Evaluation of DIBH and VMAT in Hypofractionated Radiotherapy for Left-sided Breast Cancers After Breast-conserving Surgery: a Planning Study

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Research

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

Posted Date: February 16th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-203486/v1>

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Abstract

Background This paper aims to compare dosimetric parameters of the organs at risk (OARs) among three 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 radiotherapy (3DCRT) and volumetric modulated arc therapy (VMAT) plans were generated for each patient in the DIBH position. A 3DCRT plan was also created in the FB position. Dose-volume histogram (DVH) was used to analyze each evaluation index of OARs. The principal outcome was heart dose, left anterior descending coronary artery (LADCA) dose and left lung dose.

Results For the 3D-CRT plans, significant dose reductions were demonstrated in all evaluation parameters to heart, LADCA and left lung dose in the DIBH position compared with the FB position ($p < 0.05$). In DIBH position, significant dose reductions were founded in heart and LADCA in VMAT plan compared to 3DCRT plan ($p < 0.05$). There were no significant differences between 3DCRT and VMAT plan for the left lung dose in DIBH position.

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

Background

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). Despite advances in radiation techniques and methods, the toxicities of RT still inevitably occur. RT involves some radiation exposure of the heart and lung, serious side effects can pose competing risks of mortality, especially for patients with left breast cancer. Researches [2–4] has reported that an increase in 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 right-sided RT. Radiation-induced side effects are correlated with the absorbed dose and irradiated volume. So it is important and necessary to reduce exposure to the organs at risk (OARs) to decrease the incidence rate of side effects and improve survival.

Some modern treatment techniques could reduce the cardiac toxicity of left-sided breast irradiation. Deep inspiration breath-hold (DIBH) is a RT method that patients take a deep breath before treatment, and hold breath while the radiation is delivered. Lungs fill with air and heart will move away from chest wall by DIBH. With the rapid development of hardware and software in the field of RT, in addition to three-dimensional radiotherapy (3DCRT), volumetric modulated arc therapy (VMAT), intensity-modulated

radiotherapy (IMRT) has been developed and widely applied in clinic nowadays. VMAT is a new RT technique which can achieve highly conformal dose distributions in the target volume coverage and protect normal breast tissue simultaneously [5]. It is currently widely used in RT, but rarely for breast cancer.

In this study, we evaluated the effect of DIBH irradiation and VMAT plans under DIBH on OARs dose deposition through the comparison of dosimetric parameters of OARs in different irradiation plans in patients with left-sided breast cancer after BCS. It will be helpful to identify a rational strategy for the selection in 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 study. The patients are all female, aged 30 to 60 years old. All patients underwent FB and DIBH CT scans at intervals of 2.0–2.5 mm in the supine position with left arm above their head. All mammary glandular tissue was delineated as the clinical target volume (CTV). The planning target volume (PTV) was generated by expanding the CTV with an additional 10 mm circular margin. 3DCRT plan was conventionally treated with a tangential field 4–6 MV photon beam. Dynamic wedge filters and/or field in field technique were used to obtain a homogeneous dose distribution. In 3DCRT, 42.4 Gy in 16 fractions of 2.65 Gy was prescribed to isocenter. VMAT plan used dual partial arcs of 40–50° with collimator angle 30°, treatment couch angle 0°, rotating in opposite directions. In VMAT, 42.4 Gy in 16 fractions covering 50% of the PTV were prescribed. The maximum dose rate 1400 MU/min for 6X-FFF beams. The principal outcome was heart dose, LADCA dose, and left lung dose. The following evaluation parameters were used to compare: mean dose (Dmean), maximum dose (Dmax), the volume receiving at least 20 Gy (V20), the volume receiving at least 10 Gy (V10), and the volume receiving at least 5 Gy (V5) to the left lung; Dmean, Dmax, V5 to the heart; Dmean, Dmax, the volume receiving at least 2 Gy (V2) to the LADCA. All treatment plans were designed and calculated via the Analytical Anisotropic Algorithm (AAA) algorithm of the Eclipse planning system (version 13.6, Varian Medical Systems, Palo Alto, CA). 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). $P < 0.05$ was considered statistically significant.

Results

In different breathing maneuvers, lung volume and the spatial position of the heart have changed as shown in Fig. 1. The deep inspiration causes downward displacement of the heart and the expansion of the lung. Figure 2 show the beam arrangement and isodose distribution of three plans for the cases

based on one patient sample. Compared with 3DCRT plan, the area receiving 95% of total dose (thick red line) in VMAT plan much more fit breast morphology, and conformity to the planning target are better.

Dose-volume histograms (DVH) of OARs for three plans is illustrated in Fig. 3. For heart and LADCA, it is significant that higher relative volume is getting the same dose in FB plan and 3DCRT plan as compared to DIBH plan and VMAT plan, respectively. For left lung, VMAT plan get lower relative volume compared to 3D-CRT at higher dose regions (e.g., V20) but not at lower dose regions (e.g., V5). At the same dose, relative volume in DIBH plan is lower than that in FB plan.

The results for the dose to the OARs are summarized in Table 1.

DIBH vs FB

For the 3DCRT plans, significant dose reductions were demonstrated in all evaluation parameters to heart, LADCA and left lung dose in the DIBH position compared with the FB position ($p < 0.05$). Compared to FB position, heart Dmean reduced by 0.64 Gy (1.52 Gy vs. 0.88 Gy, $p < 0.01$) significantly. The relative V5 reduced by 91.4% (2.68% vs. 0.23%, $p < 0.01$). The difference in mean dose (3.04 Gy vs. 2.21 Gy, $p < 0.01$) and V2 (58.42% vs. 49.49%, $p = 0.03$) for LADCA approached statistical significance. The left lung Dmean reduced by 1.52 Gy (6.29 Gy vs. 4.77 Gy, $p < 0.01$). Left lung Dmax for DIBH is slightly better (41.20 Gy vs. 40.42 Gy, $p = 0.04$) than that for FB. The relative V20 reduced by 33.22% (12.13% vs. 8.10%, $p < 0.01$), V10 reduced by 29.98% (15.81% vs. 11.07%, $p < 0.01$), V5 reduced by 18.98% (23.23% vs. 18.82%, $p < 0.01$) significantly with DIBH as compared to those for FB.

3DCRT vs VMAT

In DIBH position, significant dose reductions were founded in heart and LADCA in VMAT plan compared with 3DCRT plan ($p < 0.05$). 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 plan and VMAT plan for the left lung dose in DIBH position. For the VMAT plan, Dmean (4.77 Gy vs. 4.34 Gy, $p = 0.51$), Dmax (40.42 Gy vs. 39.96 Gy, $p = 0.72$), V20 (8.10% vs. 5.52%, $p = 0.05$) of the left lung were slightly lower, and V5 (18.82% vs. 23.39%, $p = 0.05$), V10 (11.07% vs. 14.05%, $p = 0.06$) of the left lung were higher than those for 3DCRT plan. LADCA Dmean reduced by 0.78 Gy (2.21 Gy vs. 1.43 Gy, $p < 0.01$) significantly. Relative V2 decreased by 59.16% (49.49 Gy vs. 20.21 Gy, $p < 0.01$).

Table 1
Comparison of dosimetry metrics of OARs for all 11 patients (Mean $\pm$ SD)

	Dosimetric parameter	FB-3DCRT	DIBH-3DCRT	DIBH-VMAT	p-value	
					DIBH vs FB	3DCRT vs VMAT
					with 3D-CRT	for DIBH
Heart	Dmean (Gy)	1.52 $\pm$ 0.35	0.88 $\pm$ 0.15	0.47 $\pm$ 0.15	< 0.01	< 0.01
	Dmax (Gy)	29.33 $\pm$ 2.73	13.80 $\pm$ 8.42	5.32 $\pm$ 2.39	< 0.01	< 0.01
	V5(%)	2.68 $\pm$ 1.19	0.23 $\pm$ 0.18	0.04 $\pm$ 0.07	< 0.01	< 0.01
Left Lung	Dmean (Gy)	6.29 $\pm$ 1.35	4.77 $\pm$ 0.86	4.34 $\pm$ 0.97	< 0.01	0.51
	Dmax (Gy)	41.20 $\pm$ 1.39	40.42 $\pm$ 1.25	39.96 $\pm$ 2.91	0.04	0.72
	V20(%)	12.13 $\pm$ 3.65	8.10 $\pm$ 2.51	5.52 $\pm$ 2.27	< 0.01	0.05
	V10(%)	15.81 $\pm$ 4.05	11.07 $\pm$ 2.86	14.05 $\pm$ 3.31	< 0.01	0.05
	V5(%)	23.23 $\pm$ 4.03	18.82 $\pm$ 2.82	23.39 $\pm$ 5.22	< 0.01	0.06
LAD	Dmean (Gy)	3.04 $\pm$ 0.75	2.21 $\pm$ 0.33	1.43 $\pm$ 0.35	< 0.01	< 0.01
	Dmax (Gy)	12.29 $\pm$ 5.92	5.94 $\pm$ 2.15	3.76 $\pm$ 1.63	< 0.01	< 0.01
	V2(%)	58.42 $\pm$ 15.72	49.49 $\pm$ 15.34	20.21 $\pm$ 14.73	0.03	< 0.01

Discussion

In this study, we evaluated the effect of DIBH and VMAT irradiation techniques on OARs dose deposition through the comparison of dosimetric parameters of OARs in different irradiation plans in patients with left-sided breast cancer after BCS. We found that DIBH irradiation significantly reduced the heart, LADCA and left lung dose compared to FB irradiation. Moreover, compared with the 3DCRT plans, VMAT made an additional significant further dose reduction for the heart and LADCA in DIBH irradiation. It implies that the DIBH and VMAT technique could reduce the risk of radiation-induced toxicity, especially cardiac morbidity.

Radiation pneumonia and radiation heart disease are more 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, increases the risk of ischemic heart disease and coronary artery disease occurring generally years after RT [6]. Radiation pneumonitis is a subacute inflammatory reaction of radiation-induced lung injury which often occurs mainly between 4 and 12 weeks after RT course[7]. Its incidence rate is frequently correlated with the irradiated V20 and mean lung dose [8]. Most patients with radiation pneumonitis have no symptoms. Severe conditions may affect the quality of life by symptoms like dry cough, dyspnea, pleuritic pain, low-grade fever, chest discomfort, radiation fibrosis. Reducing exposure to the heart and lungs is helpful to decrease side effects and improve quality of life.

In the DIBH position, the distance between the heart and the breast target area also increases as the heart moves down. Several studies have confirmed that DIBH can reduce the heart dose by displacing the heart from the treatment field resulted from the expansion of the lung while not compromise the dose to the target [9, 10]. In the DIBH position, the lung volume increases significantly, so that the proportion of lung volume that actually receives radiation was reduced effectively. Compared to FB, RT with DIBH after BCS for left breast cancer has the advantage of significantly reducing the irradiation volume and dose of important organs around the target area, such as heart, LAD and ipsilateral lung, and reduce 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 has broad clinical application value. In clinical work, patient breathing mode training should be strengthened, and patients should be trained as much as possible to use DIBH breathing mode, in order to obtain the best effect of protecting normal tissues around the breast. RT with the DIBH may not benefit all patients, as some patients will have minimal heart volume within the tangential fields and limit ability to hold breath. Given the demonstrated benefits of DIBH, we still suggest this technique should be offered indiscriminately to all patients who may benefit.

VMAT has better dose coverage and uniformity than 3DCRT plan. In our results, VMAT plans significantly reduce all indicators of heart and LADCA compared with 3DCRT plan in DIBH position. VMAT technique slightly but insignificantly reduce the Dmean, Dmax and V20 of the left lung. Compared with 3DCRT plan, VMAT plan reduces the high dose volume of the left lung but increases the low dose volume simultaneously because of the scattered radiation increased. The similar result could also be founded in other study [11].Hypofractionated whole breast irradiation is confirmed to be safe, and could achieve equivalent treatment results compared with conventional fractionated RT while reducing visiting times to hospitals and medical expenses [12, 13]. Especially during coronavirus disease 2019 (COVID-19) pandemic, reducing visiting times to hospitals could help reduce risk of infection.

There also have limitations in our study. The number of patients in this study is relatively young and the number of patients is small. With population aging and the increasing prevalence, there are more elderly patients with breast cancer. The breast shape and size of elderly patients are different from younger patients, it could cause an uneven dose distribution. So it may need a larger cohort study in order to achieve greater clinical value. Besides, we lack evaluation of late toxicity in RT. Long-term follow-up of

adverse effects and survival outcomes is needed to determine the dosimetric benefits of DIBH and VMAT to left breast RT robustly.

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.

Abbreviations

RT: Radiotherapy; **BCS:** Breast-conserving surgery; **3DCRT:** Three-dimensional 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.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Tohoku University Hospital, with patient consent not required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding for the research or any one of the authors.

Authors' contributions

All authors performed the treatment planning. LT and KJ were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

Figure 1

The spatial position differences of the heart and lung between the two CT simulations in the FB and DIBH position in a left-sided breast cancer case (a)Coronal section; (b)Sagittal section (Lung: cyan curve; Heart: red curve; Left: FB; Right: DIBH)

Figure 2

The beam arrangement and isodose distribution of three plans for the cases based on one patient sample. (Left: FB-3DCRT; Middle: DIBH-3DCRT; Right: DBIH-VMAT; Thick red line: the volume receiving 95% of total dose)

Figure 3

Dose volume histograms (DVH) of OARs for three plans for the cases based on one patient sample.
(a)Heart;(b) LADAC;(c) Lung