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Factors Affecting Heart and Anterior Descending Coronary Artery Radiation Dose during Left Breast Irradiation (Dosimetric Retrospective Study)

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Abstract

Background: Breast cancer is the commonest cancer in females. Radiotherapy is one of the important factors in treatment of breast cancer. Heart and coronary artery are radio-biologically serial organs. Radiation toxicity in the treatment of breast cancer showed significant clinical problem and increased cardiac morbidity and mortality.
Aim of the Work: Assessing Factors affecting heart and anterior descending coronary artery dose during left breast irradiation in 3D technique.
Patients and Methods: This study included 69 patients with left breast cancer received radiotherapy to the chest wall or breast tissue at Clinical Oncology Department, Al-Hussein University hospital.
Results: heart size and Maximum heart distance included in tangential fled had a relation between mean of heart and ADCA. Heart size rang (442.4 -898.9) with mean 623±104 cm3 we found when heart size increase the mean dose to heart and ADCA decrease with significant p value 0.017 and 0.016 respectively. Maximum heart distance that when if it was ≤3cm, the mean of the ADCA was 18.5±10.9 Gy while when if it was >3cm, the mean of the ADCA was 27.9±9.1 Gy with a p-value 0.030 which is statistically significant.
Conclusion: Maximum heart distance included in tangential field and Heart size were only Factors can Affect mean of Heart and ADCA Radiation Dose During Left Breast Irradiation while BSA, WT, BMI, HT, RTH dose, number of fractions, number of segments, para sternal tissue thickness, Breast Size, Shortest distance between heart and ANT chest wall, Site, Extent, Type surgery, Boost, Bolus and stage were insignificant.

Keywords: *Factors; Heart; Coronary; Breast; Irradiation.*

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INTRODUCTION

Breast cancer is the most common malignant disease in women around the world accounting 25.1% of all cancer in Egypt 32% of female cancer.[1]

The use of adjuvant radiation therapy (ART) as per guidelines has contributed to significant improvements in disease free survival and overall survival for patients with early stage breast cancer, and even in selected patients with ductal carcinoma in situe.[2,3]

Breast surgery followed by postoperative radiotherapy is the current standard therapy for early operable breast cancer, almost in all patients after breast-conserving surgery (BCS) and most patients after modified radical mastectomy (MRM), Typically radiotherapy is administrated after finishing the adjuvant chemotherapy in these patients to reduce the risk of distant metastasis, while concurrent administration of chemotherapy and radiotherapy have been recently suggested.[4]

WBRT is associated with acute toxicities that involve the area treated (e.g., skin, muscle, and internal organs), although these complications are relatively uncommon. WBRT can also result in long-term complications, including cardio toxicity, lung injury and second malignancies, which can occur many years after treatment. However, improvements in radiation techniques over time have likely reduced the incidence of these long-term toxicities.[5]

In a recent meta-analysis included 39 studies (1.2 million breast cancer patients), adjuvant radiotherapy found to increase the risk of coronary artery disease (relative risk [RR] 1.3, 95% CI 1.13-1.49) and cardiac death (RR 1.38, 95% CI 1.18-1.62). However, the absolute risk increase for coronary artery disease and cardiac death was relatively low (76 and 126 cases, respectively, per 100,000 person-years). For coronary artery disease, the risk increased within the first decade, and for cardiac mortality, it increased in the second decade.[6]

Tangential left breast/chest wall fields likely irradiate ALAD artery, two clinical studies had showed a correlation between the site of coronary stenosis and irradiated coronary arteries after left breast irradiation, when compared with patients received right breast radiotherapy and patients who didn't receive any adjuvant radiotherapy.[7,8]

Many factors may affect the radiotherapy dose received by heart and coronary artery, some of them are related to the patient and other to the disease itself or radiotherapy technique, in this dosimetric study, we will investigate the factors that may affect doses received by the heart and LADCA with left breast irradiation.

This study is conducted to assess factors affecting heart and anterior descending coronary artery dose during adjuvant left breast irradiation with 3D technique.

PATIENTS AND METHODS

This dosimetric retrospective study included 69 patients with left breast cancer received adjuvant radiotherapy to the chest wall or whole breast from Jan 2017 to Jan 2019 and finished at Jun 2019, at the Clinical Oncology Department, Al-Hussein University Hospital. All patient included in this trial meet the following inclusion criteria; histopathologically proven breast cancer, stage I-IIIB, underwent surgery and has an indication for adjuvant radiotherapy.

Charts of included patients have been retrieved from the archive to collect the following patients and disease related data; Age, sex, weigh, high, quadrant of the mass, clinical extent of the disease, type of breast surgery, histopathology details (stage, capsular invasion..), chemotherapy (if received) and radiotherapy (Dose/fractions, boost and use of bolus,..)

CT simulation of the included patients have been retrieved from the planning system (Eclipse planning system version15.6), then target volumes and organs at risk (including ADCA) had been delineated once again by single radiotherapy physician (according to RTOG breast atlas delineation guidelines),[9] while ADCA was delineated according the guidelines published by Duane et al,[10] and radiotherapy plan has been reinitiated by single physicistwith same radiotherapy technique for all patients (according to the primary treating doctor prescription).

After plan approval for target volumes coverage and organs at risk constrains the dose to the heart and anterior descending coronary artery have be recorded along with the following data; breast size, heart volume, Shortest distance between heart and anterior chest wall, Maximum heart distance included inside the tangential fields, Number of segmental fields used in each plan.

STATISTICAL METHODS

Data were coded and entered using the statistical package SPSS version 23. Data was summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Survival interval conspired as time between the date of histological diagnosis and the date of the last follow-up (for censored observations) or the date of death (for uncensored observations), while progression free interval was considered as time between date of the first treatment and the date of the last follow-up (for censored observations) or; date of death or disease progression whichever happen first (for uncensored observations).One-sided log-rank of Kaplan—Meier survival estimates was used for statistical analysis of overall survival and progression free survival, while the unpaired T test and one-way ANOVA test were used in the univariate analysis of the variables. Results of P-value less than 0.05 were considered statistically significant.

ETHICAL APPROVAL

The current investigation had been approved by the ethical committee, Faculty of Medicine, Al-Azhar University, Cairo, Egypt, before the start of this study.

RESULTS

This study included 69 patients with median age 49 years (ranges: 28 -71); most of them were postmenopausal (58%). patients subjected to CBS about 24 pts (34.8%) while who subjected to MRM were 45pts (65.2%) While patients that received Chemotherapy 65 pts (94.2%) while who not received chemotherapy were 4 pts (5.8 %). All patients received the same dose 40Gy /15f), some of them received RTH with boost (34.8 %) and another received RTH with bolus to Chest wall to increase the skin dose with boulse (14.1%). (Table 1) (Figures 1-3)

	Mean	SD	Median	Minimum	Maximum
Age	49.2	10.1	49	28	71

Table 1: age statistics

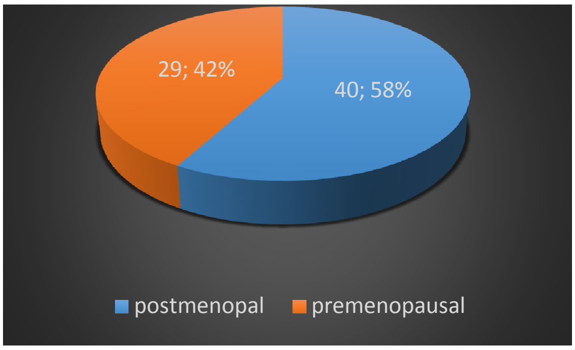

Fig. 1: Menopausal state (40.58% premenopausal, 29.4% postmenopausal)

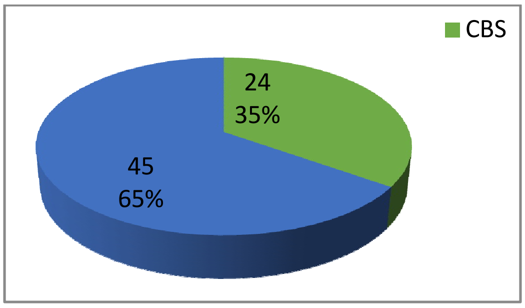

Fig. 2: Type of surgery (35%CBS, 65%MRM)

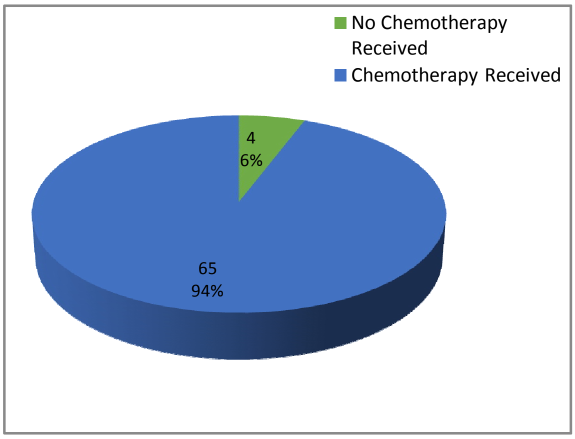

Fig. 3: Received chemotherapy (94% received chemotherapy, 6% not received chemotherapy)

TNM staging explained in (Table 2).

T1	**13**	**18.80%**
T2	**39**	**56.50%**
T3	**9**	**13.00%**
T4	**7**	**10.10%**
TX	**1**	**1.40%**
N0	**16**	**23.20%**
N1	**29**	**42.00%**
N2	**14**	**20.30%**
N3	**10**	**14.50%**
M0	**69**	**100%**

Table 2: TNM stage

Capsular invasion of LNs presented in 28 of pts while 41 pts were with no capsular invasion. (Figure 4)

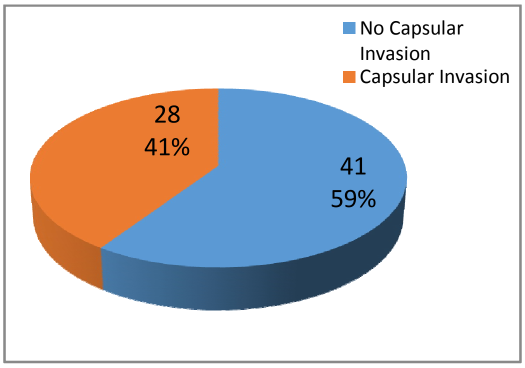

Fig. 4: Capsular invasion (59% with capsular invasion, 41%wihout capsular invasion)

The median BMI of the patients were 33.3 (range; 23.1 to 51), median of breast size was 1044 cm3 (range: 512–1787), the heart size median was 608 cm3 (range: 442 - 899), Para sternal tissue thickness median was 3 cm (range1.95 – 5), the median shortest distance between heart and ant. Chest wall was 0.3cm (range: 0.1-2), while maximum heart distance median was 1.9 cm (range: 0 - 3.3). (Table 3)

	Mean	SD	Median	Minimum	Maximum
WT	85.9	19.5	89	63	115
HT	161	9	160	145	185
BMI	34.25	5.87	33.3	23.1	51
No. of segments	4	2	3	0	8
BSA	1.8	-	1.8	1.6	2
Breast Size	1078.7	349.7	1044	511.9	1787
Heart Size	623	104.8	608	442.4	898.9
para sternal tissue thickness	3	0.63	3	1.95	5
Shortest distance between heart and ANT chest wall	0.37	0.3	0.3	0.1	2
max heart distance	1.76	0.74	1.9	0	3.3
Breast Size	1078.7	349.7	1044	511.9	1787

Table 3: Factors affecting to heart and ADCA

The maximum heart distance included in tangential filed and heart size were the only factors that affect significantly both mean heart dose and mean ADCA dose, while capsular invasion was having significant effect on mean heart dose only, on other hand none of other studied factor(Age, BSA, WT, BMI, HT, RTH dose, Number of fractions, para sternal tissue thickness, Breast Size, Shortest distance between heart and ANT chest wall, Site, Extent, Type surgery, Boost, Bolus and stage) showed significant influence on the mean heart dose and ADCA mean dose. (Table 4)

	Pearson Correlation	p value	Pearson Correlation	p value
	Heart Dose Mean		ADCA mean %	
Age	-0.092	0.453	-0.172	0.158
BSA	-0.08	0.657	-0.193	0.281
WT	0.282	0.112	0.211	0.238
BMI	0.158	0.381	-0.043	0.813
HT	0.159	0.378	0.199	0.268
RTH dose	0.131	0.285	-0.034	0.779
Number of fraction	0.145	0.234	-0.027	0.826
Number of segments	0.066	0.588	0.203	0.095
para sternal tissue thickness	0.089	0.465	-0.161	0.187
Breast Size	0.025	0.839	-0.162	0.183
Heart Size	0.286	0.017	0.289	0.016
Shortest distance between heart and ANT chest wall	0.09	0.461	-0.027	0.828
Max Heart Distance	0.713	<0.001	0.732	<0.001

Table 4: Factors affecting to mean of heart and ADCA

We studied the factors can affect V100 (volume that received 100% of radiation dose) and V90 of the heart (volume that received 90% of radiation dose).

The maximum heart distance included in tangential filed was the only factor that affected significantly both heart V100 % and V90 %,while heart size was having significant effect on heart V100 % only, on other hand none of other studied factor (age, BSA, WT, BMI, HT, RTH dose, number of fractions, para sternal tissue thickness, breast size, shortest distance between heart and ANT chest wall, site, extent, type surgery, boost, bolus and stage) showed significant influence on the Heart V100 % and V90 %. (Table 5)

	Pearson Correlation	p value	Pearson Correlation	p value
			heart V90%	
Age	-0.053	0.664	-0.198	0.104
BSA	-0.082	0.649	0	0.998
WT	0.165	0.358	0.086	0.633
BMI	-0.052	0.773	-0.102	0.571
HT	0.244	0.171	0.267	0.133
RTH dose	0.008	0.951	0.108	0.377
Number of fraction	0.017	0.888	0.122	0.317
Number of segments	-0.042	0.732	0.06	0.624
Para Sternal Tissue Thickness	0.026	0.834	-0.079	0.516
Breast Size	0.042	0.732	-0.019	0.874
Heart Size	0.245	0.042	0.206	0.090
Shortest Distance Between Heart and ANT Chest Wall	-0.104	0.393	-0.141	0.249
Max Heart Distance	0.342	0.004	0.681	<0.001
Stage	T1T2N0 (n=16)	.449		0.848
	T3T4/ T1T2N+ (n=53)			

Table 5: Factors affecting to V100 and V90 of heart

We studied the factors can affect V100 (volume that received 100% of radiation dose) and V90 of ADCA (volume that received 90% of radiation dose).

The maximum heart distance included in tangential filed and heart dose mean % were the only factor that affect significantly both ADCA V100 % and ADCA V90%,while heart size was having significant effect on ADCA V90% only, on other hand none of other studied factor (age, BSA, WT, BMI, HT, RTH dose, number of fractions, para sternal tissue thickness, breast size, shortest distance between heart and ANT chest wall, site, extent, type surgery, boost, bolus and stage) showed significant influence on the ADCA V100 % and ADCA V90 %. (Table 6)

We had studied Maximum heart distance in relation with ADCA dose mean and we found the significant effect started at >3cm.

The effect of Maximum heart distance was studied showing that when it was ≤3cm, the mean dose of the ADCA was 18.5±10.9 Gy while if it was >3cm, the mean dose of the ADCA was 27.9±9.1 Gy with a p-value 0.030 which is statistically significant. (Table 7)

The effect of Maximum heart distance was studied showing that when it was ≤ 2cm, the mean dose of the ADCA was 17.4±11.1 Gy while it was > 2cm, the mean dose of the ADCA was 25.7±10.1 Gy with a p-value 0.074 which is statistically non-significant. (Table 8)

	Pearson Correlation	p value	Pearson Correlation	p value
	ADCA V100 %		ADCA V90 %	
Age	-0.098	0.422	-0.151	0.217
BSA	-0.086	0.634	-0.259	0.146
WT	0.063	0.727	0.247	0.165
BMI	-0.156	0.386	-0.046	0.799
HT	0.215	0.228	0.187	0.298
RTH dose	-0.016	0.894	0.026	0.831
Num. of fraction	-0.016	0.899	0.032	0.793
Heart dose mean%	0.405	0.001	0.736	<0.001
Num. of segments	-0.078	0.525	-0.016	0.894
Para Sternal Tissue Thickness	-0.227	0.061	-0.163	0.18
Breast Size	-0.087	0.479	-0.081	0.511
Heart Size	0.198	0.102	0.24	0.047
Shortest Distance Between Heart and ANT Chest Wall	-0.196	0.107	-0.162	0.183
Max Heart Distance	0.258	0.032	0.633	<0.001
Stage	T1T2N0 (n=16)	0.809		0.887
	T3T4/ T1T2N+ (n=53)			

Table 6: Factors affecting to V100 and V90 of ADCA

Maximum heart distance	Lt ADCA Dmean (mean±SD)	p-value
≤3cm	18.5±10.9 Gy	0.030
>3cm	27.9±9.1 Gy	

Table 7: Maximum heart distance at 3cm effect on coronary artery D_{mean}

Maximum heart distance	Lt ADCA Dmean (mean±SD)	p-value
≤ 2cm	17.4±11.1 Gy	0.074
> 2cm	25.7±10.1 Gy	

Table 8: Maximum heart distance at 2cm effect on coronary artery D_{mean}

DISCUSSION

Data obtained from patients files including clinico-epidemiological and treatment, 48 patients (69.6%) were above 50 and 21 were below 50 years (30.4%) in which median age was 49 years slightly higher than other national studies done at the National cancer institute (NCI), the median age was 46 years.[13]

Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease, this increase is proportional to the mean dose to the 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.[7] After breast radiotherapy, the early focus has been on ischemic cardiac disease, and since the LAD is the closest major coronary vessel to tangential breast fields, it stands to reason that it may be most often affected.

Because LADA delineation is not a routine work in breast irradiation, a single radiation oncologist had delineated all cases using the guidelines provided by University of Michigan Medical Center that published detailed cardiac atlas consisting of images, with and without intravenous contrast, and written instructions describing the anatomy.[11] And there cently published detailed cardiac atlas for heart & its chambers delineation by a UK group.[10]

The CTV volume of the breast is different vary among patients with early stage who having T1-2 N0 breast cancer and has conservative breast cancer received radiotherapy on the breast tissue without inclusion of the chest wall in the CTV volume, although that our study did not show a significant difference between this group of patients and the other remaining patients (who had chest wall included in the CTV volume) in term of mean dose to the heart and ADCA.

Because the obesity among our Egyptian population is of high rate, We have investigated the relation between body mass index (BMI) and breast size on one side; and the received dose by the heart and LADA one the other side; BMI ranged from (23 to 51) in this study, with 62 patients (90%) has BMI above 30 while 7 patients (10%) has BMI below 30, which is higher than the reported results by WHO on 2008, that showing that the percentage of Egyptian females suffering obesity (BMI ≥30) was 39.5% while the percentage of Egyptian females who had BMI <30 was 58.5this difference may return to the patient selection criteria in our study.

Although this very high rate of obese patients in this study, no significant statically correlation was found between either BMI or breast size and mean dose to the heart or ADCA.

There is no consensus on the dose tolerance of the heart and ADCA in literatures, the QUANTEC has summarized that, mean dose (D_{mean}) of the heart is of good value as long as it is <26 Gy[12], While the ongoing NSABP B-51 trial set the heart D_{mean} at <4 Gy, The D_{mean} of the heart in our study was 5Gy ± 5.1% (2.4Gy) with median value 2.3% (1.1 Gy).

Regarding relation between heart size and mean of heart and ADCA. Heart size rang (442.4 -898.9) with mean 623±104 cm3 we found when heart size increase the mean dose to heart and ADCA decrease with significant p value 0.017 and 0.016 respectively. Regarding v100 and v90 of heart and factor that may affect the percentage of them and the only factor that affect significant is max heart distance included in tangential fled.

While the mean value of the LAD coronary artery D_{mean} was 56.1% (25 Gy) ± 19.7% (8.5 Gy) with a median value 59.6% (25.0 Gy) with range (9.6% 4G-90%39.5G) could be explained by several factors (hear size, para sternal tissue thickness, Breast Size, Shortest distance between heart and ANT chest wall, Site, Extent, Type surgery, Boost, Bolus, maximum heart distance, capsular invasion).

Which is higher the dose suggested by Clinical Trial Service Unit, Oxford, United Kingdom which suggested that the average mean dose to the Left-sided 3D conformal irradiated patients was 7.6 Gy& also higher than the dose (18.6 Gy) suggested by department of clinical oncology, Leiden University Medical Center in The Netherlands.[14]

The effect of Maximum heart distance was studied showing that when if it was ≤ 3cm, the mean of the Lt ADCA D_{mean} was 18.5±10.9 Gy while when if it was > 3cm, the mean of the Lt ADCA D_{mean} was 27.9±9.1 Gy with a *p*-value 0.030 which is statistically significant. Note that the mean MHD in our study was 2.9 which is higher than the mean value suggested by Clinical Trial Service Unit, Oxford, United Kingdom which was 0.59 cm.[15]

The effect of body mass index was studied showing that statistically non-significant to mean heart dose with p value 0.381 or mean ADCA with p value 0.813.

Putting in consideration that increased body weight has been associated with an increased risk of morbidity and mortality from coronary heart disease (CHD) in several populations. Individuals with increased BMI have greater prevalence, extent, and severity of CAD. Also, WHO Global Database on Body Mass Index on 2009 showed that the BMI was ≥ 30 in 39.5% of the whole Egyptian.[16]

So our study pays attention to the importance of caring about delineation of ADCA & calculating the dose received by ADCA in obese patients with BMI ≥ 30, small heart volume and if max heart distance is less than 3 cm.

IMRT results in a significant additional decrease of dose in the heart and LAD-region in both breath-hold and free-breathing.[17]

CONCLUSION

Maximum heart distance included in tangential field and heart size were the only obvious factors that affected the heart and ADCA radiation dose during left breast irradiation while BMI, HT, number of fractions, number of segments, para sternal tissue thickness, breast size, shortest distance between heart and ANT chest wall, site, extent, type surgery, boost, bolus and stage were insignificant.

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