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Original Research Article

Cardiac death after breast radiotherapy and the QUANTEC cardiac guidelines

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ABSTRACT

Background: Breast/chest wall irradiation (RT) increases risk of cardiovascular death. International Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines state for partial heart irradiation a "V25Gy <10% will be associated with a <1% probability of cardiac mortality" in long-term follow-up after RT. We assessed whether women treated with breast/chest wall RT 10-years ago who died of cardiovascular disease (CVD) violated QUANTEC guidelines.

Materials/methods: A population-based database identified all cardiovascular deaths in women with early-stage breast cancer <80 years, treated with adjuvant breast/chest wall RT from 2002 to 2006. Ten-year rate of cardiovascular death was calculated using a Kaplan-Meier method. Patients were matched on a 2:1 basis with controls that did not die of CVD. For left-sided cases, the heart and left anterior descending (LAD) artery were retrospectively delineated. Dose-volume histograms were calculated, and heart V25Gy compared to QUANTEC guidelines.

Results: 5249 eligible patients received breast/chest wall RT from 2002 to 2006: 76 (1.4% at 10-years) died of CVD by June 2015. Forty-two patients received left-sided RT (1.7% CVD death at 10-years), 34 right-sided RT (1.3% at 10-years). Heart V25Gy did not exceed 10% in any left-sided cases. No cardiac dosimetry parameter distinguished left-sided cases from controls.

Conclusions: QUANTEC guidelines were not violated in any patient that died of CVD after left-sided RT. The risk of radiation induced cardiac death at 10-years appears to be very low if MHD is <3.3 Gy and maximum LAD dose ($EQD2_3$ Gy) is <45.4 Gy. Further studies are needed to evaluate heart and LAD constraints in the CT-planning era.

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1. Introduction

Adjuvant radiotherapy (RT) for breast cancer patients reduces the risk of local relapse and improves overall survival [1,2]. However, breast and chest wall RT have been shown to increase the risk of cardiovascular death [3–7]. The most recent update from the Early Breast Cancer Trialists' Collaborative Group showed a 30% increased risk of mortality from heart disease [7]. This increased risk has been shown to be detectable within 10-years after RT [6–8].

Historical studies based on populations of breast cancer patients treated with RT have assessed mean heart dose (MHD) as a measure of radiation exposure [6,9–11]. However, RT techniques have improved since the era described in these studies, and previous estimates of cardiac risk and radiation exposure may be outdated. Modern computerized tomography (CT) based planning now enables sub-volumes of the heart within the RT field to be calculated. As a result, a number of cardiac atlases are available to aid in contouring of the heart and coronary arteries [12–14]. International Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines have subsequently been developed, which aimed to predict risk of cardiac mortality due to RT [15]. QUANTEC guidelines state that for partial heart irradiation a "V25Gy <10% will be associated with a <1% probability of cardiac mortality" in long-term follow-up after RT. However, uncertainty remains as to which region of the heart is functionally the most

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important for RT-induced cardiac toxicity. Previous studies have shown that MHD was a better predictor for major coronary events than mean dose to the left anterior descending (LAD) artery [6]. Yet studies have also shown an increase in high grade coronary artery stenosis in the LAD in women who received left-sided RT for breast cancer, indicating a direct link between RT and coronary artery stenosis [16]. It is also increasingly recognised that risk of RT-associated cardiovascular disease (CVD) may be affected by a patient's baseline CVD risk factors (RFs) [6,7,11,17,18]. Dosimetric data on patients treated in the modern CT-based planning era is however lacking, as is the assessment of underlying CVD RFs in patients who died of CVD after RT.

We assessed whether women treated with RT 10-years ago, who died of CVD disease, had RT plans that violated QUANTEC guidelines. In order to define safe doses for the heart and LAD likely to be associated with a low cardiac-death event rate, we compared heart and LAD doses in patients who died of CVD to those who did not. Finally, in case and control patients, we assessed the presence of CVD RFs at the time of RT.

2. Materials and methods

2.1. Study design

BC Cancer provides all radiotherapy, chemotherapy and hormone therapy (HT) for patients with breast cancer in the province of British Columbia. CT-based planning for breast RT has been available in most of the province since 2002. The BC Cancer Breast Cancer Outcomes Unit manages a prospectively collected database containing patient, tumour and treatment details, as well as clinical outcomes on all breast cancer patients diagnosed since 1989. All women with the following criteria were identified from this database: <80 years at diagnosis, early-stage breast cancer (pTis-T2N0-2M0 and pT3N0), and received adjuvant RT to breast/chest wall between January 1, 2002 and December 31, 2006.

Women whose cause of death was coded as 'cardiovascular' were classified as cases. Cardiovascular deaths included: coronary artery disease (CAD), myocardial infarction (MI), congestive heart failure, cardiomyopathy, arrhythmias, pericardial disease, and 'other' heart disease. Controls were defined as patients who did not die of CVD (either alive or non-cardiac death) and selected from all eligible women in the study population. Controls were matched for age (within a three-year age range), year of diagnosis, laterality, use of HT, and use of adjuvant chemotherapy (none, anthracycline-based and non-anthracycline-based). Controls were randomly selected using a computer-generated random number sequence after matching in a 2:1 manner to cardiovascular death cases. For each case, time to death was measured from start of RT.

2.2. Cardiovascular disease risk factors

A chart review was performed for all cases and matched controls to document baseline CVD RFs. Pre-existing diagnoses of diabetes, hypertension, hypercholesterolemia, cardiac or stroke history, and smoking status were collated. If a specific RF was not documented, the patient was presumed not to have it unless they were documented as taking medications for that RF.

2.3. Radiation dosimetry

Individual CT-based RT plans were reviewed for all available left-sided cases and controls in Eclipse (Varian Medical Systems, Palo Alto, CA). The heart and LAD were retrospectively manually delineated on individual CT scans by a radiation oncologist (LB) using a published peer-reviewed cardiac atlas [12]. A 1 cm planning risk volume (PRV) was added around the LAD to account for heart motion and difficulty in identifying LAD location. Dose-volume histograms (DVH) were created for each structure (heart, LAD, LAD PRV) using the original RT plan. In addition, ten patients were randomly selected for review of reliability of LAD contouring. This process is outlined in further detail in Appendix A.

For each left-sided patient (with dosimetry data available) the original RT plan was used to calculate the volume of the heart receiving 25 Gy or more (V25), in addition to mean and maximum doses to the heart, LAD, and LAD PRV [10]. Circumferential coverage (i.e. the entire LAD contour on a given slice) of the LAD on at least one slice by the 25 Gy and 40 Gy isodose ($EQD2_3Gy$) was recorded. Equivalent doses in 2 Gy per fraction ($EQD2_3Gy$) [15] were calculated for maximum doses using the standard formula [19].

2.4. Statistical analyses

Baseline CVD RFs, patient tumour and treatment factors were compared between cases and controls and between left and right-sided cases using Chi-square test and Fisher's exact text. Cumulative risk of death from CVD was calculated using a Kaplan-Meier method. Survival distributions for left and right-sided cases were compared using log-rank test. For left-sided patients only, cardiac dosimetric parameters were compared between cases and controls using Wilcoxon rank sum test. All statistical tests were 2-sided, and results considered significant at $p < 0.05$. Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary NC). This study was reviewed and approved by the BC Cancer Research Ethics Board.

3. Results

3.1. Baseline characteristics

Between 2002 and 2006, 5249 women < 80 years, with early-stage breast cancer received adjuvant RT. Radiotherapy was used for 2644 left and 2605 right-sided breast cancers. At time of registry sampling for cardiac death, 77% of patients had received RT at least 10-years prior (range 8.4–13.2 years). Cumulative risk of cardiovascular death at 10-years was 1.4% (1.7% for left-sided, 1.3% for right-sided, log-rank $p = 0.30$). At time of censoring, 76 patients had died of CVD; 42 received left-sided and 34 right-sided RT. One hundred and fifty-three control patients were identified and all but three cases matched for all variables (Fig. 1). Baseline patient and tumour characteristics are listed in Table 1. Types of cardiac death are shown in Table 2.

3.2. Cardiovascular disease risk factors

Baseline CVD RFs for cases and controls are shown in Table 3. There was a statistically higher proportion of cases with hypertension ($p < 0.01$), stroke/TIA ($p < 0.01$), ischemic heart disease (IHD)/circulatory disease ($p < 0.01$) and smoking history ($p = 0.04$) than controls (Table 4).

3.3. Cardiac dosimetric parameters (left-sided patients only)

For dosimetric analysis CT-based RT plans were available for 31/42 cases (73%), and 64/85 controls (75%) (Fig. 1). The heart V25 did not exceed 10% in any left-sided case or control. No cardiac dosimetry parameter assessed distinguished left-sided cases from controls, with cases overall receiving lower radiation doses to the heart and LAD (Fig. 1a–c).

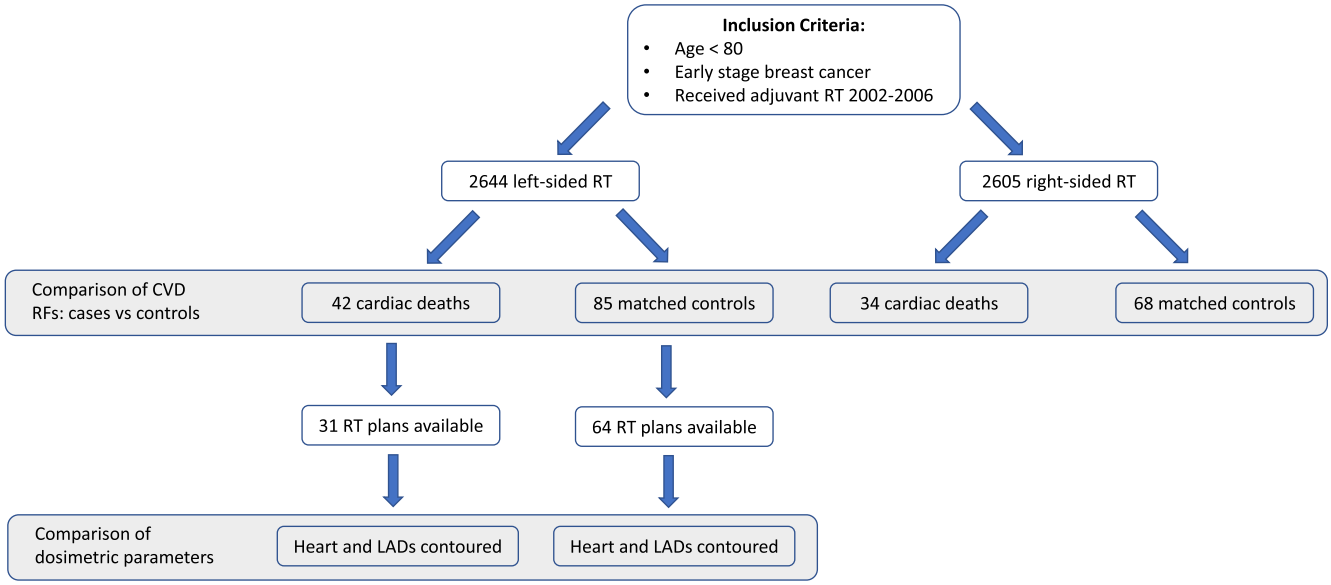

Fig. 1. Study schema. Abbreviations: RT, radiotherapy; CVD, cardiovascular disease; RFs, risk factors; LAD, Left Anterior Descending Artery

Table 1
Patient and tumour baseline characteristics.

Characteristic		Cardiac death cases			Cases and controls		
		Left n = 42	Right n = 34	*p* value	Cases n = 76	Controls n = 153	*p* value
Age	Median (range)	73 (47–79)	73 (48–79)	0.84	74 (47–79)	74 (47–79)	
	<40	0	0	0.92	0 (0%)	0	0.99
	40–60	4 (9%)	3 (9%)		7 (9%)	14 (9%)	
	61–79	38 (91%)	31 (91%)		69 (91%)	139 (91%)	
ER status	Positive	33 (79%)	24 (71%)	0.19	57 (75%)	132 (86%)	0.33
	Negative	4 (9%)	7 (21%)		11 (15%)	17 (11%)	
	Unknown[¶]	5 (12%)	3 (8%)		8 (10%)	4 (3%)	
Her-2 status	Positive	0 (0%)	2 (6%)	0.48	2 (2%)	11 (7%)	0.22
	Negative	16 (38%)	15 (44%)		31 (41%)	60 (39%)	
	Unknown[¶]	26 (62%)	17 (50%)		43 (57%)	82 (54%)	
Behaviour	DCIS	5 (12%)	3 (9%)	0.67	8 (10%)	10 (6%)	0.29
	Invasive ductal	37 (88%)	31 (91%		68 (90%)	143 (94%)	
Grade	1	19 (45%)	8 (23%)	0.11	27 (35%)	55 (36%)	0.92
	2	15 (36%)	16 (47%)		31 (41%)	66 (43%)	
	3	7 (17%)	10 (30%)		17 (22%)	31 (20%)	
	Unknown[¶]	1 (2%)	0 (0%)		1 (1%)	1 (1%)	
Surgery	BCS	39 (93%)	30 (88%)	0.48	69 (91%)	138 (90%)	0.89
	Mastectomy	3 (7%)	4 (12%)		7 (9%)	15 (10%)	
Tumour size	<5 mm	5 (12%)	3 (9%)	0.62	8 (11%)	7 (5%)	0.06
	5–10 mm	10 (24%)	5 (15%)		15 (20%)	51 (33%)	
	11–20 mm	14 (33%)	16 (47%)		30 (39%)	64 (42%)	
	21 mm-50 mm	12 (29%)	10 (29%)		22 (29%)	30 (20%)	
	>50 mm	0 (0%)	0 (0%)		0 (0%)	1 (1%)	
	Unknown[¶]	1 (2%)	0 (05)		1 (1%)	0 (0%)	
Number positive nodes	0	15 (36%)	19 (56%)	0.56	34 (45%)	93 (61%)	0.04
	1–3	15 (36%)	10 (30%)		25 (33%)	32 (21%)	
	≥4	1 (2%)	1 (3%)		2 (3%)	2 (1%)	
	Unknown	11 (26%)	4 (12%)		15 (20%)	26 (17%)	
Radiation	40–44 Gy/15–16	30 (71%)	3 (9%)	0.06	33 (43%)	119 (78%)	0.96
	45–50 Gy/25–28	12 (29%)	27 (79%)		39 (51%)	31 (20%)	
	Other	0 (0%)	4 (12%)		4 (5%)	3 (2%)	
Boost	Yes	16 (38%)	6 (17%)	0.05	22 (29%)	45 (29%)	0.94
	No	26 (62%)	28 (82%)		54 (72%)	108 (71%)	
Regional nodal RT	Yes	8 (19%)	9 (26%)	0.44	17 (22%)	30 (20%)	0.63
	No	34 (81%)	25 (74%)		59 (78%)	123 (80%)	
Adjuvant HT	Yes	27 (64%)	22 (65%)	0.58	49 (65%)	102 (67%)	0.74
	No	15 (36%)	12 (35%)		27 (35%)	51 (33%)	
Adjuvant Chemotherapy	Anthracycline	4 (10%)	4 (12%)	0.26	8 (10%)	18 (12%)	0.45
	Non-anthracycline	0 (0%)	2 (6%)		2 (3%)	1 (1%)	
	No chemotherapy	38 (90%)	28 (82%)		66 (87%)	134 (88%)	
Adjuvant Herceptin	Yes	0 (0%)	1 (3%)	0.26	1 (1%)	3 (2%)	0.73
	No	42 (100%)	33 (97%)		75 (99%)	150 (98%)	

[¶] Note: Unknowns removed before computing statistical tests.

Table 2
Types of cardiac deaths.

Type of cardiac death	ICD 10 code	Left n = 42	Right n = 34	*p* value
Coronary artery disease		24 (57%)	15 (44%)	0.26
Acute myocardial infarction	I21	17 (40%)	9 (26%)	0.20
Coronary artery disease, not otherwise specified	I25.0, I25.1, I25.9, I70.9	7 (17%)	6 (18%)	0.91
Cardiac arrest	I46	1 (2%)	0 (0%)	0.34
Congestive Heart Failure and Cardiomyopathy	I25.5, I42, I50	6 (14%)	4 (12%)	0.75
Conduction disorders and arrhythmias	I44, I45, I47-149	5 (12%)	3 (9%)	0.66
Valvular Heart disease	I05, I34, I35	1 (2%)	4 (12%)	0.10
Other heart disease**	I10-11, I38-9, I70, I71.0-I71.2, E78.4-5	5 (12%)	8 (24%)	0.18

** Includes cardiomegaly, endocarditis, hypertension, hypertensive heart disease, and hyperlipidaemia.

Table 3
Baseline cardiovascular risk factors.

Cardiovascular risk factors		Cases			Cases and controls		
		Left n = 42	Right n = 34	*p* value	Cases n = 76	Controls n = 153	*p* value
Diabetes	Yes	8 (19%)	7 (21%)	0.87	15 (20%)	18 (12%)	0.11
	No	34 (81%)	27 (79%)		61 (80%)	135 (88%)	
Hypertension	Yes	33 (78%)	24 (70%)	0.42	57 (75%)	74 (48%)	<0.01
	No	9 (21%)	10 (30%)		19 (25%)	79 (52%)	
Previous Stroke/TIA	Yes	7 (17%)	3 (9%)	0.32	10 (13%)	5 (3%)	<0.01
	No	35 (83%)	31 (91%)		66 (87%)	148 (97%)	
Previous myocardial infarction	Yes	5 (12%)	3 (9%)	0.66	8 (10%)	7 (5%)	0.10
	No	37 (88%)	31 (91%)		68 (90%)	146 (95%)	
Elevated cholesterol	Yes	13 (31%)	9 (27%)	0.67	22 (29%)	48 (31%)	0.71
	No	29 (69%)	25 (73%)		54 (71%)	105 (69%)	
Smoking history	Never	16 (38%)	8 (24%)	0.21	24 (32%)	80 (52%)	0.02
	Prior	9 (21%)	13 (38%)		22 (29%)	37 (24%)	
	Current	9 (21%)	7 (21%)		16 (21%)	18 (12%)	
	Unknown	8(19%)	6 (18%)		14 (18%)	18 (12%)	
Smoking history	Yes	18 (43%)	20 (59%)	0.17	38 (50%)	55 (36%)	0.04
	No	24 (57%)	14 (41%)		38 (50%)	98 (64%)	
History of IHD/circulatory disease*	Yes	16 (38%)	16 (47%)	0.43	32 (42%)	27 (18%)	<0.01
	No	26 (62%)	18 (53%)		44 (58%)	126 (82%)	
Total no: CVD risk factors	0	1 (2%)	1 (3%)	0.73	2 (3%)	33 (22%)	<0.01
	1–2	26 (62%)	18 (53%)		44 (58%)	85 (56%)	
	>3	15 (36%)	15 (44%)		30 (40%)	35 (23%)	

* Includes angina, CAD, valvular heart disease, arrhythmia.

Table 4
Left-sided cases vs. left-sided controls.

CVS risk factors	Cases N = 42	Controls N = 85	p value
Diabetes	8 (19%)	9 (11%)	0.19
Hypertension	33 (79%)	40 (47%)	<0.01
Previous Stroke/TIA	7 (17%)	2 (2%)	<0.01
Previous Myocardial infarction	5 (12%)	2 (2%)	0.03
Elevated cholesterol	13 (31%)	27 (32%)	0.93
Smoking history			
Never	16 (38%)	46 (54%)	0.10
Prior	9 (21%)	22 (26%)	
Current	9 (21%)	8 (9%)	
Unknown	8 (19%)	9 (11%)	
Smoking history			
Yes	18 (43%)	30 (35%)	0.41
No	24 (57%)	55 (65%)	
History of IHD/circulatory disease*	16 (38%)	12 (14%)	<0.01
Total no: CVS risk factors			
0	1 (2%)	17 (20%)	<0.01
1–2	26 (62%)	52 (61%)	
>3	15 (36%)	16 (19%)	

* Includes angina, CAD, valvular heart disease, arrhythmia.

Median MHD was 1.9 Gy (25–75%tile, 1.2–2.7) in left-sided cases and 2.3 Gy (25–75%tile, 1.6–3.3) in controls ($p = 0.11$). Twenty-three percent of cases and 33% of controls received a MHD >3 Gy. Median maximum LAD dose ($EQD2_3$ Gy) was 36.4 Gy (25–75%tile, 4.4–44.9) in left-sided cases and 41.3 Gy (25–75%tile, 18.9–45.4) in controls ($p = 0.08$). Median maximum heart dose ($EQD2_3$ Gy) was 42.3 Gy (25–75%tile 26.4–46.1) in the cases and 44.7 Gy (25–75%tile, 42.2–47.6) in controls (p = 0.04). The LAD was circumferentially irradiated to more than 25 Gy ($EQD2_3$ Gy) on at least one axial slice in 45% of cases and 53% of controls (p = 0.5); and to more than 40 Gy in 23% of cases and 37% of controls (p = 0.15). Only 6% of cases had >1 cm of continuous circumferential dose to the LAD of >40 Gy (Table 5).

4. Discussion

In this retrospective case-control matched study, we have shown that women who died of CVD 8–13 years after breast/chest wall RT did not have plans that violated QUANTEC guidelines. Despite analysing individual patient dosimetric data, we did not see a difference in any dosimetric parameter studied between those that died of CVD to those that did not. We did, however, demonstrate that there was a higher proportion of cases than controls with a history of hypertension, stroke/TIA, IHD or smoking history and that these RFs remained significant when left-sided cases were compared to controls. We found lower cardiac doses in left-sided cases versus controls, leading us to suspect that the radiation oncologists who planned the cases may have deliberately spared the heart in patients with a past history of cardiac disease or multiple CVD RFs.

Although several studies have found an association between RT and cardiac morbidity and mortality [3–6,18,20], there are also

Table 5
Left-sided patients (dosimetric analysis).

Dosimetric characteristic	Cases n = 31	Controls n = 64	*p* value
Patients with V25 Gy > 10%	0 (0%)	0 (0%)	
Patients with V25 Gy > 5%	1 (3%)	13 (20%)	0.03
Mean Heart dose:			
Median (25th-75th percentile)	1.9 (1.2–2.7)	2.3 (1.6–3.3)	0.11
Patients (n) with MHD > 3 Gy	7 (23%)	21 (33%)	0.35
Maximum heart dose: $EQD2_3$ Gy			
Median (25th–75th percentile)	42.3 (26.4–46.1)	44.7 (42.2–47.6)	0.04
Mean LAD dose:			
Median (25th–75th percentile)	8.4 (2.5–21.0)	16.3 (6.5–29.0)	0.01
Maximum LAD dose: $EQD2_3$ Gy			
Median (25th–75th percentile)	36.4 (4.4–44.9)	41.3 (18.9–45.4)	0.08
Mean LAD PRV dose:			
Median (25th–75th percentile)	12.3 (3.8–21.9)	14.2 (8.7–22.4)	0.07
Maximum LAD PRV dose: $EQD2_3$ Gy			
Median (25th–75th percentile)	45.8 (42.5–49.2)	48.1 (45.1–50.3)	0.07
Length of LAD with circumferential coverage > 25 Gy ($EQD2_3$ Gy)			
0 cm	17 (55%)	30 (47%)	0.59
0.1–1.0 cm	5 (16%)	8(13%)	
1.1–2 cm	2 (6%)	4 (6%)	
>2 cm	7(23%)	22 (34%)	
Length of LAD with circumferential coverage > 40 Gy ($EQD2_3$ Gy)			
0 cm	24 (77%)	40 (63%)	0.22
0.1–1.0 cm	5 (16%)	10 (16%)	
1.1–2 cm	1 (3%)	2 (3%)	
>2.1 cm	1 (3%)	12 (19%)	

studies that have found no significant increase in risk [8,21–24]. The landmark analysis by Darby et al demonstrated that the rate of major coronary events increased by 7.4% for each increase of 1 Gy in MHD. They modelled scenarios of increased risk with a threshold MHD of 3 Gy, implying an attributable absolute increased cardiac mortality of 0.5 to 0.7% for women <50 years depending on number of cardiac RFs. In our series, a quarter of patients exceeded 3 Gy MHD, but this did not distinguish cases from controls. Darby et al also showed that MHD was a better predictor of coronary events than mean dose to the LAD [6]. However, their study assessed patients in the pre-CT planning era, and individual dosimetric information was not available. Merzenich et al recently demonstrated there was no difference in cardiac mortality between women who received radiotherapy for left versus right-sided breast cancer between 1998 and 2008. Detailed analysis of 769 individuals showed an average MHD for left-sided RT of 4.6 Gy versus 1.7 Gy for right-sided RT. Furthermore, on multivariable analysis only pre-existing cardiac disease predicted for cardiac death [8].

In our study, we assessed QUANTEC guidelines, based on the risk of cardiac mortality in relation to a whole-heart dose-volume constraint. This constraint was not breached in any of our cases, although all patients were treated prior to publication of QUANTEC guidelines. With more modern RT techniques dose to the heart and LAD is reduced, and as a result, risk of cardiac toxicity has decreased over time [7,10,25–28]. It may be that in the CT-planning era such volume constraints are no longer as predictive of RT-induced cardiac damage. Dosimetry studies have shown that left-tangential irradiation delivers a high mean radiation dose to the LAD due to its location [10,29]. A higher incidence of coronary artery stenosis in the LAD has also been shown after left-sided breast RT [16,30]. In our analysis, individual CT-based information was used to assess a number of dosimetric parameters. Despite this, we did not see a correlation between any cardiac dose parameter and cardiac death. This raises the question as to whether any of the cardiac deaths in our cohort were related to dose of RT to the heart or LAD. Furthermore, it remains unclear what dose constraint to place on these structures. In our study, for the left-sided cases we report upper quartile doses of 2.7 Gy for MHD, and 44.9 Gy for maximum LAD dose ($EQD2_3$ Gy). Only 6% of cases had more than 1 cm of continuous circumferential dose to the LAD of >40 Gy. Our controls received higher cardiac doses with an upper quartile MHD of 3.3 Gy and maximum LAD dose ($EQD2_3$ Gy) of 45.4 Gy (Fig. 2). Although we were not able to define a threshold dose to the LAD, or heart, above which cardiac risk is increased, we can state that in our cohort, the risk of cardiac mortality from RT appears to be very small if we keep plans within the dose constraints of our controls.

This study does have limitations. Firstly, cases were selected on cause of death from death certificate data. Although additional chart reviews were performed, original source documents for verification were often unavailable, and coding may have been suboptimal. While we matched cases to controls on baseline patient and tumour factors, we were unable to match for CVD RFs, as this information was not available in the electronic database used for matching. CVD RFs were subsequenlty documented from a detailed chart review, but it is possible that not all CVD RFs were initially recorded. Furthermore, approximately 25% of cases in our series did not have CT plans available for analysis. This therefore limits the statistical power of our study, as there could be a difference in cardiac parameters not detected with our small sample size. Recent studies have also suggested that dose to the left ventricle is an important prognostic dose-volume parameter [31,32]. However, in this study we focused on dose to the heart and LAD. Our study also included few women <60 years at time of diagnosis. Perhaps in our older population, the risk of cardiac death is driven more by competing CVD RFs rather than RT dose. Although cardiac injury has historically been thought to be a long-term toxicity [3,5], recent studies have suggested that cardiac injury may manifest with the first five years post-RT [6–8,33,34]. Nonetheless, it may be that our analysis at 8–13 years post-RT was too early to assess cardiac mortality attributable to radiotherapy, particularly in younger patients [35]. Our plan is therefore repeat this analysis in 5-years' time to allow for 15-years of follow-up data.

Risk of cardiac death has decreased over time as increasingly effective cardiovascular preventative and re-vascularization therapies have developed. During the same period, improved RT planning has lowered dose to the heart and LAD. It may be that with modern RT techniques, and modern cardiac care, the actual risk

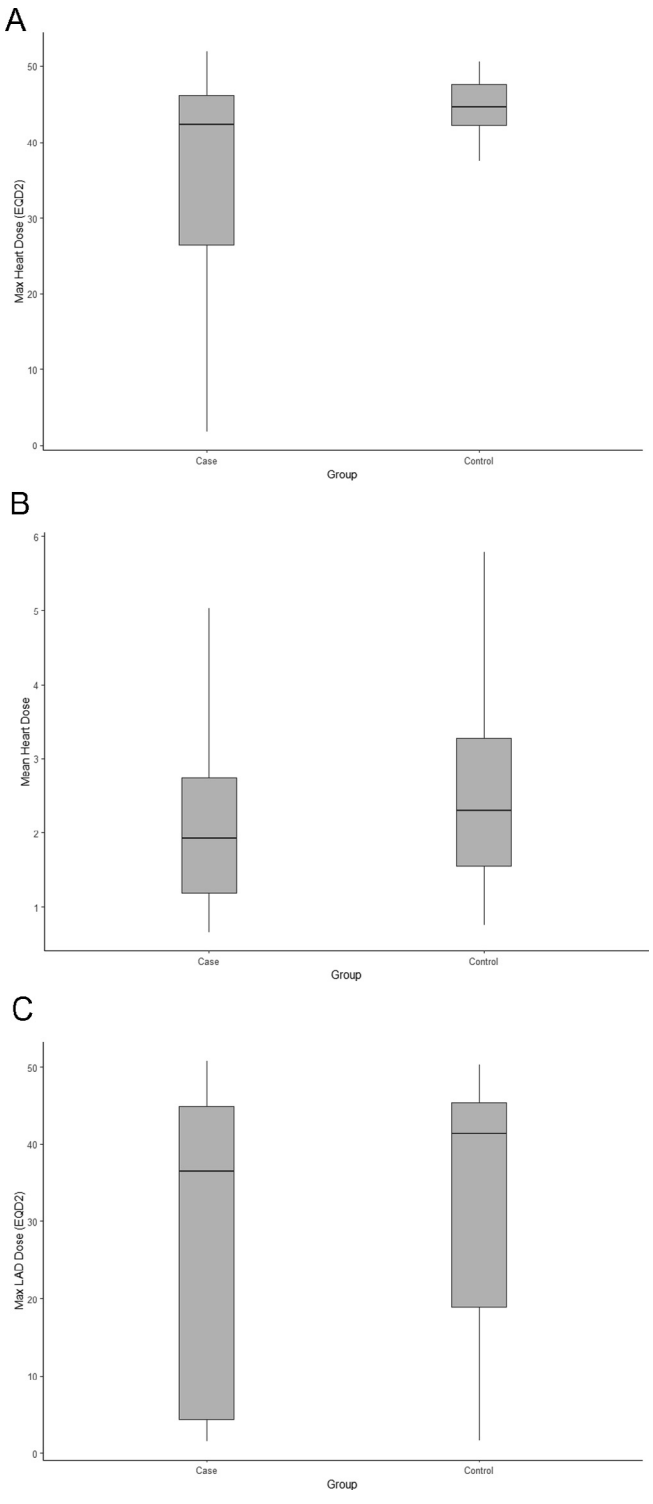

Fig. 2. Box and whisker plot of left-sided cases vs controls: A) Maximum heart dose ($EQD2_3$ Gy), B) Mean heart dose (MHD), C) Left-anterior descending artery (LAD) dose $EQD2_3$Gy.

of cardiac death post-RT is minimal. It may also be that there is greater correlation between cardiac dose and cardiac morbidity and focusing on fatal heart disease may give an incomplete picture of the risk [11]. It also remains unclear whether there is a threshold dose, to either the heart or LAD, above which risk increases. What is clear, is that we need further dosimetric data on cardiac substructures (including the LAD and left ventricle) linked to post-treatment cardiac events in large, modern era trials, and a better understanding of the pathophysiology of RT-induced cardiac damage in all age groups to be confident of the dosimetric correlates of cardiac risk. In the future, large population-based research databases should record cardiac RFs in patients treated for breast cancer. This would allow future studies to match cases and controls on cardiac RFs to eliminate bias due to systematic differences in treatment planning by radiation oncologists who are aware of the patients' pre-existing cardiac risk. In the meantime, we have confirmed that baseline cardiac RFs predict for cardiac death in breast cancer patients. It is therefore important to ensure that breast cancer patients undergo cardiovascular evaluation at time of diagnosis, in order to alter modifiable RFs. However, until further dosimetric data are available, dose to the heart and LAD should be kept as low as reasonably achievable.

5. Conclusions

In this study, women treated with breast/chest wall RT 8–13 years ago, who died of CVD, did not have RT plans that violated QUANTEC guidelines. No cardiac or coronary dosimetry was clearly associated with risk of death from cardiac disease. In our series, a quarter of patients exceeded 3 Gy MHD, but this did not distinguish cases from controls. The risk of radiation induced cardiac death at 10-years appears to be very low if MHD is <3.3 Gy, maximum LAD dose ($EQD2_3$ Gy) is <45.4 Gy and V25 <5%. Baseline CVD RFs predict for cardiac death and should be recognized and modified in breast cancer patients. Further studies are required to determine cardiac dose constraints in the modern RT era, with a wider range of cardiac doses and longer follow-up.

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Declaration of Competing Interest

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Provisional results presented at ASTRO 2016 in poster format.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2019.08.001.

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