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Evaluation of DIBH and VMAT in Hypofractionated Radiotherapy for Left-Sided Breast Cancers After Breast-Conserving Surgery: A Planning Study

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Abstract

Background: Dosimetric parameters of the planning target volume (PTV) and organs at risk (OARs) were compared among 3 different radiotherapy (RT) modalities in left breast cancer patients after breast-conserving surgery (BCS). **Methods:** Eleven patients with left breast cancer after BCS were enrolled and underwent CT simulation in the free breathing (FB) and deep inspiration breath-hold (DIBH) position. Three-dimensional conformal RT (3DCRT) and volumetric modulated arc therapy (VMAT) plans were generated for each patient in the DIBH positions. A 3DCRT plan was also created in the FB position. A dose-volume histogram (DVH) was used to analyze each evaluation index of PTV and OARs. The principal outcomes were PTV dose, heart dose, right breast dose, left anterior descending coronary artery (LADCA) dose, and left lung dose. **Results:** For 3DCRT plans, significant dose reductions were demonstrated in all evaluation parameters of the heart, LADCA, and left lung doses in the DIBH position compared with those in the FB position ($P < 0.05$). In the DIBH position, significant dose reductions were found in the heart and LADCA in VMAT plans compared to those in 3DCRT plans ($P < 0.05$). For the right breast, VMAT reduced Dmean significantly (0.32 Gy vs 0.08 Gy, $P < 0.01$). There were no significant differences between 3DCRT and VMAT plans for the left lung dose in the DIBH position. The indicators of PTV had no significant difference between the 3 plans. **Conclusion:** DIBH and VMAT could reduce dosimetric parameters of the OARs in left breast cancer patients after BCS. RT plans for left breast cancer after BCS can be optimized by DIBH and VMAT techniques to minimize radiation-induced toxicity.

Keywords

breast cancer, radiotherapy, deep inspiration breath hold, volumetric modulated arc therapy

Abbreviations

RT, radiotherapy; BCS, breast-conversing surgery; 3DCRT, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; IMRT, intensity-modulated radiotherapy; CTV, clinical target volume; DIBH, deep inspiration breath hold; FB, free breathing; LADCA, left anterior descending coronary artery; OAR, organ at risk; PTV, planning target volume; SD, standard deviation; V20Gy, volume receiving at least 20 Gy; V10Gy, volume receiving at least 10 Gy; V5Gy, volume receiving at least 5 Gy; V2Gy, volume receiving at least 2 Gy

Introduction

Breast cancer is the most common type of cancer among women worldwide.[1] Radiotherapy (RT) is a vital component in the management of breast cancer and has become one of the standard treatment choices for many patients with early-stage breast cancer after breast-conserving surgery (BCS).

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Despite advances in radiation techniques and methods, toxicities of RT still inevitably occur. RT involves some radiation exposure of the heart and lung, and serious side effects can pose competing risks of mortality, especially for patients with left breast cancer. Previous studies[2-4] showed increases in the incidences of acute myocardial infarction, ischemic heart disease, stenosis in the left anterior descending coronary artery (LADCA), angina pectoris, pericarditis, and valvular heart disease after left-sided RT compared to those after right-sided RT. Radiation-induced side effects are correlated with the absorbed dose and irradiated volume. It is therefore important to reduce exposure of organs at risk (OARs) in order to decrease the incidence rate of side effects and improve survival.

Some modern treatment techniques can reduce the cardiac toxicity of left-sided breast irradiation. Deep inspiration breath-hold (DIBH) is an RT method in which patients take a deep breath before treatment and hold their breath while the radiation is delivered. Lungs fill with air and the heart will move away from the chest wall by DIBH. With the rapid development of hardware and software in the field of RT, in addition to three-dimensional conformal RT (3DCRT), volumetric modulated arc therapy (VMAT) and intensity-modulated RT (IMRT) have been developed and are widely used now in clinics. VMAT is a new RT technique that can achieve highly conformal dose distributions in the target volume coverage and protect normal breast tissue simultaneously.[5] It is currently used widely for prostate, head, and neck cancer, but is less used for breast cancer in Japan.

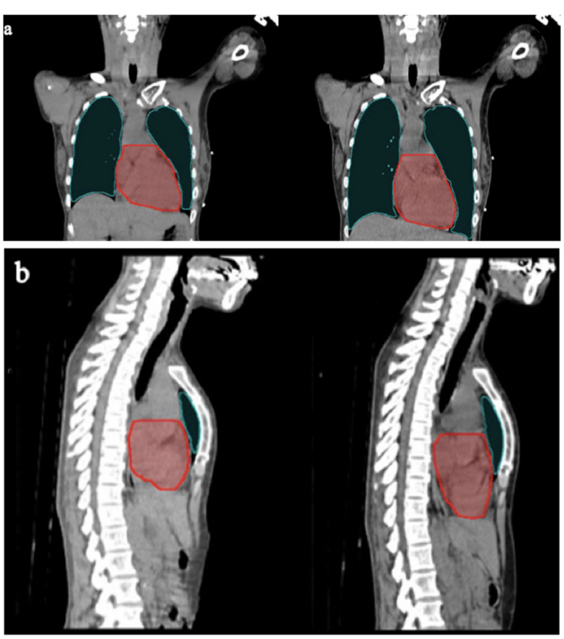

Figure 1. The spatial position differences of the heart and lung between the 2 CT simulations in the FB and DIBH position in a left-sided breast cancer case. (a) Coronal section and (b) Sagittal section (lung: cyan curve; heart: red curve; left: FB; right: DIBH). Abbreviations: FB, free breathing; DIBH, deep inspiration breath hold.

In this study, we evaluated the effects of DIBH irradiation and VMAT plans under DIBH on OAR dose deposition through a comparison of dosimetric parameters of OARs in different irradiation plans in patients with left-sided breast cancer after BCS. Our results will be helpful for determining a rational strategy for patients with left-sided breast cancer.

Materials and Methods

Patients: Eleven patients who received BCS for left-sided breast cancer were included in this planning stud, which was approved by our institutional review board and ethics committee (approval number: 20531. The patients were all females aged 30 to 60 years. All of the patients underwent FB and DIBH CT scans at intervals of 2.0 to 2.5 mm in the supine position with their left arm above their head. All mammary glandular tissue was delineated as the clinical target volume (CTV): the upper border was the second rib insertion, the lower border at the plane where glandular tissue disappears, the medial border was the lateral edge of the sternum, the lateral border was the lateral breast fold. The planning target volume (PTV) was generated by expanding the CTV with an additional 10-mm circular margin, but within 2 mm of the skin surface. A 3DCRT plan was conventionally treated with tangential fields 4 to 6 MV photon beam. Dynamic wedge filters and/or the field in field technique were used to obtain a homogeneous dose distribution.[6,7] In 3DCRT, 42.4 Gy in 16 fractions of 2.65 Gy was prescribed to the isocenter. A VMAT plan used dual partial arcs of 40° to 50° with a collimator angle of 30° and treatment couch angle of 0°, rotating in opposite directions. In VMAT, 42.4 Gy in 16 fractions covering 95% of the PTV was prescribed. The maximum dose rate was 1400 MU/min for 6X-FFF beams. The OARs like heart, LADCA, left lung and right breast were generated in accordance with the European Society for RT and Oncology (ESTRO) guidelines.[8] The principal outcomes were PTV dose, right breast dose, heart dose, LADCA dose, and left lung dose. The following evaluation parameters were used for comparison: mean dose (Dmean), maximum dose (Dmax), volume receiving at least 20 Gy (V20), volume receiving at least 10 Gy (V10), and volume receiving at least 5 Gy (V5) to the left lung; Dmean, Dmax, and V5 to the heart; Dmean, Dmax, and volume receiving at least 2 Gy (V2) to the LADCA; Dmean, Dmax, and V2 to the right breast; Dmean, Dmax, volume receiving at least 95% of total dose (V95), and volume receiving at least 90% of total dose (V90) to PTV. All treatment plans were designed and calculated by the Analytical Anisotropic Algorithm (AAA) of the Eclipse planning system (version 13.6, Varian Medical Systems, Palo Alto, CA). The calculation grid size was 2 mm. The plans were compared according to dose-volume histogram (DVH) analysis.

Statistical analysis: Doses and volume differences between the treatment plans were evaluated by the Wilcoxon signed-rank test. Data analyses were conducted using SPSS 26 (IBM SPSS). $P < .05$ was considered statistically significant.

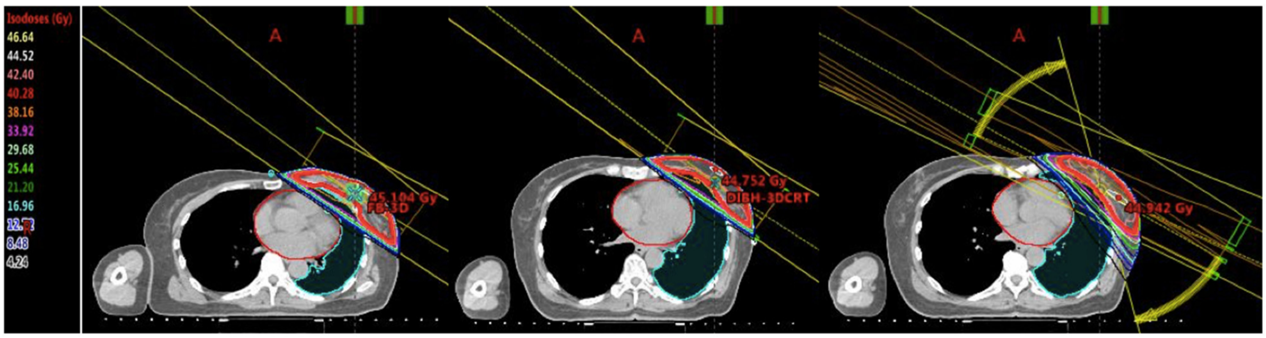

Figure 2. The beam arrangement and isodose distribution of 3 plans for the cases based on 1 patient sample.

Results

Lung volume and spatial position of the heart changed in different breathing maneuvers as shown in Figure 1. Deep inspiration causes downward displacement of the heart and expansion of the lungs. Figure 2 shows the beam arrangement and isodose distribution of the 3 plans for cases based on 1 patient sample. Compared with 3DCRT plans, the area receiving 95% of the total dose (thick red line) in VMAT plans fitted breast morphology much better.

Dose-volume histograms (DVHs) of OARs and PTV for 3 plans in a case are shown in Figure 3. For the heart, LADCA, and right breast, the DIBH plans were better than the FB plan and the VMAT plan was better than the 3DCRT plan on DVH. For the left lung, the VMAT plan had lower relative volume compared to that in the 3DCRT plan at higher dose regions (eg, V20) but not at lower dose regions (eg, V5). At the same dose, relative volume in the DIBH plan was lower than that in the FB plan. For the PTV, no obvious differences were found between the 3 plans, there was a lower dose in the higher dose region (over 100% of total dose) and maximum dose with the VMAT plan.

The results for doses to OARs and PTV are summarized in Table 1.

DIBH versus FB

For the 3DCRT plans, significant dose reductions were demonstrated in all evaluation parameters of the heart, LADCA, and left lung doses in the DIBH position compared with those in the FB position ($P < 0.05$). Compared to that in the FB position, heart Dmean was significantly reduced by 0.64 Gy (1.52 Gy vs 0.88 Gy, $P < 0.01$). Relative V5 was reduced by 91.4% (2.68% vs 0.23%, $P < 0.01$). The differences in mean dose (3.04 Gy vs 2.21 Gy, $P < 0.01$) and V2 (58.42% vs 49.49%, $P = 0.03$) for the LADCA approached statistical significance. Left lung Dmean was reduced by 1.52 Gy (6.29 Gy vs 4.77 Gy, $P < 0.01$). Left lung Dmax for DIBH was slightly better (41.20 Gy vs 40.42 Gy, $P = 0.04$) than that for FB. Relative V20 was significantly reduced by 33.22% (12.13% vs 8.10%, $P < 0.01$), V10 was significantly reduced by 29.98% (15.81% vs 11.07%, $P < 0.01$), and V5 was significantly reduced by 18.98% (23.23% vs 18.82%, $P < 0.01$) with DIBH compared to those for FB. The indicators of PTV and right breast had no significant difference between groups.

3DCRT versus VMAT

In the DIBH position, significant dose reductions were found in the heart and LADCA in VMAT plans compared with those in 3DCRT plans ($P < 0.05$). Dmean (0.88 Gy vs 0.47 Gy, $P < 0.01$) for the heart was significantly improved with VMAT, and V5 decreased by 82.61% (0.23% vs 0.04%, $P < 0.01$). There were no significant differences between 3DCRT and VMAT plans for the lung dose. For VMAT plans, Dmean (4.77 Gy vs 4.34 Gy, $P = 0.51$), Dmax (40.42 Gy vs 39.96 Gy, $P = 0.72$), and V20 (8.10% vs 5.52%, $P = 0.05$) of the left lung were slightly lower and V5 (18.82% vs 23.39%, $P = 0.05$) and V10 (11.07% vs 14.05%, $P = 0.06$) of the left lung were higher than those for 3DCRT plans. LADCA Dmean was significantly reduced by 0.78 Gy (2.21 Gy vs 1.43 Gy, $P < 0.01$). Relative V2 decreased by 59.16% (49.49% vs 20.21%, $P < 0.01$). For the right breast, VMAT reduced Dmean significantly (0.32 Gy vs 0.08 Gy, $P < 0.01$). Dmax and V2 were lower than that in 3DCRT but with no significant difference ($P = 0.11$, $P = 0.05$). VMAT had no significant impact on PTV indicators compared with 3DCRT plans.

Discussion

In this study, we evaluated the effects of DIBH and VMAT irradiation techniques on OAR dose deposition through a comparison of dosimetric parameters of OARs in different irradiation plans for patients with left-sided breast cancer after BCS. We found that DIBH irradiation significantly reduced the heart, LADCA, and left lung doses compared to those with FB irradiation. Moreover, compared with 3DCRT plans, VMAT plans provided an additional significant further dose reduction for the heart and LADCA in DIBH irradiation. The PTV results indicated that the treatment efficacies of the 3 plans were compatible. This suggests that the DIBH and VMAT technique

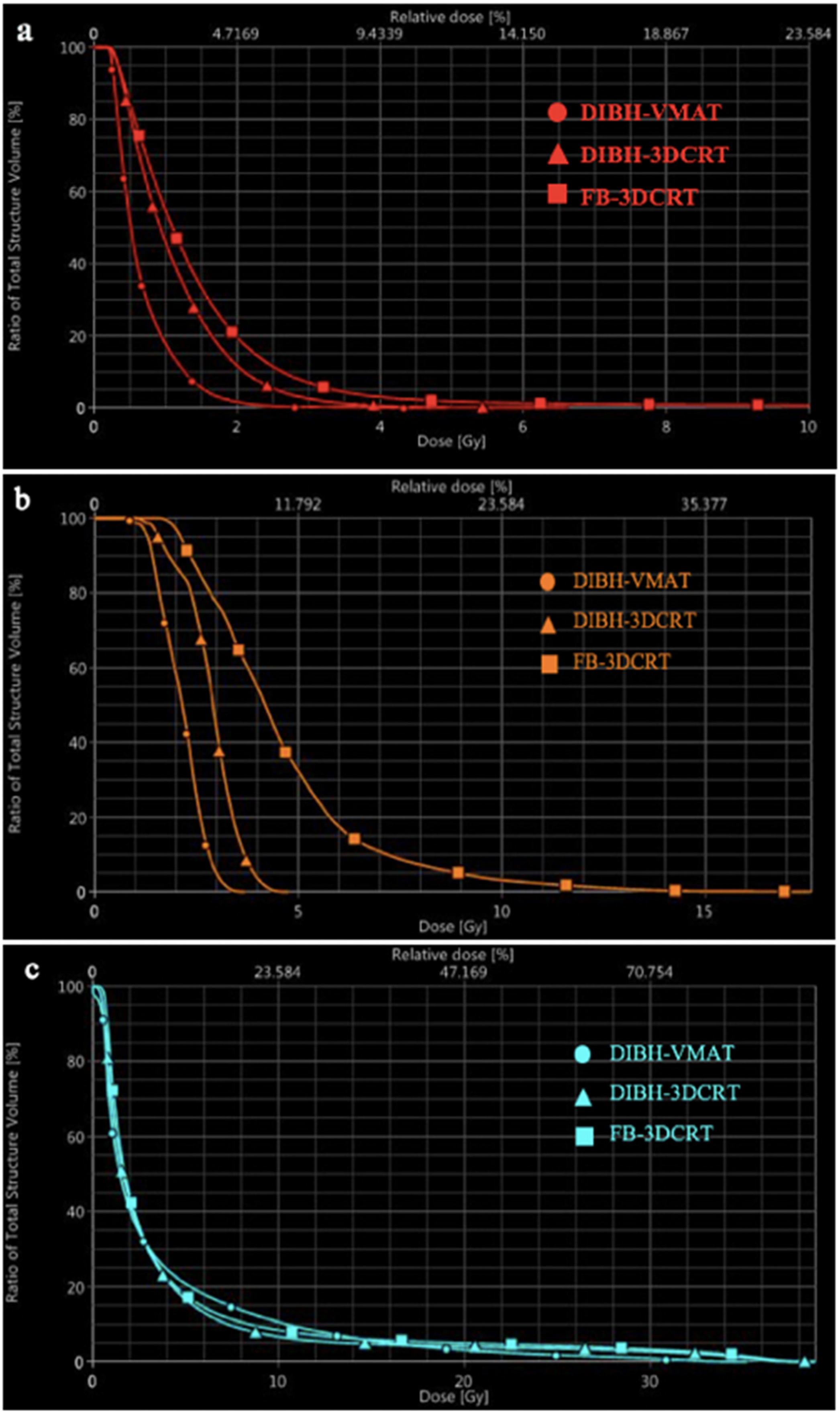

Figure 3. DVHs of OARs for 3 plans for the cases based on 1 patient sample. (a) Heart, (b) LADAC, (c) Lung, (d) Right breast, and (e) PTV. Abbreviations: DVH, dose-volume histogram; OARs, organs at risk; LADAC, left anterior descending coronary artery; PTV, planning target volume.(continued)

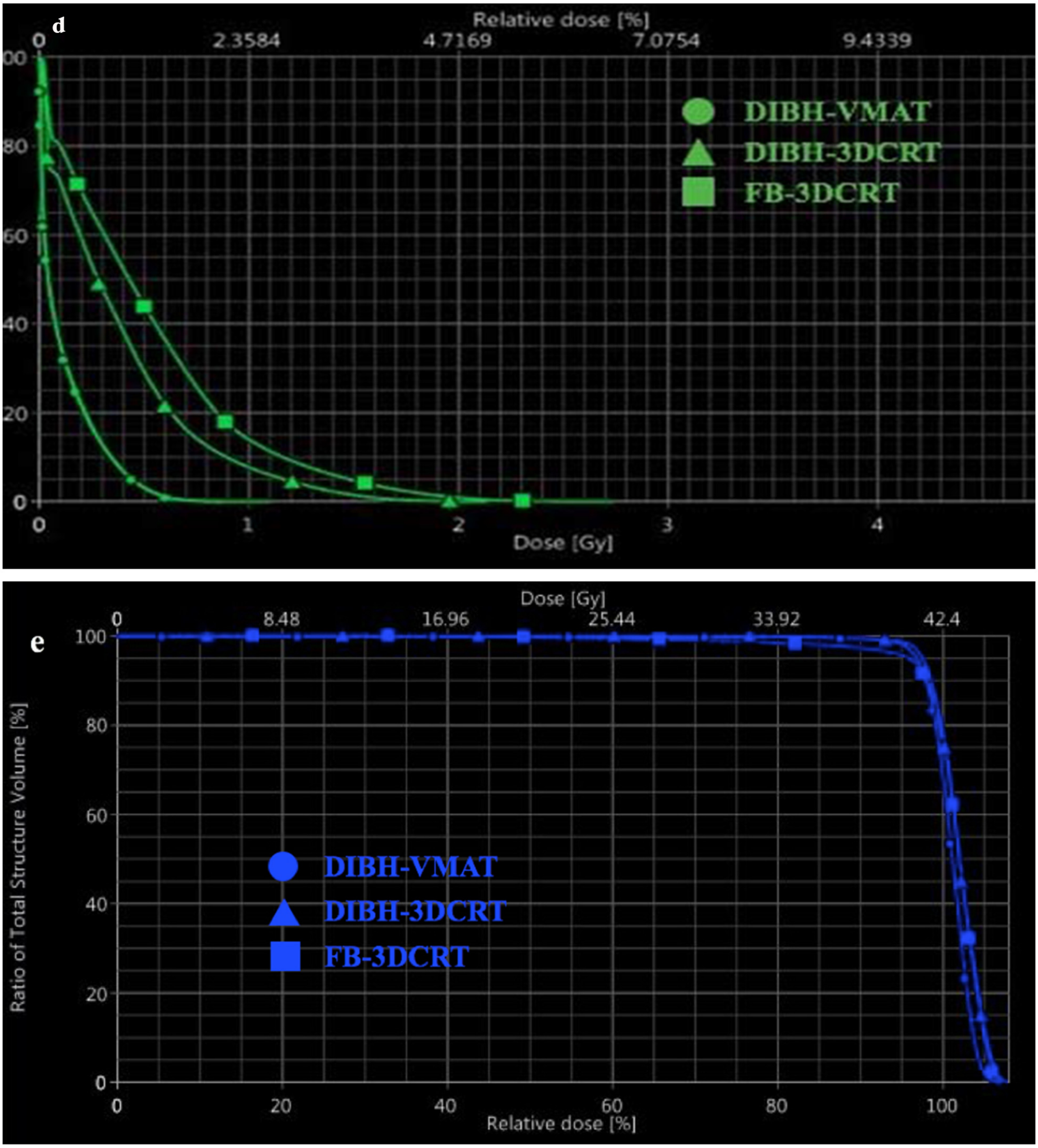

Figure 3. Continued.

could reduce the risk of radiation-induced toxicity, especially cardiac morbidity.

There are other studies on dose distribution with DIBH and VMAT techniques in RT of left-sided breast cancer.[9-13] We reached a similar conclusion that DIBH and VMAT techniques could reduce the dose to heart, left lung, and LADAC while remains the PTV coverage. Our dosimetric parameters were lower than theirs because we used the hypofractionated RT dose scheme. For 3DCRT and VMAT plan, our results showed that VMAT plans significantly reduced doses to the heart and LADCA compared with those in 3DCRT plans. Compared with 3DCRT plans, the VMAT technique slightly but insignificantly reduced Dmean, Dmax, and V20 of the left lung. VMAT plans reduced the high dose volume of the left lung but increased the low dose volume simultaneously because of the increase in scattered radiation. For the dose to

Table 1. Comparison of dosimetry metrics of OARs for all 11 patients (Mean ± SD).

	Dosimetric parameter	FB-3DCRT	DB-3DCRT	DB-VMAT	*P*-value: DIBH versus FB with 3DCRT	*P*-value: 3DCRT versus VMAT for DIBH
Heart	Dmean (Gy)	1.52 ± 0.35	0.88 ± 0.15	0.47 ± 0.15	<0.01	< 0.01
	Dmax (Gy)	29.33 ± 2.73	13.80 ± 8.42	5.32 ± 2.39	<0.01	<0.01
	V5 (%)	2.68 ± 1.19	0.23 ± 0.18	0.04 ± 0.07	< 0.01	<0.01
Lung-L	Dmean (Gy)	6.29 ± 1.35	4.77 ± 0.86	4.34 ± 0.97	<0.01	0.51
	Dmax (Gy)	41.20 ± 1.39	40.42 ± 1.25	39.96 ± 2.91	0.04	0.72
	V20 (%)	12.13 ± 3.65	8.10 ± 2.51	5.52 ± 2.27	<0.01	0.05
	V10 (%)	15.81 ± 4.05	11.07 ± 2.86	14.05 ± 3.31	<0.01	0.05
	V5 (%)	23.23 ± 4.03	18.82 ± 2.82	23.39 ± 5.22	<0.01	0.06
LADCA	Dmean (Gy)	3.04 ± 0.75	2.21 ± 0.33	1.43 ± 0.35	< 0.01	<0.01
	Dmax (Gy)	12.29 ± 5.92	5.94 ± 2.15	3.76 ± 1.63	<0.01	<0.01
	V2 (%)	58.42 ± 15.72	49.49 ± 15.34	20.21 ± 14.73	0.03	<0.01
Breast-R	Dmean (Gy)	0.32 ± .12	0.32 ± 0.13	0.08 ± 0.03	0.89	<0.01
	Dmax (Gy)	2.59 ± 0.63	2.61 ± 0.46	2.11 ± 1.24	0.82	0.11
	V2 (%)	0.29 ± 0.34	0.19 ± 0.30	0.09 ± 0.21	0.48	0.05
PTV	Dmean (Gy)	41.00 ± 2.28	40.76 ± 2.80	41.02 ± 0.92	0.59	0.59
	Dmax (Gy)	45.35 ± 0.58	45.08 ± 0.45	45.22 ± 0.89	0.16	0.06
	V95 (%)	95.14 ± 1.90	95.86 ± 1.77	96.95 ± 1.76	0.72	0.93
	V90 (%)	97.93 ± 3.23	98.17 ± 2.32	98.91 ± 3.49	0.42	0.21

Abbreviations: DVH, dose-volume histogram; OARs, organs at risk; LADAC, left anterior descending coronary artery; PTV, planning target volume; 3DCRT, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; IMRT, intensity-modulated radiotherapy; DIBH, deep inspiration breath hold; FB, free breathing.

the right breast, our study showed that VMAT reduced the Dmean significantly. However, several differences exist which might restrict comparisons between studies. Jensen et al[9] reported that the Dmean of the right breast in the VMAT plan was higher but acceptable than that in the 3DCRT plan. The difference may be caused by the breast size of enrolled patients or the partial arc range, beam angel, central location of VMAT. Compared with continuous VMAT with a semicircle beam, tangential VMAT with 2 small tangential arc segments beams reduce the contralateral breast mean dose.[13] Zhao et al[14] had reported that the Dmean of heart in the VMAT plan was not significantly different from that in the 3DCRT plan. Differences between studies in gantry rotation angle, heart size of enrolled patients, the ability of breath-holding (the percentage increase of the lung volume), isocenter position will influence reported Dmean of heart. Besides, DIBH greatly reduces irradiated cardiac volume, the range of VMAT to further reduce the heart dose by optimization may decrease. In the DIBH position, the distance between the heart and the breast target area increases as the heart moves down. Several studies have shown that DIBH can reduce the heart dose by displacing the heart from the treatment field that results from the expansion of the lungs while not compromising the dose to the target.[11,15] In the DIBH position, the lung volume increases significantly, and the proportion of the lung volume that actually receives radiation is therefore effectively reduced. Compared to FB, RT with DIBH after BCS for left breast cancer has the advantage of significantly reducing the irradiation volumes and doses of important organs around the target area, such as the heart, LAD, and ipsilateral lung, and reducing radiation-induced damage. It is expected to further reduce the occurrence of RT complications and improve the long-term quality of life for patients, and it has a broad clinical application value.

Radiation pneumonia and radiation heart disease are serious side effects caused by RT. Cardiac radiation exposure can cause microvascular injury of small vessels and macrovascular injury of the coronary artery, which can lead to myocardial fibrosis, increasing the risk of ischemic heart disease and coronary artery disease occurring generally years after RT.[16] Radiation pneumonitis is a subacute inflammatory reaction of radiation-induced lung injury that often occurs mainly between 4 and 12 weeks after the RT course.[17] Its incidence rate is frequently correlated with the irradiated V20 and mean lung dose.[18] Most patients with radiation pneumonitis have no symptoms. Severe conditions may affect the quality of life by symptoms such as dry cough, dyspnea, pleuritic pain, low-grade fever, chest discomfort, and radiation fibrosis. Reducing exposure to the heart and lungs is helpful for reducing side effects and improving the quality of life.

VMAT plan has the advantages of better dose coverage and uniformity than a 3DCRT plan. However, VMAT plans need a longer time to design because the parameters are adjusted and optimized repeatedly. It can reduce our work efficiency considerably. Besides, the cost of VMAT is higher than 3DCRT. Patients with the VMAT plan may face more financial pressure. RT with DIBH may not benefit all patients since some patients will have minimal heart volume within the tangential fields and limited ability to hold their breath. In clinical work, patient breathing mode training should be strengthened, and patients should be trained as much as possible to use the DIBH breathing mode in order to obtain the best effect for protecting normal tissues around the breast. Given the demonstrated benefits of DIBH, we still suggest that this technique should be offered indiscriminately to all patients who may benefit from it.

There are some limitations to our study. The average age of enrolled patients was 45 years old. The patients in this study were relatively young and the number of patients was small. With population aging and the increasing prevalence of breast cancer, there are more elderly patients with breast cancer. They have a higher risk of treatment-related toxicity and preexisting disease due to body aging and function decline. The breast shape and size of elderly patients are different from those of younger patients, the difference might cause an uneven dose distribution.[19,20] Therefore, a larger cohort study may be needed to achieve greater clinical value. Another limitation is that we did not evaluate the late toxicity of RT. We are conducting clinical trials to evaluate effectiveness and safety. Long-term follow-up of adverse effects and survival outcomes is needed to precisely determine the dosimetric benefits of DIBH and VMAT for left breast RT.

Conclusion

DIBH and VMAT could reduce dosimetric parameters of the OARs in left breast cancer patients after BCS. RT plans for left breast cancer after BCS can be optimized by DIBH and VMAT techniques in order to minimize radiation-induced toxicity.

Author Contribution

LT and KJ carried out statistical analysis and manuscript editing, all authors contributed to design treatment plans.

Ethics Approval

Ethical approval was obtained from the Ethics Committee of Tohoku University Hospital (approval number: 20531).

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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