Received:
22 March 2018

Revised:
20 June 2018

Accepted:
26 June 2018

<https://doi.org/10.1259/bjr.20180287>

Cite this article as:

Ueda Y, Gerber NK, Das IJ. Model-based cardiac dose estimation in radiation treatment of left breast cancer. *Br J Radiol* 2018; **91**: 20180287.

FULL PAPER

Model-based cardiac dose estimation in radiation treatment of left breast cancer

¹YOSHIHIRO UEDA, MS, ²NAAMIT K GERBER, MD, PhD and ²INDRA J DAS, PhD, FACR, FASTRO

¹Department of Radiation Oncology, Osaka International Cancer Institute, Osaka, Japan

²Department of Radiation Oncology, New York University Health & Laura and Isaac Perlmutter Cancer Center, New York, NY, USA

Address correspondence to: Prof Indra J Das

E-mail: indra.das@nyumc.org

Objective: To develop a mathematical model for cardiac dose estimation for patients who have been treated for left-sided breast cancer without CT data.

Methods: After obtaining institutional review board approvals, 147 patients with left-sided breast cancer were selected that were treated supine with opposed tangents. The heart blocks from the tangential fields were removed and dose calculations were performed with 6 MV beams using an advanced algorithm. This study was performed with CT data with DRR to represent a radiographic simulator image of yesteryear treatments. The beam's eye-view images showing delineated breast, lung and heart were created to represent views on radiograph. The maximum heart distance (MHD) was recorded and irradiated heart area (AREA) was computed by combination of triangles and rectangles. Based on accurate 3D dose calculation, mean dose (D_{mean}) and V_{10} to V_{50} of heart were analyzed with respect to MHD and AREA for dosimetric parameters using linear and quadratic fit.

Results: The treatment parameters calculated by MHD and segments using 2D radiographs were within 2% of the actual dosimetric parameters computed from the 3D

planning system. The MHD and AREA vs D_{mean} , V_{10} , V_{20} , V_{30} and V_{50} showed very good correlation with linear model ($R^2 > 0.91$); however the correlation was significantly better with quadratic model ($R^2 > 0.92$). The analysis of the dosimetric error with our linear and quadratic model is remarkable within <3% error for most cases.

Conclusion: The proposed mathematical model for the cardiac dose estimation is accurate within $\pm 3\%$ using a radiograph without CT data. This provides avenues for patient pooling in future studies related to radiation dose and cardiac toxicity. These results will help in estimating cardiac dose analysis accurately from previous studies as well as in centers still using 2D planning.

Advances in Knowledge: The evidence of cardiac risk following radiotherapy continues to be one of the important considerations for the management of left-sided breast cancer patients. One of the problem in the estimation of dose-risk effects is the reconstruction of heart dose for pre-CT treatments. In this study, a simple mathematical model is presented that could estimate cardiac dose within $\pm 3\%$ in left breast cancer treatment from 2D radiograph where CT data do not exist.

INTRODUCTION

It is now well known that adjuvant radiation improves local control and overall survival in early stage breast cancer.^{1,2} Excellent cure rates are testament of success but data have emerged with long-term cardiac complication associated with radiation dose. Advances in radiation oncology for breast cancer focus on minimizing dose to normal tissue, most notably the heart and more so to its components like left ventricle (LV) and left anterior descending artery (LAD). However, the vast majority of older data sets (from 1955 to 1994) were treated with Co-60 without volumetric or CT data and the lack of heart shielding. Thus they cannot be used for toxicity analyses, with regard to dose-volume constraints. The only data for these patients treated before CT are treatment parameters that can be obtained from a

2D radiograph such as chest wall separation (s), central lung distance (CLD), maximum heart distance (MHD) and other treatment field parameters: width, length, wedge angle, weight, gantry angle etc.^{3,4}

The long-term survival of patients with breast cancer has shown that there is a higher rate of cardiac complication in patients with left breast cancer, and has been attributed to the radiation dose to the heart.⁵⁻¹⁹ According to Darby et al,²⁰ the increase in the rate of ischemic heart disease after radiotherapy for breast cancer is proportional to the mean heart dose, and this increased risk begins within a few years after exposure that continues for at least 20 years. However, the dosimetric accuracy in this article was limited as it was based on a very small subset of patients' data that were

dosimetrically analyzed. Owing to this difficulty, the data were retrospectively reanalyzed and presented recently by Taylor et al.²¹ Cardiac toxicity is a sequelae of chemotherapy and outdated radiation techniques such as Co-60 without heart block, but current data point to the fact that dosimetric parameters are linked to cardiac toxicity regardless of these other factors.^{13,22–25} Many correlative studies have estimated irradiated lung and heart volumes based on the CLD and have reported various methods to reduce the dose to the heart and lungs.^{4,18,26–33}

To properly estimate heart and lung volume, volumetric CT data is needed. Unfortunately, patients treated prior to the emergence of CT-simulation³⁴ do not have CT data. In addition, the radiation treatment techniques of yesteryear typically resulted in higher dose to the heart through internal mammary and wider tangential fields without any consideration of heart shielding. In older days of 2D and 3DCRT, most radiation oncologists preferred the non-divergent posterior edges of the tangential fields,^{35,36} which can be accomplished either using a half beam block or through various other techniques^{37–46} that could minimize cardiac dose. The availability of CT-simulators in 1993 led to the wide use of CT imaging for most diseases, but it was a critical step for breast cancer because treatment fields could be tailored, and lung and heart doses could be minimized or avoided.^{4,47–54}

At present, breast cancer patients in some countries are followed much more closely with vast amount of data being accumulated for survival and lung and heart complications.^{55–58} However,

there still remains a critical need to determine the radiation dose to the heart and other structures in breast cancer treatments.⁵⁹ In prone breast treatment Cooper et al⁶⁰ showed that cardiac separation from chest wall is a good indicator of max dose to LAD. Unfortunately, there is very little information that can correlate irradiated heart volumes from planar radiographs. Heart area, as seen in tangential radiographs, has been used as a surrogate for volume; however, it is a poor indicator of treated volume and dosimetry can be uncertain. Lorenzen et al⁶¹ used randomly selected 20 patients from Danish Breast Cancer Cooperative Group to and provided a logarithmic correlation with MHD from planar tangential field radiograph. There is still a critical need for the estimation of actual volumes and dose in the treatment fields as dose is directly related to the cardiac complication. It is desirable to link one-dimensional data, such as CLD or MHD, to the actual heart volume. It is also beneficial to correlate the two-dimensional irradiated heart area (AREA) with real three-dimensional (3D) data of the irradiated heart volume.

The estimation of irradiated heart volume is essential for pre-CT datasets to be used in modern analysis. This study provides data that could be used for populations where CT-data does not exist. The overall purpose of this study is to determine parameters extracted from the 2D images and provide mathematical model to estimate accurately heart dose volume parameters for future cardiac toxicity estimation retrospectively with older data set.

Figure 1. A method to calculate the MHD and the MHL, and the heart area in the breast treatment field (AREA) (a) the overview of the breast treatment field. (b) The enlarged view of a heart in the field showing MHL, MHD and THL. The AREA in the field includes two triangles and one square. The AREA is calculated using Eq (1). MHD, maximum heart distance; MHL, maximum heart length; THL, top of heart length.

Figure 2. Relationships between gantry angle and AREA in 4 cases indicating parabolic variation.

METHODS AND MATERIALS

With institutional review board approval, 147 cancer patients that were treated using external beam irradiation for left breast carcinoma in supine position with tangential breast techniques were selected. In some patients, field-in-field was used. Patient's records were made available for retrospective analysis. Most patients were immobilized on a breast board or a vacuum-lock angle board (typically at 10°). Radio-opaque wires were placed mid-sternum for the medial border, 1 cm below the clavicular head for the superior border, 2 cm below the inframammary fold for the inferior border and in the mid-axilla for the lateral border. These markers were used to create the tangential field. The CT images of all patients were acquired using a Phillips Ultra-Z CT simulator (Philips Medical Systems, Milpitas, CA) in spiral mode with a 3 mm slice thickness. The patient surface and a heart outline were contoured manually.

The patient planning and dose calculation were performed with Eclipse v. 11.0 (Varian Medical Systems, Palo Alto, CA). The analytical anisotropic algorithm (AAA) was used for dose calculation for inhomogeneity correlation whereas pencil beam algorithm was used for without inhomogeneity correction. This exercise was performed as older treatments did not account the inhomogeneity correction. The energy used was 6 MV photons, the total dose was 40.05–50.40 Gy, and the fraction dose was 1.80–2.67 Gy. For some patient plans, a multileaf collimator (MLC) was also used to decrease the heart and lung dose. For this analysis, the MLCs were removed from all plans and recalculated with the same MU values in the treatment plan for the sake of uniformity. Dosimetric parameters of the heart, *i.e.* mean

Table 1. The coefficients of fitting parameters along with R^2 for each of the investigated parameter

		Coefficient			(R^2)	
	Prediction model	Linear	Quadratic		Linear	Quadratic
X	Y	α	α	β		
MHD	D_{mean}	5.96	4.83	0.25	0.911	0.924
	V10	7.98	6.75	0.27	0.878	0.887
	V20	6.03	4.12	0.41	0.878	0.906
	V30	5.61	3.61	0.44	0.865	0.901
	V50	5.13	2.97	0.48	0.848	0.897
MHL	D_{mean}	2.04	-0.42	0.281	0.468	0.601
	V10	2.75	-0.52	0.379	0.476	0.607
	V20	2.01	-1.20	0.366	0.445	0.626
	V30	1.86	-1.30	0.360	0.428	0.618
	V50	1.68	-1.37	0.348	0.407	0.607
AREA	D_{mean}	0.90	1.01	-0.003	0.925	0.931
	V10	1.21	1.36	-0.004	0.899	0.903
	V20	0.92	0.95	-0.0007	0.929	0.929
	V30	0.86	0.85	0.0004	0.924	0.925
	V50	0.79	0.73	0.002	0.922	0.925

MHD, maximum heart distance; MHL, maximum heart length.

heart dose (D_{mean}), V10, V20, V30 and V50, were extracted from the dose volume histogram (DVH). Due to variability in prescription dose, a normalized approach was used. Thus most parameters are expressed in percent for comparison with other studies. D_{mean} represents percent average dose to the heart. The parameters V10, V20, V30 and V50 represented the volume of the heart receiving 10%, 20%, 30% and 50% of the prescribed dose, respectively.

The 2D parameters, *i.e.* MHD, the maximum distance of the cardiac silhouette perpendicular to the longitudinal edge (maximum heart length, MHL) and the top heart length (THL) were measured from the digitally reconstructed radiograph (DRR) of the tangential field in each case, as shown in Figure 1 in free breathing. In this study, no attempts were made for reducing heart dose by breath hold or other techniques. If there was no heart in the radiation field, the MHD was a negative value. The heart area in the radiation field was created using a rectangle and triangles as needed (Figure 1). The heart area was estimated using the equation (1) below.

$$\begin{aligned} \text{Area} &= \text{Area (square)} + \sum_{i=1}^2 \text{Area (triangle)}_i \\ &= \frac{1}{2} \times \text{MHD} \times (\text{MHL} + \text{THL}) \end{aligned} \quad (1)$$

As projected area in DRR is dependent on the gantry angle, analysis of the area in various clinically relevant breast treatment angles was evaluated. Correlations between dose-volume parameters (D_{mean} , V10, V20, V30 and V50) as Y axis and the MHD, MHL and AREA as X axis were evaluated using regression analysis for linear and quadratic models along with R^2 to determine statistical significance.

$$Y = \alpha X \quad (2a)$$

$$Y = \alpha X + \beta X^2 \quad (2b)$$

Where α and β are the fitting coefficients for linear and linear quadratic models. The ability to predict heart dose with the MHD and AREA was also evaluated using both linear and quadratic models. Additionally, 15 patients from a different hospital were chosen to evaluate the accuracy of model based on Eq 2 for AREA and MHD independently of the original data set.

RESULTS

It is observed that irradiated cardiac area is dependent on the beam's eye view which is dependent on the tangential beam as shown in Figure 2. The AREA data from wide range of gantry angles (70 to -40 degrees) are shown for completeness and not necessary clinically applicable. The graph is nearly parabolic. This is further evaluated in terms of cardiac dose for our patient population where beam angle is rather limited.

Using the treatment planning system (TPS), the mean $\pm$ SD of heart volume was $705 \pm 162 \text{ cm}^3$. The mean $\pm$ SD (min-max) of the dosimetric parameters, D_{mean} , V10, V20, V30 and V50, were $13.4 \pm 11.4\%$ (1.5%–47.2%), $17.9 \pm 15.6\%$ (0.4%–64.6%), $12.6 \pm 12.8\%$ (0%–51.1%), $11.6 \pm 12.2\%$ (0%–49.0%) and

Figure 3. Correlations between the D_{mean} and each 2D parameter ((a) MHD, (b) MHL and (c) AREA). Data points are the D_{mean} detected by DVHs in treatment planning. The solid lines represent the linear regressions and dotted lines represent the quadratic regressions with R^2 values.

$10.4 \pm 11.5\%$ (0%–47.0%), respectively. The difference in the calculated MU between planning with and without inhomogeneity correction was relatively small (within 2%) due to small

Figure 4. Distributions of prediction errors for the D_{mean} obtained using the formulas shown in (a) linear prediction model with MHD and AREA, (b) quadratic prediction model with MHD and AREA. MHD, maximum heart distance.

amount of lung in treatment volume. The mean $\pm$ SD (min – max) of the 2D parameters, MHD, MHL, THL and AREA, were 2.3 ± 1.7 (–1.2–8.5) cm, 7.1 ± 2.9 (0–12.5) cm, 2.7 ± 1.6 (0–7.8) cm and 14.1 ± 13.1 (0–60.3) cm², respectively.

For each dosimetric parameter, such as the D_{mean} , V10, V20, V30 and V50, the predicted dose was calculated and compared with the measured dose from the CT planning scan. In the case of a negative value for MHD, MHD was defined as zero. Figure 2 describes the relationship between AREA and the angle of gantry. This indicates that the area of the heart in the radiation field is inversely related to the gantry angle up to zero angle e.g. ipsilateral side of the breast.

Table 1 shows the coefficients of fitting parameters for each of the investigated parameter. There were strong positive linear and quadratic correlations. In all cases, AREA had excellent correlations compared to MHD and MHL. Compared to linear, quadratic model had stronger correlations with all parameters. There was a smaller difference between the linear and quadratic coefficients in AREA compared to in MHD. The MHD, MHL and AREA were strongly correlated with mean heart dose (Figure 3). MHL was the least predictive parameter of the three on the 2D radiograph.

Figure 4 shows the histograms of the linear and quadratic prediction errors for the D_{mean} from entire data set. When MHD was used to predict the D_{mean} with the linear model, 19 cases (13%) had a prediction error of more than 5%. When AREA was used to predict the D_{mean} with the linear model, 17 cases (12%) had a prediction error of more than 5%. With the quadratic model for MHD, 14 cases (9.5%) had a prediction error of more than 5%. For MHD, the quadratic model was more accurate than the linear model. For AREA, there was a small difference between the linear and quadratic models. There were 18 cases (12%) that had a prediction error of more than 5% using the quadratic model.

Table 2 shows the results for the prediction errors based on equation 2 for linear and quadratic models for cardiac dose. A positive value indicates that the predicted dose is less than the measured dose. The rate of change within prediction errors is described in Figure 5. Linear models with MHD for the dose volume

Table 2. The results for the prediction errors based on the linear and quadratic models for cardiac dose showing mean range and confidence interval

X	Prediction model	Linear			Quadratic		
	Y	Mean (SD)	Range [min/max]	95% CI	Mean (SD)	Range [min/max]	95% CI
MHD	D_{mean}	0.5 (3.4)	–9.9/6.6	[–0.06, 1.04]	0.0 (3.1)	–9.9/11.8	[–0.55, 0.48]
	V10	0.7 (5.4)	–21.0/11.4	[–0.20, 1.57]	0.1 (5.2)	–21.9/16.3	[–0.75, 0.96]
	V20	1.4 (4.2)	–15.1/8.4	[0.67, 2.05]	0.5 (3.9)	–11.7/19.6	[–0.13, 1.13]
	V30	1.5 (4.3)	–15.5/8.2	[0.77, 2.16]	0.5 (3.8)	–11.9/20.2	[–0.90, 1.16]
	V50	1.5 (4.2)	–15.3/7.7	[0.86, 2.23]	0.5 (3.7)	–12.1/19.6	[–0.60, 1.13]
AREA	D_{mean}	–0.7 (3.0)	–10.3/10.3	[–1.21, –0.22]	–1.5 (3.0)	–13.2/9.2	[–2.01, 1.03]
	V10	–0.9 (4.9)	–25.0/14.1	[–1.71, –0.11]	–0.4 (4.8)	–24.7/15.2	[–1.23, 0.35]
	V20	0.3 (3.4)	–11.8/11.4	[–0.28, 0.82]	0.3 (3.4)	–11.8/11.6	[–0.21, 1.10]
	V30	0.5 (3.3)	–11.5/10.9	[–0.52, 1.03]	0.4 (3.3)	–11.6/10.8	[–0.11, 0.98]
	V50	0.7 (3.1)	–11.1/10.4	[0.20, 1.22]	0.5 (3.1)	–11.4/10.5	[–0.03, 0.99]

CI, confidence interval; MHD, maximum heart distance; SD, standard deviation. The values are in % normalized to prescription dose.

Figure 5. Prediction accuracy for each method represented as cumulative frequency, (a) D_{mean} , (b) V10, (c) V20, (d) V30 and (e) V50. Horizontal axes represent prediction errors. Vertical axes are cumulative case rate within prediction errors.

parameters had larger errors compared with the quadratic model with MHD and both models with AREA. The predictive accuracy for the linear model with MHD decreases with a higher dose volume. Prediction models with AREA had a greater accuracy than those with MHD for all dose volume parameters.

The independent verification of the model was performed on 15 patients from a different hospital comprising of a new data set for radiograph. Table 3 shows the accuracy of the model with AREA for D_{mean} indicating that linear and quadratic model can predict cardiac dose accurately to within $1.88 \pm 0.93\%$ and $1.34 \pm 0.84\%$ respectively. Similar findings were also noted for the MHD where cardiac dose was predicted to be within $-0.21 \pm 2.61\%$ and $0.78 \pm 2.65\%$ for the linear and quadratic models respectively. As can be seen that our model can predict cardiac dose to within 3% accuracy.

DISCUSSION

The patients in this series were treated with lung and heart blocks, but these were removed for the estimation of dose for

model fitting. This was performed for the sake of uniformity as heart block is individualized. Additional investigation is needed regarding the correlation between mean heart dose and other cardiac parameters and long-term cardiac toxicity in breast cancer patients treated with radiotherapy. Unfortunately, the latent period for cardiac complications is relatively long and prior to 1992 volumetric information is not available. The 2D radiographs are the only imaging data available for the majority of surviving patients, and these need to be correlated with cardiac toxicity and DVH. The present study provides this link by using a retrospective analysis of patient data planned in the modern era and correlating this with a representative 2D DRR to represent the pre-CT era. A relatively good correlation for 2D to 3D was found in this study, and this information will be vital for future studies on this issue.

MHD and AREA models were selected in this study to predict cardiac dose. MHL model is relatively poor with $R^2 = 0.4681$ and hence not useful entity for cardiac dose estimation [Figure 3 (b)]. The other method for the prediction of heart dose utilizes the MHD, an important parameter for breast radiotherapy. Many approaches from different investigators^{4,53,62,63} have provided mathematical formula for calculating the mean heart dose from the MHD. As noted in their studies, mean heart dose has a strong linear correlation with MHD. Kong et al⁵⁷ also analyzed irradiated volumes, such as V10, V20, V30 and V40. The percent volume (%) of the irradiated heart at 10, 20, 30, and 40 Gy was approximately 6 times the MHD (cm). In their analyzed MHD range, most MHD were less than 3.0 cm, which was too small to calculate cardiac toxicity. Borger et al⁶⁴ assessed the risk of cardiovascular disease (CVD) after adjuvant radiation in 1601 patients. With a median follow-up of 16 years, they found no significant trend that increasing the MHD increased the risk of CVD. Patients with an MHD of 3 cm did have a higher risk of ischemic cardiac events; however, these findings were not statistically significant. The analysis of MHDs of more than 3 cm is needed for prediction of the risk of CVD. Notably, our analysis used a large number of cases (147) and a wide range of MHD (from -1.2 to 8.5 cm) with the advanced calculation algorithm. The larger MHD (8.5 cm) is not clinical rather artefact of the removal of the MLC blocking heart to calculate dose in this study. Few studies have been conducted with more than 100 cases for the prediction of heart dose. It is evident from our analysis that the quadratic model is more accurate than the linear model in the prediction of cardiac dose with 2D parameters.

To calculate dosimetric parameters of the heart, a new method using heart area with a radiograph is proposed. In predictive models with the D_{mean} and irradiated volume, we found that this method using heart area had stronger correlations and offered more accurate prediction than using the MHD. Prediction accuracy decreased in the method using the MHD, particularly with higher doses and increased irradiated volumes. In contrast, in the method using area, the accuracy was constant regardless of irradiated volume (V10–V50). Gagliardi et al¹² found that if 5% of the heart receives 40 Gy, the risk of cardiac mortality exceeds 2% in their clinical study. The risk of pericarditis in esophageal cancer patients treated with radiation and chemotherapy was

Table 3. Validation of model from independent patients from a different institution

Patient	AREA	Heart dose (Dmean) %	Calc dose (linear) %	% diff (linear)	Calc dose (quadratic)%	% diff (quadratic)
1	2.2	3.1	2.0	1.1	2.2	0.9
2	1.8	3.3	1.7	1.6	1.8	1.5
3	1.5	3.8	1.4	2.4	1.5	2.3
4	4.3	5.2	3.8	1.4	4.2	1.0
5	4.0	5.5	3.6	1.9	3.9	1.6
6	6.0	6.5	5.5	1.0	6.0	0.5
7	6.0	6.7	5.4	1.3	5.9	0.8
8	6.6	6.8	6.0	0.8	6.5	0.3
9	9.4	8.9	8.5	0.4	9.2	-0.3
10	8.3	9.7	7.5	2.2	8.1	1.6
11	12.3	14.1	11.1	3.0	11.9	2.2
12	17.4	19.1	15.7	3.4	16.6	2.5
13	20.5	21.2	18.5	2.7	19.4	1.8
14	20.0	21.2	18.1	3.1	19.0	2.2
15	25.3	22.8	22.9	-0.1	23.6	-0.8
			Average	1.88		1.34
			SD	0.93		0.84

SD, standard deviation.

Dose (%) is normalized to prescription dose.

reported by Wei et al.⁶⁵ In this study, increases in a variety of dose parameters, such as mean pericardium dose >26 Gy, and V30 >46%, increased the risk of pericarditis. Aznar et al.⁶⁶ indicated that the most important parameters for long-term cardiac mortality were V20 <10% and V40 <5%. According to these results, it is evident that irradiated volume is critically important to predict toxicity, and the area method is superior to the MHD method in predicting irradiated volume.

Goody et al.⁶⁷ provided portal imaging-based data for CLD and MHD in left breast cancer patient and showed that in many cases even with good intent a large MHD variation was noticed in daily imaging. Our model can be used to provide cumulative cardiac dose of entire treatment without recalculation of dosage in treatment planning.

There are some limitation in this study such as only heart dose is considered, while there is emerging data that other cardiac structures such as LV and LAD dose could also be critical for the late cardiac effects. This omission was due to the fact that LV and LAD are hard to delineate on 2D radiographs of tangential fields. Additionally, many pre-CT treatments were delivered using Co-60 beams without immobilization. In post-CT, most patients are immobilized with slightly different technique that may impact the dosimetry. From nearly 1980s, Co-60 treatment has been replaced with megavoltage photon beams in most developed countries where cardiac risk data have been evaluated. Thus the fitting parameters presented in the paper is only applicable to 6 MV X-ray beam.

Additional concerns are the cardiac structure delineation in some radiographs may not be possible or accurate since window and level options as in the digital image (DRR) is not possible. The accuracy of area estimation may have some variability than volume delineation variability as shown by many investigations even with modern tools.^{68,69} This may lead our method a greater chance of dosimetric variability than our estimated 3% value from the model.

CONCLUSIONS

In this study, simple mathematical models with MHD and AREA on a radiograph are provided to estimate cardiac dose parameters. Such a correlation is useful for analyzing older data sets where 3D volumetric data are not available. These models created by 3D CT data and advanced inhomogeneity corrected dose for a large patient population show that either MHD or AREA could be used for accurately estimate dose from a simple radiograph for estimation of cardiac toxicities thus eliminating ambiguity of risk. For a 6 MV treatment, our model can predict cardiac dose within $\pm 3\%$ with a radiograph alone if heart can be visualized and area estimated accurately.

FUNDING

This article was supported by the JSPS Core-to-Core Program (No.23003) and the JSPS KAKENHI (No. 17K15817) to Yoshihiro Ueda. The data were collected from Indiana University School of Medicine under institutional review board approval when YU and IJD were part of the IUSM.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2000; **355**: 1757–70.
2. Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000; **18**: 1220–9. doi: <https://doi.org/10.1200/JCO.2000.18.6.1220>
3. Das IJ, Cheng CW, Fein DA, Fowble B. Patterns of dose variability in radiation prescription of breast cancer. *Radiation Oncol* 1997; **44**: 83–9. doi: [https://doi.org/10.1016/S0167-8140\(97\)00054-6](https://doi.org/10.1016/S0167-8140(97)00054-6)
4. Das IJ, Cheng EC, Freedman G, Fowble B. Lung and heart dose volume analyses with CT simulator in radiation treatment of breast cancer. *Int J Radiat Oncol Biol Phys* 1998; **42**: 11–19. doi: [https://doi.org/10.1016/S0360-3016\(98\)00200-4](https://doi.org/10.1016/S0360-3016(98)00200-4)
5. Brosius FC, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am J Med* 1981; **70**: 519–30.
6. Corn BW, Trock BJ, Goodman RL. Irradiation-related ischemic heart disease. *J Clin Oncol* 1990; **8**: 741–50. doi: <https://doi.org/10.1200/JCO.1990.8.4.741>
7. Gyenes G, Fornander T, Carlens P, Rutqvist LE. Morbidity of ischemic heart disease in early breast cancer 15–20 years after adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 1998; **28**: 1235–41. doi: [https://doi.org/10.1016/0360-3016\(94\)90500-2](https://doi.org/10.1016/0360-3016(94)90500-2)
8. Gyenes G, Gagliardi G, Lax I, Fornander T, Rutqvist LE. Evaluation of irradiated heart volumes in stage I breast cancer patients treated with postoperative adjuvant radiotherapy. *J Clin Oncol* 1997; **15**: 1348–53. doi: <https://doi.org/10.1200/JCO.1997.15.4.1348>
9. Gyenes G. Radiation-induced ischemic heart disease in breast cancer--a review. *Acta Oncol* 1998; **37**: 241–6. doi: <https://doi.org/10.1080/028418698429522>
10. Stewart JR, Fajardo LE, Gillette SM, Constine LS. Radiation injury to the heart. *Int J Radiat Oncol Biol Phys* 1995; **31**: 1205–11. doi: [https://doi.org/10.1016/0360-3016\(94\)00656-6](https://doi.org/10.1016/0360-3016(94)00656-6)
11. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 1994; **12**: 447–53. doi: <https://doi.org/10.1200/JCO.1994.12.3.447>
12. Gagliardi G, Lax I, Ottolenghi A, Rutqvist LE. Long-term cardiac mortality after radiotherapy of breast cancer--application of the relative seriality model. *Br J Radiol* 1996; **69**: 839–46. doi: <https://doi.org/10.1259/0007-1285-69-825-839>
13. Paszat LE, Mackillop WJ, Groome PA, Boyd C, Schulze K, Holowaty E. Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries. *J Clin Oncol* 1998; **16**: 2625–31. doi: <https://doi.org/10.1200/JCO.1998.16.8.2625>
14. Rutqvist LE, Johansson H. Mortality by laterality of the primary tumour among 55,000 breast cancer patients from the Swedish Cancer Registry. *Br J Cancer* 1990; **61**: 866–8. doi: <https://doi.org/10.1038/bjc.1990.193>
15. Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. *Int J Radiat Oncol Biol Phys* 1992; **22**: 887–96. doi: [https://doi.org/10.1016/0360-3016\(92\)90784-F](https://doi.org/10.1016/0360-3016(92)90784-F)
16. Valagussa P, Zambetti M, Biasi S, Moliterni A, Zucali R, Bonadonna G. Cardiac effects following adjuvant chemotherapy and breast irradiation in operable breast cancer. *Ann Oncol* 1994; **5**: 209–16. doi: <https://doi.org/10.1093/oxfordjournals.annonc.a058795>
17. Yu X, Prosnitz RR, Zhou S, Hardenbergh PH, Tisch A, Blazing MA, et al. Symptomatic cardiac events following radiation therapy for left-sided breast cancer: possible association with radiation therapy-induced changes in regional perfusion. *Clin Breast Cancer* 2003; **4**: 193–7.
18. Levitt SH. Cardiac damage following radiation treatment of primary breast cancer: assessing the risk, exploring the cause. *Int J Radiat Oncol Biol Phys* 1992; **22**: 1157–8. doi: [https://doi.org/10.1016/0360-3016\(92\)90824-2](https://doi.org/10.1016/0360-3016(92)90824-2)
19. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, Peto R, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 1994; **12**: 447–53. doi: <https://doi.org/10.1200/JCO.1994.12.3.447>
20. Darby SC, Ewertz M, Hall P. Ischemic heart disease after breast cancer radiotherapy. *N Engl J Med* 2013; **368**: 2527. doi: <https://doi.org/10.1056/NEJMc1304601>
21. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* 2017; **35**: 1641–9. doi: <https://doi.org/10.1200/JCO.2016.72.0722>
22. Fowble B, Fein DA, Hanlon AL, Eisenberg BL, Hoffman JP, Sigurdson ER, et al. The impact of tamoxifen on breast recurrence, cosmesis, complications, and survival in estrogen receptor-positive early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 1996; **35**: 669–77. doi: [https://doi.org/10.1016/0360-3016\(96\)00185-X](https://doi.org/10.1016/0360-3016(96)00185-X)
23. Ray GR, Fish VJ, Marmor JB, Rogoway W, Kushlan P, Arnold C, et al. Impact of adjuvant chemotherapy on cosmesis and complications in Stages I and II carcinoma of the breast treated by biopsy and radiation therapy. *Int J Radiat Oncol Biol Phys* 1984; **10**: 837–41. doi: [https://doi.org/10.1016/0360-3016\(84\)90385-7](https://doi.org/10.1016/0360-3016(84)90385-7)
24. Hardenbergh PH, Recht A, Gollamudi S, Come SE, Hayes DF, Shulman LN, et al. Treatment-related toxicity from a randomized trial of the sequencing of doxorubicin and radiation therapy in patients treated for early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1999; **45**: 69–72. doi: [https://doi.org/10.1016/S0360-3016\(99\)00127-3](https://doi.org/10.1016/S0360-3016(99)00127-3)
25. Canney PA, Sanderson R, Deehan C, Wheldon T. Variation in the probability of cardiac complications with radiation technique in early breast cancer. *Br J Radiol* 2001; **74**: 262–5. doi: <https://doi.org/10.1259/bjr.74.879.740262>
26. Mallik R, Fowler A, Hunt P. Measuring irradiated lung and heart area in breast tangential fields using a simulator-based computerized tomography device. *Int J Radiat Oncol Biol Phys* 1995; **31**: 411–7. doi: [https://doi.org/10.1016/0360-3016\(94\)00280-X](https://doi.org/10.1016/0360-3016(94)00280-X)
27. Sixel KE, Aznar MC, Ung YC. Deep inspiration breath hold to reduce irradiated heart volume in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2001; **49**: 199–204. doi: [https://doi.org/10.1016/S0360-3016\(00\)01455-3](https://doi.org/10.1016/S0360-3016(00)01455-3)
28. Janjan NA, Gillin MT, Prows J, Arnold S, Haasler G, Thorsen MK, et al. Dose to the cardiac vascular and conduction systems in primary breast irradiation. *Med Dosim* 1989; **14**: 81–7. doi: [https://doi.org/10.1016/0958-3947\(89\)90176-3](https://doi.org/10.1016/0958-3947(89)90176-3)
29. Marks LB, Spencer DP, Bentel GC, Ray SK, Sherouse GW, Sontag MR, et al. The utility of SPECT lung perfusion scans in minimizing and assessing the physiologic consequences

- of thoracic irradiation. *Int J Radiat Oncol Biol Phys* 1993; **26**: 659–68. doi: [https://doi.org/10.1016/0360-3016\(93\)90285-4](https://doi.org/10.1016/0360-3016(93)90285-4)
30. Fuller SA, Haybittle JL, Smith RE, Dobbs HJ. Cardiac doses in post-operative breast irradiation. *Radiother Oncol* 1992; **25**: 19–24. doi: [https://doi.org/10.1016/0167-8140\(92\)90190-6](https://doi.org/10.1016/0167-8140(92)90190-6)
 31. Roberson PL, Lichter AS, Bodner A, Fredrickson HA, Padikal TN, Kelly BA, et al. Dose to lung in primary breast irradiation. *Int J Radiat Oncol Biol Phys* 1983; **9**: 97–102. doi: [https://doi.org/10.1016/0360-3016\(83\)90216-X](https://doi.org/10.1016/0360-3016(83)90216-X)
 32. Bornstein BA, Cheng CW, Rhodes LM, Rashid H, Stomper PC, Siddon RL, et al. Can simulation measurements be used to predict the irradiated lung volume in the tangential fields in patients treated for breast cancer? *Int J Radiat Oncol Biol Phys* 1990; **18**: 181–7. doi: [https://doi.org/10.1016/0360-3016\(90\)90282-O](https://doi.org/10.1016/0360-3016(90)90282-O)
 33. Smitt MC, Li SD, Shostak CA, Chang W, Boyer AL. Breast-conserving radiation therapy: potential of inverse planning with intensity modulation. *Radiology* 1997; **203**: 871–6. doi: <https://doi.org/10.1148/radiology.203.3.9169719>
 34. Coia LR, Schultheiss TE, Hanks GE. *A Practical Guide to CT Simulation*. Madison, WI: Advanced Medical Publishing; 1995.
 35. Harris JR, Hellman S. Put the “hockey stick” on ice. *Int J Radiat Oncol Biol Phys* 1988; **15**: 497–9. doi: [https://doi.org/10.1016/S0360-3016\(98\)90034-7](https://doi.org/10.1016/S0360-3016(98)90034-7)
 36. Marks LB, Hebert ME, Bentel G, Spencer DP, Sherouse GW, Prosnitz LR. To treat or not to treat the internal mammary nodes: a possible compromise. *Int J Radiat Oncol Biol Phys* 1994; **29**: 903–9. doi: [https://doi.org/10.1016/0360-3016\(94\)90584-3](https://doi.org/10.1016/0360-3016(94)90584-3)
 37. Solin LJ, Danoff BF, Schwartz GF, Galvin JM, Goodman RL. A practical technique for the localization of the tumor volume in definitive irradiation of the breast. *Int J Radiat Oncol Biol Phys* 1985; **11**: 1215–20. doi: [https://doi.org/10.1016/0360-3016\(85\)90072-0](https://doi.org/10.1016/0360-3016(85)90072-0)
 38. Siddon RL, Buck BA, Harris JR, Svensson GK. Three-field technique for breast irradiation using tangential field corner blocks. *Int J Radiat Oncol Biol Phys* 1983; **9**: 583–8. doi: [https://doi.org/10.1016/0360-3016\(83\)90080-9](https://doi.org/10.1016/0360-3016(83)90080-9)
 39. Svensson GK, Bjärngard BE, Larsen RD, Levene MB. A modified three-field technique for breast treatment. *Int J Radiat Oncol Biol Phys* 1980; **6**: 689–94. doi: [https://doi.org/10.1016/0360-3016\(80\)90224-2](https://doi.org/10.1016/0360-3016(80)90224-2)
 40. Conte G, Nascimben O, Turcato G, Polico R, Idi MB, Belleri LM, et al. Three-field isocentric technique for breast irradiation using individualized shielding blocks. *Int J Radiat Oncol Biol Phys* 1988; **14**: 1299–305. doi: [https://doi.org/10.1016/0360-3016\(88\)90410-5](https://doi.org/10.1016/0360-3016(88)90410-5)
 41. Podgorsak EB, Gosselin M, Kim TH, Freeman CR. A simple isocentric technique for irradiation of the breast, chest wall and peripheral lymphatics. *Br J Radiol* 1984; **57**: 57–63. doi: <https://doi.org/10.1259/0007-1285-57-673-57>
 42. Legendik JJ, Hofman P. A standardized multifield irradiation technique for breast tumours using asymmetrical collimators and beam angulation. *Br J Radiol* 1992; **65**: 56–62. doi: <https://doi.org/10.1259/0007-1285-65-769-56>
 43. Rosenow UF, Valentine ES, Davis LW. A technique for treating local breast cancer using a single set-up point and asymmetric collimation. *Int J Radiat Oncol Biol Phys* 1990; **19**: 183–8. doi: [https://doi.org/10.1016/0360-3016\(90\)90152-A](https://doi.org/10.1016/0360-3016(90)90152-A)
 44. Marshall MG. Three-field isocentric breast irradiation using asymmetric jaws and a tilt board. *Radiother Oncol* 1993; **28**: 228–32. doi: [https://doi.org/10.1016/0167-8140\(93\)90062-D](https://doi.org/10.1016/0167-8140(93)90062-D)
 45. Galvin JM, Powlis W, Fowble B, Goodman RL. A new technique for positioning tangential fields. *Int J Radiat Oncol Biol Phys* 1993; **26**: 877–81. doi: [https://doi.org/10.1016/0360-3016\(93\)90504-O](https://doi.org/10.1016/0360-3016(93)90504-O)
 46. Chu JC, Solin LJ, Hwang CC, Fowble B, Hanks GE, Goodman RL. A nondivergent three field matching technique for breast irradiation. *Int J Radiat Oncol Biol Phys* 1990; **19**: 1037–40.
 47. Buchali A, Geismar D, Hinkelbein M, Schlenger L, Zinner K, Budach V. Virtual simulation in patients with breast cancer. *Radiother Oncol* 2001; **59**: 267–72. doi: [https://doi.org/10.1016/S0167-8140\(01\)00322-X](https://doi.org/10.1016/S0167-8140(01)00322-X)
 48. Neal AJ, Torr M, Helyer S, Yarnold JR. Correlation of breast dose heterogeneity with breast size using 3D CT planning and dose-volume histograms. *Radiother Oncol* 1995; **34**: 210–8. doi: [https://doi.org/10.1016/0167-8140\(95\)01521-H](https://doi.org/10.1016/0167-8140(95)01521-H)
 49. Butker EK, Helton DJ, Keller JW, Hughes LL, Crenshaw T, Davis LW. A totally integrated simulation technique for three-field breast treatment using a CT simulator. *Med Phys* 1996; **23**: 1809–14. doi: <https://doi.org/10.1118/1.597763>
 50. Vincent D, Beckham W, Delaney G. An assessment of the number of CT slices necessary to plan breast radiotherapy. *Radiother Oncol* 1999; **52**: 179–83. doi: [https://doi.org/10.1016/S0167-8140\(99\)00072-9](https://doi.org/10.1016/S0167-8140(99)00072-9)
 51. Aref A, Thornton D, Youssef E, He T, Tekyi-Mensah S, Denton L, et al. Dosimetric improvements following 3D planning of tangential breast irradiation. *Int J Radiat Oncol Biol Phys* 2000; **48**: 1569–74. doi: [https://doi.org/10.1016/S0360-3016\(00\)00808-7](https://doi.org/10.1016/S0360-3016(00)00808-7)
 52. Landau D, Adams EJ, Webb S, Ross G. Cardiac avoidance in breast radiotherapy: a comparison of simple shielding techniques with intensity-modulated radiotherapy. *Radiother Oncol* 2001; **60**: 247–55. doi: [https://doi.org/10.1016/S0167-8140\(01\)00374-7](https://doi.org/10.1016/S0167-8140(01)00374-7)
 53. Kong FM, Klein EE, Bradley JD, Mansur DB, Taylor ME, Perez CA, et al. The impact of central lung distance, maximal heart distance, and radiation technique on the volumetric dose of the lung and heart for intact breast radiation. *Int J Radiat Oncol Biol Phys* 2002; **54**: 963–71. doi: [https://doi.org/10.1016/S0360-3016\(02\)03741-0](https://doi.org/10.1016/S0360-3016(02)03741-0)
 54. Lu XQ, Sullivan S, Eggleston T, Holupka E, Bellerive M, Abner A, et al. A three-field breast treatment technique with precise geometric matching using multileaf collimator-equipped linear accelerators. *Int J Radiat Oncol Biol Phys* 2003; **55**: 1420–31.
 55. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347**: 1233–41. doi: <https://doi.org/10.1056/NEJMoa022152>
 56. Solin LJ, Kurtz J, Fourquet A, Amalric R, Recht A, Bornstein BA, et al. Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. *J Clin Oncol* 1996; **14**: 754–63. doi: <https://doi.org/10.1200/JCO.1996.14.3.754>
 57. Santiago RJ, Wu L, Harris E, Fox K, Schultz D, Glick J, et al. Fifteen-year results of breast-conserving surgery and definitive irradiation for Stage I and II breast carcinoma: the University of Pennsylvania experience. *Int J Radiat Oncol Biol Phys* 2004; **58**: 233–40. doi: [https://doi.org/10.1016/S0360-3016\(03\)01460-3](https://doi.org/10.1016/S0360-3016(03)01460-3)
 58. Harris EE, Schultz D, Bertsch H, Fox K, Glick J, Solin LJ. Ten-year outcome after combined modality therapy for inflammatory breast cancer. *Int J Radiat Oncol Biol Phys* 2003; **55**: 1200–8. doi: [https://doi.org/10.1016/S0360-3016\(02\)04201-3](https://doi.org/10.1016/S0360-3016(02)04201-3)
 59. Krueger EA, Schipper MJ, Koelling T, Marsh RB, Butler JB, Pierce LJ. Cardiac chamber and coronary artery doses associated with postmastectomy radiotherapy techniques

- to the chest wall and regional nodes. *Int J Radiat Oncol Biol Phys* 2004; **60**: 1195–203. doi: <https://doi.org/10.1016/j.ijrobp.2004.04.026>
60. Cooper BT, Li X, Shin SM, Modrek AS, Hsu HC, DeWyngaert JK, et al. Preplanning prediction of the left anterior descending artery maximum dose based on patient, dosimetric, and treatment planning parameters. *Adv Radiat Oncol* 2016; **1**: 373–81. doi: <https://doi.org/10.1016/j.adro.2016.08.001>
 61. Lorenzen EL, Brink C, Taylor CW, Darby SC, Ewertz M. Uncertainties in estimating heart doses from 2D-tangential breast cancer radiotherapy. *Radiother Oncol* 2016; **119**: 71–6. doi: <https://doi.org/10.1016/j.radonc.2016.02.017>
 62. Taylor CW, McGale P, Povall JM, Thomas E, Kumar S, Dodwell D, et al. Estimating cardiac exposure from breast cancer radiotherapy in clinical practice. *Int J Radiat Oncol Biol Phys* 2009; **73**: 1061–8. doi: <https://doi.org/10.1016/j.ijrobp.2008.05.066>
 63. Das IJ, Andrews JZ, Cao M, Johnstone PA. Correlation of 2D parameters to lung and heart dose-volume in radiation treatment of breast cancer. *Acta Oncol* 2013; **52**: 178–83. doi: <https://doi.org/10.3109/0284186X.2012.673737>
 64. Borger JH, Hooning MJ, Boersma LJ, Snijders-Keilholz A, Aleman BM, Lintzen E, et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: the role of irradiated heart volume. *Int J Radiat Oncol Biol Phys* 2007; **69**: 1131–8. doi: <https://doi.org/10.1016/j.ijrobp.2007.04.042>
 65. Wei X, Liu HH, Tucker SL, Wang S, Mohan R, Cox JD, 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. doi: <https://doi.org/10.1016/j.ijrobp.2007.10.056>
 66. Aznar MC, Korreman SS, Pedersen AN, Persson GF, Josipovic M, Specht L. Evaluation of dose to cardiac structures during breast irradiation. *Br J Radiol* 2011; **84**: 743–6. doi: <https://doi.org/10.1259/bjr/12497075>
 67. Goody RB, O'Hare J, McKenna K, Dearey L, Robinson J, Bell P, et al. Unintended cardiac irradiation during left-sided breast cancer radiotherapy. *Br J Radiol* 2013; **86**: 20120434. doi: <https://doi.org/10.1259/bjr.20120434>
 68. Hurkmans CW, Borger JH, Pieters BR, Russell NS, Jansen EP, Mijnheer BJ. Variability in target volume delineation on CT scans of the breast. *Int J Radiat Oncol Biol Phys* 2001; **50**: 1366–72. doi: [https://doi.org/10.1016/S0360-3016\(01\)01635-2](https://doi.org/10.1016/S0360-3016(01)01635-2)
 69. Li XA, Tai A, Arthur DW, Buchholz TA, Macdonald S, Marks LB, 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. doi: <https://doi.org/10.1016/j.ijrobp.2008.10.034>