery (BCS) without radiation was commonly performed in Japan. In the 1990s, BCS spread rapidly and in 2003 the rate exceeded that of mastectomy in Japan. It was demonstrated that breast radiation significantly reduces ipsilateral breast recurrence in several important reports, and this treatment has been spreading in Japan. As a result, the rate of BCT without radiation has been decreasing and was 22.2% in 2003, although it might not be high enough (1). In PCS, the data from only patients who underwent radiation was collected but we could catch the general current of the process in BCT.

As regards patient characteristics, in JPCS-2 there was an older age distribution compared with JPCS-1. The shift could be a reflection of greater acceptance of conservative

Table 9. Technical details of whole breast radiotherapy

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Breast irradiation		
Performed	857/865 (99.1%)	745/746 (99.9%)
Not performed	8/865 (0.9%)	1/746 (0.1%)
Missing	0/865 (0%)	0/746 (0%)
Beam type for breast irradiation		
Orthovoltage	0/857 (0%)	16/745 (2.1%)
^{60}Co	124/857 (14.5%)	19/745 (2.6%)
Photons <4 MV	5/857 (0.6%)	11/745 (1.5%)
Photons ≥4 MV, <6 MV	406/857 (47.4%)	401/745 (53.8%)
Photons ≥6 MV, <8 MV	217/857 (25.3%)	268/745 (36.0%)
Photons ≥8 MV, <10 MV, with bolus	0/857 (0.0%)	0/745 (0.0%)
Photons ≥8 MV, <10 MV, without bolus	1/857 (0.1%)	1/745 (0.1%)
Photons ≥10 MV, with bolus	39/857 (4.6%)	4/745 (0.5%)
Photons ≥10 MV, without bolus	38/857 (4.4%)	15/745 (2.0%)
Photons ≥10 MV, bolus unknown	2/857 (0.2%)	0/745 (0.0%)
Electrons	23/857 (2.7%)	9/745 (1.2%)
Mixed	1/857 (0.1%)	1/745 (0.1%)
Missing	1/857 (0.1%)	1/745 (0.1%)
Matching of the dorsal margin of tangential fields		
None	144/833 (17.3%)	104/720 (14.4%)
Half beam used	181/833 (21.7%)	142/720 (19.7%)
Tilting	476/833 (57.1%)	458/720 (63.6%)
Others	0/833 (0%)	12/720 (1.7%)
N/A/unknown/missing	32/833 (3.8%)	5/720 (0.7%)
Use of beam modifiers on tangent breast fields		
Wedge on both fields	385/833 (46.2%)	429/720 (59.6%)
Wedge on lateral fields only	2/833 (0.2%)	21/720 (2.9%)
Compensators on both fields	1/833 (0.1%)	1/720 (0.1%)
No beam modifiers	392/833 (47.1%)	248/720 (34.4%)
Unknown/missing	53/833 (6.4%)	20/720 (2.8%)
Total dose for breast	4882.31 ± 327.41	4930.855 ± 214.17
<4400 cGy	12/851 (1.4%)	16/731 (2.2%)
4400–4599 cGy	79/851 (9.3%)	37/731 (5.1%)
4600–4799 cGy	91/851 (10.7%)	44/731 (6.0%)
4800–4999 cGy	29/851 (3.4%)	25/731 (3.4%)
5000–5199 cGy	629/851 (73.9%)	594/731 (81.3%)
≥5200 cGy	11/851 (1.3%)	15/731 (2.1%)
Missing	6	14
Max	6000	6000
Number of tangents treated/day		
Both	632/833 (75.9%)	614/720 (85.3%)
One only	157/833 (18.9%)	84/720 (11.7%)
Unknown/N/A/missing	44/833 (5.3%)	22/720 (3.1%)

Table 10. Technical details of primary site boost

	JPCS-1 ($n = 857$)	JPCS-2 ($n = 745$)
Boost was given to:		
Margin positive	35/65 (53.9%) Missing: 2/65 (3.1%)	81/97 (83.5%) Missing: 0/97 (0%)
Margin close (2 mm or less)	18/39 (46.2%) Missing: 0/39 (0%)	25/39 (64.1%) Missing: 0/39 (0%)
Margin negative	78/657 (11.9%) Missing: 42/657 (6.4%)	90/581 (15.5%) Missing: 0/581 (0%)
Margin unknown/missing	14/96 (14.6%) Missing: 10/96 (10.4%)	8/28 (28.6%) Missing: 0/28 (0%)
Boost dose	972.87 ± 172.3	1033.27 ± 242.0
<400 cGy	0/129 (0.0%)	1/199 (0.5%)
400–599 cGy	6/129 (4.7%)	5/199 (2.5%)
600–799 cGy	5/129 (3.9%)	9/199 (4.5%)
800–999 cGy	7/129 (5.4%)	31/199 (15.6%)
1000–1199 cGy	102/129 (79.1%)	113/199 (56.8%)
1200–1399 cGy	4/129 (3.1%)	5/199 (2.5%)
1400–1599 cGy	5/129 (3.9%)	25/199 (12.6%)
1600–1799 cGy	0/129 (0.0%)	10/199 (5.0%)
1800–1999 cGy	0/129 (0.0%)	0/199 (0%)
Missing	16	5
Max	1400	1600
Electron energy for boost		
<6	0/127 (0%)	11/189 (5.8%)
6–8 MeV	29/127 (22.8%)	86/189 (45.5%)
9–11 MeV	69/127 (54.3%)	71/189 (37.6%)
12–14 MeV	15/127 (11.8%)	16/189 (8.5%)
≥15MeV	7/127 (5.5%)	3/189 (1.6%)
Unknown/missing	7/127 (5.5%)	2/189 (1.1%)
Max	18 MeV	15 MeV

surgery and irradiation for older women as well as younger women. As regards evaluation, the rate of mentioning menstrual status rather than change of the status should be noted. Menstrual status is one of the most important factors in making the decision to use systemic therapy, but the data was unknown or missing in 17.8% of JPCS-1 patients. The rate was significantly decreased to 10.2% in JPCS-2, although it is still high.

The extent of surgical resection was significantly diminished and the rate of positive or close surgical margin was increased correlatively. This might be a result of reliance on breast irradiation. The rate of axillary dissection decreased in the second survey compared with the previous survey, which is consistent with the use of sentinel node biopsy (SNB). In 1996, sentinel lymph node (SLN) biopsy was introduced in Japan and has rapidly spread in Japan as in Western countries. It was reported that 21.5% of breast cancer patients in Japan underwent SLN biopsy in 2003 (7). However, in this study 61.8% of patients who underwent SNB also underwent axillary dissection.

The timing of the second survey was probably during the validation process for SNB by institutional surgeons. The use of SNB without axillary dissection will increase because current studies (8) have suggested that axillary dissection is not necessary for patients with negative sentinel nodes. Over the last few decades, there has been a major shift towards less invasive local treatment of breast cancer and BCT has largely replaced mastectomy as the surgical treatment of choice for early-stage breast cancer. In this trend, SLN biopsy will be accepted as an effective method of assessing axillary nodal status and avoiding unnecessary axillary dissection in patients with node-negative breast cancer. We therefore need to continue monitoring SNB.

The administration of tamoxifen was previously independent of the hormone receptor status, but was individualized according to the receptor status in the second survey. The trend was more significant in A facilities than in B facilities. Chemotherapy was given to more patients in the present study than in the previous one. However, the oral administration of 5-FU or its derivatives, which has been commonly used in Japan, was still carried out for 43.1% of the patients, and chemotherapy such as CMF or regimens including anthrathycline was uncommon. In Japan, medical oncology has not been established as a profession, and surgeons decide regimens under the present conditions. However, surgeons have been adopting the guidelines for Western countries to decide the chemotherapy regimens. Therefore, the rate of standard regimens will probably increase in the near future.

CT-based planning of irradiation to the conserved breast has been common compared with that in the United States (3). CT scans were used to generate isodose curves in 60.0% of JPCS-1 and 62.9% of JPCS-2 cases, and the rate was much higher than in the United States (22.9%). CT-based planning enables the decision to be made of individualized beam arrangements to adjust for variation in body habitus. Thereby, it can improve dose homogeneity throughout the target volume and generates dose–volume histograms of critical organs.

On the other hand, planning without the aid of CT or X-ray simulation was not unusual in JPCS-1. The present survey showed an increase in the use of CT-based or X-ray simulation. Regarding parameters for treatment planning such as a fixation system, matching of the dorsal margin of tangential fields or beam modifiers, suboptimal radiation therapy was performed on some patients in JPCS-1. Although it has been improved to some degree, there is space for improvement in some aspects of JPCS-2.

As expected, most patients in JPCS-2 underwent whole breast irradiation. The use of boost irradiation was

significantly increased in the present study, especially for patients with a positive surgical margin. The guidelines for BCT published by the JBCS recommend that boost irradiation to the tumor bed should be performed for patients with a positive or close surgical margin. Following these guidelines might result in an increase in the use of boost irradiation. Boost irradiation tends to be common even for patients with a negative surgical margin in Western countries, since usefulness of boost irradiation has been shown in two randomized trials (9,10). In the United States PCS, 88.7% of patients who underwent BCT received boost irradiation whether margin status was positive or not. However, it has not been accepted yet in Japan and this may have be a result of differences in the policies of margin assessment.

The current study revealed high levels of compliance with guidelines; however much more improvement is required in some points of radiation therapy. For example, a cast or shell for immobilization was used in only 52.9% of the patients in JPCS-2, although the rate was significantly higher than in JPCS-1. Regarding simulation, the clinical set-up of the radiation treatment was planned without the aid of CT or X-ray simulation for 5.8% of JPCS-2 cases, although the rate was decreased compared with JPCS-1.

In conclusion, the second survey revealed a rapid change in the trend of BCT treatment process in Japan. Although it also showed high compliance with the guidelines, there is room for improvement in the treatment process of BCT.

Conflict of interest statement
None declared.

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ORIGINAL ARTICLE

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Regional hyperthermia combined with radiotherapy for locally advanced non-small cell lung cancers: a multi-institutional prospective randomized trial of the International Atomic Energy Agency

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Abstract
Background. An International Atomic Energy Agency (IAEA)-sponsored, multi-institutional prospective randomized trial was conducted to clarify whether the combination of hyperthermia and radiotherapy improves the local response rate of locally advanced non-small cell lung cancer (NSCLC) compared with that obtained by radiotherapy alone.
Methods. Between October 1998 and April 2002, 80 patients with locally advanced NSCLC were randomized to receive either standard radiation therapy alone (RT) or radiation therapy combined with hyperthermia (RT + HT). The primary endpoint was the local response rate. The secondary endpoints were local progression-free survival and overall survival.
Results. The median follow-up period was 204 days for all patients and 450 days for surviving patients. There were no significant differences between the two arms with regard to local response rate ($P = 0.49$) or overall survival rate ($P = 0.868$). However, local progression-free survival was significantly better in the RT+HT arm ($P = 0.036$). Toxicity was generally mild and no grade 3 late toxicity was observed in either arm.
Conclusion. Although improvement of local progression-free survival was observed in the RT+HT arm, this prospective randomized study failed to show any substantial benefit from the addition of hyperthermia to radiotherapy in the treatment of locally advanced NSCLC.

Key words Lung cancer · Hyperthermia · Radiation therapy · Randomized controlled trial

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Introduction

Lung cancer is one of the most common cancers worldwide, and more than 1 000 000 deaths were estimated to have been due to lung cancer in 2000.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancers.[2] Because various studies of screening for lung cancer have failed to demonstrate unequivocal reduction of mortality, none of the major advisory organizations recommends screening for lung cancer at the present time. Consequently, the majority of the patients with NSCLC present with advanced disease.[3] The standard treatment of locally advanced NSCLC has not yet been well established. For resectable disease, surgical resection has been tried but the results have been considerably less favorable than those for more limited disease.[4] Radiation therapy has been used for medically inoperable patients with stage II disease and most of those with stage III disease, which is usually nonresectable. The results of radiotherapy alone have been devastating, with a 5-year survival of less than 20% for stage II disease and around 5% for stage III disease.[5,6] Various contrivances, such as altered fractionation and the addition of chemotherapy, have been explored to increase the efficacy of radiotherapy.[5] The addition of hyperthermia to radiotherapy is one such effort.