Post mastectomy adjuvant radiotherapy in breast Cancer: A comparison of cardiac toxicity in hypo-fractionated and normal fractionation protocols.

Hagar A. Al Agizy and Mahmoud A. Elshenawy*

Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Menoufia University, Shebin El Kom 32511, Egypt.
Mahmoudelshenawy78@gmail.com, Mahmoudelshenawy@med.menofia.edu.eg

Abstract: Background: Post mastectomy radiotherapy (PMRT) with hypo-fractionation protocols has been widely used because of less frequent treatment sessions with comparable efficacy to the conventional fractionation protocols. Late PMRT induced toxicities, especially cardiac toxicities, with hypo-fractionation protocols remained under investigation. Purpose of our study was to compare risk of PMRT induced cardiac toxicities with hypofractionation and conventional fractionation protocols. **Patients and methods:** This was a prospective randomized clinical trial done in our department. Between August 2009 and June 2010, breast cancer female patients eligible for PMRT underwent 1:1 randomization into 2 groups; **group A:** conventional fractionation (50 Gy/25fractions/5weeks; 2Gy/fraction). **Group B:** Hypofractionation (40Gy/15 fractions/3 weeks; 2.67Gy/fraction).

Echocardiography (ECHO) and Electrocardiography (ECG) were performed at base line before chemotherapy, at start of radiotherapy, after 6 months, then annually. **Results:** At a median follow up duration of 60 months (range 25- 70),120 patients were randomized equally in both groups A & B. Median age was 47 years in both groups [ranges (23-70) & (25-68) in groups A & B respectively]. No significant statistical difference was found between both groups regarding hypertension (25% vs 21.7% group A & B respectively). Also, no difference was found between both groups regarding base line and follow up ECHO & ECG. Patients with left sided breast cancer and/or hypertension showed significant decline in ejection fraction (EF) in both groups ($p < 0.05$). 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 decline in baseline EF from 65% 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 decline in baseline EF from 64% to 59%. Only 1 recorded death due to heart failure however, she was 70 years old and had history of hypertension and diabetes mellitus. **Conclusion:** PMRT with hypofractionation protocols has no additional cardiac toxicity in comparison to conventional fractionation.

[Hagar A. Al Agizy and Mahmoud A. Elshenaw. **Post mastectomy adjuvant radiotherapy in breast Cancer: A comparison of cardiac toxicity in hypo-fractionated and normal fractionation protocols.** *Cancer Biology* 2019;9(1):38-42]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). http://www.cancerbio.net. 5. doi:10.7537/marscbj090119.05.

Keywords: breast cancer, hypofractioned radiotherapy, cardiac toxicity.

1. Introduction:

The main concern of PMRT in breast cancer is late toxicities especially cardiac toxicities that might occur up to 15 years or more after finishing treatment, especially in women with a long-life expectancy and an unhealthy lifestyle (1).

Patients with left sided breast cancer who received anthracycline based chemotherapy in the neoadjuvant or adjuvant setting are at higher risk of late life-threatening cardiac toxicities occurring 10 to 15 years after end of PMRT (2).

Data supporting the use of PMRT with hypofractionation protocols are based mainly on results of 6 randomized clinical trials (RCTs) comparing hypofractionated to conventionally fractionated protocols; START A, START B, Spooner 2012, UK FAST, Canadian and RMH/GOC trials (3–6).

After follow up duration of 15 years, there was no significant difference in incidence of cardiac toxicities between hypofractionation and conventional fractionation protocols in 5,334 patients with left-sided early breast cancer who received adjuvant breast or chest wall irradiation (7).

The increasing use of modern radiotherapy techniques nowadays had led to increase safety of PMRT with fewer incidences of cardiac toxicities (1).

The aim of this study was to compare the risk of PMRT induced cardiotoxicity with conventional and hypofractionation protocols.

2. Patient and Methods:

Patients:

Eligible patients were females between 18 and 75 years old. All have pathologically confirmed breast cancer (T2, T3 or T4 primary lesion and N1, N2, N3, Nx, N0 nodal status) and underwent modified radical

mastectomy (MRM). All the patients had complete metastatic work up including chest X-ray, abdominal ultrasound or computed tomography (CT) of chest, abdomen and pelvis if indicated and isotope bone scan. Patients with radiological evidence of metastasis were excluded from the study. Adjuvant chemotherapy was completed before start of radiation.

Trial Design:

This was a prospective randomized trial of PMRT using hypofractionation and conventional fractionation protocols. Randomization in a 1:1 ratio was performed and the patients were divided equally into 2 groups A and B. Group A patients received conventional fractionation; 50 gray (Gy),2 Gy per fraction in 25 fractions for 5 weeks and group Bpatients received hypofractionation; 40 Gy,2.67 Gy per fraction in 15 fractions for 3 weeks. Patients in both groups 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 field to the supraclavicular and axillary areas was planned.

Echocardiography (ECHO), Electrocardiography (ECG) were performed for all patients in both groups at base line before chemotherapy, at start of PMRT, after 6 months, then annually.

This trial was approved by the ethical committee in our faculty and all the patients provided a written informed consent.

Statistical analysis:

Data were statistically analyzed in terms of median, mean and percentages. Independent t and chi-square tests were used for comparing variables. SPSS program (Inc. Chicago, IL, USA) version 16 for windows was used for analysis.

3. Results:

Patients:

From August 2009 and through June 2010, a total of 120 patients were randomly assigned to both treatment protocols with equal distribution between both groups A and B.

Median age was 47.5 years (range: 23-70) for group A and 47 years (range: 25-68) for group B. Most of the patients were post-menopausal; 70% and 73.4% in groups A and B respectively. Both treatment groups were comparable regarding age, performance status, stage and menopausal status. Table 1 summarizes clinicopathological criteria of patients in both groups.

Adjuvant systemic treatment:

Adjuvant chemotherapy given to patients in both groups are summarized in table 2. At the time of the study, Trastuzumab was not available in our department due to governmental issues regarding reimbursement, so that patients with positive HER2neu didn't receive it. Patients with positive hormonal status were given 5 years adjuvant Tamoxifen or Aromatase inhibitors (AIs) if applicable. Table 2 summarizes different adjuvant systemic treatments given to patients in both groups.

Table1. Clinico-pathological criteria of both groups.

	Group A (n=60)	**Group B** (n=60)
Age (years)		
Mean	48.8	48.5
Median	47.5	47
Range	(23-70)	(25-68)
Sidedness of primary tumor		
Left breast	32 (53.3%)	35 (58.3%)
Right breast	28 (46.7%)	25(41.7%)
Stage		
II	33 (55%)	35 (58.3%)
III	27 (45%)	25 (41.7%)
Menopausal Status		
Pre-menopausal	18 (30%)	16 (26.6%)
Post-menopausal	42 (70%)	44 (73.4%)
ER		
Positive	49 (82%)	52 (87%)
Negative	11(18%)	8(135)
HER 2neu		
Positive	8 (13%)	10 (17%)
Negative	37 (62%)	37 (61%)
Unknown	15 (25%)	13 (22%)
Hypertension		
Yes	13(21.7%)	15(25%)
No	47(88.3%)	45(75%)

n: number; ER: estrogen receptor; HER2neu: epidermal growth factor receptor 2

Assessment of cardiac toxicity:

There was no significant difference between both groups regarding EF during follow up; meanwhile decrease in EF didn't exceed 10% in both groups. Table 3 summarizes results of EF in patients of both groups upon base line and in different follow up visits.

Decline in median EF >10 and <20 was noticed in 5 patients with known history of hypertension (3 patients were in group A and 2 were in group B).

Hypertension was an influencing factor in declining of EF in both treatment groups. 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 decline in baseline EF from 65% 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 decline in baseline EF from 64% to 59%.

After 3 years of follow up, congestive heart failure was noticed in a 70 years old patient in group A who had history of uncontrolled hypertension.

Patients with left sided breast cancer has a significant decrease in EF in correlation with right side in both groups however it didn't exceed 10 % (Table 4).

Table2. Types of adjuvant systemic treatment received in both groups.

	Group A (n=60)	**Group B** (n=60)
Chemotherapy		
FEC (6cycles)	48 (80 %)	45 (75%)
FEC (3cycles) followed by Docetaxel (3cyles)	6 (10%)	4 (7%)
Hormonal treatment	(23-70)	(25-68)
Tamoxifen	15(31%)	19(36%)
AIs	34(69%)	33(64%)

FEC:5 Fluorouracil, Epirubcin, Cyclophosamide; AIs: Aromatase inhibitors

Table 3. Correlation of ejection fraction (EF) during follow up between two groups.

	Group A	**Group B**	**P Value**
Base-line EF	63.3	64.9	0.6
2nd	61.9	63.2	0.1
3rd	60.9	62	0.1
4th	60.2	60.7	0.6
5th	59.4	59.3	0.9
Last follow up EF	58.8	58.1	0.6

EF: ejection fraction

Table 4. Correlation between right side and left side in both groups.

	Right SIDE (n=57)		**LEFT SIDE (n=63)**		**p.value**
EF	**Mean**	**SD**	**Mean**	**SD**	
Base line	64.5	4.8	63.8	4.6	0.4
2nd follow up	63.4	4.8	61.7	4.5	0.04
3rd follow up	62.6	4.8	60.6	4.4	0.02
4th follow up	61.9	5.2	59.1	4.6	0.003
5th follow up	61.1	5.6	57.8	4.3	0.01
Last follow up	60.6	5.7	56.5	4.5	0.001

EF: ejection fraction; SD: standard deviation

4. Discussion:

The use of PMRT hypofractionation protocols in breast cancer patients is rapidly growing in the last two decades because of its proven efficacy as per start A and B trials (4,5) and it is cost effective especially in developing countries that might not have adequate number of radiotherapy equipment. Clinical trials had been initiated to evaluate the efficacy of PMRT hypofractionation protocols in our department.

There is a major concern regarding PMRT induced cardiac toxicity especially in patients with left sided breast cancer. This concern is mainly in 2 D planning contouring of the chest wall as some portion of the heart might be included in the tangential portals. Also, use of adjuvant anthracycline based chemotherapy protocols in our routine clinical practice and other comorbid conditions might carry additional risk of cardiac toxicities in those patients.

Our study showed that Left breast cancer patients in both groups didn't have a significant difference of PMRT induced cardiac toxicities. These findings coincide with results of a study done by **Haviland, et al in 2013** that showedno major difference of incidence of adjuvant radiotherapy induced cardiac toxicities between both fractionation protocols in women with left breast cancer. It was also noted that there was a cardiac sensitivity to radiation whatever fractionation used with no lower dose threshold for adverse effects (7).

A commentary on the 2013 START trial results agreed with the START trial authors that protection of the heart is important for both adjuvant conventional and hypofractionated radiotherapy protocols and the choice of fractionation should not be affected by whether the tumor is in the right or left breast (10).

A retrospective study from Ontario with a median follow-up of 13.2 years aimed to compare cardiac toxicities in adjuvant radiotherapy for breast cancer patients with hypofractionation (40-44 Gy in 16 fractions) and conventional fractionation (45-50 Gy in 25 fractions or 50.4 Gy in 28 fractions). This study showed that 15-year cumulative hospital-related morbidity from cardiac causes was not different between the two radiotherapy protocols (both 21%, p=0.93). The difference was also not significant for right breast cancer (hypofractionation 18%, conventional 19%; p=0.76). The 15-year cumulative mortality before first cardiac hospitalization between hypofractionation and conventional fractionations protocols was not statistically different; 20.7% vs. 23.8% respectively (p= NR). Right breast cancer patients were also not significantly different. The difference in cardiac mortality rates between both fractionation protocols was not statistically significant (4.8% and 4.2 % for hypofractionation and conventional fractionation, p = 0.74). Also, this difference was not significant for right breast cancer cases (4.9% and 3.2 % for hypofractionation and conventional fractionation, p = 0.21) (8).

Although in our study there was a significant difference between EF regarding sidedness of the primary tumor (right vs left breast) there was no difference between both groups however, the cumulative long-term effect needs further follow up.

A retrospective case-control study compared 20-year risk of death from ischemic heart disease (IHD) in two adjuvant radiotherapy hypofractionation protocols [4.3 Gy x 10 given as 2 weekly fractions (n=1107) and 2.5 Gy x 20 given as 4 weekly fractions (n=459)]. Multivariate analysis of this study showed that 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 breast cancer did not have increased risk of dying from IHD compared with right breast cancer (9).

In 2007 **Marhin et al** reported no significant correlation in risk of PMRT cardiac mortality regarding age [≤60 vs. >60 years], tumor sidedness [left vs. right breast] and dose per fraction [≤2 vs. >2 Gy]. The relative risk of adjuvant radiotherapy induced cardiac mortality for left relative to right breast cancer with >2 Gy fractions was 1.07 (95% CI 0.68-1.69) (10).

Absence of a difference in PMRT induced 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.

In our study only one patient died due to congestive heart failure, she was 70 years old and had history of uncontrolled hypertension and diabetes mellitus. Although a 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 received the hypo-fractionation protocols (11).

In our study there was no significant correlation between cardiotoxicity and use of tamoxifenvs AIs, although patients above 50 years showed more reduction in EF which wasn't statistically significant.

Median follow up duration of 60 months (range 25- 70) might be considered as a limitation of our study as late cardiac toxicities might take up to 15 years to be seen and most of trials addressing that issue had median follow up durations of more than 10 years. Other limitations to this study are small number of patients recruited in both treatment arms and the use 2D planning techniques that might add to cardiac toxicities because of higher possibility of involving portion of the heart in the radiation fields.

Conclusion:

Data collected from multiple trials and from our study suggest that there is no difference between breast cancer adjuvant hypofractionation and conventional radiotherapy protocols in regard to cardiac toxicity. Longer follow up is mandatory to detect late effects. The use of more advanced high precision radiotherapy techniques can also reduce the risk of PMRT cardiac complications especially in left sided breast cancer.

Acknowledgement:

We would thank all patients enrolled to this study and their families. We also thank all staff of radiation and physics unit in our department for their generous help in this study.

Conflict of interest:

Both authors dedicated no potential conflicts of interest.

Authorship:

Both authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

Abbreviations:

PMRT: post mastectomy radiotherapy; ECHO: echocardiography; ECG: electrocardiography; EF: Ejection fraction; RCT: randomized clinical trials; MRM: modified radical mastectomy; CT: computed tomography; CLD: central lungdistance; Gy: gray; ER: estrogen receptor; HER2neu: epidermal growth

factor receptor 2; AIs: aromatase inhibitors; IHD: ischemic heart disease.

References:

1. Nitsche M, Pahl R, Huber K, Eilf K, Dunst J. Cardiac Toxicity after Radiotherapy for Breast Cancer: Myths and Facts. Breast Care [Internet]. 2015;10(2):131–5. Available from: https://www.karger.com/Article/FullText/376560.
2. Paszat LF, Mackillop WJ, Groome PA, Schulze K, Holowaty E. Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: a population-based study in Ontario, Canada. Int J Radiat Oncol Biol Phys [Internet]. 1999 Mar 1;43(4):755–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10098430.
3. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol [Internet]. 2006 Jun;7(6):467–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16750496.
4. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet (London, England) [Internet]. 2008 Mar 29;371(9618):1098–107. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18355913
5. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol [Internet]. 2008 Apr;9(4):331–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18356109.
6. Spooner D, Stocken DD, Jordan S, Bathers S, Dunn JA, Jevons C, et al. A randomised controlled trial to evaluate both the role and the optimal fractionation of radiotherapy in the conservative management of early breast cancer. ClinOncol (R CollRadiol) [Internet]. 2012 Dec;24(10):697–706. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23036277.
7. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol [Internet]. 2013 Oct;14(11):1086–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24055415.
8. Chan EK, Woods R, McBride ML, Virani S, Nichol A, Speers C, et al. Adjuvant hypofractionated versus conventional whole breast radiation therapy for early-stage breast cancer: long-term hospital-related morbidity from cardiac causes. Int J Radiat Oncol Biol Phys [Internet]. 2014 Mar 15;88(4):786–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24606848
9. Tjessem KH, Johansen S, Malinen E, Reinertsen K V, Danielsen T, Fosså SD, et al. Long-term cardiac mortality after hypofractionated radiation therapy in breast cancer. Int J Radiat Oncol Biol Phys [Internet]. 2013 Oct 1;87(2):337–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23886416.
10. Marhin W, Wai E, Tyldesley S. Impact of fraction size on cardiac mortality in women treated with tangential radiotherapy for localized breast cancer. Int J Radiat Oncol Biol Phys [Internet]. 2007 Oct 1;69(2):483–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17601680.
11. Whelan TJ, Pignol J-P, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med [Internet]. 2010 Feb 11;362(6):513–20.

1/25/2019