Breast Cancer: Basic and Clinical Research

ORIGINAL RESEARCH

Dose Distribution in the Heart and Cardiac Chambers Following 4-field Radiation Therapy of Breast Cancer: a Retrospective Study

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Abstract

Purpose: To evaluate cardiac doses in breast cancer patients with stage II/III treated with 4-field radiotherapy based on computed tomography (CT) dose planning.

Methods and Materials: Based on archived CT images, whole heart and cardiac chamber radiation doses were analyzed in 216 (111 left-sided and 105 right-sided) mastectomized or lumpectomized breast cancer patients treated at a single institution, the Norwegian Radium Hospital, between 2000–2002. Individual dose volume histograms for the whole heart and for the four cardiac chambers were obtained, and mean, median and maximum doses to these structures were calculated. The dose (Gy) delivered to the 5% of the volume of each cardiac structure ($D_{5\%}$), and the volume percentage of each structure receiving $\geq$ 25 Gy (V_{25Gy}) were reported. Normal tissue complication probability (NTCP) calculations were used to estimate the risk for ischemic heart disease (IHD).

Results: Cohort-based medians of the whole heart mean dose (D_{mean}) for left- and right-sided tumors were 3.2 Gy and 1.3 Gy, respectively, with similar ventricular but lower atrial values. The atrial doses did not differ according to laterality of the breast tumor. In 13 patients with left-sided cancer, 5% of the heart volume was exposed to >25 Gy. The NTCP estimates were generelly low, with a maximum of 2.8%.

Conclusions: During adjuvant CT-based locoregional radiotherapy of women with breast cancer, the cardiac radiation doses are, at the group level, below recommended threshold values ($D_{5\%}$ < 25 Gy), though individual patients with left-sided disease may exceed these limits.

Keywords: heart, cardiac chambers, breast cancer and radiation therapy

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Introduction

A number of large randomized trials have shown a small but statistically significant risk of cardiac mortality associated with locoregional irradiation of breast cancer.[1–3] In the Early Breast Cancer Trialists' Collaborative Group meta-analysis, radiotherapy (RT) compared with no RT was associated with excess mortality (rate ratio 1.27) from heart disease.[4] In many of the included trials, older techniques were applied such as Cobalt-60 (Co-60) or orthovoltage radiation, and treatment was based on manual planning. Other studies have shown that modern techniques and dose planning recommendations result in much smaller cardiac radiation doses.[5–7] However, even with modern techniques, a subgroup of patients with left-sided breast cancer might receive cardiotoxic doses.[6,8–10] Further, considerable variation in the cardiac doses according to the use of different RT treatment regimens has been pointed out.[11] On the other hand, Correa et al[12] have concluded that cardiac toxicity could be avoided by use of proper field arrangements and choice of beam energy. The application of CT-based dose planning, breath-hold techniques and intensity-modulated RT thus represents an important step to reduce long-term cardiac risk in breast cancer survivors.

Dose-response relationships based on cardiac mortality data have been produced using a radiobiological model.[8] Model-based estimates predict that $V_{25} < 10\%$ (V_{25}: heart volume receieving 25 Gy or more) is associated with a <1% probability of cardiac mortality 15 years after radiotherapy.[13] The Norwegian Breast Cancer Group (NBCG) recommends that $V_{25} < 5\%$ (http://www.nbcg.no), and The National Danish Breast Cancer Group states that no part of the left anterior descending artery (LAD) should be irradiated with 20 Gy or more, with $V_{40} < 5\%$ and $V_{20} < 10\%$ for the heart (http://www.dbcg.dk).

To our knowledge, no detailed dosimetric data from a large routinely treated patient cohort are available in which the radiation exposure to the cardiac chambers using modern radiotherapy techniques for a large cohort of real-life patients has been documented. Furthermore, most commonly radiation-induced cardiotoxicity is described as abnormal function of the left ventricle, as demonstrated by echocardiography.[14] In recent years, reduced diastolic function[14] has gained increasing attention as a parameter of early cardiotoxicity, and assessment of atrial radiation doses has become a goal of future research. Such data should be analyzed together with long-term atrial and ventricular morbidity in breast cancer survivors.

We plan to investigate the relationship between cardiac doses applied during adjuvant irradiation of breast cancer stage II/III and cardiotoxicity in 10-year breast cancer survivors. As a first step, we report here total ventricular as well as atrial cardiac doses for future estimation of radiation-induced complication probabilities among the patients in question. The aim of the current descriptive study was to measure radiation doses to all 4 cardiac chambers based on archived CT images established when planning adjuvant radiotherapy in breast cancer patients.

Material and Methods

Patients

Breast cancer survivors eligible for the present study were all consecutive patients who, from 2000 to 2002, had CT-based adjuvant radiotherapy at the Norwegian Radium Hospital after modified mastectomy or lumpectomy for breast cancer stage II/III and who were included in an ongoing longitudinal survey.[15] All patients consented by signature to participate in the study of longterm problems after breast cancer. The evaluation of radiotherapy techniques presented in this paper was a part of this larger project. Medical and demographic data were extracted from medical records (Table 1). Of 216 patients, all of whom were Caucasian women, 111 had left-sided breast cancer, and 105 had right-sided breast cancer. Sixty-one of the patients had had a lumpectomy. One hundred and fifty-six of these patients underwent systemic chemotherapy prior to irradiation, but none of them received trastuzumab. At the time of diagnosis, only 3 women used any medications for cardiac problems.

The study was approved by the ethical committee of the South Health Region South in Norway.

4-field radiation technique

All women were treated with 4-field RT where the target volume included the breast (after lumpectomy) or the chest wall (after mastectomy), the ipsilateral supraclavicular and infraclavicular fossa, the

Table 1. Patient demographics and treatment related characteristics for 216 included breast cancer patients.

Characteristic	Left-sided	Right-sided
No of patients	111	105
Age (yrs)		
<50	47	49
>50	64	56
Median	51	51
Range	34–72	27–69
Surgery		
Mastectomy	78	77
Lumpectomy	33	28
BMI		
BMI ≤ 25	40	38
BMI > 25	58	58
Hight		
Median (range)	126 (156–176)	156 (150–180)
Weight		
Median (range)	68 (50–96)	71 (50–100)
RT (Gy)		
50 Gy	95	90
50+10 Gy[a]	14	12
50+16 Gy[a]	2	3
Chemo		
FEC	76	63
Other	5	12
No	20	20
Tamoxifen		
Yes	20	13
No	91	92

Note: [a]Adjuvant radiotherapy to the thoracic wall and lymph nodes regions+ boost to the lumpectomy area.

ipsilateral internal mammary nodes (IMNs), and the ipsilateral axillary nodes. Respiratory gating was not used. The RT planning was based on noncontrast enhanced transverse CT scans covering the region from the 6th cervical vertebra to the middle part of the abdomen, the CT-slice thickness being 1 cm. Wing board with headrest was employed. Treatment planning and dose calculation were performed using the Helax-TMS (Version 6.0 or higher) system applying a pencil beam algorithm. The voxel size of the dose calculation matrix was $0.5 \times 0.5 \times 1.0$ cm^3.

The beam arrangement consisted of four half-beams with two tangential beams covering the caudal part of the target volume, one anterior-posterior field (0°) and one oblique field, 110° to 115°, covering the cranial part of the target volume (Figs. 1 and 2). Field 1 and 2 were intended to treat the ipsilateral supraclavicular and infraclavicular, axillary, and internal mammary lymph nodes (IMNs) and the cranial part of the breast/breast wall, while tangential fields 3 and 4 treated the caudal part of the breast/breast wall. The beam angles, apertures, weights, and dynamic wedges were optimized by standard (forward) planning. In the longitudinal direction, the isocentre was placed immediately caudal of the IMNs, which typically was 2 to 3 cm caudal of the carina. The photon beam energy was mainly 6 MV using a Siemens or Varian linear accelerator. The dose plans were normalized to the mean dose to the CTV. The breast/chest wall received a total dose of 50 Gy, and the regional lymph nodes, 46 to 50 Gy. Thirty-six lumpectomized women, all younger than 50 years of age, received a boost of 10 or 16 Gy to the tumor bed (9–12 MeV) using a circular field with a diameter of 5 to 9 cm. Mastectomized women with stage III breast cancer and patients with stage II breast cancer with tumor-positive resection margins had bolus covering the whole breast wall; otherwise, a bolus of 6 cm width covering only the mastecomy scar was applied. The impact of boost on cardiac radiation doses was not investigated in this study.

Cardiac volume definition

During the routine dose planning procedure, a clinical oncologist had delineated the heart on the CT images, but for the purpose of this study, cardiac delineation was redone by a radiologist using the archived CT images. With applied CT scan technique, the coronary arteries were not consistently visible; hence, coronary arteries were not contoured. The cranial limit of the heart included the right atrium and excluded the pulmonary trunk and coronary arteries. The caudal contour of the heart was the caudal myocardial border. The pericardium was included in the heart volume; the inferior caval vein was excluded. The right and left heart atria and ventricles were contoured separately. The atrial septum was well discernible on the available scans as it had lower attenuation than the surrounding blood and myocardium. Cardiac motion and lack of contrast made it difficult to reliably identify the valves and the interventricular septum. To have reproducible results, we defined these borders from certain

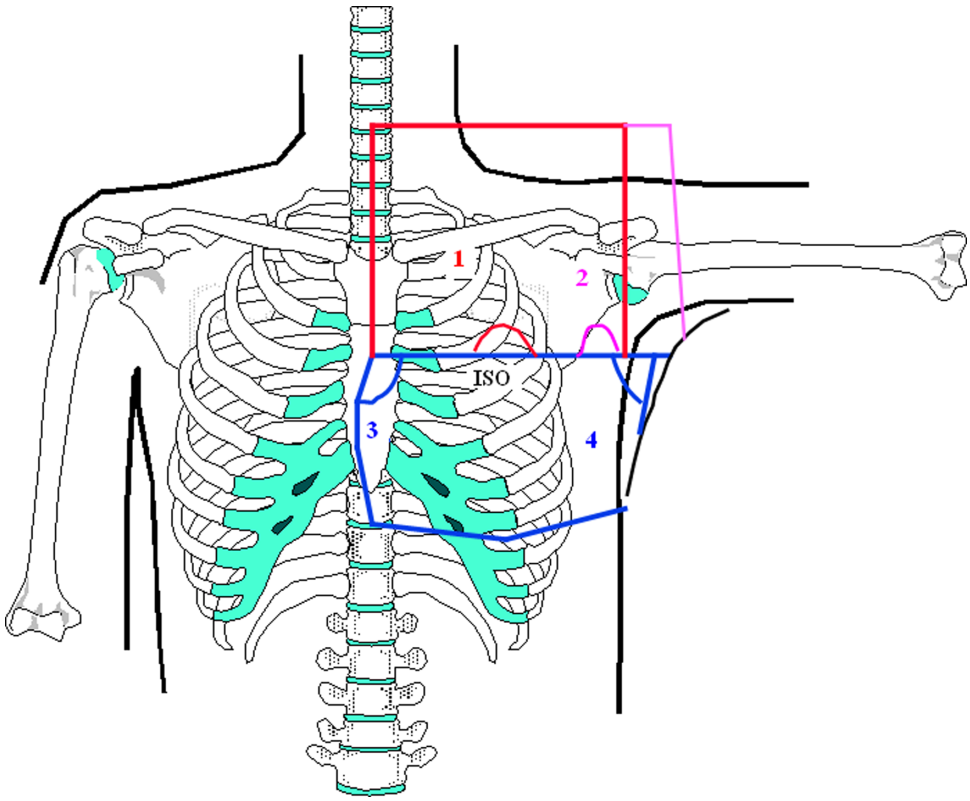

Figure 1. The 4-field arrangement used in CT-RT shown schematically.
Notes: The red field borders depict the anterior-posterior field (1), the pink color indicates the oblique field (2), and the blue color illustrates the location of the tangential fields (3 and 4).

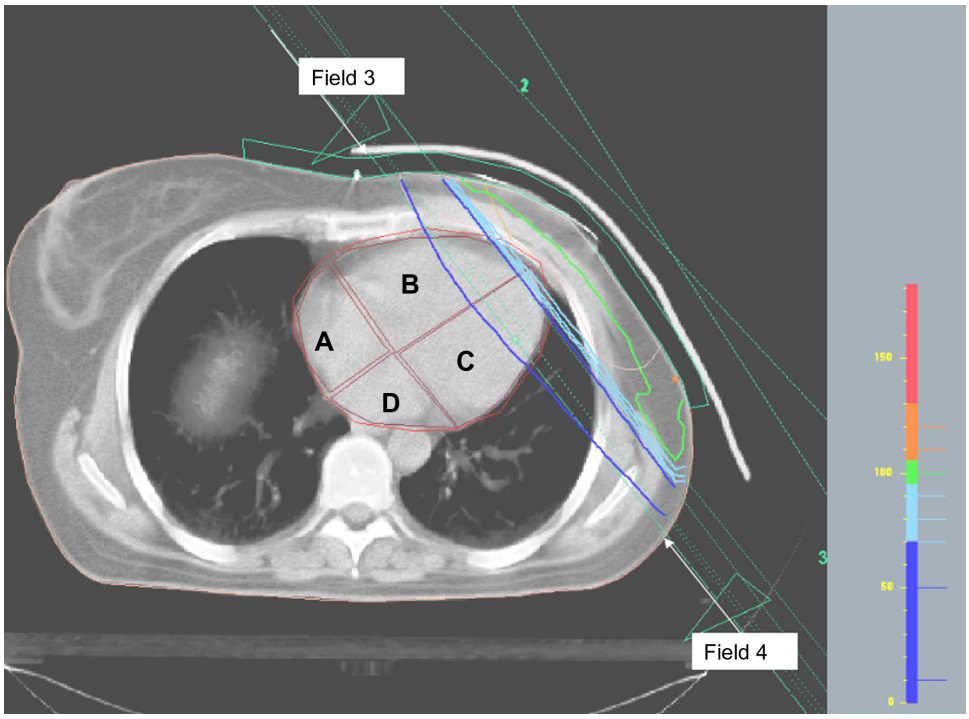

Figure 2. Radiation fields covering the caudal part of the breast/breast wall (fields 3 and 4) are shown here.
Notes: The arrows indicate the radiation direction. Delineation of whole heart and four cardiac chambers in a patient with a left-sided breast cancer. A = right atrium, B = right ventricle, C = left ventricle, and D = left atrium.

key structures that were reliably identified on the available scans:

A. The atrioventricular groove
B. The interventricular groove/apex cordis
C. An area of fibrous/fatty tissue where the atrial septum meets the atrioventricular plane, anatomically corresponding to the trigonum fibrosum dextrum
D. The pulmonary artery bifurcation.

The border between atria and the ventricles were defined as straight lines drawn between A and C. The border between the ventricles was a straight line between B and C. The cranial border of the right ventricle was defined as the third CT-slice below D (Fig. 2).

Dose calculations

For each patient, dose volume histograms (DVHs) for the whole heart and each of the four delineated cardiac chambers were obtained from the treatment planning module supplemented by the individual mean, median, and maximum doses. Further, the individual dose (Gy) delivered to 5% of the volume of each specific cardiac structure ($D_{5\%}$) was assessed as well as the volume percentage of the respective structure receiving 25 Gy or more (V_{25Gy}).

Normal tissue complication probability

The normal tissue complication probability (NTCP), in terms of excess cardiac mortality at 15 years, was estimated using the relative seriality model.[8] This model employs the DVH for the heart and accounts for the serial and parallell architecture of tissue subunits and for the binomial nature of cell kill. The dose at 50% response, D_{50}, and the maximal relative slope, γ, were used to describe the dose-response curve. The parameters used were $D_{50} = 52.3$ Gy and $\gamma = 1.28$.[8] A fractionation sensitivity (α/β-ratio) of 3 Gy was assumed. Individual NTCP estimates were obtained for all patients based on their DVH.

Statistics

As a rule, cohort-based medians along with their ranges were established for the continous demographic and dosimetric parameters. Differences between variables in patients with right- and left-sided tumors were evaluated by the Mann–Whitney test. However, the dose-volume histograms display mean values and one standard deviation. A P value < 0.05 was considered to be statistically significant.

Results

Compared to women with right-sided tumors, those with left-sided tumors had significantly higher radiation doses to the whole heart and the ventricles (Fig. 3 and Table 2), whereas the doses to the atria did not differ according to laterality of the tumor. Significant differences also emerged for $D_{5\%}$ for the whole heart and for the left and right ventricle but not for the atria. There was a considerable interpatient variability in cardiac doses. Greater variations of the cardiac parameters were observed for patients with left-than with right-sided tumors, with exception of the right atrium. Cohort-based medians of the whole cardiac mean dose (D_{mean}) were 3.2 Gy and 1.3 Gy for patients with left- and right-sided breast cancer, respectively. In none of the patients with right-sided tumors, but in 13 (12%) of those with left-sided cancer, 5% of the heart volume was exposed to >25 Gy.

Figure 3 provides cohort-based cumulative DVHs for the whole heart and the 4 cardiac chambers. For whole heart and ventricular doses between 5 to 45 Gy, significant differences were observed comparing left-sided with right-sided tumors. No statistical differences for the dosimetric results were observed for the atria with exception of the 5 Gy point of the right atrium.

The estimated normal tissue complication probability for the whole heart was moderately higher for the patients with left-sided compared with those with right-sided disease (Table 2). Furthermore, the NTCP estimates are very low for the whole population included in this study, with a maximum probability of 2.8%.

Discussion

Cohort-based mean radiation doses to the ventricles did not differ significantly from the whole heart mean doses, but both parameters were related to the laterality of the breast cancer. No side-related differences emerged between the very low atrial doses. Further, the NTCP estimates were very low for the whole population, independent of laterality.

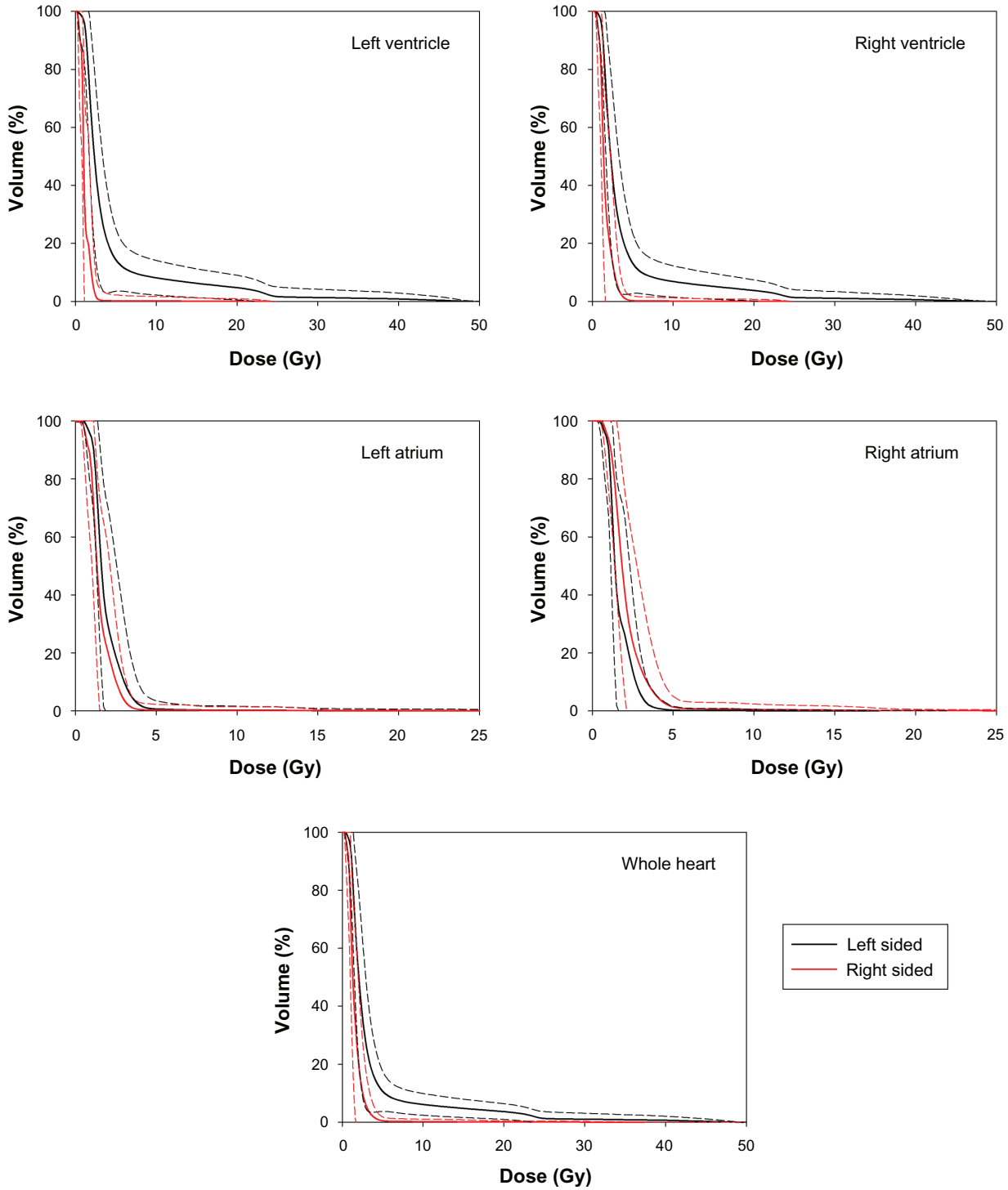

Figure 3. Mean dose-volume histograms displaying whole heart, ventricular and atrial radiation doses, in 111 patients with right-sided (red) and 105 patients with left-sided (black) tumors.
Note: The two dashed lines correspond to plus/minus one standard deviation from the cohort based mean curve (solid line).

With the recognition of the beneficial effect of adjuvant radiotherapy of breast cancer, research has increasingly dealt with long-term radiation-related adverse effects such as cardiotoxicity. Many studies have shown that tumor laterality has the greatest impact on radiation doses to the heart[8,9,12,13] with additional impact of the radiotherapy technique.[12,16–19] Not surprisingly, there has been a gradual decrease of the cardiac doses along with technical improvements during the last two decades with the introduction of

Table 2. Whole heart and cardiac chamber radiation dose, together with the normal tisuue complication probabilities (NTCP) based on the dose volume histogram for the whole heart.

	Left sided	Right sided
No. of patients	111	105
Whole heart		
D_{mean} (Gy)*	3.2 (0.7, 7.9)	1.3 (0.6, 4.1)
D_{median} (Gy)*	1.8 (0.6, 4.3)	1.2 (0.5, 2.9)
D_{max} (Gy)*	25.0 (1.8, 53.1)	3.4 (1.4, 51.5)
$D_{5\%}$ (Gy)*,†	11.6 (1.3, 44.1)	2.2 (1.1, 16.2)
V_{25Gy} (%)*	0.0 (0.0, 8.6)	0.0 (0.0, 3.3)
NTCP (%) (median, min, max)	0.03, 0.00, 2.8	0.00, 0.00, 0.5
Left ventricle		
D_{mean} (Gy)*	3.7 (0.4, 11.3)	1.0 (0.4, 5.3)
D_{median} (Gy)*	2.3 (0.4, 5.6)	1.0 (0.3, 2.7)
D_{max} (Gy)*	24.5 (0.8, 52.1)	1.4 (0.6, 24.8)
$D_{5\%}$ (Gy)*	14.8 (0.6, 46.5)	1.2 (0.5, 22.7)
V_{25Gy} (%)*	0.0 (0.0, 16.0)	0.0 (0.0, 0.0)
Right ventricle		
D_{mean} (Gy)*	3.5 (0.7, 9.1)	1.4 (0.6, 4.5)
D_{median} (Gy)*	2.1 (0.7, 4.8)	1.3 (0.6, 3.1)
D_{max} (Gy)*	24.2 (1.6, 51.0)	2.5 (1.2, 24.9)
$D_{5\%}$ (Gy)*	12.0 (1.2, 41.4)	2.0 (1.0, 22.4)
V_{25Gy} (%)*	0.0 (0.0, 11.2)	0.0 (0.0, 0.0)
Left atrium		
D_{mean} (Gy)	1.6 (0.7, 6.0)	1.3 (0.5, 4.6)
D_{median} (Gy)	1.6 (0.7, 3.9)	1.3 (0.5, 2.9)
D_{max} (Gy)	2.4 (0.9, 49.4)	2.0 (0.8, 26.9)
$D_{5\%}$ (Gy)	2.1 (0.8, 23.7)	1.8 (0.7, 15.0)
V_{25Gy} (%)	0.0 (0.0, 4.5)	0.0 (0.0, 1.6)
Right atrium		
D_{mean} (Gy)	1.4 (0.6, 3.7)	1.9 (0.8, 5.6)
D_{median} (Gy)	1.4 (0.5, 3.6)	1.8 (0.8, 4.2)
D_{max} (Gy)	2.4 (1.0, 22.2)	3.0 (1.3, 33.9)
$D_{5\%}$ (Gy)	1.8 (0.8, 10.0)	2.5 (1.2, 18.0)
V_{25Gy} (%)	0.0 (0.0, 0.0)	0.0 (0.0, 2.1)

Notes: Cohort-based medians and range are given. D_{mean} = mean dose, D_{median} = median dose, D_{max} = maximum dose, $D_{5\%}$ (Gy) = the dose (Gy) delivered to 5% of the volume of each specific cardiac structure ($D_{5\%}$) and V_{25Gy}(%) = the volume percentage of the respective structure receiving 25 Gy or more. *$P < 0.01$ comparing left-sided with right-sided tumors; †13 patients, all left-sided tumors, received $D_{5\%} > 25$Gy with a range of [28.3–44.1Gy].

CT-based radiotherapy planning, IMRT, and respiratory gating.[8,12,20] The possibility of establishing individual CT-based DVHs has also lead to official guidelines as to doses to the whole heart or its parts. In most of our patients, the NBCG's recommendation that not more than 5% of the heart's volume should receive 25 Gy has been met but with considerable interpatient variability. Lower cardiac doses may be achieved when the breast wall is irradiated by electron beams.[8,21] However, breast wall irradiation with electron beams may not provide a uniform target dose distribution. Reduction in mean cardiac dose can also be achieved by breath holding techniques, such as deep-inspiratory breath-hold introduced during the last decade.[12] Taking into account the differences in dose estimation procedures and different patient numbers, our presented figures are comparable to those for modern radiotherapy techniques published by Taylor et al[8] regarding whole cardiac mean doses (0.9–14 Gy for left-sided disease and 0.4–5 Gy for rightsided disease).

Pierce et al[21] noted that the volume of heart receiving greater than 30 Gy (V_{30}) was significantly higher with Co^{60} treatment than other linear accelerator-based methods. Based on a study of 28 patients, Fuller et al[22] recorded that when using orthovoltage radiotherapy approximately 87% of the mean cardiac volume received a BED (biologically effective dose) of 5 Gy or more in case of left-sided tumors. This share was reduced to 41% after introduction of megavoltage radiotherapy. The target volume in Fuller et al's patients[22] did not comprise the IMNs. Several studies have demonstrated a higher risk of cardiac toxicity when the internal mammary nodes were included in the treatment fields as a result of using wide tangents.[2,21–23] Janjan et al[23] showed that electron beam irradiation of the IMNs reduced the total dose to the anterior wall of the left ventricle with 30% compared with photon irradiation. Furthermore, in another study, the use of electrons in the treatment of IMNs and chest wall showed no impact on the risk for ischemic heart disease when patients with irradiated IMNs were compared with those without.[3] In the EORTC trial 22922/10925,[24] the survival and cardiac toxicity were investigated in approximately 4000 patients three years after elective irradiation of the internal mammary and medial supraclavicular nodes. The authors reported no increased cardiac toxicity related to the irradiation of these structures. However, it was suggested that a follow-up of at least 10 years was needed to determine whether cardiac toxicity is increased after radiotherapy. Thus, the indication to irradiate the IMNs and the optimal radiation technique remain controversial.[23]

Using the 4-field high-voltage photon technique, our median values for V_{25Gy} (0.0% for both left-sided and right-sided tumors) are far below those presented

by Fuller et al,[22] Gyenes et al,[6] and Taylor et al.[11] However, the great variability in our values should be emphasized, as some individuals with left-sided tumors still received rather high doses as a result of variation in internal anatomical differences, with approximately 10% of these patients exceeding a $D_{5\%}$ of 25 Gy. Most probably, interpatient variations of the individual breast and thoracic anatomy explain the wide range of cardiac doses found in our study. Due to the heart being located mainly in the left thoracic half, these influences are predominantly recognized for left-sided tumors.

The left anterior descending artery (LAD) is one of the most critical structures in relation to subsequent radiation-related cardiac infarction. In Fuller et al's series,[22] the radiation dose to LAD remained high even after the introduction of megavoltage radiotherapy, whereas the doses for the other coronary arteries were reduced. We have not calculated the individual LAD's radiation dose, as the radiologist considered it impossible to delineate the LAD without the use of contrast agents. According to Taylor et al,[11] the RT doses to LAD was 3 to 4 times higher than the mean cardiac dose. However, due to differences between the authors' older radiation technique and ours, we refrained from using these figures in our cohort.

Our study has several limitations. In the current work, we have not taken into account the contribution to heart dose of the electron boost treatment for a subgroup of 36 patients. In this case, no dose plan data was available, and the old dose planning system (Helax-TMS) does not provide reliable dose estimates from electron beams. However, patients currently receiving electron boosts at our clinic with Monte Carlo–based treatment plan calculations (using Oncentra) have typically been $D_{5\%} = 0.2$ Gy for a boost dose of 16 Gy. Admittedly, this dose contribution may be somewhat higher in patients with medially located tumors receiving electrons. Thus, the contribution to the heart dose for the electron beam is expected to be minute for the patients in question. Furthermore, respiratory gating was not used, which currently appears to be the most attractive technique for reducing cardiac doses to patients with left-sided disease. However, causes of cardiotoxic events from standard techniques have to be explored, and the results may aid decision making when introducing new techniques in the clinic. Finally, our results are based on CT images without the use of contrast and 1 cm slice thickness, limiting the demonstration of individual details. Thus, our figures should be viewed as the best achievable approximation of cardiac radiation exposure in a large retrospectively assessed series of breast cancer survivors. The main strength of our study is the large sample size of consecutive patients treated in real-life, whose cardiac conditions will be surveyed by a future clinical survey of 10-year breast cancer survivors to quantify potential cardiac risks caused by a defined cardiac dose. This clinical survey will also provide important feedback to the currently used NTCP model, which estimated that the excess cardiac mortality rate in the current cohort probably is low.

In summary, in the majority of included patients with stage II/III breast cancer whole heart $D_{5\%}$ was below 25 Gy as recommended by the national guidelines. However, women with left-sided breast cancer still represent a risk group. Our next step will be to perform cardiological examinations in these 10-year survivors relating the individual cardiac radiation exposure to the clinical findings.

Author Contributions

Conceived and designed the experiments: SDF, SJ. Analysed the data: SJ, EM. Wrote the first draft of the manuscript: SJ. Contributed to the writing of the manuscript: SJ, EM, SDF, KF, KT, TDD. Agree with manuscript results and conclusions: SDF, GB, SJ, EM, KF, KT, TDD. Jointly developed the structure and arguments for the paper: SJ, SDF. Made critical revisions and approved final version: SDF, EM, SJ. All authors reviewed and approved of the final manuscript.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and

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References

1. Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol*. 1994;12(3):447–53.
2. Høst H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer—long-term results from the Oslo study. *Int J Radiat Oncol Biol Phys*. 1986;12:727–32.
3. Rutqvist LE, Lax I, Fornander T, et al. 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.
4. Clarke M, Collins R, Darby S, et al; Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005;366:2087–106.
5. Das IJ, Cheng EC, Freedman G, et al. Lung and heart dose volume analyses with CT simulator in radiation treatment of breast cancer. *Int J Radiat Oncol Biol Phys.* 1998;42(1):11–9.
6. Gyenes G, Gagliardi G, Lax I, et al. Evaluation of irradiated heart volumes in stage I breast cancer patients treated with postoperative adjuvant therapy. *J Clin Oncol.* 1997;15:1348–53.
7. Giodano SH, Kuo YF, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst*. 2005;97:419–24.
8. Gagliardi G, Lax I, Ottolenghi A, et al. Long-term cardiac mortality after radiotherapy of breast cancer—application of the relative seriality model. *Br J Radiol*. 1996;69:839–46.
9. Darby SC, McGale P, Petro R, et al. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: nationwide cohort study of 90000 Swedish women. *BMJ*. 2003;326:256–7.
10. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. *Clin Cancer Res.* 2008;14:14–24.
11. Taylor CW, Nisbet A, McGale P, et al. Cardiac exposures in breast cancer radiotherapy: 1950s–90s. *Int J Radiat Oncol Biol Phys.* 2007;69(5): 1484–95.
12. Correa CR, Litt HI, Hwang W, et al. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clinc Oncol*. 2007;25:3031–7.
13. Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys*. 2010;76(3)(Suppl 1):77–85.
14. Lester SJ, Tajik AJ, Nishimura RA, et al. Unlocking the mysteries of diastolic function. *J Am Coll Cardiol*. 2008;51(7):679–89.
15. Reinertsen KV, Cvancarova M, Wist E, et al. Thyroid function in women after multimodal treatment for breast cancer stage II/III: comparison with controls from a population sample. *Int J Radiat Oncol Biol Phys*. 2009;75(1):764–70.
16. Overgaard M, Bentzen SM, Christensen JJ, et al. The values of NSD formula in equation of acute and late radiation complications in normal tissue following 2 and 5 fractions per week in breast cancer patients treated with postmastectomy irradiation. *Radiother Oncol*. 1987;9:1–11.
17. Rutqvist LE, Johansson H. Mortality by laterality of primary tumour among 55000 breast cancer patients from Swedish cancer registry. *Br J Cancer*. 1990;61:866–8.
18. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300000 women in US SEER cancer registries. *Lancet Oncol.* 2005;6:557–65.
19. Harris EER. Cardiac mortality and morbidity after breast cancer treatment [review]. *Cancer Control*. 2008;15:120–9.
20. Violet JA, Harmer C. Breast cancer: improving outcome following adjuvant radiotherapy. *Br J Radiol.* 2004;77:811–20.
21. Pierce LJ, Butler JB, Martel MK, et al. Postmastectomy radiotherapy of the chest wall: dosimetric comparison of common techniques. *Int J Radioat Oncol Biol Phys*. 2002;52:1220–30.
22. Fuller SA, Haybittle JL, Smith REA, et al. Cardiac doses in post-operative breast irradiation. *Radiother Oncol*. 1992;25:19–24.
23. Janjan NA, Gillin MT, Prows J, et al. Dose to the cardiac vascular and conduction systems in primary breast irradiation. *Med Dosim*. 1989;14:81–7.
24. Matzinger O, Heimsoth I, Poortmans P, et al. Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph nodes chain in stage I to III breat cancer (EORTC trial 22922/10925). *Acta Oncol.* 2010;49:24–34.