Journal of Radiation Research, Vol. 60, No. 5, 2019, pp. 694–704
doi: 10.1093/jrr/rrz052
Advance Access Publication: 31 July 2019

Intensity-modulated radiation therapy using TomoDirect for postoperative radiation of left-sided breast cancer including lymph node area: comparison with TomoHelical and three-dimensional conformal radiation therapy

Shoko Takano[1,2], Motoko Omura[1,*], Ryoko Suzuki[3], Yumiko Tayama[1], Kengo Matsui[1], Harumitsu Hashimoto[4], Hideyuki Hongo[1], Hironori Nagata[1], Kumiko Tanaka[5], Masaharu Hata[2] and Tomio Inoue[6]

[1]Shonan Kamakura General Hospital, Department of Radiation Oncology, 1370-1 Okamoto, Kamakura, Kanagawa 247-8533, Japan
[2]Yokohama City University Graduate School of Medicine, Department of Radiation Oncology, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan
[3]Cancer Institute Hospital, Department of Radiation Oncology, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan
[4]Shonan Fujisawa Tokushukai Hospital, 1-5-1 Tsujidokandai, Fujisawa, Kanagawa 251-0041, Japan
[5]Shonan Kamakura General Hospital, Department of Breast Surgery, 1370-1 Okamoto, Kamakura, Kanagawa 247-8533, Japan
[6]Shonan Kamakura General Hospital, Advanced Medical Center, 1370-1 Okamoto, Kamakura, Kanagawa 247-8533, Japan
*Corresponding author. Shonan Kamakura General Hospital, Department of Radiation Oncology, 1370-1 Okamoto, Kamakura, Kanagawa 247-8533, Japan. Tel: 81-467-46-1717; Fax: 81-467-46-9925; Email: momuram@mac.com
(Received 26 March 2019; revised 25 May 2019; editorial decision 11 June 2019)

ABSTRACT

Intensity-modulated radiation therapy (IMRT) delivers an excellent dose distribution compared with conventional three-dimensional conformal radiation therapy (3D-CRT) for postoperative radiation including the lymph nodes in breast cancer patients. The TomoTherapy system, developed exclusively for IMRT, has two treatment modes: TomoDirect (TD) with a fixed gantry angle for beam delivery, and TomoHelical (TH) with rotational beam delivery. We compared the characteristics of TD with TH and 3D-CRT plans in the breast cancer patients. Ten consecutive women with left breast cancer received postoperative radiation therapy using TD including the chest wall/residual breast tissue and level II–III axial and supraclavicular lymph node area. Fifty percent of the planning target volume (PTV) was covered with at least 50 Gy in 25 fractions. TD, TH and 3D-CRT plans were created for each patient, with the same dosimetric constraints. TD and TH showed better dose distribution to the PTV than 3D-CRT. TD and 3D-CRT markedly suppressed low-dose spread to the lung compared with TH. Total lung V5 and V10 were significantly lower, while V20 was significantly higher in the TD and 3D-CRT plans. The mean total lung, heart and contralateral breast doses were significantly lower using TD compared with the other plans. Compared with 3D-CRT and TH, TD can provide better target dose distribution with optimal normal-organ sparing for postoperative radiation therapy including the chest wall/residual breast tissue and lymph node area in breast cancer patients. TD is thus a useful treatment modality in these patients.

Keywords: breast cancer, radiation therapy; TomoTherapy; TomoDirect; TomoHelical

INTRODUCTION

Recent developments in chemotherapy have improved the disease-control rate among breast cancer patients. However, the rate remains unacceptably low in some high- or unfavorable-risk groups, including younger patients and patients with triple-negative subtype, multicentric breast cancer, positive surgical margins and lymph node involvement. Patients with positive lymph nodes are often recommended to receive postoperative radiation including the lymph node area [1–7], which can reduce the risks of both recurrence and mortality in these patients [1].

Patients with positive lymph nodes usually receive radiation therapy to their ipsilateral chest wall/residual breast, and axillary and supraclavicular lymph node areas. However, there are several problems with treatment planning for irradiating such wide and complex target volumes using conventional three-dimensional conformal radiation therapy (3D-CRT). First, it is necessary to use a combination of opposed tangential beams for the chest wall and anterior–posterior beams for the lymph node area, resulting in the potential for under-dosing at the junction, as well as over-dosing of the areas immediately adjacent to the junction. In addition, this beam arrangement may lead to inaccurate dose distribution around the junction because of daily set-up errors or the patient's breathing motion.

Second, it is difficult to achieve uniform target coverage with optimal normal-tissue sparing using this conventional technique, because the targets vary in depth and are close to radiosensitive organs/normal tissues, such as the lung, spinal cord, heart and contralateral breast. These factors may thus lead to inadequate dose distribution for the planning target volume (PTV), as well as excessive doses to the normal tissues. In addition, it is particularly difficult to manage these problems in Japanese/Asian patients, who have a relatively thin chest wall and small breasts.

Compared with conventional 3D-CRT techniques, intensity-modulated radiation therapy (IMRT) has been reported to afford an excellent dose distribution for postoperative radiation therapy including the lymph node area for breast cancer patients [8–10]. The TomoTherapy System has been developed exclusively for IMRT, and its use has spread in the last 10 years. It has several unique characteristics, including continuous movement of the couch up to 145 cm with the delivery of radiation, allowing it to treat a long field and thus avoid a field junction. This represents a great advantage in postoperative radiation therapy including the lymph node area in breast cancer patients, which usually involves a field of around 30 cm.

The TomoTherapy System also has two methods of beam delivery treatment modalities: helical TomoTherapy (TomoHelical; TH) and fixed-beam TomoTherapy (TomoDirect; TD). TH is the original beam delivery method used in the TomoTherapy System and provides rotational delivery of a fan beam [11]. Compared with 3D-CRT, TH improves target coverage with better sparing of organs at risk (OAR) in breast cancer patients, including the lung, heart and contralateral breast [12–14]. However, TH has the disadvantage of increased low-dose spread to the lung, associated with 360° rotational beam delivery.

In contrast, TD uses a fixed gantry angle instead of rotational beam delivery [3, 4]. TD may reduce the low-dose spread of radiation to intact lung tissues in patients with breast cancer, relative to the TH method. In addition, the TD system provides a 1–5 collimator leaf expansion function on the anterior edge of the beams, which helps to deliver the exact prescribed dose to the target by accounting for movement, such as breathing during irradiation [5]. TD may therefore be a more appropriate technique than TH for whole-breast irradiation. Indeed, some planning studies reported an excellent dose distribution of TD for whole-breast irradiation (without the lymph node area).

Two planning studies have compared TD and TH for postoperative radiation therapy targeting the regional lymph node area and chest wall/residual breast in breast cancer patients [15, 16]. In addition, no reports have described the clinical outcomes of such patients following radiation therapy using the TD technique. We considered that the TD technique may offer advantages in breast cancer patients with positive lymph nodes by (i) delivering high target-dose uniformity, (ii) ensuring a better dose-sparing of the lung and heart, and (iii) providing a large field covering the chest wall and lymph node area without a junction. We have therefore routinely used TD for these patients in our institution.

This study aimed to evaluate the utility of TD compared with TH and 3D-CRT for postoperative radiation therapy including the chest wall/residual breast tissue and regional lymph node area in patients with breast cancer. We also report on the preliminary clinical outcomes in terms of the feasibility and toxicity of TD in these patients.

MATERIALS AND METHODS

Patients

We have applied postoperative radiation therapy using the TomoTherapy System for all breast cancer patients in our institution since October 2010. Nineteen consecutive female breast cancer patients received postoperative radiation therapy including the chest wall/residual breast tissue and lymph node area, up to August 2014, including 10 patients with left-sided and 9 with right-sided disease. We included the 10 patients with left-sided disease in this study. Six of the 10 patients had undergone mastectomy and the others had received lumpectomy. Their median age at radiation therapy was 60.5 years (range: 39–75 years). Tumor classification was performed using the 7th edition of the UICC classification system for breast cancers. Their T and N stage were followings; T1N1 ($n = 2$), T1N2 ($n = 2$), T2N2 ($n = 2$), T2N3 ($n = 1$), T4N1 ($n = 1$) and T4N2 ($n = 2$). No patients had distant metastases. All patients gave their written informed consent for radiation therapy and retrospective evaluation of their clinical data. This retrospective study was approved by our institutional ethics committee (TGE01162-024).

Imaging

Computed tomography (CT) images were obtained using a LightSpeed Ultra 8 Slice system (General Electric Healthcare, Pewaukee, WI, USA). Patients were instructed to lie in a supine position with their arms raised above their head using an arm support and to breathe naturally. A 0.5 cm-thick-bolus was applied on the chest wall of patients who had undergone radical mastectomy

to deliver the dose at the skin surface. CT images were taken at 2.5-mm intervals.

Contouring

All contours were drawn using Pinnacle[3] (version 9.2; Philips Medical Systems, Eindhoven, The Netherlands) based on the Radiation Therapy Oncology Group (RTOG) Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions [17].

The clinical target volume (CTV) consisted of two parts the chest wall and/or residual breast (CTV breast), and level II–III of the axial and supraclavicular lymph node area (CTV LNs). The tumor bed was also delineated by reference to preoperative CT images, operative notes and surgical wounds. The PTV was generated by adding a 5 mm margin around each CTV (PTV breast and PTV LNs) excluding a 2-mm strip of skin, as well as the lung and heart tissue. PTV ALL was defined as the combined PTV breast and PTV LNs. The PTV ring was delineated at 3 cm around the PTV ALL to suppress the dose outside the PTV. The delineated OAR included the lungs, heart, contralateral breast tissue, thyroid and spinal cord. The CT images and volume contours were transferred to the planning station described below.

Dose prescriptions and constraints

For the planning study, a set of treatment plans using TD, TH and 3D-CRT were generated for each patient based on the CT images acquired for actual treatment performed in the clinical practice setting. One set of CT images was shared for the three plans (TD, TH and 3D-CRT plans). Dose constraints for planning target volume and organs at risk during planning are shown in Table 1. Fifty percent of the PTV was covered with prescribed dose, 50 Gy in 25 fractions. The first priority of the planning goals was set to deliver >95% of the prescribed dose to >95% of the PTV. Dose–volume histogram (DVH) points were adjusted throughout the optimization to best meet the OAR dose constraints without compromising the PTV coverage mentioned above.

TomoDirect and TomoHelical planning

TD and TH plans were generated using a TomoTherapy Hi-ART planning station (version 4.0, TomoTherapy Inc., WI, USA). All plans were optimized using a jaw width of 2.5 cm and a modulation factor of 2.0, with pitches of 0.25 and 0.287 for TD and TH plans, respectively. The dose calculation grid size was set to 'fine'. The same parameters for dose calculation were initially used for both TD and TH plans and then modified during plan optimization.

TomoDirect planning

A representative TD plan is shown in Fig. 1a. For PTV breast, the paired tangential beam angles were first determined based on a technique for a conventional linear accelerator. The beam angles were arranged to include the PTV and to minimize the doses to OARs. An additional four beams were then generated with modified gantry angles of ±5° from the original tangential beam set. For PTV LNs, four anterior beams and one posterior beam were used. To avoid a field junction, one of the six beams for PTV breast was shared with one of the four anterior beams for PTV LNs (Fig. 1b).

Table 1. Dose constraints for planning target volume and organs at risk during radiation therapy planning

PTV		
	D50% = 50Gy	(prescribed dose)
	D95% ≥47.5 Gy	
	D99% ≥43.5 Gy	
OARs		
Ipsilateral lung	V20 Gy < 30%–35%	
	V15 Gy < 50%	
Contralateral lung	V20 Gy < 0%	
	V15 Gy < 15%	
Heart	V15 Gy < 50%	
	Mean < 20 Gy	
Contralateral breast	Max < 5 Gy	
Spinal cord	Max < 25 Gy	
Body	Max < 55 Gy	

PTV = planning target volume, OARs = organs at risk, Dx% = percent receiving dose ≥ x% of the volume (minimum dose covering x% of the concerning volume), VxGy = percent volume receiving ≥xGy.

TomoHelical planning

A representative TH plan is shown in Fig. 2. To avoid low-dose spread to the lung, we applied dose-limiting volumes (DLVs) for the right breast, lung and 2 cm-expanded spinal cord, excluding the PTV ring. The DVLs were defined as 'blocking' the beam on the entrance side (a directional block) but not the exit side.

Three-dimensional conformal radiation therapy planning

3D-CRT treatment plans were generated using Pinnacle[3] (version 9.0; Philips Medical Systems). The plans consisted of anterior–posterior beams for PTV LNs and opposed tangential beams for PTV breast. Both sets of beams were arranged to match at the line of the lower edge of the clavicle head, using a half-beam block. Using the field-in-field technique, four sub-fields were applied for PTV breast and two for PTV LNs, to improve the dose distribution. A dose of 50 Gy was prescribed for each dose reference point for PTV breast and for PTV LNs. Each dose reference point was arranged to cover 95% of the PTV with 95% of the prescribed isodose line.

Treatment plan evaluation

The dose distribution and dose volume parameters for the PTV ALL and OARs in the TD plan were compared with those for the TH and 3D-CRT plans, respectively. We evaluated the D50%, D90%, D95% and Dmean of PTV ALL. To characterize the dose

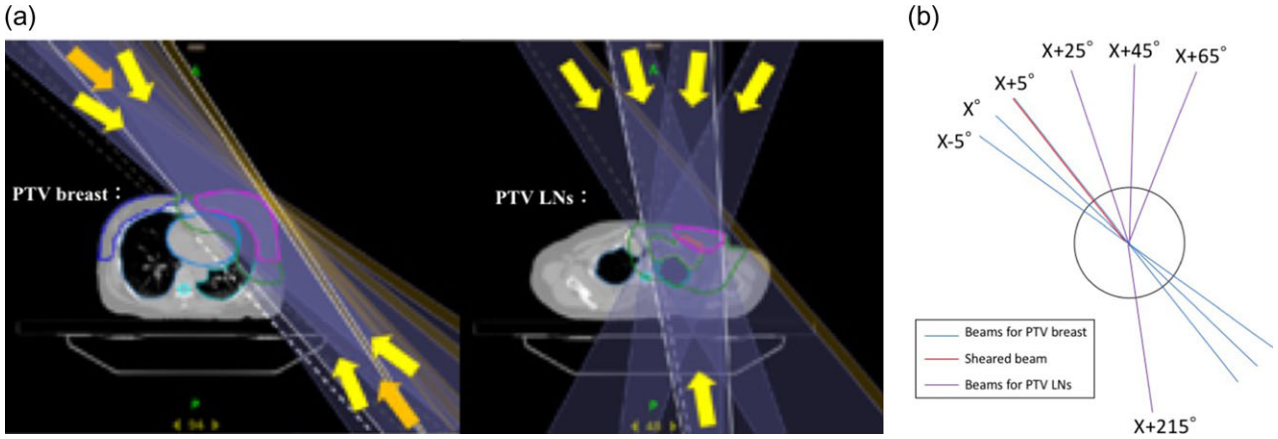

Fig. 1. TomoDirect (TD) planning. (a) **Representative TD plan.** (b) **Beam settings for TD plan. For planning target volume (PTV) breast, paired tangential beam angles were determined based on a conventional linear accelerator technique** [(a) **orange arrows; (b) X°)**] **and an additional four beams were then generated with modified gantry angles of ± 5°** [(a), **yellow arrows, (b), X ± 5°**]. **For PTV LNs, four anterior beams and one posterior beam were used** [(a), **yellow arrows; (b) X+25, 45, 65, 125°**]. **To avoid a field junction, one of the six beams for PTV breast was shared with one of the four anterior beams for PTV LNs** [(b), **X+5°**].

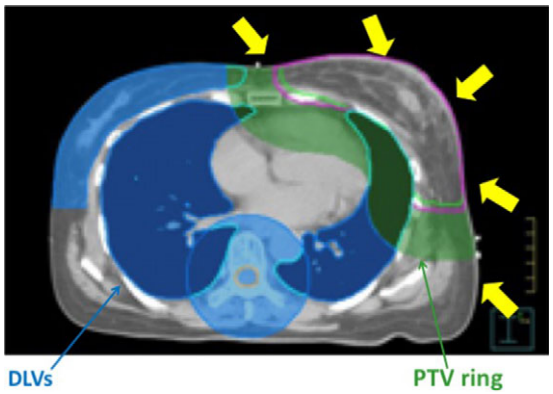

Fig. 2. TomoHelical (TH) planning. Representative TH plan. The planning target volume (PTV) ring was delineated around the PTV ALL at 3 cm to suppress the dose outside the PTV (green area). Dose-limiting volumes (DLVs) were applied to the right breast, lung and 2 cm-expanded spinal cord, excluding the PTV ring (blue area). DVLs were defined as blocking the beam on the entrance side only (directional block). The beams cannot enter the body from the blue area. The yellow arrows indicate the direction in which the beams can enter.

distributions to the targets, the heterogeneity index (HI) was defined as PTV ALL (D2%–D98%)/D50%.

The V5, V10, V15 and V20 for the ipsilateral, contralateral and total lung and their mean doses were evaluated. We also evaluated the V15, 25, 30 and 35 Gy for the heart, D1ml and Dmean for the contralateral breast, maximum dose to the spinal cord and maximum dose and V5 to the body. Dose parameters of the three plans were compared using Wilcoxon's signed-rank test. A *P*-value of <0.05 was considered statistically significant.

Patient characteristics and clinical outcomes were evaluated retrospectively. TD plans were applied in 9 of the 10 patients, and the remaining patient was treated by the TH plan.

RESULTS

Representative dose distributions of the TD, TH and 3D-CRT plans are shown in Fig. 3. The mean dosimetric parameters of the three plans in the 10 patients are summarized in Tables 2 and 3. Cumulative dose–volume histograms for the three plans are shown in Figs. 4–10.

Target volume

There were no significant differences in average D95% and D90% of PTV ALL among the TD, TH and 3D-CRT plans, because the treatment planning goals were all defined to achieve D95% > 95% of the prescribed dose (Table 2 and Fig. 4).

The average D50, Dmean and HI for PTV ALL were similar in the TD and TH plans, but significantly higher in the 3D-CRT plans. The 3D-CRT plan involved excessive radiation above the prescribed dose of 50 Gy to achieve the PTV coverage defined as the planning goal (Fig. 4). Compared with the TD and TH plans, the standard deviation (SD) of PTV ALL was greater for 3D-CRT, indicating large inter-individual differences (Fig. 5).

Dosimetry of organs at risk

Cumulative dose–volume histograms for OARs in the three plans are compared in Figs 6–10, and the mean dosimetric parameters are summarized in Table 3.

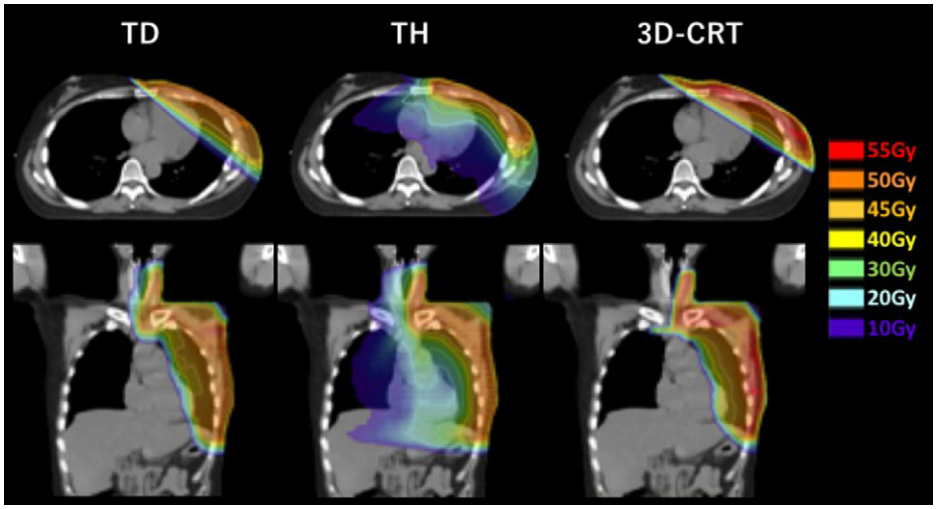

Fig. 3. Isodose distribution of TomoDirect (TD), TomoHelical (TH) and three-dimensional conformal radiation therapy (3D-CRT) plans in a representative patient.

Table 2. Statistical analysis of planning target volume distribution for TomoDirect (TD), TomoHelical (TH), and three-dimensional conformal radiation therapy (3D-CRT) plans

Structure		TD	TH	3D-CRT	*P*-value		
	Metric	Mean ± SD	Mean ± SD	Mean ± SD	TD vs TH	TD vs 3D-CRT	TH vs 3D-CRT
PTV All	D50% (Gy)	50.01 ± 0.06	50.04 ± 0.06	51.91 ± 0.50[b,c]	0.33	*0.01*	*0.01*
	D90% (Gy)	48.65 ± 0.34	48.63 ± 0.19	48.45 ± 0.56	0.88	0.11	0.29
	D95% (Gy)	47.56 ± 0.71	47.56 ± 0.39	47.15 ± 0.60	0.96	0.17	0.11
	Dmean (Gy)	49.74 ± 0.19	49.87 ± 0.08	51.46 ± 0.41[b,c]	*0.03*	*0.01*	*0.01*
	HI (-)	0.13 ± 0.04	0.12 ± 0.01	0.18 ± 0.02[b,c]	0.24	*0.01*	*0.01*

PTV = planning target volume, TD = TomoDirect, TH = TomoHelical, 3D-CRT = three-dimensional conformal radiation therapy, SD = standard deviation, Dx% = percent dose received by ≥x% of volume (minimum dose covering x% of the concerning volume), Dmean = mean dose, HI = homogeneity index derived by (D2%−D98%)/D50%. [a]Significant overdose compared with 3D-CRT ($P \leq 0.05$); [b]significant overdose compared with TH ($P \leq 0.05$); [c]significant overdose compared with TD ($P \leq 0.05$). Italic letters indicate significant differences.

Total lung

TD and 3D-CRT plans showed better dose sparing (< 17 Gy) of the total lung compared with TH (Fig. 6 and Table 3), but the TH plans spread a higher dose distribution. The total lung V5 and V10 were significantly higher in the TH compared with the TD and 3D-CRT plans, and V20 was significantly higher in the TD and 3D-CRT plans. The mean total lung doses for TD, TH and 3D-CRT were 7.84 ± 1.09, 12.88 ± 1.45 and 8.67 ± 1.48 Gy, respectively. TD had the lowest mean lung dose of the three plans. The dose distribution and parameters for the ipsilateral lung were similar to those for the total lung (Fig. 7 and Table 3).

Contralateral lung

There were apparent differences in the contralateral lung between TH and the other two plans (Fig. 8 and Table 3). The dose to the contralateral lung was reduced to nearly 0% in the TD and 3D-CRT plans, while the TH plan did not spare the contralateral lung. The TD and 3D-CRT plans showed significantly lower contralateral lung V5–V20 and Dmean values compared with TH.

Heart

The TH plan spread a higher dose distribution to the heart, while the TD plan delivered a lower dose, as in the lung (Fig. 9 and Table 3). The 3D-CRT plan showed a similar pattern of dose distribution to the heart as the TD plan, but the irradiated volume of the heart was higher in any dose area compared with TD.

The heart V30 values were 12.39 ± 5.0, 20.22 ± 5.95 and 17.47 ± 6.86 Gy in the TD, TH and 3D-CRT plans, respectively. V15, V25 and V30 were significantly lower in the TD compared with the other plans. Similarly, the mean heart doses were 8.54 ± 2.79, 21.09 ± 2.62 and 11.19 ± 3.55 Gy in the TD, TH and 3D-CRT plans, respectively, and were significantly lower in the TD compared with the other plans.

Table 3. Statistical analysis of sparing organs at risk with TomoDirect (TD), TomoHelical (TH), and three-dimensional conformal radiation therapy (3D-CRT) plans

Structure		TD	TH	3D-CRT	*P*-value		
	Metric	Mean ± SD	Mean ± SD	Mean ± SD	TD vs TH	TD vs 3D-CRT	TH vs 3D-CRT
Total lung	Dmean (Gy)	7.84 ± 1.09[a,b]	12.88 ± 1.45	8.67 ± 1.48[b]	*0.01*	*0.04*	*0.01*
	V5Gy (%)	22.49 ± 2.69[b]	94.59 ± 4.26	23.31 ± 3.11[b]	*0.01*	0.65	*0.01*
	V10Gy (%)	19.43 ± 2.73[b]	45.83 ± 13.02	19.49 ± 3.03[b]	*0.01*	0.88	*0.01*
	V15Gy (%)	17.52 ± 2.62	20.08 ± 4.38	17.81 ± 3.02	0.07	0.96	0.17
	V20Gy (%)	15.87 ± 2.49	13.63 ± 3.17[a,c]	16.68 ± 2.99	*0.02*	0.80	*0.02*
Ipsilateral lung	Dmean (Gy)	17.79 ± 2.19[a]	18.32 ± 2.24	19.64 ± 3.04	0.45	*0.05*	0.20
	V5Gy (%)	53.36 ± 5.13[b]	99.62 ± 0.69	55.37 ± 5.37[b]	*0.01*	0.58	*0.01*
	V10Gy (%)	46.52 ± 5.63[b]	65.27 ± 11.44	46.56 ± 5.98[b]	*0.01*	0.80	*0.01*
	V15Gy (%)	41.94 ± 5.38	39.80 ± 6.62	42.62 ± 6.25	0.58	0.88	0.20
	V20Gy (%)	37.98 ± 5.08	31.50 ± 5.90[a,c]	39.95 ± 6.34	*0.02*	0.80	*0.01*
Contralateral lung	Dmean (Gy)	0.70 ± 0.11[a,b]	8.95 ± 1.38	0.83 ± 0.13[b]	*0.01*	*0.03*	*0.01*
	V5Gy (%)	0.36 ± 0.38[b]	91.01 ± 7.27	0.35 ± 0.29[b]	*0.01*	0.95	*0.01*
	V10Gy (%)	0.01 ± 0.01[a,b]	31.72 ± 17.70	0.11 ± 0.12[b]	*0.01*	*0.03*	*0.01*
	V15Gy (%)	0.00 ± 0.00[a,b]	5.85 ± 4.09	0.06 ± 0.08[b]	*0.01*	*0.03*	*0.01*
	V20Gy (%)	0.00 ± 0.00[a,b]	0.75 ± 0.78	0.04 ± 0.06[b]	*0.01*	*0.04*	*0.01*
Heart	Dmean (Gy)	8.54 ± 2.79[a,b]	21.09 ± 2.62	11.19 ± 3.55[b]	*0.01*	*0.01*	*0.01*
	V15Gy (%)	17.21 ± 6.65[a,b]	63.24 ± 13.46	21.32 ± 7.64[b]	*0.01*	*0.01*	*0.01*
	V25Gy (%)	13.76 ± 5.50[a,b]	30.07 ± 7.75	18.68 ± 7.13[b]	*0.01*	*0.01*	*0.01*
	V30Gy (%)	12.39 ± 5.03[a,b]	20.22 ± 5.95	17.47 ± 6.86[b]	*0.01*	*0.01*	0.88
	V35Gy (%)	11.04 ± 4.59[a]	12.74 ± 4.56	16.19 ± 6.59	0.96	*0.01*	0.29
Contralateral breast	D1ml (Gy)	7.36 ± 3.78[a]	8.80 ± 2.70[a]	33.38 ± 12.11	0.07	*0.01*	*0.01*
	Mean (Gy)	1.11 ± 0.41[a,b]	5.24 ± 1.32	2.09 ± 0.80[b]	*0.01*	*0.01*	*0.01*
	V5	2.90 ± 3.46[b]	50.80 ± 35.20	5.55 ± 3.06[b]	*0.01*	0.09	*0.01*
Spinal cord	Max (Gy)	13.99 ± 5.34[a]	16.24 ± 3.01[a]	36.08 ± 11.82	0.09	*0.01*	*0.01*
Body	Max (Gy)	54.15 ± 0.73[a]	53.87 ± 0.57[a]	56.29 ± 0.43	0.33	*0.01*	*0.01*
	V5Gy (%)	21.91 ± 2.32[b]	58.94 ± 8.82	18.84 ± 2.44[b,c]	*0.01*	*0.01*	*0.01*

TD = TomoDirect, TH = TomoHelical, 3D-CRT = three-dimensional conformal radiation therapy, SD = standard deviation, Dx% = percent dose received by ≥x% of volume (minimum dose covering x% of the concerning volume), VxGy = percent volume receiving ≥xGy, D1ml = dose covering 1 ml of the volume, Dmean = mean dose to the volume, Drax = maximum dose to the volume. [a]Significantly improved over 3D-CRT ($P \leq 0.05$); [b]significantly improved over TH ($P \leq 0.05$); [c]significantly improved over TD ($P \leq 0.05$). Italic letters indicate significant differences.

Contralateral breast

The TD plans showed a lower dose distribution to the contralateral breast (Fig. 10 and Table 3). V5 was significantly higher in the TH compared with the other two plans. D1ml, representing the maximum dose to the contralateral breast, was significantly higher in the 3D-CRT compared with the other two plans. The mean doses were 1.11 ± 0.41, 5.24 ± 1.32 and 2.09 ± 0.80 Gy in the TD, TH and 3D-CRT plans, respectively, with TD showing the lowest mean dose to the contralateral breast.

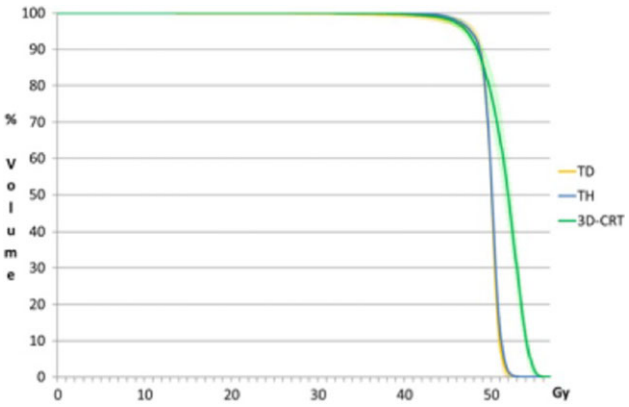

Fig. 4. Dose–volume relationship of planning target volume ALL. TD, TomoDirect; TH, TomoHelical; 3D-CRT, three-dimensional conformal radiation therapy. The green, blue, and orange areas indicate the standard deviations.

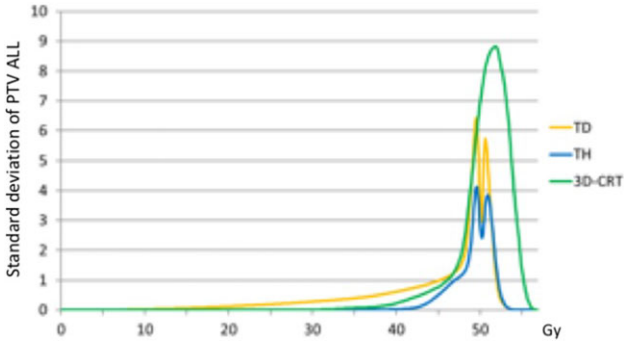

Fig. 5. Dose–volume relationship of standard deviation (SD) of planning target volume ALL. The SD was most marked for 3D-CRT, indicating large inter-individual differences. TD, TomoDirect; TH, TomoHelical; 3D-CRT, three-dimensional conformal radiation therapy.

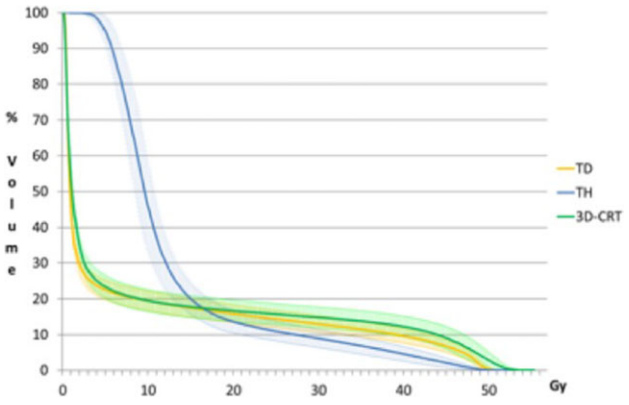

Fig. 6. Dose–volume relationship for total lung. TD, TomoDirect; TH, TomoHelical; 3D-CRT, three-dimensional conformal radiation therapy. The green, blue, and orange areas indicate the standard deviations.

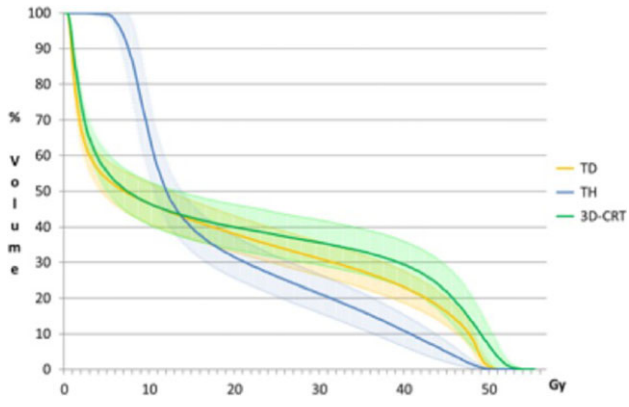

Fig. 7. Dose–volume relationship for ipsilateral lung. TD, TomoDirect; TH, TomoHelical; 3D-CRT, three-dimensional conformal radiation therapy. The green, blue, and orange areas indicate the standard deviations.

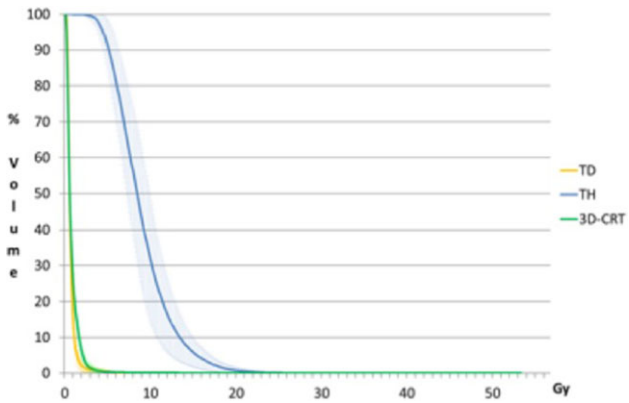

Fig. 8. Dose–volume relationship for contralateral lung. TD and 3D-CRT showed significantly lower contralateral lung V5–V20 and Dmean values compared with TH. TD, TomoDirect; TH, TomoHelical; 3D-CRT, three-dimensional conformal radiation therapy. The green, blue, and orange areas indicate the standard deviations.

Other tissues

TH and TD showed comparable maximum doses to the spinal cord and body (Table 3). The maximum dose of the 3D-CRT plan to the spinal cord was significantly higher than those of the other two plans. Low-dose exposure to the body (V5) was highest in the TH plan.

Clinical outcomes

The median follow-up time among the 10 patients was 43.9 months (range: 21.8–67.2 months). Nine of the 10 patients in the current study were treated with almost identical TD plans. None of the 10 patients had grade ≥3 acute toxicity. No patients experienced radiation pneumonitis or exclusive local recurrence. Two patients finally developed regrowth of the lymph nodes inside the radiation field,

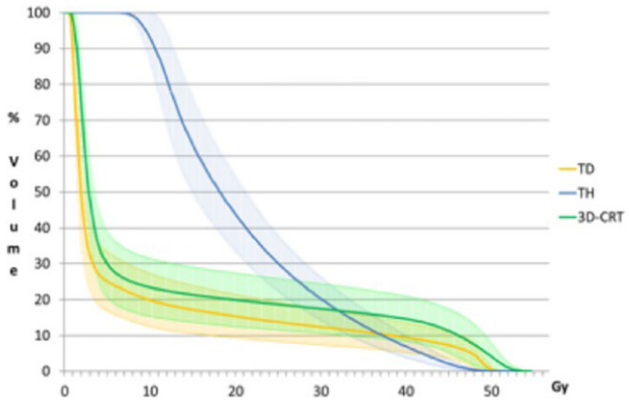

Fig. 9. Dose–volume relationship for whole heart. The dose distribution to the heart was significantly lower in TD compared with the other plans. TD, TomoDirect; TH, TomoHelical; 3D-CRT, three-dimensional conformal radiation therapy. The green, blue, and orange areas indicate the standard deviations.

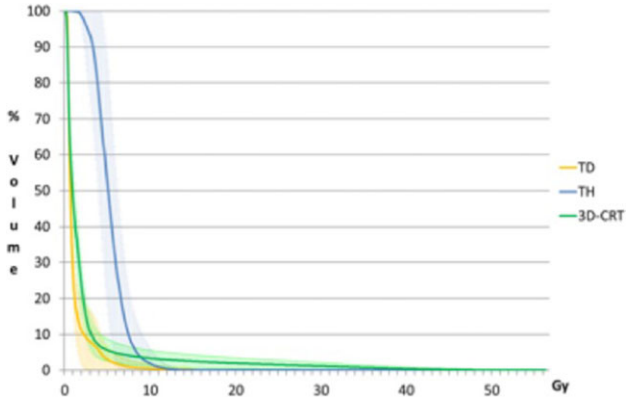

Fig. 10. Dose–volume relationship for contralateral breast. TD showed the lowest mean dose to the contralateral breast. TD, TomoDirect; TH, TomoHelical; 3D-CRT, three-dimensional conformal radiation therapy. The green, blue, and orange areas indicate the standard deviations.

but had already developed multiple bone, lung and/or liver metastases at least 6 months before in-field recurrence.

DISCUSSION

The present study demonstrated the usefulness of TD for postoperative radiation therapy targeted to the chest wall/residual breast tissue and lymph node area in patients with left-sided breast cancer. TD showed better dose sparing to the lungs, heart and contralateral breast than 3D-CRT, while maintaining adequate dose coverage to the PTV. TD plans also apparently regulated low-dose spread to OARs compared with TH plans.

In line with our study, Jones *et al.* [15] also concluded that fixed-beam TD using 11 beam angles may provide high-quality dosimetry compared with HT targeted to the affected chest wall/residual breast tissue and lymph node area for patients with left-sided breast cancer. Other studies also presented the dosimetric advantage of fix beam IMRT over rotation beam IMRT [18]. Compared with the doses in the planning study by Jones *et al.*, doses to OARs such as the contralateral breast and lung were relatively higher in the present study. The difference may be attributed to careful contouring of the target and OARs. In their study, the contour of the lymph node area was modified individually from the patients' CT images [15]. Previous studies showed great variabilities in intra- and inter-observer target and OAR contouring for breast irradiation, even for experienced radiation oncologists [19–22], resulting in clinically and dosimetrically significant differences [12]. The RTOG consensus contouring atlas was established to address these issues [13, 14]. In our study, target contouring was carried out according to the RTOG atlas, and each plan achieved its planning goal for sufficient dose distribution to the PTV.

To the best of our knowledge, this was the first planning study to use strict contouring based on the RTOG atlas for postoperative radiation therapy including the regional lymph node area in patients with breast cancer, using TD and TH modes. The results suggested that TD plans were clinically feasible, with acceptable short-term clinical outcomes, indicating that TD may be suitable for clinical application in these patients. Since the number of patients in the current study is too small for definitive conclusions, further study with a larger group of patients is required to demonstrate clinical application of TD.

Jones *et al.* [15] also reported that the average duration of TD plan using 11 beam angles was 10.3 min. The average duration in our study was 8.7 min (range, 7.9–9.8; data not shown) despite the fact that we used a similar number of beams as in their study. A shorter treatment time is safe and desirable for immobilization of patients during treatment.

Qi *et al.* [16] compared Elekta volumetric modulated arc therapy (VMAT), TH, TD and 3D-CRT for advanced left-sided breast cancer requiring regional nodal treatment. Their study showed that the VMAT and TH plans offer certain dosimetric advantages over TD. Similar results have been reported in other studies [23]. Consistent with our findings, they described that TD showed better dose sparing of the right lung and breast, and provided a shorter delivery time compared with the other plans. However, in contrast to our study, significantly greater heart sparing was found in rotational delivery techniques, such as VMAT and TH, than in TD [16]. We suggest that this difference may be caused by two possible factors. First, the body shape is quite different between Western and Asian women. Second, the lymph node area in the study by Qi *et al.* [16] included the internal mammary node, which is close to the heart. These differences may explain the higher dose distribution to the heart when using TD than when using VMAT and TH in their study. They concluded that it is important to judiciously select an appropriate delivery technique specifically for patients with certain risk factors to provide individualized care [16]. We agree with their recommendation.

The present results showed that both TomoTherapy plans (TD and TH) had better target-dose distributions than 3D-CRT. TomoTherapy demonstrated several advantages over 3D-CRT,

including the ability to deliver radiation continuously with no field junction. To avoid dose deficiency at the field junction in 3D-CRT, it is necessary to accept that areas immediately above and below the junction might receive higher doses, resulting in an overdose to the PTV with 3D-CRT. Evaluation of the dose at a field junction is often ambiguous and remains a problem, even using other IMRT methods. TomoTherapy thus offers the advantage of being able to treat a long field, without a field junction.

In addition, TomoTherapy planning (TD and TH) resulted in a D50 and mean dose around the prescribed dose, while 3D-CRT delivered more than the prescribed dose to achieve the planning goal of PTV D95 > 95%. The HI was also significantly better in the TomoTherapy compared with the 3D-CRT plans. IMRT using TomoTherapy thus demonstrates advantages over 3D-CRT in providing a uniform dose distribution over a complex shape of PTV.

Finally, the SD values of DVH for PTV were smaller for TomoTherapy compared with the 3D-CRT plan (Fig. 5), indicating that plan quality varied more among patients for 3D-CRT compared with TomoTherapy. This suggests that 3D-CRT was less able to adapt to anatomical differences among patients in terms of individual body shape, while TomoTherapy plans demonstrated greater flexibility.

Although the TD and TH plans showed similar target-dose distributions, TD had some advantages in terms of dose distribution to OARs compared with TH. First, TD reduced low-dose spread to normal tissues. Since the development of IMRT, low-dose spread, represented by lung V5, has been recognized as an important factor predicting lung toxicity, in addition to the conventional dosimetric factors such as V20 and mean lung dose [24–26]. In the current study, TD markedly suppressed V5 compared with TH, with no great increase in lung V20.

Low-dose spread also affects the induction of second primary cancers. Santos *et al.* estimated the risk of second primary cancer following postoperative radiation therapy for breast cancer and concluded that the lungs and contralateral breast had high life-attributed risk estimates [27]. Furthermore, Ng and Shuryak reviewed organ-specific second primary cancer risk and showed that breast tissue had a much higher estimated relative risk than other organs [28]. In a study of women who received radiation therapy for breast cancer between 1985 and 1999, Stovall *et al.* showed that the risk of secondary breast cancer in the contralateral breast was increased in women younger than 40 years who received >1.0 Gy maximum dose to the breast tissue [29]. These results suggest that low-dose spread should be avoided as much as possible. In the current study, TD reduced the dose to contralateral breast tissue compared with either TH or 3D-CRT.

According to Darby *et al.*, the risk of a major coronary event increased linearly with increasing mean dose to the heart [30], with a magnitude of risk of 7.4% per gray, with no apparent threshold below which there was no risk. Another study also examined the relationship between the relative volumes of irradiated heart or pericardium and late cardiac toxicity [31]. In the present study, TD significantly reduced the mean heart dose and V30 (or the dose to less than 30% volume of the heart) compared with TH. Recent publications have discussed the evaluation of dose to coronary artery (LDA) and left ventricle (LV) and this is an important issue [32, 33]. The dose constraints were not assigned to LDA and LV in the optimization process of this planning study, and further study is required to assess the superiority of TD or TH for heart.

TD also has the advantage of a leaf expansion function, compared with TH. This technique is exclusive to TD, making it appropriate for chest wall/breast irradiation. Furthermore, TD shares some characteristics of treatment planning with 3D-CRT. The pattern of DVHs and dose distribution of TD resemble those of 3D-CRT, because both modalities use static beams and similar arrangement of beam angles. Given that 3D-CRT has been routinely used for postoperative radiation therapy including the lymph node area in patients with breast cancer, its effects and toxicities are well known, and the equivalent effects/toxicities of TD plans can thus be predicted based on experiences with 3D-CRT plans. In contrast, TH plans have not been widely applied for these patients, and some unexpected side effect might thus occur.

In summary, the advantages of TD over 3D-CRT and TH suggest that TD should be recommended for postoperative radiation therapy including the regional lymph node area in patients with breast cancer. Given that the recurrence risk in patients requiring this type of radiation is relatively high, the benefits of improving dose distribution to the PTV while sparing OARs may be to help prevent locoregional recurrence, improve clinical outcomes and prolong survival.

This study had some limitations. It was a retrospective study with a small number of patients and short follow-up times. However, no patients developed locoregional recurrence or any adverse events >grade 2, including radiation pneumonitis. Further longer-term studies in more patients are needed to confirm these results and establish the role of TD in these patients. Some studies demonstrated a longer favorable clinical outcome of postoperative radiation therapy including the regional lymph node area in patients with breast cancer using fix beam IMRT rather than TD using TomoTherapy [34]. These data support the application of TD to this disease.

In conclusion, compared with 3D-CRT and TH, TD provides better target-dose distribution with optimal OAR sparing for postoperative radiation including the chest wall/residual breast tissue in patients with breast cancer. TD was shown to be clinically acceptable, suggesting that it should be considered as a useful treatment modality in patients with breast cancer and positive lymph nodes. However, further studies are required to clarify the usefulness of TD in these patients.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

We thank the all staff of the Department of Radiation Oncology at Shonan Kamakura General Hospital for their continued assistance. Oral presentation at the 26th Annual Meeting of the Japan Society for Radiation Oncology.

REFERENCES

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127–35.
2. Dragun AE, Huang B, Gupta S et al. One decade later: trends and disparities in the application of post-mastectomy radiotherapy since the release of the American Society of Clinical Oncology clinical practice guidelines. *Int J Radiat Oncol Biol Phys* 2012;83:e591–6.
3. Sautter-Bihl ML, Sedlmayer F, Budach W et al. DEGRO practical guidelines: radiotherapy of breast cancer III—radiotherapy of the lymphatic pathways. *Strahlenther Onkol* 2014;190:342–51.
4. Taylor ME, Haffty BG, Rabinovitch R et al. ACR appropriateness criteria on postmastectomy radiotherapy expert panel on radiation oncology-breast. *Int J Radiat Oncol Biol Phys* 2009;73:997–1002.
5. Truong PT, Olivotto IA, Whelan TJ et al. Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional post-mastectomy radiotherapy. *CMAJ* 2004;170:1263–73.
6. Yarnold J. Early and locally advanced breast cancer: diagnosis and treatment National Institute for Health and Clinical Excellence guideline 2009. *Clin Oncol (R Coll Radiol)* 2009;21:159–60.
7. Fortin A, Dagnault A, Blondeau L et al. The impact of the number of excised axillary nodes and of the percentage of involved nodes on regional nodal failure in patients treated by breast-conserving surgery with or without regional irradiation. *Int J Radiat Oncol Biol Phys* 2006;65:33–9.
8. Woo TC, Pignol JP, Rakovitch E et al. Body radiation exposure in breast cancer radiotherapy: impact of breast IMRT and virtual wedge compensation techniques. *Int J Radiat Oncol Biol Phys* 2006;65:52–8.
9. Beckham WA, Popescu CC, Patenaude VV et al. Is multibeam IMRT better than standard treatment for patients with left-sided breast cancer? *Int J Radiat Oncol Biol Phys* 2007;69:918–24.
10. Selvaraj RN, Beriwal S, Pourarian RJ et al. Clinical implementation of tangential field intensity modulated radiation therapy (IMRT) using sliding window technique and dosimetric comparison with 3D conformal therapy (3DCRT) in breast cancer. *Med Dosim* 2007;32:299–304.
11. Mackie TR, Holmes T, Swerdloff S et al. Tomotherapy: a new concept for the delivery of dynamic conformal radiotherapy. *Med Phys* 1993;20:1709–19.
12. Li XA, Tai A, Arthur DW et al. Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG multi-institutional and multiobserver study. *Int J Radiat Oncol Biol Phys* 2009;73:944–51.
13. Rudra S, Al-Hallaq HA, Feng C et al. Effect of RTOG breast/chest wall guidelines on dose-volume histogram parameters. *J Appl Clin Med Phys* 2014;15:4547.
14. Yang J, Woodward WA, Reed VK et al. Statistical modeling approach to quantitative analysis of interobserver variability in breast contouring. *Int J Radiat Oncol Biol Phys* 2014;89:214–21.
15. Jones R, Yang W, Read P et al. Radiation therapy of post-mastectomy patients with positive nodes using fixed beam tomotherapy. *Radiother Oncol* 2011;100:247–52.
16. Qi XS, Liu TX, Liu AK et al. Left-sided breast cancer irradiation using rotational and fixed-field radiotherapy. *Med Dosim* 2014;39:227–34.
17. RTOG (Radiation Therapy Oncology Group). Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions. https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx (26 March 2019, date last accessed).
18. Wang J, Yang Z, Hu W et al. Intensity modulated radiotherapy with fixed collimator jaws for locoregional left-sided breast cancer irradiation. *Oncotarget* 2017;8:33276–84.
19. Landis DM, Luo W, Song J et al. Variability among breast radiation oncologists in delineation of the postsurgical lumpectomy cavity. *Int J Radiat Oncol Biol Phys* 2007;67:1299–308.
20. Struikmans H, Warlam-Rodenhuis C, Stam T et al. Interobserver variability of clinical target volume delineation of glandular breast tissue and of boost volume in tangential breast irradiation. *Radiother Oncol* 2005;76:293–9.
21. Pitkanen MA, Holli KA, Ojala AT et al. Quality assurance in radiotherapy of breast cancer—variability in planning target volume delineation. *Acta Oncol* 2001;40:50–5.
22. Hurkmans CW, Borger JH, Pieters BR et al. Variability in target volume delineation on CT scans of the breast. *Int J Radiat Oncol Biol Phys* 2001;50:1366–72.
23. Xu Y, Wang J, Hu Z et al. Locoregional irradiation including internal mammary nodal region for left-sided breast cancer after breast conserving surgery: dosimetric evaluation of 4 techniques. *Med Dosim* 2018;18:S0958–3947.
24. Allen AM, Czerminska M, Janne PA et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. *Int J Radiat Oncol Biol Phys* 2006;65:640–5.
25. Chen J, Hong J, Zou X et al. Association between absolute volumes of lung spared from low-dose irradiation and radiation-induced lung injury after intensity-modulated radiotherapy in lung cancer: a retrospective analysis. *J Radiat Res* 2015;56:883–8.
26. Song CH, Pyo H, Moon SH et al. Treatment-related pneumonitis and acute esophagitis in non-small-cell lung cancer patients treated with chemotherapy and helical tomotherapy. *Int J Radiat Oncol Biol Phys* 2010;78:651–8.
27. Santos AM, Marcu LG, Wong CM et al. Risk estimation of second primary cancers after breast radiotherapy. *Acta Oncol* 2016;55:1331–7.
28. Ng J, Shuryak I. Minimizing second cancer risk following radiotherapy: current perspectives. *Cancer Manag Res* 2015;7:1–11.
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. Darby SC, Ewertz M, McGale P et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;36:987–98.
31. Wei X, Liu HH, Tucker SL et al. Risk factors for pericardial effusion in inoperable esophageal cancer patients treated with

definitive chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2008;70:707–14.
32. Duma MN, Herr AC, Borm KJ et al. Tangential field radiotherapy for breast cancer—the dose to the heart and heart subvolumes: what structures must be contoured in future clinical trials? *Front Oncol* 2017;7:1–6.
33. Jacob S, Camilleri J, Derreumaux S et al. Is mean heart dose a relevant surrogate parameter of left ventricle and coronary arteries exposure during breast cancer radiotherapy: a dosimetric evaluation based on individually-determined radiation dose (BACCARAT study). *Radiat Oncol* 2019;14:1–10.
34. Ho AY, Ballangrud A, Li G et al. Long-term pulmonary outcomes of a feasibility study of inverse-planned, multibeam intensity modulated radiation therapy in node-positive breast cancer patients receiving regional nodal irradiation. *Int J Radiat Oncol Biol Phys* 2019;103:1100–8.