Evaluation of cardiotoxicity five years after 2D planned, non-simulated, radiation therapy for left breast cancer

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Introduction: Radiation treatment has been associated with radiation induced cardiotoxicity, especially with older, long-outdated, techniques. Such complications include pericarditis, myocardial fibrosis, valvular injury, ischemic heart disease, and myocardial infarction.

Aim: To assess the effect of outdated breast radiation therapy (RT) – using a diagnostic CT scanner in the absence of a CT simulator – on cardiac function in women with stage II left breast cancer.

Patients and Methods: Sixty-two women under 65 with stage II left breast cancer who received post-operative RT using a diagnostic computed tomography scanner were studied between 1997 and 2001. Participants underwent a clinical interview, ECG, and echocardiography before and 6 months and 5 years after RT.

Results: There was no serious cardiotoxicity at 6 months and 5 years after radiotherapy. A 23% increase in hypertensive patients, and a slight decrease (2.3%) in ejection fraction was observed after 5 years, with 3 patients (5%) developing abnormalities. Two patients presented abnormal electrocardiographic findings within 6 months of RT.

Conclusion: Our study showed that RT for left breast cancer was not associated with significant alteration in heart morbidity or mortality within 5 years of treatment, despite the lack of a simulator.

Keywords: radiotherapy, breast cancer, cardiotoxicity, acute myocardial infraction, ischemic heart disease

Introduction

Adjuvant radiation therapy (RT) in patients with early breast cancer significantly reduces locoregional recurrence in up to 60% of cases (Gyenes 1998). The most recent systematic overview, conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTCG), indicated that post-mastectomy RT reduces absolute breast cancer mortality by an average of 5% at 10 years (EBCTCG 2000). The relative benefits are similar after mastectomy or breast conservation surgery in the presence or absence of adjuvant systemic therapies as well as in axillary node-negative and -positive patients.

However, RT has been associated with radiation-induced cardiotoxicity, especially with older, long-outdated, techniques (Gyenes 1998; Carlson et al 1991; Cutuli 2000). Such complications include pericarditis, myocardial fibrosis, valvular injury, ischemic heart disease, and myocardial infarction, and have been observed particularly in the literature on photon radiation of post-mastectomy chest-wall and direct internal mammary lymph nodes (Rutqvist et al 1992; Gyenes et al 1994). A meta-analysis by Cuzick (2005) showed a 62% increase in cardiac death in women receiving RT. Similarly, EBCTCG found a 30% increase in vascular mortality in women receiving RT

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for breast cancer (Clarke et al 2005). Some authors reported no increased risk for patients with left breast disease treated with techniques used approximately since 1975 (Hojris et al 1999; Rutqvist et al 1998), while others claimed a 2-fold risk of fatal myocardial infarction for left-sided treatment compared with right-sided (Paszat et al 1998).

At present, there is a controversy as to whether modern RT techniques are also cardiotoxic, especially in cases of left breast cancer. Gustavsson et al (1999) found that women younger than 50 years at the time of adjuvant RT following mastectomy for early breast cancer had no serious cardiac sequelae 13 years on. On the contrary, Paszat et al (1998) suggested that adjuvant RT for left-sided breast cancer diagnosed in women younger than 60 is associated with a higher risk of fatal myocardial infarction 10 to 15 years later compared with adjuvant RT for right-sided cases. Moreover, Harris et al (2006) proposed that irradiation to the left breast is not associated with a higher risk of cardiac death up to 20 years after treatment, but is associated with an increased rate of diagnoses of coronary artery disease and myocardial infarction compared with right breast treatment.

The aim of our study is to assess the effect of outdated breast RT – using a diagnostic CT scanner in the absence of a computed tomography (CT) simulator – on cardiac function in women with stage II left breast cancer, using non invasive techniques such as electrocardiogram (ECG) and echocardiography.

Patients and methods

We studied 62 women younger than 65 years with stage II left breast cancer between 1997 and 2001, who received post-operative RT in the department of Radiation Oncology in AHEPA University Hospital, Thessaloniki, Greece. None of them underwent radical mastectomy before RT. At the time of diagnosis, all patients were younger than 65 years (mean age 56 years, range 48–64).

Participants underwent clinical interview, ECG, and echocardiography before and 6 months and 5 years after RT. Patients with ECG abnormalities, previous cardiovascular disease, or echocardiographic abnormalities were excluded from the study. Thyroid stimulating hormone (TSH) was measured in all patients before and after RT to establish that they were all euthyroidic.

Using echocardiography, LVIDd (left ventricular internal dimension in diastole), LVIDs (left ventricular internal dimension in systole), IVSd (interventricular septum in diastole), IVSs (interventricular septum in systole), EDV (end diastolic volume), ESV (end systolic volume), EF (ejection fraction) as well as the presence of pericardial fluid was assessed.

Radiotherapy technique

Accurate patient-specific anatomic information of the breast is a prerequisite for planning and implementing the delivery of radiation to the entire breast while minimising exposure to critical structures such as lungs, ribs and heart. In our department, conventional or CT simulators were unavailable, so the image data from the patients' breasts were taken by a diagnostic multi-slice spiral CT scanner with a flat couch and a gantry opening 80 cm in diameter, which could be restrictive for setting up patients with immobilization devices in the treatment position.

During RT all patients were placed supine with both hands up and behind their head in a precise reproducible position of treatment. The anterior and lateral isometric lines and other landmarks were marked on the patients' skin by radiopaque markers or lead beads.

From all diagnostic CT slices, the central one was chosen as the one in where the disease was most extensive. Thereafter, we delineated the target area as well as the organs at risk, and these data were input to a 2-dimensional (2D) computer treatment planning. The entire breast was included in the planning target volume (PTV) with a 1 cm margin around palpable breast tissue. The physician and the radiotherapist could then select the treatment beam directions. The objective was to treat the PTV disease tissue plus a 1 cm margin to a tumoricidal dose while limiting the dose to the surrounding normal tissues. If critical tissues were located nearby, the aim was to keep the dose to these organs to a level within the acceptable limit of complication. The reference point (100% dose) was located in the centre of the PTV and in the junction of the axes of the tangential fields. The dose variation permitted inside the PTV was between –5% and +10%. In order to further adjust doses and to prevent radiation of sensitive healthy tissues such as lungs and pericardium, axes with a deviation larger than 180° as well as wedges of different angles (15°, 30°, 45°, 60°) were employed.

Radiotherapy was delivered with a Cobalt-60 1.25 MV treatment unit using a pair of opposed tangential beams (medial and lateral). The daily dose was 200 cGy, the total dose on the PTV was 50 Gy in 25 fractions over 5 weeks without boost, while in some patients a boost dose of 5 to 6 Gy was given as necessary. None underwent RT to the internal mammary chain.

Results

Table 1 summarizes the clinical symptoms as well as ECG and echocardiographic findings in our patients before and 6 months and 5 years after RT. SPSS 11.0 has been used for the statistical analysis of data.

No patient developed angina pectoris or other manifestations of coronary heart disease at 6 months or 5 years after RT. However, there was a 23% increase in hypertensive patients within a period of 5 years after RT.

Only 2 patients showed ECG abnormalities within 6 months of RT (ST depression and right bundle bunch block respectively). Conversely, there were only 3 patients who developed QRS and/or ST abnormalities within 5 years of RT.

Pericardial fluid was present in only 1 patient at 6 months after RT. However, this finding was not permanent, since it did not reappear at 5 years after RT.

There was a slight decrease (2.3%) in EF within 5 years after RT. However, there was no significant change in the other echocardiographic parameters included in our study.

Thyroid function could not be evaluated due to lack of data for 27 patients. The other 35 patients remained euthyroidic.

Discussion

This study was undertaken under difficult circumstances because modern technologies such as a conventional simulator or a CT, connected online to a 3D computerized treatment planning, were not available in our department. Instead, we tried to substitute for the lack of a CT simulator by using a diagnostic CT scanner, which was the closest equivalent to a simulator. However, many of the advantages of a conventional simulator were lacking, and only one slice could be input to the 2D computerized treatment planning, so planning and measuring the given dose according to the heart volume were not possible. Another disadvantage was that no correlation existed between the incidence of cardiac sequela in the women of our study and that of women irradiated on the right breast.

Reported data from studies on the comprehensive examination of the long-term cardiac mortality and morbidity after left breast irradiation using contemporary RT techniques indicate a significant association with an increased incidence of coronary artery disease and myocardial infraction 20 years after RT treatment. However, our study shows only a 23% increase in hypertensive patients 5 years after RT. Furthermore, none of the patients developed myocardial infraction or coronary artery disease. Also, the slight decrease in EF may be attributed to the aging of the patients, rather than the long-term effect of RT. All other echocardiographic parameters remained practically unchanged, showing that RT did not affect them. Pericardial fluid was present in only 1 case at 6 months after RT, an effect that was temporary.

Table 1 Clinical manifestations, ECG changes, and echocardiographic parameters 6 months before and 5 years after radiotherapy for left breast cancer

	Before RT (n = 62)	Six months after RT (n = 62)	Five years after RT (n = 62)
Clinical symptoms			
Angina	0	0	0
Hypertension	24	25	31 ($p < 0.05$)
ECG changes			
QRS and/or ST changes	0	1	3
Other ECG changes	0	1	2
Echocardiographic findings			
Pericardial fluid	0	1	0
EDV (mL)	111.5 ± 17.9	112.5 ± 13.7	117.5 ± 17.1
ESV (mL)	43.8 ± 7.5	43.9 ± 8.4	45.8 ± 9.5
EF (%)	65.7 ± 7.9	65.3 ± 6.8	63.4 ± 7.1
LVIDd (cm)	5.1 ± 0.4	5.2 ± 0.8	5.4 ± 0.5
LVIDs (cm)	3.7 ± 0.7	3.8 ± 0.9	3.9 ± 0.6
LVPwd (cm)	0.71 ± 0.2	0.72 ± 0.2	0.74 ± 0.1
IVSd (cm)	0.75 ± 0.3	0.76 ± 0.1	0.79 ± 0.1
IVSs (cm)	1.01 ± 0.2	1.02 ± 0.3	1.04 ± 0.2

Abbreviations: EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; IVSd, interventricular septum in diastole; IVSs, interventricular septum in systole.

These results contrast with those in most other publications. In the most recent population-based case-cohort study (Paszat et al 2007), the authors concluded that in addition to risk factors such as increasing age at diagnosis, smoking history, and history of acute myocardial infarction before post-operative RT, anatomic characteristics of RT such as RT for left-sided tumors, the use of an anterior internal mammary field, and increased area of an anterior left breast boost field are associated with increased risk of acute myocardial infarction (Paszat et al 2007).

The discrepancy could most likely be explained by the small total number of participants, the short follow-up period, the absence of internal mammary irradiation, and, especially, the younger mean age of patients at the time of diagnosis (56 years).

To conclude, our study showed that RT for left breast cancer was not associated with significant alteration in heart morbidity and mortality within 5 years of treatment despite the lack of a simulator. However, a 20-year follow-up of these patients and a comparison with work that includes the same methods of treatment and RT techniques for the right breast would be helpful in order to better evaluate our results.

Disclosures

None of the authors have any conflicts of interest to disclose.

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