

Cardiac toxicity of hypofractionated radiotherapy in left breast cancer

Tamer M Samy¹, Samia Abdelkareem², Marwa Abdelgawad², Shima Ahmed¹.

¹ Radiation Oncology, South Egypt Cancer Institute (SECI), Asyut University, Egypt.

² Clinical Oncology, Faculty of Medicine, Asyut University, Egypt.

shimaayoussif04@gmail.com

Abstract: Background: Adjuvant postoperative breast radiotherapy improve local control and overall survival. Based on radiobiological and clinical data analysis, hypofractionated radiotherapy had comparable survival to conventional regimen radiotherapy. One of the major limitations of breast radiotherapy is cardiac toxicity that more significant in patients has left breast cancer. **Methods:** This retrospective study recruited 200 patients with left non-metastatic breast cancer. All patients underwent surgery followed by adjuvant 3D hypofractionated radiotherapy with different hypofractionation schedules with no cardiac or other comorbidity, Patients ≥ 18 years, were eligible. Patients with tumor size more than 1 cm or with lymph node involvement received adjuvant chemotherapy and those with positive estrogen and/ or progesterone receptors received hormonal therapy with either estrogen receptor modulator like tamoxifen or aromatase enzyme inhibitors like letrozole according to patient menopausal state and those with Her2neu Over-expression received trastuzumab. The cardiac toxicity was evaluated by measuring the left ventricular ejection fraction (LVEF) prior to treatment and repeated 3 years after radiation therapy or when indicated. **Results:** Median age was 55 years, 25% less than 50 years, T2 detected in 47.5% of patients, N1 in 40%, while positive hormonal receptors reported in 75%. Her2neu Over-expression reported in 20% and these patients received trastuzumab. At 94 months median follows up period, ten-year LRR-FS was 93.9%, DM-FS was 80.8%, and OAS was 88.9%. Grade I cardiac toxicity reported in 12 patients (6%), the univariate analysis of factors associated with significantly increased cardiac toxicity is only concurrent trastuzumab and none other factors were significant. **Conclusion:** The results of our study suggest that hypofractionation radiotherapy not associated with increased risk of cardiac toxicity in left-sided breast cancer patients and there is no difference between different hypofractionation radiotherapy protocol as regard cardiac toxicity with the comparable result as regard LRR, DM and survival. Trastuzumab increased cardiac toxicities during hypofractionated radiotherapy and this should study in large randomized trials with long-term follow-up to confirm these findings.

[Tamer M. Samy, Samia Abdelkareem, Marwa Abdelgawad, Shima Ahmed. **Cardiac toxicity of hypofractionated radiotherapy in left breast cancer.** *Cancer Biology* 2018;8(2):65-72]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). <http://www.cancerbio.net>. 8. doi:[10.7537/marscbj080218.08](https://doi.org/10.7537/marscbj080218.08).

Keywords: left sided Breast cancer, Hypofractionation radiotherapy, cardiac toxicity.

1: Introduction:

Breast cancer in women is the most life-threatening cancer, it remains leading cause of women death among less developed countries, however in developed countries, it the second cause of women cancer deaths after lung cancer, it is accounted for 29 % of all cancer in the United States [1]. Breast cancer in Egypt, it represents 32% of cancer deaths in women [2].

Breast-conserving therapy (BCT) is the standard treatment for early breast cancer as it had survival rates comparable to that of mastectomy [3], [4]. Radiation therapy established to be an important treatment strategy after mastectomy with axillary clearance significantly decreased the rate of locoregional recurrence. The absolute reduction in locoregional recurrence was greater in lymph node positive than in lymph node negative (17% versus 4%) [5]. Adjuvant radiation after breast conservative surgery is considered standard as it decreased locoregional recurrences by 70% [6] and women

deaths by 9-12% [5]–[7]. The total dose of 45 to 50 Gy (Gray) as adjuvant radiotherapy to the breast using conventional fractionation (1.8 to 2 Gy) [3] delivered in 5 weeks with additional 1-2 weeks in cases of treatment boost. Such long treatment schedule has the disadvantages of poor patient convenience and increasing the overload on radiation departments where treatment of many patients with such long radiation schedules will take more time and affect the radiation machine turnover and maintenance.

Hypofractionation is a strategy to decrease over all period of radiation therapy. This method involves higher fraction doses (above 2 Gy) as compared to conventional radiotherapy, the dose delivered in few numbers of fractions. Therefore, the total dose decreased. Based on radiobiological reasons, the α/β ratio value for breast cancer has been estimated at 4 Gy, whereas the α/β ratio value for soft tissues is approximately 3.5 Gy. Therefore, the sensitivity of breast cancer to radiotherapy is like that of healthy tissues responding. high fraction doses may be more

efficient in destroying tumour cells, however, that higher fraction doses may also increase the frequency and severity of late post-radiation reactions [8]. Prospective randomized clinical trials have shown promising results with hypofractionated schedules for WBI, [9]. In each of these studies, the goal was to deliver a hypofractionated dose schedule that is biologically equivalent to the standard radiation fractionation dose of 50 Gy in 25 fractions of 2 Gy. With 5-10 year follow up of these studies, there has been similar in-breast local control between the hypofractionated and standard fractionated arms.

It is well known since the first meta-analysis by Cuzick and colleague [10] that postoperative radiation therapy in breast cancer may have adverse effects on long-term survivors, an increased mortality was observed in long-term survivors based on Scandinavian studies and cancer registries, a higher rate of cardiac deaths could be identified as the cause for increased long-term mortality. This was significant only in patients with left-sided breast cancer. Therefore, the radiation exposure of the heart was suspected as the cause. Detailed studies primarily from Scandinavia were able to demonstrate a clear dose-response relationship.

This dose effect was already detected in the 2005 meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [5]. The analysis published in the New England Journal of Medicine confirms the facts known for years, which stated that Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease. The increase is proportional to the mean dose of heart, begins within a few years after exposure, and continues for at least 20 years. Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women [11]

The aim of our retrospective study is to evaluate the effect of large dose per fraction used in different hypofractionation regimen 40.05Gy/15, 39Gy/13 and 42.4Gy/16 on the cardiac toxicity of left-sided breast cancer patients and the secondary endpoint is to estimate the local control and 5 years overall survival of hypofractionated radiotherapy.

2: Patients and Methods:

This retrospective study recruited 200 patients with left non-metastatic breast cancer. treated in the Clinical oncology department, faculty of medicine and radiation oncology department of south Egypt cancer institute, Asyut University, Egypt between February 2005 and April 2015. All patients underwent surgery followed by adjuvant 3D hypofractionated radiotherapy with different hypofractionation

schedules with no cardiac or other comorbidity and not metastatic, Patients ≥ 18 years, were eligible. Patients with tumour size >1 cm or with lymph node involvement received adjuvant chemotherapy and those with positive estrogen and/ or progesterone receptors received hormonal therapy with either estrogen receptor modulator like tamoxifen or aromatase enzyme inhibitors like letrozole according to patient menopausal state and those with Her2neu Over-expression received trastuzumab.

Radiotherapy technique:

We used CT simulation for the localization and determination of the target volumes, the organ at risk, and the field arrangement. The CT scans done in the supine position, starting from the level of the larynx to the upper abdomen including both lungs with thickness 5 mm. delineation of all target volumes and organs at risk (OAR) to the planning system on all CT cuts, after mastectomy chest wall, mastectomy scar and +/- regional lymph node were included and after conservation surgery the whole breast, lumpectomy boost and +/- regional lymph node were included, IMLNS were included in tangential beam when indicated.

The heart and ipsilateral lung considered OARs (organs at risk). The heart was contoured from the pulmonary trunks superiorly to its base and included the pericardium. The major blood vessels were excluded. The ipsilateral lung was contoured in all its extension. Treatment plans for the whole breast were generated using two opposed tangential beams. Beam weighting, gantry angles, wedges, and beam energies were determined to achieve optimal dose conformity and homogeneous dose distribution as well as maximal avoidance of the heart and ipsilateral lung, the volume of the heart that received at least 40 Gy not allowed to exceed 30 %.

Assessment and Follow up:

According to patient's files, patients evaluated clinically before and during treatment then every 3 months in the first 2years then every 6months for 3 years then annually. regarding cardiac toxicity, The cardiac toxicity was evaluated by measuring the left ventricular ejection fraction (LVEF) prior to treatment and repeated 3 years after radiation therapy or when indicated, a fall of more than 10% in ejection fraction is considered as a significant reduction in LVEF as proposed by the Cardiac Review and Evaluation Committee[12].

Statistical analysis:

Statistical analysis of data was done by the statistical package for the social science (SPSS) version 20. Descriptive statistics were used as median, mean, number and percentage. Kaplan-Meier test [13] used for survival analysis and Log-rank test was used to evaluate the significant differences between

variables. Chi-square test was used to evaluate the relationship between variables and treatment response. P value was double sided and considered significant if was ≤ 0.05 .

3: Results

Patient's characteristics were listed in Table 1, Median age was 55 years, 25% < 50 years old, 47.5% had T2, 40% N1, 94% G2, 75% had positive hormonal receptors, 20% had her2neu overexpression.

Table 1: patients characteristics

Variable	No.	%
1.Age		
<50 years	50	25%
≥ 50 years	150	75%
Median	55	
2.Tumour grade		
Grade 1	1	0.5%
Grade 2	188	94%
Grade 3	11	5.5%
3.Tumour histopathology		
IDC	190	95%
ILC	10	5%
4.T stage:		
T1	25	12.5%
T2	95	47.5%
T3	50	25%
T4	30	15%
5.Node stage:		
N0	20	10%
N1	80	40%
N2	60	30%
N3	40	20%
6.Hormonal receptors:		
Positive	150	75%
Negative	50	25%
7.Her 2 new		
Negative	160	80%
Positive	40	20%

Treatment characteristics listed in Table 2, 75% underwent MRM. Regarding chemotherapy, 50% received AC-Taxol and (4%) not received chemotherapy at all. Regarding radiotherapy 59.5% received 4240cGy/16 fraction and 29.5% received 3900cGy/13 fraction and 11% received 4005cGy/15 fraction. Regarding Hormonal therapy, 50% received aromatase inhibitors and regarding target therapy 20% received trastuzumab.

In our study, the median follows up period was 94 months ranged from 45 to 158 months and the 10-year LRR free survival was 93.9% as shown in figure (1). the 10-year distant metastasis-free survival was

80.8% as shown in figure (2). and the 10 years overall survival was 88.9% as in figure (3) Univariate analysis of the factors which may affect the 10 years LRR free survival, 10 years DM free survival and 10 years overall survival were the age, T stage, N stage, hormonal receptor status and radiotherapy doses showed that T stage, N stage and hormonal status had significant effect on the patients LRR free survival, DM free survival and overall survival as shown in tables (3-4-5) respectively.

Table 2: treatment characteristics

Variable	No.	%
1.Surgery:		
MRM	150	75%
BCS	50	25%
2.Chemotherapy:		
No	8	4%
FAC	42	21%
FEC	40	20%
AC-Taxol	100	50%
CMF	10	5%
3.Radiotherapy		
4240c Gy/16	119	59.5%
3900 cGy/13	59	29.5%
4005 cGy/15	22	11%
4.Hormonal therapy		
TAM	15	7.5%
AI	100	50%
Switched TAM to AI	35	17.5%
No	50	25%

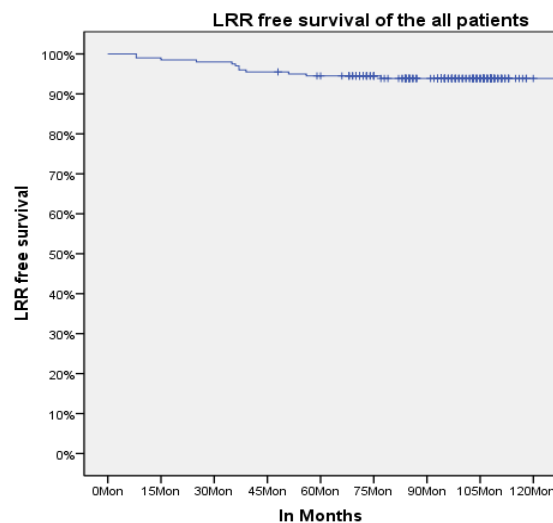


figure 1: LRR free survival of all patient

Table 3: Univariate analysis of 10 years LRR free survival

Variable		10 year LRR FS %	P value
Age	<50 yrs (50)	92%	0.497
	≥50 yrs (150)	94.5%	
T stage	T1 (25)	96%	<0.001
	T2 (95)	98.5%	
	T3(50)	94%	
	T4(30)	76.7%	
Nodal stage	N0 (20)	100	0.001
	N1 (80)	98.3%	
	N2(60)	95%	
	N3(40)	80%	
Hormonal status	+ve (150)	97.3%	0.001
	-ve (50)	83.7%	
Radiotherapy doses	4240/16 (119)	93.3%	0.563
	3900/13 (59)	96.6%	
	4005/15 (22)	89.8%	

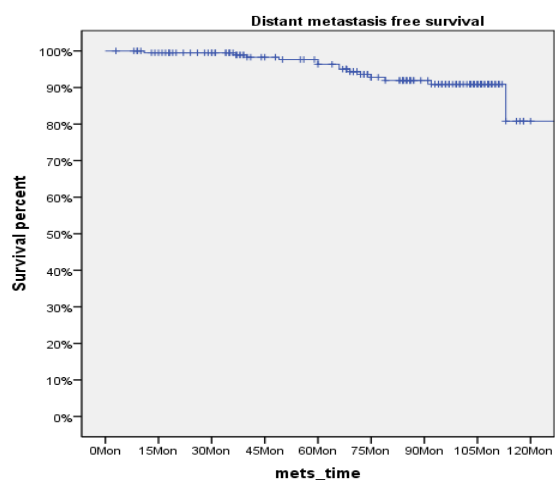


figure 2: DM free survival

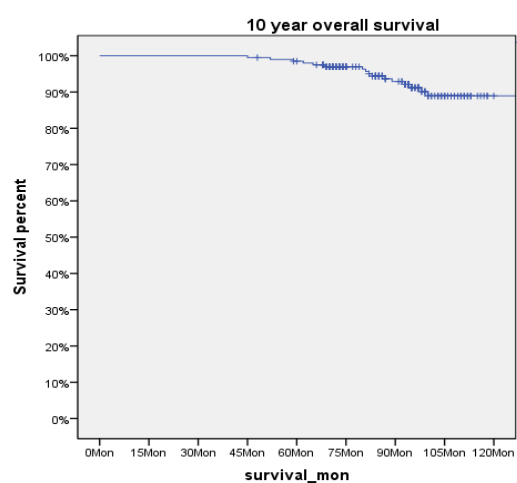


figure 3: overall survival.

Table 4: Univariate analysis of the 10 years Distant metastasis-free survival

Variable		10-year DM FS %	P value
Age	<50 yrs (50)	89.7%	0.979
	≥50 yrs (150)	76.3%	
T stage	T1 (25)	100	<0.001
	T2 (95)	96.5%	
	T3(50)	88.1%	
	T4(30)	72.3%	
Nodal stage	N0 (20)	91.7%	0.002
	N1 (80)	95.8%	
	N2(60)	93.4%	
	N3(40)	72.5%	
Hormonal status	+ve (150)	96%	<0.001
	-ve (50)	75.3%	
Radiotherapy doses	4240/16 (119)	90.8%	0.866
	300/13 (59)	90.4%	
	4005/15 (22)	87.1%	

Table 5: Univariate analysis of the 10 years OS:

Variable		10-year OS %	P value
Age	<50 yrs (50)	83.9%	0.444
	≥50 yrs (150)	91.2%	
T stage	T1 (25)	95.8%	<0.001
	T2 (95)	95.6%	
	T3(50)	89.7%	
	T4(30)	64.6%	
Nodal stage	N0 (20)	94.7%	0.002
	N1 (80)	96.4%	
	N2(60)	88.1%	
	N3(40)	72.7%	
Hormonal status	+ve (150)	94.2%	0.001
	-ve (50)	75.6%	
Radiotherapy doses	4240/16 (119)	89.2%	0.977
	3900/13 (59)	90%	
	4005/15 (22)	89.4%	

Cardiac Toxicity:

Twelve patients (6%) had grade I ejection fraction affection (>10%) patient receiving concurrent trastuzumab was the only significant prognostic factors that affecting cardiac toxicity based on univariate analysis of factors and there are no other significant factors (Table 6).

4: Discussion:

Based on radiobiological models, breast cancer had α/β ratio closer to that of late-reacting tissues range between 3 and 4 Gy, This may suggest a therapeutic benefit from accelerated schedules using a larger dose/fraction, the adjuvant hypofractionated radiation of breast cancer offer equivalent local control

to standard conventional radiation therapy by giving larger doses per fraction in a shorter period of time[14]. There are many potential benefits from hypofractionated radiotherapy as it is more convenient for patients, decreased the treatment cost and increase utilization of existing radiotherapy resource. many retrospective studies of hypofractionated RT showed satisfactory outcomes as regard tumour control and late adverse events[15]. In our current study, we evaluate the effect of large dose perfraction used in different hypofractionation regimen 40.05Gy/15, 39Gy/13 or 42.4Gy/16 on the cardiac toxicity of left-sided breast cancer patients and the secondary endpoint is to estimate the local control and 5 years overall survival of hypofractionation radiotherapy.

Table 6: Univariate analysis of factors affecting cardiac toxicity

Variable		G1 toxicity No (%)	P value
Age	<50 yrs (50)	4 (8)	0.492
	≥50 yrs (150)	8(5.3)	
Hormonal therapy	TAM (15)	2 (13.3)	0.229
	AI (100)	4 (4)	
	Switched (35)	4 (11.4)	
	No (50)	2 (4)	
Nodal stage	N0 (20)	0 (0)	<0.169
	N1 (80)	3 (3.75)	
	N2(60)	4 (6.6)	
	N3(40)	5 (12.5)	
Her 2 new Over-expression	+ve (160)	4 (2.5)	<0.001
	-ve (40)	8 (20)	
Radiotherapy doses	4240/16 (119)	4 (3.3)	0.112
	3900/13 (59)	5 (8.4)	
	4005/15 (22)	3 (13.6)	
Surgery	MRM (150)	9 (6)	0.651
	BCS (5)	3 (6)	
Chemotherapy	No (8)	0 (0)	0.885
	FAC (42)	2 (4.8)	
	FEC (40)	2 (5)	
	AC -T (100)	7 (7)	
	CMF (10)	1 (10)	

The median age of our patients was 55 years with age ranged from 25 to 76 years and 75% of patients were ≥ 50 years of age. This is comparable to that reported in START trial A and B where median age 57 years and patient ≥ 50 years old was 77% in START A and 79% in START B trial [9], [16].

In our study, a median follow-up period was 94 months ranged from 45 to 158 months. The 10-year LRR free survival was 93.9%. This is comparable to the result of Canadian trial by Whelan et al [17], which showed 10-year local recurrence of 6.7% among 612 women assigned to standard irradiation and 6.2% among the 622 women assigned to hypofractionation schedule. Similar results ($> 90\%$ 10-year LRR free survival) were reported by the START trialists group [9], [16]. According to the prognostic factors that might affect the LRR free survival, it was found that tumor stage, N stage and hormonal receptor state significantly affect the survival rates (P -value < 0.05). This could be confirmed by Rosen et al [18], who reported that there was a significant association between tumor size and 20-year locoregional recurrence-free survival and by NSABP trial by Fisher et al [19] who reported that there is a relation between the number of positive axillary nodes and the risk of recurrence and lastly our result confirmed by NSABP-06 trial by Fisher et al [20] who reported that hormonal receptors positive tumors had a significant effect on locoregional free survival.

In our study, the 10-year DM free survival was 80.8%. This is comparable to the result of START trialists group [9], [16] the 10-year DM

free survival was 82% and 84% in START A and B respectively.

According to the prognostic factors that might affect the DM free survival, it was found that tumor stage, N stage and hormonal receptor state significantly affect the survival rates (P value < 0.05). This could be confirmed by Carter et al. who reported that there was a significant association between tumor size and distant recurrence rate as distant recurrence rates increasing with larger tumor size [21], also Saez et al [22] who reported that there is a direct significant relationship between the number of involved axillary nodes and the risk for distant recurrence and lastly our result confirmed by NSABP-06 trial by Fisher et al [20] who reported that hormonal receptors positive tumors had a significant effect on distant recurrence rate.

In our study, the 10-year overall survival was 88.9%. This is comparable to the result of START B trial [9], [16] the 10-year overall survival was 84.1%.

According to the prognostic factors that might affect the overall survival, it was found that tumor

stage, N stage and hormonal receptor state significantly affect the survival rates (P -value < 0.05). This could be confirmed by Carter et al [21], NSABP trial by Fisher et al [19] and NSABP-06 trial by Fisher et al [20].

We evaluated the cardiac toxicity in our patients by measuring the LVEF using Echocardiography 3 years after radiotherapy and a fall of more than 10% in ejection fraction is considered as a significant reduction in LVEF as proposed by the Cardiac Review and Evaluation Committee.

We reported that 12 patients (6%) developed asymptomatic drop in the LVEF of more than 10% below the baseline. Univariate analysis of the factors that affect cardiac toxicity, only trastuzumab receiving is associated with increased risk of cardiac toxicity, 2.5% in patients not receiving Trastuzumab versus 20% in patients receiving Trastuzumab which is similar to Cao L et al, [23] where Grade 1 LVEF dysfunction (an asymptomatic decline in LVEF of at least 10% but less than 20% from baseline) occurred in 4.1% of left-sided patients who did not receive trastuzumab versus 7.8% in patients receiving trastuzumab [23]. In our result there is no difference in cardiac toxicity between various protocols of hypofractionated radiotherapy which is similar to Shahid et al [24] reported that cardiac toxicity occurred in 5%, 6% and 5% in patients of various hypofractionated schedules.

Conclusion:

The results of our study suggest that hypofractionation radiotherapy is not associated with increased risk of cardiac toxicity in left-sided breast cancer patients and there is no difference between different hypofractionation radiotherapy protocols as regard cardiac toxicity with comparable results as regard LRR, DM and survival. Trastuzumab increased cardiac toxicities during hypofractionated radiotherapy and this should be studied in large randomized trials with long-term follow-up to confirm these findings.

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