Radiotherapy and Oncology 122 (2017) 60–65

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Breast radiotherapy

Risk of pacemaker or implantable cardioverter defibrillator after radiotherapy for early-stage breast cancer in Denmark, 1982–2005

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ARTICLE INFO

Article history:
Received 1 May 2016
Received in revised form 2 July 2016
Accepted 29 August 2016
Available online 15 September 2016

Keywords:
Breast cancer
Radiotherapy
Heart disease
Arrhythmia
Cardiac conduction abnormality
Pacemaker

ABSTRACT

Background and purpose: To examine the risk of cardiac conduction abnormalities or severe ventricular arrhythmias requiring implantation of a cardiac implantable electronic device (CIED), either a pacemaker or an implantable cardioverter-defibrillator, subsequent to breast cancer (BC) radiotherapy (RT).
Material and methods: All women treated for early-stage BC in Denmark from 1982 to 2005 were identified from the Danish Breast Cancer Cooperative Group. By record linkage to the Danish Pacemaker and ICD Registry information was retrieved on CIED implants subsequent to RT. Standardized incidence ratios (SIR) of CIED implantation were estimated for women receiving RT and compared to women not receiving RT for BC. Uni- and multivariate Poisson regression models were used to estimate incidence rate ratios (IRR) among irradiated women compared to non-irradiated.
Results: Of 44,423 BC patients, 179 had a CIED implanted among 18,251 women who received RT, and 401 had a CIED in 26,172 who did not receive RT. The unadjusted IRR was 1.09 (0.91–1.30 95% CI) for CIED implants among women receiving RT compared to non-irradiated women and the IRR was 1.13 (0.93–1.38 95% CI) when adjustments were made.
Conclusions: BC RT as practiced in Denmark in 1982–2005 did not increase the risk of CIED implants. This indicates that RT for BC does not increase the risk of severe ventricular arrhythmias or cardiac conduction abnormalities.

Breast cancer (BC) after non-melanoma skin cancer is the most frequent malignant disease among women in Denmark as well as in the world [1]. Treatment modalities for early stage BC include surgery, radiotherapy (RT), and systemic medical treatment.

The benefits of postoperative RT in early stage BC have been documented in randomized clinical trials and include moderate reductions in BC mortality and substantial reductions in local recurrence, resulting in considerable improvements in BC survival [2–4].

However, one of the main concerns regarding RT is the radiation dose to the heart. Data from Denmark and Sweden suggest a linear relationship between an increasing risk of ischemic heart disease and an increasing dose to the heart [5]. Though doses to the heart have been reduced in modern RT regimens, the mean heart dose is around 3.3 Gy for right-sided and 5.4 Gy for left-sided BC but with a wide variation between regimens and countries [6].

The first report of electrocardiogram (ECG) changes after mediastinal radiation was published in 1925 [7]. Since then, ECG changes have been documented after mediastinal RT for Hodgkin's lymphoma (HL) [8–14]. Evidence is more sparse after RT for BC. A study of 69 Swedish BC patients comparing ECG before and after RT showed that there was a high incidence of T-wave changes 6 months after RT for left-sided BC but the ECG changes were reversible. The perimyocardial damage was functionally insignificant at long-term follow-up [15].

ECG changes constitute a quite heterogeneous pattern. They range from transient and harmless (single supra ventricular premature complexes, T-wave inversion) without a need for treatment, to severe and life-threatening (high degree AV-block, sinus node dysfunction and ventricular tachyarrhythmias) with an indication for either a pacemaker or an implantable cardioverter defibrillator [16]. The aim of this study was to examine if BC RT was associated with a risk of so severe arrhythmias and conduction abnormalities that implantation of a cardiovascular implantable electronic device (CIED), was needed.

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http://dx.doi.org/10.1016/j.radonc.2016.08.024
0167-8140/

Methods

Study design and subject selection

This is a register based cohort study. Data were ascertained through three Danish national registries; The Danish Breast Cancer Cooperative Group Registry (DBCG), The Danish Pacemaker and ICD Registry (DPIR), and the Danish National Patient Register (LPR).

DBCG has registered all women with primary, early-stage BC in Denmark since 1977. More than 80,000 women are registered and the registry has been validated to have close to complete ascertainment [17]. The DBCG registry includes individual patient information on demographic and histopathological variables, treatment modalities (surgery, medical treatment and RT) and follow-up for recurrence and death. All Danish hospitals involved in diagnosis and treatment of BC patients (breast surgeons, pathologists and oncologists) are reporting to this registry.

We identified 64,071 women diagnosed with histologically verified, early-stage (stage I-IIIC/non-metastatic) BC in Denmark from 1st January 1982 to 31st December 2005 and without prior malignancies (Fig. 1). A total of 2099 women were excluded since they only had a breast biopsy, 1311 patients because of bilateral BC, 2024 women due to unknown BC laterality, 2768 patients because of old age (more than 80 years at the time of the diagnosis) and 322 with a follow-up of less than 6 months. Additionally, 8492 patients were excluded due to lack of valid information on RT. Patients were selected for RT according to the guidelines from the DBCG [18]. RT was not recommended as a standard treatment for patients over the age of 70 years after a mastectomy but for all patients after breast conserving surgery. From 1982 to 1989, there were three regimens after mastectomy, 50 Gy in 25 fractions over 5 weeks, 48 Gy in 24 fractions over 5 weeks, and 36 Gy in 20 fractions over 4 weeks, the latter with orthovoltage. After breast conserving surgery 50 Gy was given in 25 fractions over 5 weeks some with an additional boost of 10–24 Gy. From 1989 to 2005 after breast conserving surgery, all patients were given 48 Gy in 24 fractions over 4.5 weeks with boost doses of 10–16 Gy in 5–8 fractions to the tumor bed. Endocrine therapy included tamoxifen only, initially for 1–2 years, later for 5 years, from 1977 to 2007 [17].

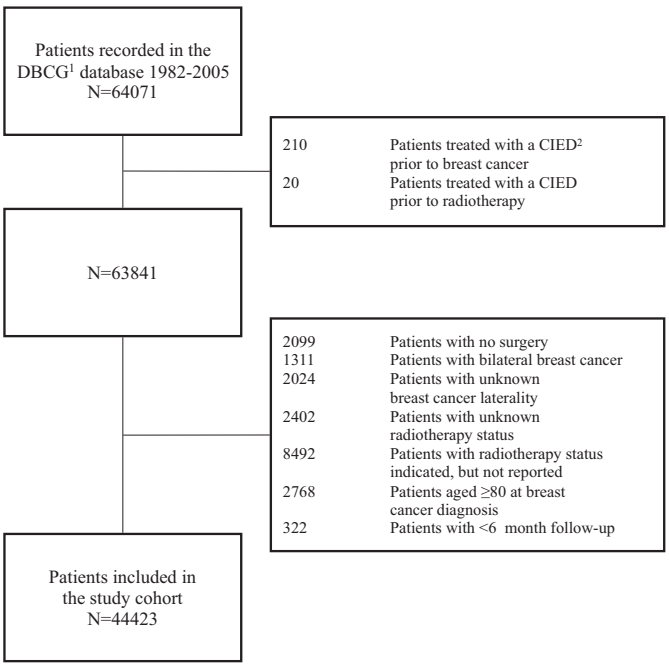

Fig. 1. Inclusion and exclusion flowchart. [1]The Danish Breast Cancer Cooperative Group. [2]Cardiovascular Implantable Electronic Device.

DPIR started in 1982 and has registered all CIEDs including permanent pacemakers (PMs), implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy devices with defibrillators (CRT-Ds) or without (CRT-Ps). More than 30,000 Danish women are registered in the DPIR, which includes individual patient information of new implants, re-implants, indication for the implant, and clinical symptoms of the patient [19].

The Danish personal identification number enabled a linkage between DBCG and DPIR. Hereby, information on CIED among women treated with radiation for BC were retrieved [20]. We identified 210 patients with a CIED implanted prior to the BC diagnosis and 20 patients who had a CIED implanted within 6 months post diagnosis. These were excluded.

LPR was established in 1977, and the register has been expanded over the years, from originally covering only somatic inpatients to covering somatic as well as psychiatric in- and outpatients in all hospitals in Denmark today. The registry has been maintained by a public enterprise under the Danish Ministry of Health [21]. Information about prior cardiac disease was identified from the LPR and was defined as having any of the following ICD-codes at least 30 days before the BC diagnosis; conduction abnormality/arrhythmia, ICD8 427.90–427.98/ICD10 I44, 45, I47-49, other cardiac diseases, ICD8 390.00–429.99/ICD10 I00-I52 (ICD-codes for conduction abnormality/arrhythmia not included).

The Danish Health and Medicines Authority and the Danish Data Protection Agency approved the study.

Statistical methods

Differences in patient characteristics between BC patients who had received RT and BC patients who had not received RT were tested using the χ^2-test. Level of significance was set to 5%. Crude standardized incidence ratios (SIR) were estimated for CIED implants as the observed numbers of CIED implants divided by the expected number of CIED implants. The expected number of implants was estimated from accumulated person-year at risk and CIED implant rates of the general Danish female population in five-year calendar-time and age groups. Ninety-five percent confidence intervals (CI) were formed assuming the expected numbers to be Poisson-distributed. Time at risk started 6 months after BC diagnosis, to avoid inclusion of CIED implants during RT for arrhythmias and conduction abnormalities prevalent prior to RT. Time at risk ended at death, emigration, CIED implant or at last date of follow-up (1st July 2014), whichever occurred first. Poisson regression models were applied to assess the incidence rate ratio (IRR) and standard likelihood ratio tests comparing Poisson's regression models were used to test for heterogeneity across subgroups. Univariate analysis of the parameters included follow-up time. The multivariate model further included RT, calendar year of diagnosis, age at diagnosis, time since diagnosis, axillary lymph nodal status, estrogen receptor status, laterality of BC, adjuvant medical treatment and prior cardiac disease.

The calendar years of BC diagnosis were divided into three groups according to different treatment strategies. The first group covers the period 1982–1989, when anthracyclines were not used in standard chemotherapy. The second group covers the period 1990–2002. As anthracyclines were used in a trial study by the end of 1989, and became standard as of 1999 onward. The third group covers the period 2003–2005, when it was decided that the internal mammary nodes should be irradiated only for women with right-sided BC, in order to reduce the radiation dose to the heart for left-sided BC.

Analyses were made with STATA 14 [22].