Post Mastectomy Adjuvant Radiotherapy in Breast Cancer: A Comparison of Cardiac Toxicity in Hypofractionated and Normal Fractionation Protocols

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Abstract

Background: Postoperative radiotherapy (RT) for breast cancer is an essential part of adjuvant cancer treatment. RT reduces the risk of local recurrence by 50% and the risk of breast cancer mortality by 16%. Hypofractionated regimens are increasingly being used as they involve fewer treatment sessions and, in terms of tumor control, the effects of conventionally fractionated and hypofractionated radiotherapy seem to be comparable. However, the concern for late toxicity especially cardiac toxicity is still under investigation. In our study, we evaluated cardiac toxicity of two radiotherapy fractionation techniques.

Patients and methods: This is a prospective randomized clinical trial conducted at clinical oncology department–Menoufia University to assess cardiac toxicity of two fractionation techniques. Between August 2009 and June 2010, 120 patients were randomized into two groups each group 60 patient. Group A: Conventional fractionation radiation (50 Gy/25 fractions/5 weeks, at 2 Gy/fraction). Group B: Hypofractionated radiotherapy (HFR) was 40 Gy in 15 fractions over 3 weeks, at 2.67 Gy per fraction. Echocardiography (ECHO), Electrocardiography (ECG) was performed at base line before chemotherapy, at start of radiotherapy, after 6 months, then annually.

Results: A total of 60 patients indicated for postoperative radiotherapy were included in each arm with median follow-up time 60 months range (25-70). Median age is 47 ranges (23-70), (25-68) in group A and B respectively. No significant statistical difference was found between two groups regarding hypertension 25% vs. 21.7% group A and B respectively, also no difference was found between two groups regarding base line and follow-up ECHO and ECG. Patients with left sided breast cancer and/or hypertension showed significant decline in ejection fraction in both groups P value <0.05. In (Group A) hypertensive patients had a median base line EF 63% which declined to 54% at last follow-up in comparison to non-hypertensive patients who had baseline EF 65% which declined to 54% at last follow-up in comparison to non-hypertensive patients who had baseline EF 64% which declined to 59%. Only one patient died to heart failure patient was 70 years old and had history of hypertension and diabetes mellitus.

Conclusion: Hypofractionation radiotherapy in the adjuvant setting for treatment of breast cancer has no additional cardiac toxicity in comparison to normal fractionation technique.

Keywords: Breast cancer; Hypofractionated radiotherapy; Cardiac toxicity

Introduction

Current clinical results of hypo-fractionated breast irradiation support its introduction into clinical routine soon. Hypofractionation offers an alternative to standard fractionation regimens at least in a subset of patients. There is now a clear radiobiological basis for the use of moderate hypofractionation with a decrease in the number of fractions by about 50% [1].

The topic-specific guideline Recommendations for use of hypofractionation radiotherapy for the treatment of (operable) breast cancer is based on evidence from six randomized clinical trials (RCTs) comparing hypofractionated radiotherapy to conventionally fractionated radiotherapy; Start A, Start B, Spooner 2012, UK FAST trial, Canadian trial, and RMH/GOC trial [2-5].

Since most radiotherapy-associated cardiac side effects occur after 15 years or more, currently available results must be assessed with caution, especially in women with a long-life expectancy and an Unhealthy lifestyle. However, no significant cardiotoxicity has been observed in modern norm fractionated radiotherapy for breast cancer with current radiotherapy techniques making it now safer than in the past [6].

A 15-year follow-up of cardiac injury, comparing hypo fractionation vs. norm fractionation in left-sided early-stage breast cancer patients. In 5,334 patients receiving breast or chest wall irradiation, no statistically significant difference in cardiac mortality was detected [7].

Another important factor in this regard is the administration of anthracyclines which again cause cardiotoxicity. Different techniques have been used in different trials to assess the cardio toxicity of chest wall radiotherapy. They include, ECG, echocardiography, cardiac perfusion imaging, infarction and cardiac deaths.

Radiotherapy following mastectomy has been seen to increase...
the risk of death due to cardiac reasons at almost 10-15 years after treatment [8].

This study aims to evaluate the cardiotoxicity of two fractionation protocols in the adjuvant setting of breast cancer.

Patients and Methods

This is a prospective randomized trial conducted at clinical oncology department-Menoufia University the objectives of this study were to compare the cardiotoxicity of hypofractionated protocol vs. normal fractionation protocol in post-mastectomy breast cancer patients in adjuvant setting. Between August 2009 and June 2010, 120 patients who were indicated for adjuvant radiotherapy was randomized into two groups each group 60 patient.

Group A: conventional fractionation radiation (50 Gy/25 fractions/5 weeks, at 2 Gy/fraction).

Group B: Hypo-fractionated radiotherapy (HFR) (40 Gy in 15 fractions over 3 weeks, at 2.67 Gy/fraction). Patients were included if female between 18 and 75 years. T2, T3 or T4 primary lesion and N1, N2, N3, Nx, N0 nodal status. Post modified radical mastectomy status.

Metastatic work up including isotope bone scan, chest X-ray and abdominal ultrasound or CT chest and pelviabdominal if indicated. Adjuvant chemotherapy was completed before radiation. Patients were planned on 2D planning system and Treated on Linac machine 6 Mev. Two tangential portals for the chest wall were planned on simulator with central lung distance (CLD) not exceeding 2.5 cm. if indicated direct anterior filed to the supraclavicular and axillary areas was planned.

Echocardiography (ECHO), Electrocardiography (ECG) was performed at base line before chemotherapy, at start of radiotherapy, after 6 months, then annually. Written consent was taken before starting the treatment. Data was statistically described in terms of median, mean and percentages. Independent t test and chi square were used for comparing variables. SPSS program (inc. Chicago, IL, USA) version 16 for windows was used for analysis.

Results

One hundred and twenty patients were randomized into two groups, the age ranges from (23-70) median 47.5 years group A, and 25-68) median 47 for group B. Both treatment groups were comparable as regard age, performance status, stage, menopausal status. Most of the patients were post-menopausal 70% in group A vs. 73.4% in group B (Table 1). At the time of the study Trastuzumab was not available for patients treated with government reimbursement so patients with +ve HER2neu didn’t receive it, also most of the patients in two arms received Anthracyclin based regimen without Taxanes (Table 2). There was no significant difference between two fractionation protocols in regard to EF during follow-up; allow median decrease in EF didn’t exceed 10% in both groups. However 5 patients has a decrease > 10 but <20% three patients treated with government reimbursement so patients with +ve HER2neu didn’t receive it, also most of the patients in two arms received Anthracyclin based regimen without Taxanes (Table 2).

Discussion

The use of hypofractionation in the adjuvant setting of breast cancer has gained a lot of popularity during the last two decades. A lot of trials have proven its efficacy and comparable side effects like Start A & Start B trials. It’s also proved to be a cost effective protocol especially in developing countries given the lack of adequate numbers of machines.

In our department a number of clinical trials has been started to evaluate the value of hypofractionation radiotherapy especially post modified radical mastectomy since it’s the most common type of operations performed here and since most of the studies done was post breast conservative surgery (BCS). Concerning post radiotherapy side effects there has always been a deep concern about cardio toxicity especially in patients with left sided breast cancer. Due to the contour of the chest wall some portion of the heart must be included in the...
tangential portals. Also the addition of anthracyclines and comorbid conditions poses and additional factor.

It was concluded that the START A and B trial results showed that although follow-up was still shorter than would be desired for cardiac events, there was no major difference between the fractionation schedules for the number of cases of heart disease in women with left-sided primary tumors [9]. These findings coincide with our data in which there was no difference between two groups regarding it side. It was noted that the heart is sensitive to radiation whatever fractionation is used with no lower dose threshold for adverse effects.

In our study the presence of hypertension was an influencing factor in declining of EF in both arms. Patients with hypertension showed significant decline in ejection fraction in both groups P value <0.05. In (Group A) hypertensive patients had a median base line EF 63% which declined to 54% at last follow-up in comparison to non-hypertensive patients who had baseline EF of 65% and declined to 60%. In (Group B) hypertensive patients had a median baseline EF 62% which declined to 54% at last follow-up in comparison to non-hypertensive patients who had baseline EF 64% which declined to 59%. Only 5 patients has a decrease in EF>10% but <20% three patients in group A, two patients in group B, all 5 patients were hypertensive.

Only one patient died due to heart failure patient was 70 years old and had history of hypertension and diabetes mellitus. A commentary on the 2013 Start trial results agreed with the sart trial authors that techniques to protect the heart are important for both radiotherapy schedules and the choice of fractionation should not be affected by whether the tumor is in the right or left breast [10]. A population-based retrospective study it was reported in two 2014 publications. The first paper aimed (median follow-up 13.2 years; Ontario) to determine if there is an increase in hospital-related morbidity from cardiac causes with either hypofractionated radiotherapy (40-44 Gy in 16 fractions) or conventional radiotherapy (45-50 Gy in 25 fractions or 50.4 Gy in 28 fractions). Seven for left-sided cases, 15-year cumulative hospital-related morbidity from cardiac causes was not different between the two radiotherapy regimens (both 21%, p=0.93). The difference was also not significant for right-sided cases (hypofractionated 18%, conventional 19%, p=0.76). The 15-year cumulative mortality before first cardiac hospitalisation between hypofractionated radiotherapy and conventional radiotherapy was not statistically different; 20.7% vs. 23.8% respectively (p=NR). Right-sided cases were also not significantly different [11].

Although in our study there was a significant difference between EF in regard to site (right vs. left side ) there was no difference between the two groups, the cumulative long term effect needs more follow-up, in the study done by The authors concluded that for women with left-sided early-stage breast cancer who received postoperative radiation therapy to the whole breast or chest wall, there was no difference at 15-years follow-up, the rate of cardiac mortality for hypofractionated radiotherapy was 4.8% and for conventional radiotherapy it was 4.2%, this difference was not statistically significant (p=0.74). The difference was also not significant for right-sided cases (hypofractionated 4.9%, conventional 3.5%, p=0.21).

The use of tamoxifen vs. aromatase inhibitors didn't increase the risk of cardiac toxicity in terms of EF decline or ECG changes in both treatment groups. In our study there was no significant correlation between cardio toxicity and the use of Tamoxifen vs. Aromatase Inhibitors although patients above 50 years shows more reduction in EF though not statistically significant.

Appelt et al. [12] analyzed dose plans for 60 left-sided breast cancer patients to compare fraction size-corrected dose distributions to the heart for four hypo-fractionated schedules with the normo-fractionated schedule of 50 Gy in 25 fractions.

The authors concluded that for standard tangential field whole breast irradiation, most of the examined hypo-fractionated schedules are estimated to spare the heart when compared with normo-fractionation. The dose to the heart, adjusted for fraction size using the linear quadratic model, will generally be lower after hypo-fractionated compared with normo-fractionated schedules, even for very low values of α/β values [12].

The retrospective case-control study that analyzed the 20-year risk of death from ischemic heart disease (IHD) in breast cancer patients who received hypofractionated locoregional radiotherapy at the Norwegian Radium Hospital between 1975 and 1991 (median follow-up: all patients 4.5yrs, surviving patients 20yrs). Two hypofractionated radiotherapy regimens were used: 4.3 Gy × 10 given as 2 weekly fractions (n=1107) and 2.5 Gy × 20 given as 4 weekly fractions (n=459). In multivariate analysis the 4.3 Gy still had an associated increased risk of IHD but with borderline significance only (HR=2.90, 95%, CI 0.97-8.76, p=0.057).

Patients treated for left-sided cancer did not have increased risk of dying of IHD compared with right-sided breast cancer. The authors concluded that at least two decades is needed to evaluate safety of such irradiation [13].

The same results were found in a study done by Marhin et al. [14]. The study reported there was no significant difference in cardiac mortality for women ≤ 60 or >60 years of age who received adjuvant radiotherapy for left-sided vs. right-sided cancer. There was no difference in cardiac mortality for women who received adjuvant radiotherapy with fraction sizes ≤ 2 vs. >2 Gy for left- or right-sided cancer. The study reported that the risk of cardiac death for left- relative to right-sided radiotherapy with >2 Gy fractions was 1.07 (95%, CI 0.68-1.69).

An additional randomized study of 60 patients, although the study population was small and had limited results. The authors concluded hypo-fractionated radiotherapy decreased cardiac toxicity though not statistically significant; however, it is more cost effective and time consuming [15].

In the absence of a difference in cardiac mortality between women treated for breast cancer with hypo-fractionated vs. conventional fractionated radiotherapy adds further support to the efficacy of hypo-fractionated regimens in this clinical setting. The Canadian trial did not report results for left- and right-sided breast cancers, the authors did note that at a median follow-up of 12 years few cardiac-related deaths were observed and no increase occurred in patients who received the hypo-fractionated regimen [16].

In our study only one cardiac related death occurred which was a patient died due to congestive heart failure patient was 70 years old and had history of uncontrolled hypertension and diabetes mellitus.

**Conclusion**

Data collected from multiple trials and data from our study (though small number of patients with relatively short follow-up) suggest that there is no difference between two protocols regarding cardiac toxicity. Longer follow-up is mandatory to detect late effects. The use of IMRT Planning can also reduce the risk of cardiac complications especially in left side.
References


