RADIATION ONCOLOGY—ORIGINAL ARTICLE

Ischaemic heart disease following conventional and hypofractionated radiation treatment in a contemporary breast cancer series

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Abstract

Introduction: We report the incidence of ischaemic cardiac toxicity in a contemporary cohort of patients receiving conventional (CFRT) or hypofractionated (HFRT) radiation after surgery for early breast cancer and investigate the interplay of cardiac risk factors and fractionation.
Methods: Included were patients receiving external beam radiation treatment from 2002 to 2006 at the Christchurch public hospital. Hospital coding databases, oncology databases and medical records were reviewed for baseline characteristics, treatment details and outcomes. The primary outcome was cardiac toxicity (including myocardial infarction, admission for cardiac chest pain, coronary angiogram positivity and ischaemic cardiac death). Kaplan-Meier methods were used to derive ischaemic cardiac event free and overall survival. Predefined univariate and multivariate analysis was performed to investigate interaction with radiation fraction size, cardiac risk factors, age and side of cancer. Standardised mortality ratios were constructed.
Results: Five hundred and one patients were identified, 220 treated with CFRT and 281 with HFRT. The median age was 56 and median follow-up 10.33 years. The 10-year breast cancer specific survival was 81.8% (95% CI %.78.1–85.0). The 10-year freedom from cardiac death was 98.6% (95% CI 96.9–99.4). There were 27 post radiation cardiac events including 5 cardiac deaths and 19 cases of acute myocardial infarction. 265 (53%) had at least one cardiac risk factor. Twenty five of the 27 patients with a cardiac event had cardiac risk factors. On univariate and multivariate analysis, fractionation schedule was not significantly associated with a post radiation ischaemic event, however, there was a significant relationship with age and the presence of a cardiac risk factor. The standardised mortality ratio was 0.89 (95% CI: 0–3.13).
Conclusions: Our study has shown a low rate of ischaemic cardiac disease for both CFRT and HFRT in women treated for breast cancer with no evidence of an effect with fractionation schedule. Coexisting cardiac risk factors are common in the population.

Key words: breast cancer; cardiac risk factors; heart disease; hypofractionation; radiotherapy.

Introduction

Radiation therapy has an important role in the management of early breast cancer. There is high level evidence that after breast conservation treatment, radiation decreases the risk of local recurrence risk by 50% and decreases the 15-year risk of breast cancer death from 25.2% to 21.4% (2p = 0.00005).[1] After mastectomy, radiation decreases the 20-year breast cancer death risk by 8.1% (66.4% vs 58.3%) (2p = 0.01) and reduces

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overall mortality in node positive disease (RR 0.89, 95% CI 0.81–0.97, 2p = 0.01).[2]

It is possible that some benefits of radiation may be outweighed by increases in cardiac toxicity and potentially even cardiac death. A recent case-controlled study indicated that cardiac toxicity is increased for women treated with radiation treatment for breast cancer with the risk of a major coronary event increased linearly with the mean dose to the heart. The magnitude of the risk was 7.4% per Gray, with no threshold below which there was no risk. The risk increased within the first 5 years and continued for at least 20 years.[3]

Traditionally breast cancer radiation was prescribed as 50 Gy in 25 fractions at 2 Gy per fraction over 5 weeks. This is known as conventional fractionation (CFRT) Following breast conservation, a number of randomised controlled trials comparing CFRT and a shorter hypofractionated schedule (HFRT) of breast radiation treatment using 39–42.9 Gy in 13–16 fractions over 3 weeks. These trials report that HFRT provides similar local control without cosmetic impairment.[4–6] as well as wait time improvements and cost savings.[7] Only the START trials report long term ischaemic heart disease as an outcome.[4]

Although randomised evidence comparing HFRT versus CFRT following mastectomy is lacking, long term outcome data from HFRT series indicate good breast cancer outcomes. One series reports a 5-year local recurrence-free survival of 97.6%, 5-year overall survival of 74.7% and 5-year breast cancer survival of 77.7%.[8] This compares favourably with figures for CFRT after a mastectomy. Late toxicity and especially cardiac toxicity for HFRT following a mastectomy, however, is not well documented.

We conducted a retrospective audit of cardiac toxicity in patients who received CFRT or HFRT after surgery for early breast cancer at Christchurch Public Hospital between 2002 and 2006 to investigate the interplay of risk factors on cardiac outcomes in our population. This time period was chosen to allow for at least 10 years of follow-up data.

Methods

Patient characteristics

All patients who received CFRT or HFRT for early breast cancer at Christchurch Public Hospital, between 1 January 2002, and 31 December 2006 and who resided in the Christchurch region, were identified using the oncology database.

The protocol for the HFRT schedule required a separation size of less than 25 cm (defined as a separation between the central axes of the breast tangents). This was not the case for our CFRT protocol. To minimise potential bias, separation measurements were collected from planning data and patients with a separation greater than 25 cms were excluded. We also excluded those with locally advanced disease.

We retrospectively collated information regarding each patient's baseline and breast cancer characteristics, radiation treatment details, adjuvant/neoadjuvant chemotherapy and hormonal treatment, systemic treatments on relapse, clinical admissions, angiography results and date and cause of death.

Surgical treatment

Patients underwent a modified radical mastectomy or a wide local excision (lumpectomy, quadrantectomy). A level two axillary clearance was standard.

Adjuvant treatment

Treatment decisions regarding type of adjuvant systemic therapy were discussed at the breast multidisciplinary meeting and individualised considering systemic risk and patient preference.

Radiation treatment

Hypofractionated radiation treatment patients received 42.5 Gy in 16 fractions following breast conservation or 40 Gy in 16 fractions following mastectomy. An additional 10 Gy in 4–5 fractions was delivered, where there was increased risk of local recurrence (boost dose). Patients treated with CFRT received either 50 Gy in 25 fractions with a possible additional boost dose of 10 Gy in five fractions or 46.8 Gy in 26 fractions at 1.8 Gy per fraction with a possible boost dose of 14 Gy in seven fractions.

All patients were treated supine with arms elevated. A clinical breast mark-up was performed guided by anatomical landmarks. Computerised tomography (CT) simulation was performed and target volumes adjusted to include the breast tissue visualised on CT. The patients were 3D planned and treated with either 6 or 10 MV tangential fields.

The dose was prescribed to the reference point (a point midway along the central plane and 2/3 of the distance from the skin to the base of the tangent fields). The treatment plans were optimised using wedges and segment fields (clinically significant maxima <112% were accepted). If indicated, nodal regions were CT planned using anatomical landmarks and treated with separate anterior and or posterior fields. Radiation to the supraclavicular fossa was given if four or more axillary nodes involved. Axillary and supraclavicular radiation treatment was given if 10 or more axillary nodes or more than 90% of nodes were involved. The internal mammary lymph nodes were not treated.

'Boost' radiation was to be given to the tumour bed after breast conservation if the patients age was <50 or the pathological margin was less than 2 mm. The boost was based on scar position and information from radiological imaging and treated with electrons. For post

mastectomy patients 'boost' radiation was reserved for close pathological margins.

Outcomes assessed

The primary outcome was cardiac toxicity, defined as any myocardial infarction, admission for chest pain proven to be cardiac related (ECG changes, cardiac enzyme rise or positive stress test), coronary angiogram positive for ischaemic disease and ischaemic cardiac death. Cardiac death is defined as those who died without a previously diagnosed cardiac condition, whose cause of death was reported as a cardiac event.

Relevant cardiac catheterisation databases and Christchurch hospital clinical coding databases were searched. The ICD-10-AM codes searched were I20–I25 Ischaemic heart diseases; I60–I69 Cerebrovascular disease and I70–I79 diseases of the arteries, capillaries and arterioles.

Hospital coding was also used to identify cardiac risk factors and in addition hospital records were hand searched. Patient ischaemic heart disease risk at the time of radiotherapy were identified including Z720, Z8643, F172 smoking (prior to and at the time of breast cancer diagnosis), I10–I15 hypertension (diagnosed at surgery or treated prior to surgery), E66 Obesity (Body Mass Index >25), E09–E14 diabetes mellitus (identified by blood test investigations), E78 hypercholesterolaemia (identified by blood test investigations) and I20–I25 previous ischaemic cardiac history.

Statistical methods

Ischaemic cardiac event-free survival and overall survival were estimated using Kaplan-Meier methods. In the survival analyses, all events were measured from the commencement of radiation to the end points associated with each event. The data were censored at the date of last follow-up.

Predefined univariate and multivariate analysis was performed to investigate interaction with left/right sided treatment, age at diagnosis, known cardiac risk factors, type of surgery and radiation dose and dose per fraction.

In order to compare cardiac mortality with the NZ female population, standardised mortality ratios were constructed comparing the expected deaths based on weighted population rates with the observed deaths in the breast cancer population studied. We took into account person years of observation by age, year and follow-up period. Data for the NZ population was obtained from NZ ministry of health and numbers within population groups obtained from NZ census data.

Results

There were 501 early breast cancer patients identified, 220 treated with CFRT and 281 with HFRT. The median age of the CFRT group was 55, similar to the HFRT group at 56. There was a similar number of left and right cases (See Table 1 for demographic detail).

Table 1. Patient demographics

Category	Options	CFRT (%)	HFRT (%)
Fractionation		220	281
Surgery type	WLE	162 (74)	214 (76)
	Mastectomy	58 (26)	67 (24)
Radiation 'boost'	WLE	17 (8)	44 (16)
	Mastectomy	4 (2)	0 (0)
T size	1	127 (58)	186 (66)
	2	70 (32)	84 (30)
	3	16 (7)	11 (4)
	Unknown	7 (3)	0 (0)
Node status	Positive	88 (40)	112 (40)
	Negative	126 (57)	166 (60)
	Unknown	6 (3)	3 (1)
Chemotherapy	Yes	87 (40)	105 (37)
	No	130 (60)	176 (63)
Side	Right	111 (50)	140 (50)
	Left	108 (49)	140 (50)
	Unknown	1 (1)	1 (1)
Age at RT start	Under 50	156 (71)	198 (70)
	Over 50	64 (29)	83 (30)
Chemotherapy at relapse		29 (13)	17 (6)
Hormonal therapy at relapse		18 (8)	16 (7)
Median age		55 years	56 years
Median follow-up		153 months	121 months

Table 2. The type and management of the post radiation cardiac event

Diagnosis	Management	Number, $N = 501$ (%)
Angina	Medical management	6 (1)
	Bypass grafting	1 (0.2)
Unstable angina	Bypass grafting	1 (0.2)
Acute myocardial infarction	Medical management	10 (2)
	Bypass grafting	2 (0.4)
	Angioplasty	1 (0.2)
	Cardiac Stents	6 (1)
Total		27 (5.4)

The 10-year breast cancer specific survival was 81.8% (95% CI 78.1–85.0). The 10-year freedom from cardiac death was 98.6% (95% CI 96.9–99.4).

There were 27 post radiation cardiac events including 19 cases with an acute myocardial infarction (AMI). The majority of AMI cases were managed with medical management (see Table 2). There were five cardiac deaths all of which occurred following an AMI.

Of the 501 patients, 174 (35%) had one cardiac risk factor, 66 had two risk factors (13%) and 32 had three risk factors (6%). There were 46 patients where the risk factor status was unknown (11%). Of the 27 patients with an ischaemic cardiac event, 25 had cardiac risk factors present at the time of radiation.

As is seen in Table 3, on univariate analysis, age 65 years and over and the presence of a cardiac risk factor were significantly associated with a post radiation ischaemic event.

On multivariate analysis age 65 years old and above and at least one cardiac risk factor retained significance (see Table 4 for further detail).

The standardised mortality ratio in our population was as 0.89 (95% CI: 0–3.13). Thus, we found no evidence that the mortality rates were above that expected in the general population.

Discussion

Most patients in our series had small, node negative cancers, treated with a wide local excision. Most patients were over 50 years of age and the majority did not undergo chemotherapy. The CRFT and HFRT populations were similar in the median age of patients, surgery type, tumour characteristics and adjuvant therapy. The median follow-up is at least 10 years for both groups.

Table 3. Univariate analysis

		Post-RT IHD	No Post-RT IHD	*P*-value
Overall		*N* = 27 (5.39%)	*N* = 474 (94.61%)	
Age at RT start	Mean (SD)	65 (10.7)	55 (11.8)	<0.0001†
	Median (IQR)	63 (59–76)	54 (47–63)	
	Range	39–80	27–86	
Age at RT start (2gp)	Younger than 65	14 (3.6%)	377 (96.4%)	0.0007‡
	65 and above	13 (11.8%)	97 (88.2%)	
Risk factors	Mean (SD)	1.5 (0.9)	0.9 (1.0)	0.0011§
	Median (IQR)	1 (1–2)	1 (0–1)	
	Range	0–3	0–5	
Risk factors (2gp)	None	2 (1.1%)	173 (98.9%)	0.0006¶
	At least one	25 (8.9%)	255 (91.1%)	
Risk factors (2gp)	Less than two	17 (4.9%)	332 (95.1%)	0.08
	Two and more	10 (9.49%)	96 (90.6%)	
Side	Left	10 (4.0%)	239 (96.0%)	0.18
	Right	17 (6.8%)	235 (93.3%)	
Fractionation	CFRT	16 (7.3%)	204 (92.7%)	0.1
	HFRT	11 (3.93%)	270 (96.1%)	

†*P*-value is derived from Wilcoxon Rank Sum test, indicating a significant mean age difference between the two groups.

‡*P*-value is derived from Chi-square test. Patients aged 65 and above were approximately 3 times more likely to develop a post-RT IHD as compared to the rest (11.8%/3.6%≈3).

§*P*-value is derived from Wilcoxon Rank Sum test, indicating a significant mean risk score difference between the two groups.

¶*P*-value is derived from Chi-square test. Patients with at least one risk factor were approximately 8 times more likely to develop a post-RT IHD as compared to patients without any risk factor (8.93%/1.14%≈8).

Table 4. Multivariate analysis (multivariate logistic model)

	Odds ratio	95% confidence interval	*P*-value
Aged 65 and above vs Younger than 65	2.959	1.3–6.6	0.0085
At least one risk factor vs None	7.311	1.7–31.5	0.0076
Right vs Left	1.565	0.7–3.6	0.2885
CFRT vs HFRT	1.730	0.8–3.9	0.1870

The 10 year risk of cardiac death in our series was 1.4% (95% CI 0.6–3.1), similar to a comparable series which reported a 10 year risk of cardiac death of 1.5% (95% CI 0.07–3.4%) – 1.9% (95% CI 0.09–3.9%).[9]

Univariate and multivariate analysis did not indicate a statistically significant interaction between fractionation and post radiation ischaemic event or ischaemic cardiac death. This would be consistent with the START randomised controlled trials of breast fractionation which reported a low number of cardiac events after a median follow-up of 9.9 years. There were 17 deaths due to cardiac disease in 2215 women (12 with CFRT and 5 with HFRT). Of these cardiac deaths 11/17 were on the left side and potentially related to radiation exposure. There were nine confirmed cases of ischaemic heart disease in 1854 women who received CFRT to the left side (0.5%) and nine confirmed cases of ischaemic heart disease in 2597 women who received HFRT to the left side (0.35%).[4]

A concern cited against the adoption of HFRT techniques is that the heart/coronary arteries are radiobiologically late responding tissues, sensitive to increased radiation fraction size. This would open the theoretical risk of increased cardiac toxicity.

The alpha-beta ratio for the heart is estimated to be low. Alpha-beta ratios in rat heart studies have been found to be between 1–3 Gy. Appelt *et al.* studied 60 different radiation plans and studied the dose to the heart should five different fractionation schedules be applied. Dose were converted to 2 Gy fractions (EQD(2)) and using the liner quadratic equation it was found that for $\alpha/\beta = 3$ Gy, HFRT for 40 Gy/15 fractions, 39 Gy/13 fractions and 42.5 Gy/16 fractions, all gave lower equivalent dose to the heart than CFRT.[10] This would provide a theoretical explanation for why series have not found a difference in ischaemic cardiac events in those treated with HFRT.

The SMR for ischaemic cardiac death in our series compared with the general population was 0.89 (95% CI: 0–3.13). The point estimate for the SMR (although not statistically significant) is similar to other studies. A Scandinavian study found a lower number of deaths due to heart disease than would have been predicted from national death rates, with an observed to expected ratio of 0.9 (0.87–0.94).[11] A large Dutch series of breast

cancer patients similarly found that breast cancer patients had a slightly lower cardiovascular disease death risk with a standardised mortality ratio of 0.92 (95% CI 0.88–0.97).[12] The reasons for this are not clear. It is possible that patients with breast cancer may have lower baseline risk of cardiac disease, or a diagnosis of breast cancer may result in lifestyle changes which modify cardiac risk.

In our series, univariate and multivariate analysis did not indicate a significant relationship between ischaemic cardiac mortality and side of breast cancer. The effect of radiation treatment is theorised to be greater for left sided patients as the heart is located predominantly in the left hemithorax. In the large Scandinavian study of almost 35,000 women treated with radiation for breast cancer, the mean radiation dose to the heart was higher on the left at 6.3 Gy compared to the right which was 2.7 Gy. This study found that incidence ratios for left sided patients were higher for acute myocardial infarction (1.22) and angina (1.25) compared with right sided patients.[11] This corresponds to an absolute increase in risk of 0.4% for acute myocardial infarction and 0.3% for angina for left sided patients. However, no significant difference in mortality for left sided versus right sided patients was found for all or ischaemic heart disease.[13]

Other series have indicated a relationship between left sided treatment and cardiac mortality. An analysis of Surveillance, Epidemiology and End Results (SEER) registry data of 300,000 women treated for breast cancer between 1973 and 2001 has found that a cardiac mortality ratio of 1.16 (1.08–1.24), (2p = 0.00004) when left versus right sided breast cancer patients treated with radiation were compared. During the timeframe of the study, radiation techniques developed and reanalysis according to decade of treatment has found a decreasing trend for cardiac risk, which may explain the contrasting results with latter series, including our own. [14]

Risk factor assessment for cardiac disease in breast cancer patients undergoing radiation treatment is not extensively reported. In our series 53% of the patients had at least one cardiac risk factor at diagnosis. On univariate and multivariate analysis, the presence of a cardiac risk factor was significantly associated with a post radiation ischaemic cardiac event.

A series of breast cancer patients reported a significant association with any cardiac death and age, years of tobacco smoking, hypertension, hyperlipidaemia, diabetes and Framingham risk score. This risk was not modified by radiation to the left breast.[9]

A BMI of 30 or greater was found in 19% of patients for whom this data was available. The Scandinavian series found that a BMI equal or greater to 30 gave a rate ratio of 1.57 times for a major coronary event compared with a BMI < 30. [3]

A further study of breast cancer patients with prolonged follow-up (median 18 years) has found an additive relationship between smoking and radiation (HR = 3.04, 95% CI = 2.03–4.55; P for departure from additivity = 0.039).[15]

A case-controlled study reviewed the interplay of cardiac risk factors and radiation found that prior ischaemic heart disease resulted in a rate ratio for coronary events of 13.43 in the first 10 years compared to controls with no such history. With no prior ischaemic history and at least one cardiac risk factor, the rate ratio for a major coronary event was 1.96 (95% CI 1.6–2.4). When radiation was considered, the baseline risk of coronary events was higher for women with cardiac risk factors, but the percentage increase in the rate of major coronary events per Gy was similar to those with no risk factors. This study estimated that for a 50 year old woman with no cardiac risk factors and a mean heart dose of 3 Gy, her risk of death from IHD would be increased from 1.9 to 2.4% with radiation treatment, however, for a woman with at least one risk factor this would be increased from 3.4% to 4.1%. These estimates were illustrated to increase quite markedly with increased mean heart dose.[3]

Our findings reinforce the importance of minimising cardiac dose particularly for those patients with cardiac risk factors who have both a greater baseline and absolute risk of ischaemic heart disease after breast radiation treatment.

There are a number of weaknesses of our study. Cardiac toxicity is a late effect of radiation and thus requires prolonged follow-up to identify trends. The population case controlled series from Sweden and Denmark found that the increased rate of major coronary events started within 5 years after radiotherapy. Of the coronary events 44% occurred less than 10 years after the cancer diagnosis, 33% occurred 10–19 years later. It is possible that at 10 years as in our series, there may be an effect seen but the effect may be become greater with extended follow-up.[3]

A further weakness is that our series is non-randomised nor formally case controlled with relatively small numbers. Although the design is reasonable, for these reasons it cannot it exclude a small effect which may emerge with increased numbers or more rigid study design. In future years, linked data bases may allow a much larger population based study of the late effects of radiation on the heart, potentially having the power to identify small risks and particular subgroups at highest risk. This may enable us to apply risk modification treatment to a more specific group of patients. In order for this to occur, these large databases would require careful coding of cardiac events and potentially cover all institutions (including both private and public).

The Her-2 status for most patients in our series was not known as this was not routinely tested for during the time period. Adjuvant Trastuzumab was not utilised, nor was chemotherapy in 60% of patients and did not include routine use of an anthracycline. This may limit

the applicability of our results to modern patients who may be treated with an anthracycline +/– Trastuzumab. Boekel et al. found chemotherapy after 1997 following the introduction of anthracyclines increased the risk of a cardiac event, however, this was more related to congestive cardiac failure rather that ischaemic heart disease.[12] However this does provide a series where the effect of radiation on heart disease is less confounded by the effect of adjuvant therapies.

A further weakness is that we were not reliably able to collect data on a family history of heart disease, although it had been our aim to do so. It was also not possible to assess the duration and extent of smoking.

The study also included only those patients with a tangent separation not greater than 25 cms and this may not be relevant for the small group of patients with a larger separation and potentially increased heart dose particularly on the left side.

Recent evidence has indicated a benefit in breast cancer specific survival with regional nodal radiation (including internal mammary chain).[16] Our patients did not receive mammary chain radiation, however, as this usually results in increased heart dose, there is the potential that increased utilisation of radiation to this region may result in increased cardiac toxicity.[3]

In conclusion, this study has shown a low rate of ischaemic cardiac disease for both CFRT and HFRT in women treated for breast cancer. There is no evidence of an effect on rates of ischaemic heart disease with CFRT vs HFRT nor left vs right sidedness. This adds further evidence for the safety of hypofractionated routines and supports their wider application.

As expected other cardiac risk factors are prevalent in our population. Awareness of these risk factors in early breast cancer patients to be treated with radiation may assist in selecting patients with the greatest potential benefit for heart sparing techniques. It may also allow identification of patients who may benefit from close monitoring and control of cardiac risk factors to minimise the additive effects from radiation on future cardiac events.

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