RADIATION ONCOLOGY—ORIGINAL ARTICLE

Journal of Medical Imaging and Radiation Oncology

Impact of radiotherapy on cardiovascular health of women with breast cancer

Ross Lawrenson,[1] Chunhuan Lao,[1] Ahmed Ali[2] and Ian Campbell[3]

1 Waikato Medical Research Centre, The University of Waikato, Hamilton, New Zealand
2 Waikato District Health Board, Hamilton, New Zealand
3 School of Medicine, The University of Auckland, Auckland, New Zealand

R Lawrenson MBBS, MD, FRCGP, FAFPHM, FFPH; **C Lao** PhD; **A Ali** MBChB; **I Campbell** MBChB.

Correspondence
Professor Ross Lawrenson, The University of Waikato, Private Bag 3200, Hamilton 3240, New Zealand.
Email: Ross.Lawrenson@waikatodhb.health.nz

Conflict of interest: None declared.

Submitted 8 March 2018; accepted 24 October 2018.

doi:10.1111/1754-9485.12838

Abstract

Introduction: This study aims to examine the impact of radiotherapy on the cardiovascular health of women diagnosed with breast cancer in the Waikato region in New Zealand.
Methods: Women diagnosed with stage 0–III breast cancer and recorded in the Waikato Breast Cancer Registry were divided into two groups: a radiotherapy group and a no-radiotherapy group. Baseline characteristics and treatments were compared in the two groups. Kaplan–Meier survival analysis was performed to compare cardiovascular morbidity and mortality. Cox Proportional Hazard regression analysis was used to estimate the hazard ratio of radiotherapy on the risk of cardiovascular morbidity and mortality while adjusting for other factors.
Results: A total of 3528 women were included in this study, with 2303 in the radiotherapy group and 1225 in the no-radiotherapy group. At 10-year follow-up, 11.7% of women in the radiotherapy group and 19.4% in the no-radiotherapy group experienced cardiovascular events. Only 2.3% of patients who received radiotherapy died of cardiovascular disease by 10 years compared to 7.0% in the no-radiotherapy group. After adjusting for clinically significant factors, there was unexplained reduced risk of developing cardiovascular disease in the radiotherapy group compared to the no-radiotherapy group (HR 0.73, 95% CI: 0.59–0.92). No significant difference was found in cardiovascular mortality between the two groups.
Conclusions: Radiotherapy appears less likely to be offered to patients at higher risk of cardiovascular disease. No evidence of increased risk of a cardiovascular event was found in the group of women with breast cancer treated with radiotherapy and current regimens appear safe. Traditional cardiovascular risk factors remain the main culprits in this setting. Clinicians should work with patients in managing these risk factors for optimal results.

Key words: breast cancer; cardiovascular disease; morbidity; mortality; radiotherapy.

Introduction

Breast cancer is the most commonly diagnosed cancer in women in New Zealand, with 3000 new cases diagnosed in 2012 and an incidence rate of 96.9 per 100,000. New Zealand is considered to have a high incidence of breast cancer worldwide. Both incidence and survival have been increasing over the years.[1,2] This means that the number of women diagnosed with breast cancer and ultimately dying from other causes is increasing. One of the common causes of death of women with breast cancer is cardiovascular disease.[3,4] Some treatments for breast cancer can increase the risk of developing cardiovascular disease.[5–7]

Radiotherapy is one of the main treatment options for women with early breast cancer, with over half of these women undergoing radiotherapy in New Zealand. Radiation-induced heart disease (RIHD) is a well-recognized

side effect of radiation therapy observed in many cancer patients, including breast cancer and Hodgkin's lymphoma patients, since the 1950s-60s.[5,8] RIHD includes ischaemic heart disease (IHD), Myocardial infarction (MI), heart failure (HF) and valvular heart disease (VHD).[5,9] A systematic review including 40 randomized clinical trials started before 1990 demonstrated that there was around 5% cancer survival benefit from radiotherapy, but this was offset by a 30% increase in deaths from cardiovascular disease.[10] However, three studies using the U.S. National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) data only found significant increase in cardiovascular mortality in patients treated with radiotherapy in the 1960s and 1970s, and found no significant increase from 1980 onwards.[11–13]

In these studies, several factors were shown to increase the risk of RIHD, including side of irradiation, irradiation of internal mammary nodes (IMN), pre-existing cardiac disease or risk factors, and concurrent therapies used at the time of treatment. Breast cancer patients treated with hormone therapy were found to have a decreased risk of cardiovascular disease,[14,15] whilst chemotherapy and trastuzumab were shown to increase the risk.[7,16–19] This study aims to examine the impact of radiotherapy on developing cardiovascular disease in women diagnosed with breast cancer in the Waikato region in New Zealand.

Methods

Research design and data sources

This study is an observational retrospective cohort study. It included women of all ages diagnosed with stage 0–III breast cancer from 1st January 1995 to 31st December 2013 recorded in the Waikato Breast Cancer Registry (WBCR). For women who had been diagnosed with breast cancer twice within the study period, only the first diagnosis was included. Participants were divided into a radiotherapy group and a no-radiotherapy group based on the treatment record in the WBCR.

Patients' baseline demographic data, tumour characteristics, treatments and mortality were obtained from the WBCR. Age at diagnosis was divided into three categories: younger than 50 years, 50 to 64-year-old and 65 years or older. Ethnicity was classified into Māori and non-Māori. Body Mass Index (BMI) was calculated for patients who had both height and weight information available. Patients were then categorized into: normal BMI ($\leq$24.00 kg/m^2), overweight (25–29.99 kg/m^2) and obese ($\geq$30 kg/m^2). Smoking status was grouped into: current smokers, ex-smokers, never smoked or unknown. Gynaecological history was obtained from the WBCR and included history of hysterectomy, use of hormone replacement therapy (HRT) and menopausal status. The site of the cancer (left or right breast) is recorded in the cancer register.

Co-existing cardiovascular disease at the time of breast cancer diagnosis was categorized into eight cardiovascular-relevant comorbidity groups: diabetes, with or without organ damage, moderate to severe renal disease, hypertension, congestive heart failure (CHF), ischaemic heart disease (IHD), cardiac arrhythmias, valvular heart disease (VHD) and vascular disease [including peripheral vascular disease (PVD), stroke and abdominal aortic aneurysm (AAA)]. Personal identification numbers – National Health Index (NHI) – were used to cross-reference patients with another national database, the National Minimum dataset (NMDS). NMDS is a national dataset that keeps track of almost all hospitalizations, public and private, in New Zealand. The study had access to all records in the NMDS from 1995 to the end of 2014. It was used to obtain information on comorbidities between the time of tissue diagnosis and start of follow-up period, and to retrieve information on cardiovascular diseases that developed after the start of follow-up period. The dataset was searched for relevant admissions using codes from the International Classification of Disease system (ICD-9). Mortality data in the WBCR ar updated biannually from the Ministry of Health, and the latest update was on the 31st of December 2014.

Statistical analyses

Baseline characteristics and treatments were compared between the radiotherapy group and the no-radiotherapy group. Chi-square test was used to examine the differences between the two groups.

Two outcome measurements were used in this study, including cardiovascular morbidity and mortality. For morbidity, patients who had radiotherapy were followed up from the first radiotherapy session until one of the following end points: (i) development of cardiovascular morbidity, (ii) diagnosis of a second primary breast cancer before the development of a cardiovascular morbidity, (iii) death and (iv) 31st of December 2014 if alive and none of the above. Patients who did not receive radiotherapy were followed up from 160 days from date of diagnosis until one of the end points. The use of 160 days from date of diagnosis was justified as it represents the mean time required for a patient to have their first radiotherapy session in the study cohort.

Kaplan–Meier survival analysis was performed to compare the outcome between the two groups. Cox Proportional Hazard regression analysis was performed to estimate the hazard ratio (HR) of radiotherapy on the risk of cardiovascular morbidity/mortality while adjusting for other factors including age, ethnicity, menopausal status, comorbidity, side of breast cancer, aromatase inhibitors (AI), selective oestrogen receptor modulators (SERMs), ovarian ablation, chemotherapy and trastuzumab.

Ethics

The study is covered under ethics approval from the Health and Disability Ethics Committee (HDEC) – Approval Number: 12/NTA/42/AM01.

Results

A total of 3528 patients were included in this study, with 2303 women in the radiotherapy group and 1225 in the no-radiotherapy group. Table 1 summarizes and compares the patient demographics and tumour characteristics between the radiotherapy group and the no-radiotherapy group. Women who did not have radiotherapy were older, more likely to be post-menopausal, more likely to be stage 0 or stage I, and more likely to have comorbidity than women who had radiotherapy. Over 30% of the BMI information and 47% of the smoking status information was missing in the dataset.

A total of 370 (10.5%) patients experienced new cardiovascular disease, 92 (2.6%) died of CVD and 450 (12.8%) died of breast cancer during the follow-up period (Table 2). Patients in the radiotherapy group had a statistically lower incidence of cardiovascular events than patients who did not have radiotherapy (Fig. 1). At 10-year follow-up, 11.7% of women in the radiotherapy group and 19.4% in the no-radiotherapy group experienced cardiovascular events. The radiotherapy group had better survival compared to the no-radiotherapy group (Fig. 2). Only 2.3% of patients who received radiotherapy died of cardiovascular disease by 10 years compared to 7.0% of the no-radiotherapy group.

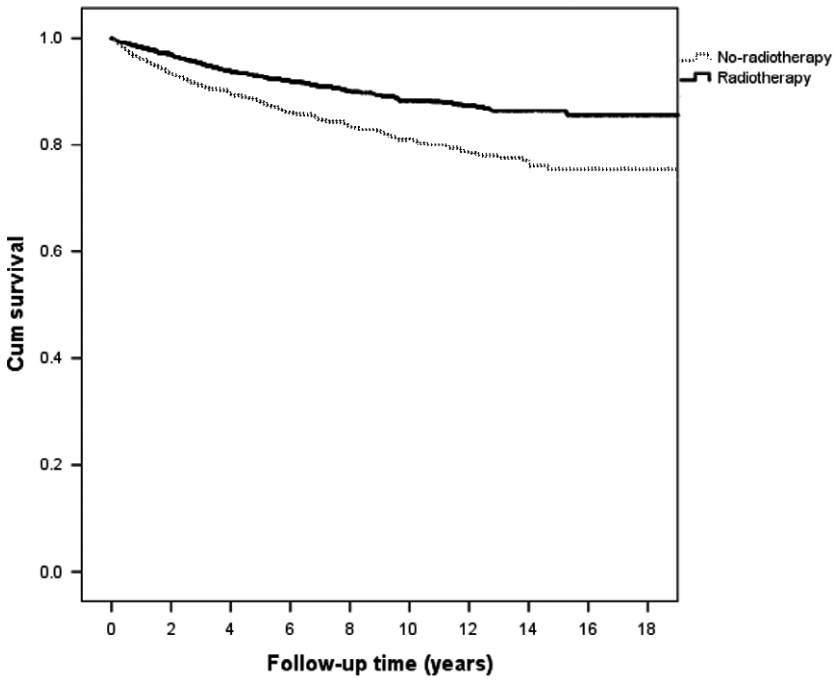
Because of the missing data in BMI and smoking status, they were not included in the multivariate analysis. Several factors had a statistically significant impact on the development of cardiovascular disease (Table 3). Increasing age and Māori ethnicity were strongly correlated with the development of cardiovascular disease (HR 1.04 and 1.51, respectively). Having at least one cardiovascular comorbidity before the start of the follow-up period also significantly correlated with an increased risk of developing cardiovascular disease subsequently (HR 2.10, 95% CI: 1.68–2.64). In terms of cancer medical treatment, only SERMS, trastuzumab and ovarian-ablation treatments had a statistically significant relationship with cardiovascular disease (HR 0.71, 2.14 and 2.43, respectively). After taking into account the available clinically relevant factors, there was still unexplained, statistically significant reduced risk of developing cardiovascular morbidity in the radiotherapy group

Table 1. Baseline characteristics in the radiotherapy group and the no-radiotherapy group

Baseline characteristics	No-radiotherapy group (%)	Radiotherapy group (%)	*P*-value (chi-square test)
Age (years)			
<50	286 (23.3)	743 (32.3)	<0.001
50–64	370 (30.2)	906 (39.3)	<0.001
65+	569 (46.4)	654 (28.4)	<0.001
BMI			
24	274 (35.6)	513 (30.3)	<0.05
25–29	267 (34.7)	580 (34.3)	>0.05
30	229 (29.7)	598 (35.4)	<0.05
Unknown	455	612	
Ethnicity			
Māori	176 (14.4)	321 (13.9)	NS
Non-Māori	1049 (85.6)	1982 (86.1)	
Smoking status			
Never smoked	294 (44.9)	564 (46.6)	NS
Ex-smoker	147 (22.4)	245 (20.2)	NS
Current smoker	214 (32.7)	401 (33.1)	NS
Unknown	570	1093	
Menopausal status			
Pre	250 (21.1)	646 (28.9)	<0.001
Peri	56 (4.7)	148 (6.6)	<0.05
Post	880 (74.2)	1442 (64.5)	<0.001
Unknown	39	67	
Stage			
Stage 0	254 (20.7)	311 (13.5)	<0.001
Stage I	403 (32.9)	967 (42.0)	<0.001
Stage II	510 (41.6)	893 (38.8)	NS
Stage III	58 (4.7)	132 (5.7)	NS
Comorbidities			
Diabetes	102 (8.3)	126 (5.5)	<0.001
CHF	75 (6.1)	34 (1.5)	<0.001
IHD/MI	122 (10.0)	76 (3.3)	<0.001
VHD	30 (2.4)	23 (1.0)	<0.001
Hypertension	366 (29.9)	522 (22.7)	<0.001
Renal	13 (1.1)	7 (0.3)	<0.05
Arrhythmia	80 (6.5)	53 (2.3)	<0.001
PVD/stroke/AA	87 (7.1)	51 (2.2)	<0.001
At least one comorbidity	501 (40.9)	654 (28.4)	<0.001
Total	1225	2303	

Table 2. The number of women who developed cardiovascular morbidity, mortality, or breast cancer mortality by stage of breast cancer

BC stage	Outcomes	No-radiotherapy group (%)	Radiotherapy group (%)	Total population (%)
Stage 0	CVD morbidity	25 (9.8)	20 (6.4)	45 (8.0)
	CVD mortality	8 (3.1)	3 (1.0)	11 (1.9)
	BC mortality	8 (3.1)	10 (3.2)	18 (3.2)
Stage I	CVD morbidity	72 (17.9)	74 (7.7)	146 (10.7)
	CVD mortality	23 (5.7)	15 (1.6)	38 (2.8)
	BC mortality	45 (11.2)	58 (6.0)	103 (7.5)
Stage II	CVD morbidity	73 (14.3)	82 (9.2)	155 (11.0)
	CVD mortality	23 (4.5)	11 (1.2)	34 (2.4)
	BC mortality	89 (17.5)	171 (19.1)	260 (18. 5)
Stage III	CVD morbidity	9 (15.5)	15 (11.4)	24 (12.6)
	CVD mortality	6 (10.3)	3 (2.3)	9 (4.7)
	BC mortality	20 (34.5)	49 (37.1)	69 (36.3)
Stage 0–III	CVD morbidity	179 (14.6)	191 (8.3)	370 (10.5)
	CVD mortality	60 (4.9)	32 (1.4)	92 (2.6)
	BC mortality	162 (13.2)	288 (12.5)	450 (12.8)



Follow-up time (years)		0	3	6	9	12	15	18
Number of women at risk	No-radiotherapy	1225	815	564	378	223	113	25
	Radiotherapy	2303	1621	1094	700	409	213	59

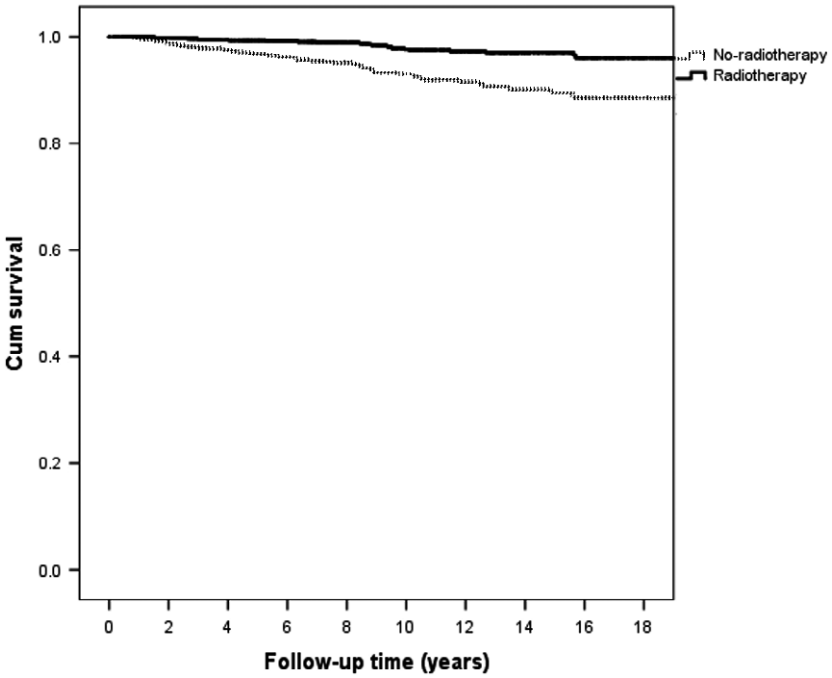
Fig. 1. Kaplan–Meier curve of new cardiovascular events in the radiotherapy group and the no-radiotherapy group.

compared to those who did not have radiotherapy (HR 0.73, 95% CI, 0.59–0.92).

The main determinants of cardiovascular mortality were increasing age, ethnicity, and pre-existing cardiovascular disease (Table 4). Radiotherapy did not have a significant effect on cardiovascular mortality. Menopausal status, ovarian ablation and trastuzumab were excluded from the multivariate analysis for cardiovascular mortality due to a lack of cardiovascular deaths in some subgroups.

Discussion

Radiotherapy did not increase the risk of cardiovascular mortality or morbidity. The risk also did not increase in women with left-sided breast cancer compared to women with right-sided breast cancer. The findings are consistent with other studies looking at women diagnosed with breast cancer in the 1980s and onwards.[12,13] However, the results are in contrast to the Danish and Swedish cohort study that included over 35,000 irradiated breast cancer patients, which found an 8% increased risk of heart disease in women with left-sided breast cancer compared to right-sided breast cancer. This increase was observed in women diagnosed between 1976 and 1989 and also in women diagnosed between 1990 and 2006.[20] A dose–response rate has also been reported from a case–control study of the same cohort of women.[11] The difference in our findings could be related to the different techniques employed in radiotherapy delivery, for example,. routine use of CT-planning in radiotherapy was not established in Sweden and Denmark until around 2000.[21] Furthermore, radiotherapy techniques have evolved over time, becoming more precise with less radiation dose to the heart.[6,22] Therefore, the effects of radiotherapy on women treated earlier, particularly before the 1990s and before the use of CT-planning, may not be representative and reflective of the effects of current radiotherapy sources and delivery techniques. Our cohort is of women diagnosed from 1995 to 2013. From 1998, we routinely used CT-planning and block protection of the heart and lungs when using radiotherapy. Thus, the expected dosage to the heart would be substantially lower than sustained in earlier studies. The vast majority of women in this paper received 50 Grey in 25 fractions plus or minus a 10 Grey boost. Boost was mainly used in younger women, or women over 50 years considered to be at high risk of recurrence. Only in the last few years of the study, did some selected women receive hypofractionated regimens of 40 Grey in 15 fractions or 42 Grey in 16 fractions.



Follow-up time (years)		0	3	6	9	12	15	18
Number of women at risk	No-radiotherapy	1225	864	604	402	235	112	25
	Radiotherapy	2303	1669	1131	718	413	208	56

Fig. 2. Kaplan–Meier curve of cardiovascular disease-specific survival (cardiovascular mortality) in the radiotherapy group and the no-radiotherapy group.

Table 3. Cox regression analysis for cardiovascular morbidity

Variable	Hazard ratio	95% CI	*P*-value
Age	1.04	1.03–1.06	<0.001
Having at least 1 comorbidity vs no comorbidity	2.10	1.68–2.64	<0.001
Trastuzumab vs no trastuzumab	2.14	1.23–3.71	<0.05
Ovarian Ablation vs no ablation	2.43	1.25–4.72	<0.05
SERMS vs no SERMS	0.71	0.55–0.92	<0.05
Māori vs Non-Māori	1.51	1.13–2.01	<0.05
Radiotherapy vs no-radiotherapy	0.73	0.59–0.92	<0.05
AI vs no AI	1.18	0.90–1.55	NS
Left-sided BC vs right-sided	0.92	0.75–1.14	NS
Menopausal status	1.07	0.58–1.96	NS
Peri vs Pre			
Post vs Pre	0.91	0.61–1.36	NS
Chemotherapy vs no chemotherapy	1.00	0.75–1.33	NS

Table 4. Cox Regression analysis for cardiovascular mortality

Variable	Hazard ratio	95% CI	*P*-value
Age	1.12	1.09–1.15	<0.001
Having at least 1 comorbidity vs no comorbidity	3.07	1.86–5.07	<0.001
Māori vs Non-Māori	2.56	1.37–4.76	<0.05
Chemotherapy vs no chemotherapy	0.49	0.19–1.26	NS
AI vs no AI	1.26	0.65–2.46	NS
Radiotherapy vs no-radiotherapy	0.75	0.47–1.19	NS
SERMS vs no SERMS	1.24	0.69–2.25	NS
Left-sided BC vs right-sided	1.04	0.69–1.58	NS

Strengths and limitations

The strengths of this study include a sizeable number of participants treated in the modern era of radiotherapy, complete breast cancer-related information from the WBCR, and including both morbidity and mortality as outcomes. The cohort was representative of the New Zealand population in terms of demographic variation and treatment options; therefore, the overall observed impact of various factors on the cardiovascular risk of women with breast cancer can be applied to New Zealand. Furthermore, the study has looked at the risk of heart disease in the context of other important determining cardiovascular risk factors.

The limitations of the study include the important fact that there is apparent treatment indication bias. Thus, the no-radiotherapy group included older and postmenopausal women and a higher proportion of women

with comorbidity compared to the radiotherapy group. These factors were included in the multivariate analyses. We did not include smoking and BMI in the analysis because of the proportion of missing data but from the information in Table 1 it is unlikely that these were significant factors. However, it is likely that residual indication bias remains, which is likely responsible for the apparent 'protective' effect of radiotherapy.

The study quantifies the risk of cardiovascular disease in a cohort of women with newly diagnosed breast cancer. Ten percent of women had experienced an event and 2.6% had died of cardiovascular disease by the end of the study period. The aim of our approach was to aid clinicians in choosing optimal treatments for the management of women with early breast cancer and breast cancer survivors, taking into account their underlying cardiovascular risk. The aim was to help improve overall quality of life and survival.

In conclusion, radiotherapy appears less likely to be offered to patients at higher risk of cardiovascular disease. We could find no evidence of increased risk of a cardiovascular event in the group of women with breast cancer treated with radiotherapy and believe that current treatment regimens are safe. Traditional cardiovascular risk factors remain the main culprits in this setting. Clinicians should work with patients in managing these risk factors for optimal results.

Acknowledgements

We would like to acknowledge the financial support from the Health Research Council of New Zealand, the Auckland and Waikato Breast Cancer Registers for providing the detailed data, and the New Zealand Breast Cancer Foundation and the Waikato Bay of Plenty Division of the Cancer Society for funding the Registers.

References

1. Cunningham R, Shaw C, Blakely T, Atkinson J, Sarfati D. Ethnic and socioeconomic trends in breast cancer incidence in New Zealand. *BMC Cancer* 2010; **10**: 674.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87–108.
3. Colzani E, Liljegren A, Johansson AL *et al.* Prognosis of patients with breast cancer: causes of death and effects of time since diagnosis, age, and tumor characteristics. *J Clin Oncol* 2011; **29**: 4014–21.
4. Hagemeister FB Jr, Buzdar AU, Luna MA, Blumenschein GR. Causes of death in breast cancer: a clinicopathologic study. *Cancer* 1980; **46**: 162–7.
5. Senkus-Konefka E, Jassem J. Cardiovascular effects of breast cancer radiotherapy. *Cancer Treat Rev* 2007; **33**: 578–93.
6. Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the heart in breast cancer radiation therapy: a systematic review of heart doses published during 2003 to 2013. *Int J Radiat Oncol Biol Phys* 2015; **93**: 845–53.
7. Visser A, van de Ven EM, Ruczynski LI *et al.* Cardiac monitoring during adjuvant trastuzumab therapy: guideline adherence in clinical practice. *Acta Oncol* 2016; **55**: 423–9.
8. Eldabaje R, Le DL, Huang W, Yang LX. Radiation-associated cardiac injury. *Anticancer Res* 2015; **35**: 2487–92.
9. Slezak J, Kura B, Ravingerova T, Tribulova N, Okruhlicova L, Barancik M. Mechanisms of cardiac radiation injury and potential preventive approaches. *Can J Physiol Pharmacol* 2015; **93**: 737–53.
10. Taylor CW, McGale P, Darby SC. Cardiac risks of breast-cancer radiotherapy: a contemporary view. *Clin Oncol (Royal College of Radiologists (Great Britain))* 2006; **18**: 236–46.
11. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005; **6**: 557–65.
12. Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN, Goodwin JS. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst* 2005; **97**: 419–24.
13. Patt DA, Goodwin JS, Kuo YF *et al.* Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol* 2005; **23**: 7475–82.
14. Boardman HM, Hartley L, Eisinga A *et al.* Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev* 2015; Cd002229.
15. Anderson GL, Limacher M, Assaf AR *et al.* Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; **291**: 1701–12.
16. Schlitt A, Jordan K, Vordermark D, Schwamborn J, Langer T, Thomssen C. Cardiotoxicity and oncological treatments. *Deutsches Arzteblatt Int* 2014; **111**: 161–8.
17. Cardinale D, Colombo A, Bacchiani G *et al.* Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation* 2015; **131**: 1981–8.
18. Seemann I, te Poele JA, Song JY, Hoving S, Russell NS, Stewart FA. Radiation- and anthracycline-induced cardiac toxicity and the influence of ErbB2 blocking agents. *Breast Cancer Res Treat* 2013; **141**: 385–95.
19. Todaro MC, Oreto L, Qamar R, Paterick TE, Carerj S, Khandheria BK. Cardioncology: state of the heart. *Int J Cardiol* 2013; **168**: 680–7.
20. McGale P, Darby SC, Hall P *et al.* Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiotherapy Oncol* 2011; **100**: 167–75.

21. Taylor CW, Bronnum D, Darby SC *et al.* Cardiac dose estimates from Danish and Swedish breast cancer radiotherapy during 1977–2001. *Radiotherapy Oncol* 2011; **100**: 176–83.

22. Yeboa DN, Evans SB. Contemporary breast radiotherapy and cardiac toxicity. *Sem Rad Oncol* 2016; **26**: 71–8.