Intensity-modulated radiotherapy using two static ports of tomotherapy for breast cancer after conservative surgery: dosimetric comparison with other treatment methods and 3-year clinical results

Aiko Nagai[1,2,*], Yuta Shibamoto[2], Masanori Yoshida[1], Koji Inoda[3] and Yuzo Kikuchi[1]

[1]Radiation Therapy Center, Fukui Saiseikai Hospital, 7-1, Funabashi, Wadanaka-cho, Fukui 918-8503, Japan
[2]Department of Radiology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan
[3]Department of Radiological Technology, Fukui Saiseikai Hospital, 7-1, Funabashi, Wadanaka-cho, Fukui 918-8503, Japan
*Corresponding author: Department of Radiology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. Tel: +81-52-853-8276; Fax: +81-52-852-5244; E-mail: love_child317@hotmail.com
Received July 5, 2016; Revised October 23, 2016; Editorial Decision December 18, 2016

ABSTRACT

This study investigated the differences in dose–volume parameters for the breast and normal tissues during TomoDirect™ (TD) intensity-modulated radiation therapy (IMRT), TD-3D conformal radiotherapy (3DCRT) and 3DCRT plans, all using two beams, and analyzed treatment outcomes of two-beam TD-IMRT for breast cancer after breast-conserving surgery. Between August 2011 and January 2015, 152 patients were treated using two-beam TD-IMRT with 50 Gy/25 fractions. Among them, 20 patients with left-sided breast cancer were randomly chosen, and two-beam TD-IMRT, TD-3DCRT and 3DCRT plans were created for each patient. The homogeneity and conformity indices and various dose–volume parameters for the planning target volume and OARs were evaluated. Clinical outcomes were evaluated at 3 years. Toxicities were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. TD-IMRT and TD-3DCRT showed better whole-breast coverage than 3DCRT ($P < 0.001$). Most of the mean values of dosimetric endpoints for OARs were better in TD-IMRT than in TD-3DCRT and 3DCRT. Overall survival rates were 97.7% and local control rates were 99.1% at 3 years. Regional control and distant metastasis control rates at 3 years were 98.6% and 96.8%, respectively. Twenty-four of the 152 patients had Grade 2 or higher acute radiation dermatitis. Four patients ($4/146 = 2.7\%$) had Grade 2 radiation pneumonitis. There were no late adverse events of Grade 2 or higher. Two-beam TD-IMRT appeared to yield better dose distribution for whole-breast external-beam radiation therapy than TD-3DCRT and two-beam 3DCRT. The treatment appeared to provide low skin toxicity and acceptable tumor control.

KEYWORDS: breast cancer, intensity-modulated radiation therapy, tomotherapy, Tomo-Direct, static tomotherapy

INTRODUCTION

Adjuvant whole-breast external-beam radiation therapy (WBRT) is an essential part of the current standard approach for early-stage breast cancer, because it yields excellent long-term local control and survival [1]. However, conventional 3D-conformal radiotherapy (3DCRT) for breast cancer occasionally causes treatment-related complications (e.g. dermatitis, pneumonitis, cardiac injuries). The severity of both acute and late dermatitis is associated with increased breast dose inhomogeneity and resultant hot spots [2]. With conventional breast radiotherapy, a portion of the breast tissue receives 110% of the prescription dose, occasionally up to 120% [2]. Intensity-modulated radiation therapy (IMRT) has been shown

to improve breast dose homogeneity by decreasing hot spots and doses to normal tissues (e.g. the lung and heart) [3]. Breast IMRT is a developing area of active research, and several publications have shown feasibility, dosimetric superiority over 3DCRT [4], decreased acute side effects compared with conventional WBRT [5], and the potential for fewer late complications [6]. In particular, two Phase III studies have shown a reduction in skin toxicity by using IMRT [7, 8]. However, the use of IMRT for breast cancer has not yet become popular in Japan.

Tomotherapy (TomoTherapy, Accuray, Madison, WI, USA) delivers IMRT with a high target-dose homogeneity, minimized doses to surrounding organs at risk [9], and a precise set-up using the onboard megavoltage (MV) computed tomography (CT) system enabling on-line image-guided radiotherapy (IGRT) [10]. TomoDirect™ (TD) is a fixed beam treatment method, allowing planning and delivery of static beams past binary multileaf collimators (MLCs) for fluence modulation [11, 12]. Recently, some clinical data on the use of helical tomotherapy (HT) and TD-IMRT in breast cancer have been reported [13–15]. TD-IMRT plans can decrease the dose for the contralateral lung and breast compared with HT plans. However, the previous reports only paid attention to dermatitis. In addition, there have been no reports that have compared the dosimetric parameters between two-beam TD-IMRT, two-beam TD-3DCRT and two-beam 3DCRT.

In Japan, breast cancer patients are usually treated with two opposed tangential fields. Since our institution has no conventional linear accelerator (linac), we have used tomotherapy for all patients. Therefore, in this study, we investigated the differences in dose–volume parameters for the breast and normal tissues during TomoDirect™ (TD) intensity-modulated radiation therapy (IMRT), TD-3D conformal radiotherapy (3DCRT) and 3DCRT plans, all using two beams, and analyzed treatment outcomes of two-beam TD-IMRT for breast cancer after breast-conserving surgery.

MATERIALS AND METHODS
Patient characteristics

Between August 2011 and January 2015, a total of 152 patients were treated at Fukui Saiseikai Hospital using TD-IMRT. All patients who underwent TD-IMRT were conventionally treated (2 Gy/day, 5 fractions/week) with two tangential fields using 6-MV photon beams to a total dose of 50 Gy/25 fractions. Our center had two tomotherapy machines but no linac. Written informed consent was obtained before treatment from all patients. Patient and tumor characteristics are shown in Table 1. Patient age ranged from 31 to 79 years (median, 52 years). All patients had a performance status score of 0. Concurrent chemotherapy was not used. We randomly chose 20 patients with left-sided breast cancer from the 152 patients for planning comparison of TD-IMRT, TD-3DCRT and 3DCRT. The Fukui Saiseikai Hospital Review Board approved this study (No. 2016-003).

CT simulation, planning target volume and organ at risk definition and contouring

Our methods of tomotherapy have previously been described in detail [16]. All patients were immobilized in a supine position with a customized Blue BAG Cushion (Medical Intelligence, Schwabmuenchen, Germany) for simulation and treatment. Planning CT images were acquired with the Activion™ 16 (Toshiba Medical Systems Corporation, Tochigi, Japan) and obtained from the midneck to the bottom of the lung with a 3-mm slice thickness under shallow breathing. All target volumes and normal structures were contoured on the Pinnacle³ workstation version 9.2 (Philips Medical Systems, Madison, WI, USA). The target for breast irradiation was determined by referring to preoperative sagittal CT and positron emission tomography (PET)-CT images. The planning target volume (PTV) for WBRT covered the superior border at the base of the manubriosternal joint and the inferior border at 1 cm below the inframammary line; the medial border was usually the midline of the sternum, and the lateral border was the midaxillary line, excluding the outermost 2 mm from the superficial skin surface. Delineated organs at risk (OARs) were the ipsilateral, contralateral and bilateral lungs, heart, contralateral breasts, and skin. The skin was defined as the volume with a depth of 2 mm from the external surface, and was automatically outlined.

Treatment plan comparison between TD-IMRT, TD-3DCRT and 3DCRT

TD-IMRT and TD-3DCRT plans for 20 patients with left-sided breast cancer were created and optimized with the TomoTherapy version 5.0.5.18 treatment planning station (Accuray, Inc, Madison, WI, USA) using a convolution/superposition dose calculation algorithm. The planning parameters used for both plans were as follows: a field width of 2.51 cm, a pitch of 0.251, a modulation factor of 1.15–1.85, and a fine calculation grid (1.96 mm × 1.96 mm × slice thickness) for both optimization and calculation. The same beam angles were selected for both plans in order to minimize doses to the OARs. To account for possible breath-related target movements, 2 MLC leaves were opened on the anterior edge of each beam. The TD-3DCRT plans were made selecting the normal tissue homogeneity option and setting the tissue compensation to low, in order to allow for a more significant comparison with TD-IMRT plans. Details of the inverse planning algorithm used, the optimization method, and several parameters associated with the optimization in the tomotherapy planning station have been described previously [17]. A prescription dose of 50 Gy in 25 fractions to 50% of the PTV was chosen.

The 3DCRT plans for 20 patients with left-sided breast cancer were created with the Pinnacle³ workstation using two open tangential 6-MV photon beams from a Varian Clinac 2100 C/D (Varian Medical System, Palo Alto, CA). Beam angles were chosen such that the edges matched those of the corresponding TD treatment beams. Adequate wedges were selected from 15, 30 and 45 degrees for the breast tissues. Final dose calculation employed a beam modeling based on the collapsed cone convolution/superposition. A prescription dose of 50 Gy in 25 fractions to the isocenter of the PTV was chosen.

Verification of treatment planning system calculations

We compared the dose profiles calculated using each planning system with the dose profiles for beam modeling and actually measured doses in order to validate the accuracy of the treatment planning

Table 1. Patient characteristics

Characteristic		Number of patients (%)
Total number of patients		152
Age (years), median [range]		52 [31–79]
Follow-up (months), median [range]		33 [1–53]
Laterality	Right/Left	76 (50)/76 (50)
Clinical stage	0/I/II/III	37 (24.4)/83 (54.6)/28 (18.4)/4 (2.6)
Histology		
Ductal/Lobular/Mucinous/Scirrhous		147 (96.7)/2 (1.3)/2 (1.3)/1 (0.7)
Estrogen receptor	Positive/Negative	32 (21.1)/120 (78.9)
Progesterone receptor	Positive/Negative	107 (70.4)/45 (29.6)
HER2	Positive/Negative	61 (40.1)/91 (59.9)
Ki-67	≥20%/<20%/Unknown	101 (66.4)/45 (29.6)/6 (4.0)
Neoadjuvant chemotherapy	Yes/No	52 (34.2)/100 (65.8)
Concurrent chemotherapy	Yes/No	0 (0)/152 (100)
Adjuvant chemotherapy	Yes/No	5 (3.3)/147 (96.7)
Neoadjuvant hormonotherapy	Yes/No	72 (47.4)/80 (52.6)
Concurrent hormonotherapy	Yes/No	84 (55.3)/68 (44.7)
Adjuvant hormonotherapy	Yes/No	92 (60.5)/60 (39.5)
Neoadjuvant molecularly targeted therapy	Yes/No	22 (14.5)/130 (85.5)
Concurrent molecularly targeted therapy	Yes/No	23 (15.1)/129 (84.9)
Adjuvant molecularly targeted therapy	Yes/No	24 (15.8)/128 (84.2)

HER2 = human epidermal growth factor receptor type 2.

systems. The dosimetric quality indices for beam profiles differ considerably between the Varian linac on Pinnacle[3] and TomoTherapy, since the latter has no flattening filter. For beam model verification of the Varian machine with a flattening filter, W_{50} (radiological width on a 50% dose level) and P_{80-20} (penumbra, defined as the distance between 80 and 20% dose levels) were used. On the other hand, full width at quarter maximum (FWQM) was used to check consistency between the beam model and the beam measurement for tomotherapy.

Planning evaluation

Dosimetric comparisons of the treatment plans were performed based on the following parameters extracted from dose–volume histograms (DVHs): homogeneity index (*HI*); conformity index (*CI*); maximum dose for the PTV (*Dmax*); dose received by 95% of the PTV (*D95%*); dose received by 2% of PTV (*D2%*); V5 Gy, V10 Gy, V20 Gy and mean lung dose (MLD) for the bilateral, ipsilateral and contralateral lungs; V10 Gy, V25 Gy, V30 Gy, V35 Gy and mean heart dose (MHD) for the heart; mean dose for the

contralateral breast; and maximum dose for the skin. Furthermore, we divided the patients into a large PTV (above-median) group and a small PTV (below-median) group (*n* = 10 for each). The median PTV for all patients was 575.1 cm³. The median PTV was 685.7 cm³ (range: 586.1–1055.5) in the large PTV group and 456.2 cm³ (361.8–564.1) in the small PTV group (*P* = 0.002 by unpaired *t*-test). Maximum dose for the skin in the large and small PTV groups was compared between TD-IMRT, TD-3DCRT and 3DCRT. The *HI* was defined as the ratio of the maximum dose in the PTV (*Dmax*) and the prescription dose in the PTV (*Drx*): HI = Dmax/Drx. The *CI*, as proposed by ICRU 62 [18], was defined as the ratio of the treated volume within the prescription isodose surface (V_{TV}) to the PTV (V_{PTV}): $CI = V_{TV}/V_{PTV}$.

Evaluation of clinical outcome

In principle, physical examination and a blood test were performed at every follow-up visit, and CT, chest radiography, mammography and/or ultrasonography was performed whenever necessary until death. PET-CT and magnetic resonance imaging

were performed when history, physical examination, CT scan, and/or tumor marker assessment yielded suspicious findings. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 4.0. Acute dermatitis and overall survival (OS) were evaluated for all 152 patients, and late dermatitis, pneumonitis, local control (LC) and regional control (RC) were evaluated for 146 patients with at least 6 months of follow-up. Cardiac injuries were evaluated for 74 patients with left-sided breast cancer followed for at least 12 months, and distant metastasis control (DMC) rates were evaluated for 126 patients who had been evaluated with follow-up CT, PET-CT and/or abdominal ultrasonography.

Statistical analysis

Comparisons of dose–volume parameters of the PTV and OARs among the three plans for 20 patients were carried out using the factorial analysis of variance (ANOVA), followed by the Tukey–Kramer *post hoc* test. OS, LC, RC and DMC rates were calculated using the Kaplan–Meier method from the start of IMRT. A two-sided P-value of ≤ 0.05 was considered to reflect statistical significance. These univariate analyses were carried out using Prism (Graph Pad Institute Inc., San Diego, CA, USA).

RESULTS
Verification of treatment planning system calculations

W_{50}, P_{80-20} and FWQM values are shown in Table 2. The difference in W_{50} between measured values and values calculated from the treatment planning systems in Pinnacle[3] was 1.4 mm, which satisfied the <2 mm criteria [19]. In the same way, the difference in P_{80-20} was 0.5 mm, which satisfied the 3 mm criteria of distance to agreement [20]. For tomotherapy, the gamma-index of 2%/1 mm was 0.271, which satisfied the <1 criteria [21].

Treatment plan analysis for 20 patients with left-sided breast cancer

PTV and OAR isodose distributions for a typical left-sided breast plan are illustrated in Fig. 1. The mean values (± SD) of the PTV and OAR dosimetric parameters of TD-IMRT, TD-3DCRT and 3DCRT plans are listed in Table 3. TD-IMRT and TD-3DCRT showed better whole-breast coverage than 3DCRT; D95% was more than 95% in all TD-IMRT and TD-3DCRT plans ($P < 0.0001$). PTV Dmax and D2% were significantly lower for the TD-IMRT and TD-3DCRT plans than 3DCRT (both $P < 0.0001$), and no significant difference was observed between

TD-IMRT and TD-3DCRT. The PTV homogeneity of TD-IMRT and TD-3DCRT plans was better than that of the 3DCRT plan ($P < 0.0001$). Most of the mean values of OAR dosimetric endpoints were significantly better in TD-IMRT than in TD-3DCRT and 3DCRT. TD-IMRT provided lower values of ipsilateral lung V5 Gy and V10 Gy, bilateral lung V5 Gy and V10 Gy, and contralateral MLD than 3DCRT ($P = $ <0.0001, 0.0091, <0.0001, 0.017 and 0.037, respectively). MHD and heart V10 Gy, V25 Gy, V30 Gy and V35Gy for TD-IMRT were significantly lower than those of TD-3DCRT ($P = $ 0.0012, 0.0029, 0.0004, 0.0002 and 0.0003, respectively). Mean dose for the contralateral breast tissue was lower in TD-IMRT than in TD-3DCRT ($P = 0.0018$). Maximum dose for the skin was lower in 3DCRT than in TD-IMRT and TD-3DCRT ($P = 0.0055$). In the small PTV group, the maximum dose for the skin was smaller in 3DCRT (mean ± SD: 48.4 ± 1.5 Gy) than in TD-IMRT (50.2 ± 0.5 Gy) and TD-3DCRT (50.2 ± 0.6 Gy; $P = 0.0007$). On the other hand, there were no significant differences in the large PTV group between the three plans (50.5 ± 0.3 Gy for TD-IMRT, 50.7 ± 0.4 Gy for TD-3DCRT, and 50.0 ± 2.1 Gy for 3DCRT; $P = 0.53$).
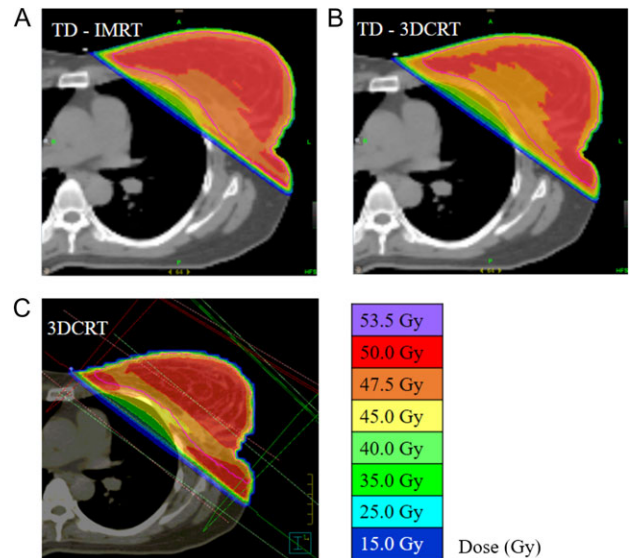

Fig. 1. Isodose distribution for a left-sided breast cancer planned with TomoDirect (TD) intensity-modulated radiation therapy (IMRT) (A), TD-3D conformal radiotherapy (3DCRT) (B) and 3DCRT (C). The pink line in (A) to (C) indicates the planning target volume.

Table 2. Verification of treatment planning system calculations for Pinnacle[3] and TomoTherapy

	Measured value	Calculated value on Pinnacle[3]	Calculated value on TomoTherapy workstation
W_{50} (mm)	101.8	100.4	–
P_{80-20} (mm)	6.6	6.1	–
FWQM (mm)	410.7	–	411.2

W_{50} = radiological width on a 50% dose level, P_{80-20} = penumbra defined as distance between 80 and 20% dose levels, FWQM = full width at quarter maximum.

Table 3. Dose parameter comparison among TD-IMRT, TD-3DCRT and 3DCRT plans for 20 left-sided breast cancer patients

Parameters		TD-IMRT	TD-3DCRT	3DCRT	*P*-value
PTV	Dmax (%)	106 ± 1.0	105 ± 1.0	113 ± 4.3	<0.0001
	D95 (%)	95.4 ± 0.3	96.0 ± 0.6	89.5 ± 2.5	<0.0001
	D2 (%)	103 ± 0.7	102 ± 0.5	109 ± 2.4	<0.0001
HI		1.8 ± 0.4	1.3 ± 0.1	4.3 ± 1.5	<0.0001
CI		0.5 ± 0.0	0.5 ± 0.0	0.6 ± 0.1	<0.0001
Bilateral lung	V5 Gy (%)	5.8 ± 1.3	6.6 ± 1.4	9.3 ± 2.7	<0.0001
	V10 Gy (%)	4.4 ± 1.1	5.2 ± 1.2	6.0 ± 2.4	0.017
	V20 Gy (%)	3.3 ± 0.9	4.0 ± 1.0	4.0 ± 2.1	0.17
	MLD (Gy)	2.1 ± 0.7	2.3 ± 0.5	2.5 ± 1.0	0.22
Right lung	MLD (Gy)	0.2 ± 0.0	0.2 ± 0.0	0.3 ± 0.1	0.037
Left lung	V5 Gy (%)	12.8 ± 3.2	14.8 ± 2.8	20.9 ± 6.1	<0.0001
	V10 Gy (%)	9.7 ± 2.6	11.6 ± 2.4	13.5 ± 5.3	0.0091
	V20 Gy (%)	7.2 ± 2.2	9.1 ± 2.1	9.1 ± 4.6	0.11
	MLD (Gy)	4.1 ± 0.9	4.9 ± 1.0	5.0 ± 2.0	0.11
Heart	V10 Gy (%)	4.1 ± 2.4	7.9 ± 3.8	5.7 ± 3.4	0.0029
	V25 Gy (%)	2.0 ± 1.5	5.3 ± 3.1	3.0 ± 2.5	0.0004
	V30 Gy (%)	1.6 ± 1.3	4.7 ± 2.8	2.5 ± 2.2	0.0002
	V35 Gy (%)	1.2 ± 1.1	4.0 ± 2.6	2.1 ± 2.0	0.0003
	MHD (Gy)	2.2 ± 0.9	3.8 ± 1.6	3.5 ± 1.4	0.0012
	Dmax (Gy)	46.7 ± 4.7	48.5 ± 1.2	47.1 ± 2.8	0.18
Right breast tissue	Dmean (Gy)	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.2	0.0018
Skin	Dmax (Gy)	50.4 ± 0.5	50.5 ± 0.5	49.3 ± 2.0	0.0055

3DCRT = 3D-conformal radiotherapy, IMRT = intensity-modulated radiation therapy, TD = TomoDirect, PTV = planning target volume, HI = homogenity index, CI = conformity index, MLD = mean lung dose, MHD = mean heart dose. *P*-values from the factorial analysis of variance (ANOVA) followed by the Tukey–Kramer *post hoc* test. Data presented as mean ± standard deviation.

Clinical outcome

The median follow-up was 38 months for all patients (range, 1–58 months). The OS, LC, RC and DMC rates at 3 years were 97.7%, 99.1%, 98.6% and 96.8%, respectively. OS rates for Stage 0, I, II and III patients at 3 years were 100%, 100%, 91.4% and 100%, respectively (Fig. 2). LC rates were 100%, 98.4%, 100% and 100% at 3 years for Stage 0, I, II and III, respectively (Fig. 3). RC rates at 3 years were 100%, 98.7%, 100% and 100%, for Stage 0, I, II and III, respectively (data not shown). DMC rates at 3 years were 100%, 97.3%, 95.8% and 75% for Stage 0, I, II and III, respectively (data not shown).

Twenty-four of the 152 (15.8%) patients had ≥Grade 2 acute radiation dermatitis. Grade 3 acute radiation dermatitis was seen in 4 of the 152 (2.6%) patients. Most patients (84.2%) had Grade 1 acute dermatitis. There was no late radiation dermatitis of Grade 2 or higher. Two of the 146 patients had Grade 2 radiation pneumonitis (1.4%). There were no acute or late adverse cardiac events of Grade 2 or higher.

DISCUSSION

In this study, dose homogeneity of PTVs in TD-IMRT and TD-3DCRT plans were better than in 3DCRT plans (both *P* < 0.001), and most of the mean values of the OAR dose parameters were better in TD-IMRT than in TD-3DCRT and 3DCRT. The maximum dose for the skin in 20 patients was lower in 3DCRT than in TD-IMRT and TD-3DCRT, but there were no significant differences in
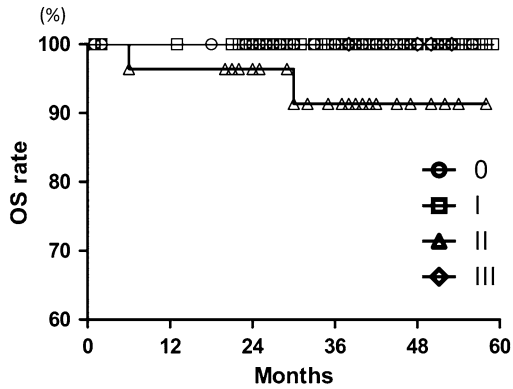
Fig. 2. Curves for overall survival (OS)
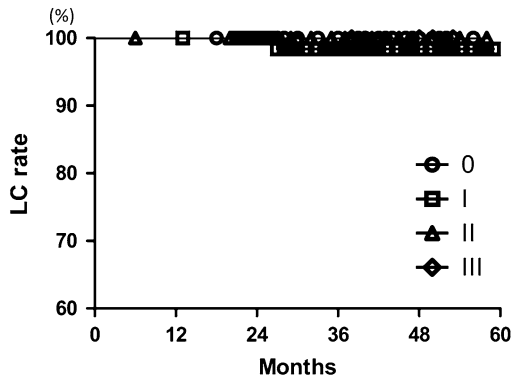according to clinical stages for all 152 patients.

Fig. 3. Curves for local control (LC) according
to clinical stages for 146 patients.

the large PTV group between the three plans. It has been reported that a larger breast size is associated with more severe dermatitis [22, 23], so the results of our study would indicate that the use of TD-IMRT might not increase the incidence of severe dermatitis. In a 3DCRT study using a 50-Gy dose, Grade 2 or higher acute dermatitis was seen in 22% [24]; that study used both 4 and 6 MV X rays, so it is not appropriate to compare the results with those obtained in our study that used 6 MV X rays only. Nevertheless, the incidence of Grade 2 or higher dermatitis of 15.8% in our study may be an acceptable level. Regarding late toxicity, palpable breast induration and negative changes in telangiectasia were reported to be reduced with breast IMRT compared with 3DCRT [25], while there was no late dermatitis in this study. TD-IMRT could also decrease bilateral V5 Gy and V10 Gy, ipsilateral V5 Gy and V10 Gy of the lung, and contralateral MLD, while bilateral MLD and V20 Gy could not be reduced. In the clinical study, the frequency of Grade 2 or higher pneumonitis (1.38%) was nearly equal to or possibly slightly higher than that in 3DCRT studies (0.9–1.28%) [19, 26]. The lung toxicity of TD-IMRT should be further investigated in future studies. Concerning doses for the heart, TD-IMRT was superior to TD-3DCRT regarding V10 Gy, V25 Gy, V30 Gy and V35 Gy. There was no pericarditis in this study, but a previous

study showed that pericarditis occurred in 3 of 831 patients (0.4%) [27]. A clinical study on IMRT showed a low rate of local relapse with mild acute/late effects [28]. Short follow-up is a limitation of our study, but the clinical outcomes obtained so far are comparable with those of the previous studies. From the above considerations, it seems that TD-IMRT provides more appropriate dose distribution for WBRT than the other two plans.

Moreover, TD-IMRT has two other advantages for breast irradiation. First, TD-IMRT is an image-guided IMRT delivery using a fixed gantry; in that respect it is thus suitable for clinical use [9]. Daily MVCT assures set-up accuracy, and it can detect changes in the skin surface and occurrence of pneumonitis during treatment, so we can make a more accurate re-plan and cope with acute adverse events immediately.

As a second advantage, compared with 3DCRT in our study TD-IMRT provided adequate target coverage of the whole breast, with a reduction of the high doses to the target and of the low doses to the contralateral tissues. The low-dose effect to the contralateral tissues is known to lead to an increased rate of radiation-induced secondary malignancies; women <40 years of age who received a radiation dose of >1.0 Gy to the contralateral breast had an elevated, long-term risk of developing a second primary contralateral breast cancer [29]. In this study, the dose to the contralateral breast was lower in TD-IMRT than in 3DCRT, but the Dmean was <1.0 Gy in both treatments, so the influence on the incidence of secondary breast cancer may be small. Regarding the dose of the MVCT, the mean dose delivered to the contralateral breast was ~26.8 cGy in 25 fractions in a previous study [30], so the influence of the MVCT dose on the contralateral breast appears to be small. However, it should be noted that daily MVCT increases MLD and MHD.

On the other hand, breast TD-IMRT has three issues that need to be improved. One is the high cost of breast IMRT, so breast IMRT is not necessarily recommended for all patients [31]. In Japan, however, the cost of two-beam IMRT is equal to that of two-beam 3DCRT, so patients there receiving two-beam therapy could benefit from IMRT in terms of clinical outcome at no additional cost. Second, the current version of tomotherapy cannot use respiration gating or deliver treatment under breath holding. It is expected that this issue will be solved in the future version of tomotherapy. Third, breast hypofractionated radiotherapy over a shorter number of treatment days (15–16 fractions) is reported to have an advantage, with equivalent or even improved outcomes and acute/late toxicities compared with conventionally fractionated radiotherapy [17, 32, 33]. However, breast hypofractionated IMRT is not as frequently employed in Japan as it is in the rest of the world. By using TD-IMRT, the daily doses to OARs could be reduced, so the adverse effects caused by using a higher dose per fraction may be alleviated. Hypofractionated IMRT using TD may be a promising topic of future investigation.

CONCLUSION
The two-beam TD-IMRT plan appeared to yield better dose distribution for WBRT than TD-3DCRT or two-beam 3DCRT. Our preliminary results for TD-IMRT suggest that the skin and other

toxicities and tumor control are acceptable, and further studies are warranted.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Clarke M, Collins R, Darby S, et al. Early Breast Cancer Trialists Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. *Lancet* 2005;366:2087–106.

2. Buchholz TA, Gurgoze E, Brice WS, et al. Dosimetric analysis of intact breast irradiation in off-axis planes. *Int J Radiat Oncol Biol Phys* 1997;39:261–7.

3. Kestin LL, Sharpe MB, Frazier RC, et al. Intensity modulation to improve dose uniformity with tangential breast radiotherapy: initial clinical experience. *Int J Radiat Oncol Biol Phys* 2000;48:1559–68.

4. Hong L, Hunt M, Chui C, et al. Intensity-modulated tangential beam irradiation of the intact breast. *Int J Radiat Oncol Biol Phys* 1999;44:1155–64.

5. Harsolia A, Kestin L, Grills I, et al. Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68:1375–80.

6. McDonald MW, Godette KD, Butker EK, et al. Long-term outcomes of IMRT for breast cancer: a single-institution cohort analysis. *Int J Radiat Oncol Biol Phys* 2008;72:1031–40.

7. Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol* 2008;26:2085–92.

8. Mukesh MB, Barnett GC, Wilkinson JS, et al. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. *J Clin Oncol* 2013;31:4488–95.

9. Coon AB, Dickler A, Kirk MC, et al. TomoTherapy and multifield intensity-modulated radiotherapy planning reduce cardiac doses in left-sided breast cancer patients with unfavorable cardiac anatomy. *Int J Radiat Oncol Biol Phys* 2010;78:104–10.

10. Beavis AW. Is Tomotherapy the future of IMRT? *Br J Radiol* 2004;77:285–95.

11. Franco P, Catuzzo P, Cante D, et al. TomoDirect: an efficient means to deliver radiation at static angles with tomotherapy. *Tumori* 2011;97:498–502.

12. Murai T, Shibamoto Y, Manabe Y, et al. Intensity-modulated radiation therapy using static ports of tomotherapy (TomoDirect): comparison with the TomoHelical mode. *Radiat Oncol* 2013;8:68.

13. Cendales R, Schiappacasse L, Schnitman F, et al. Helical tomotherapy in patients with breast cancer and complex treatment volumes. *Clin Transl Oncol* 2011;13:268–74.

14. Franco P, Zeverino M, Migliaccio F, et al. Intensity-modulated adjuvant whole breast radiation delivered with static angle tomotherapy (TomoDirect): a prospective case series. *J Cancer Res Clin Oncol* 2013;139:1927–36.

15. Zhang F, Wang Y, Xu W, et al. Dosimetric evaluation of different intensity-modulated radiotherapy techniques for breast cancer after conservative surgery. *Technol Cancer Res Treat* 2015;14:515–23.

16. Nagai A, Shibamoto Y, Yoshida M, et al. Safety and efficacy of intensity-modulated stereotactic body radiotherapy using helical tomotherapy for lung cancer and lung metastasis. *Biomed Res Int* 2014;2014:473173.

17. Sugie C, Manabe Y, Hayashi A, et al. Efficacy of the dynamic jaw mode in helical tomotherapy with static ports for breast cancer. *Technol Cancer Res Treat* 2015;14:459–65.

18. International Commission on Radiation Units and Measurements. Prescribing, recording, and reporting photon beam therapy (Supplement to ICRU Report 50). *ICRU Report 62.* ICRU, Bethesda, MD, 1999.

19. Mijnheer B, Olszewska A, Fiorino C, et al. Accuracy requirements and tolerance levels. *ESTRO Booklet No. 7: Quality Assurance of Treatment Planning Systems. Practical Examples for Non-IMRT Photon Beams.* Brussels: ESTRO, 2004, 11–20.

20. Smilowitz JB, Das IJ, Feygelman V, et al. AAPM Medical Physics Practice Guideline 5.a. Commissioning and QA of treatment planning dose calculations—megavoltage photon and electron beams. *J Appl Clin Med Phys* 2015;16:5768.

21. TomoTherapy Service Instructions. Installation Dosimetric Verification Guide (T-PSC-HB0004). Accuray, Inc. 2013. Internal document. (22 September 2016, date last accessed).

22. De Langhe S, Mulliez T, Veldeman L, et al. Factors modifying the risk for developing acute skin toxicity after whole-breast intensity modulated radiotherapy. *BMC Cancer* 2014;14:711.

23. Fernando IN, Ford HT, Powles TJ, et al. Factors affecting acute skin toxicity in patients having breast irradiation after conservative surgery: a prospective study of treatment practice at the Royal Marsden Hospital. *Clin Oncol (R Coll Radiol)* 1996;8:226–33.

24. Osako T, Oguchi M, Kumada M, et al. Acute radiation dermatitis and pneumonitis in Japanese breast cancer patients with whole breast hypofractionated radiotherapy compared to conventional radiotherapy. *Jpn J Clin Oncol* 2008;38:334–8.

25. Barnett GC, Wilkinson JS, Moody A, et al. Randomized controlled trial of forward-planned intensity modulated radiotherapy for early breast cancer: interim results at 2 years. *Int J Radiat Oncol Biol Phys* 2012;82:715–23.

26. Nozaki M, Kagami Y, Mitsumori M, et al. A multicenter investigation of late adverse events in Japanese women treated with breast-conserving surgery plus conventional fractionated whole-breast radiation therapy. *Jpn J Clin Oncol* 2012;42:522–7.

27. Pierce SM, Recht A, Lingos TI, et al. Long-term radiation complications following conservative surgery (CS) and radiation

therapy (RT) in patients with early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1992;23:915–23.

28. Keller LM, Sopka DM, Li T, et al. Five-year results of whole breast intensity modulated radiation therapy for the treatment of early stage breast cancer: the Fox Chase Cancer Center Experience. *Int J Radiat Oncol Biol Phys* 2012;84:881–7.

29. Stovall M, Smith SA, Langholz BM, et al. Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study. *Int J Radiat Oncol Biol Phys* 2008;72:1021–30.

30. Shah AP, Langen KM, Ruchala KJ, et al. Patient dose from megavoltage computed tomography imaging. *Int J Radiat Oncol Biol Phys* 2008;70:1579–87.

31. Medscape. ASTRO: 5 Radiation Oncology Practices Should Stop. www.medscape.com/viewarticle/811528 (23 September 2013, date last accessed).

32. Haviland JS, Owen JR, Dewar JA et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013;14:1086–94.

33. Chan EK, Woods R, McBride ML, et al. Adjuvant hypofractionated versus conventional whole breast radiation therapy for early-stage breast cancer: long-term hospital-related morbidity from cardiac causes. *Int J Radiat Oncol Biol Phys* 2014;15;88: 786–92.