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RESEARCH ARTICLE

CORONARY ARTERIES EXPOSURE IN LEFT SIDED BREAST CANCER RADIOTHERAPY : DOSIMETRIC STUDY

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Abstract

Purpose :The cardiac toxicities are especially important in left-sided breast cancer radiotherapy(RT) compared to the right-sided cancers. Our study aims to perform a dosimetric analysis to evaluate the effect of RT on coronary arteries and heart in breast-conserving surgery.

Methods : Through a dosimetric study we randomly selected a total of 36 patients with early stage right and left-sided breast carcinomas (T1/T2 +N0) .All patients underwent breast-conserving surgery .Whole Breast Adjuvant Radiotherapy was delivered with tumor beds boost using 3D conformal radiotherapy (3D-CRT) and computed tomography based planning .The doses for coronary arteries and heart were recorded and median values compared between groups.

Results :The highest mean of radiation dose in patients with left-sided breast cancer was to LAD 2402.48 ± 838.39 cGy, while the highest mean dose in right-sided breast cancer patients was to RV 130.18 ± 24.92 . The highest maximum dose of radiotherapy was applied to heart at left-sided breast cancer patients as well as at right-sided patients. The mean V5 of the LV was 18.68% (6.89–31.69), mean V25 of the LV was 5.22% (0.45–16.54), mean V5 in bilateral ventricles was 23.73% (2.56–26.89), and mean V25 in bilateral ventricles 6.78% (0.63–13.63).

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Introduction:-

Breast cancer is the most common cancer among women. About 1.2 million women are newly diagnosed with breast cancer each year in the world .The breast cancer remains the primary cause of cancer mortality in women after lung cancer according to global cancer statistics 2020 [1]. 12 percent of all women will be given a diagnosis of breast cancer and 3.5 percent will die of the disease. The impact of breast cancer is magnified because women are at risk from their middle to later years [2], also the incidence increased dramatically so it became a major public health problem of great interest and importance to physicians in a variety of specialties. The main methods for earlier detection of breast cancer have been mammography and physical examination performed by a trained health professional.

The established risk factors for breast cancer — a family history of breast cancer, early menarche, late age at first childbirth, late age at menopause, history of benign breast disease, and exposure to ionizing radiation — are

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generally associated with only weak or moderate elevations in risk. The exceptions occur in uncommon subgroups of these variables; for example, a family history of breast cancer at a young age or a family history of bilateral disease[3-4].

Adjuvant breast irradiation after breast-conserving surgery leads to similar oncological outcomes as mastectomy (radical mastectomy, modified radical mastectomy, or total mastectomy) in patients with early breast cancer and improves survival in comparison to breast-conserving surgery alone (wide excision, quadrantectomy, or lumpectomy)[5-6]. Adjuvant RT, especially for left-sided breast cancer was associated with cardiotoxicity and cardiovascular mortality when compared to patients treated with surgery alone[7] in particular, the left anterior descending coronary artery (LAD) receives significant radiation, being in or near the target volume[8-9].

Patients and Methods:-

Patients

This is a dosimetric study, that included 38 patients with early stage right and left-sided breast cancer (T1/T2 + N0, according to 8th edition of American Joint Committee on Cancer staging, 2017) from December 2018 to February 2021 for this dosimetric study. They had undergone breast conserving surgery. RT was delivered to the whole breast, and tumor beds were boosted using 3D-CRT with tangential fields and computed tomography (CT) based planning. Patient's age, tumor localization, stage, chemotherapy protocol and number, Radiotherapy dose and doses for coronary arteries: LAD, LCx, RV, LV and heart were recorded and summarized below [Table 1]. All patients agreed to the conditions of this study. We based on handbook and quantec to dose limits for critical organs. Handbook recommendations for breast RT is as follows: LV and combined bilateral ventricle limits: $V5 \leq 10\%$ and $V25 \leq 5\%$. Contralateral breast $D_{max} \leq 3\%$, ipsilateral lung $V30 < 15\%$, contralateral lung $V5 < 15\%$, heart $V5 < 5\%$ for R-sided tumors, and $< 40\%$ for L-sided tumors.

Treatment and Planning

All patients included in this study underwent RT for right and left-sided breast cancers at the Cheikh Khalifa International Hospital in the Radiation Oncology Department. They had undergone breast-conserving surgery followed by Adjuvant Radiotherapy. Contrast-enhanced CT scans were obtained in 3mm slices as a part of radiation planning. During simulation, each patient was immobilized, with the ipsilateral arm above her head. Radiopaque catheters were placed to delineate the breast areas and incision scar on the CT scan. Each patient's CT data was transferred to an in-house 3-dimensional treatment planning system (TPS). The Clinical Target Volumes (CTVs) were contoured by radiation oncologist. The breast CTV included the whole breast with 5mm retraction from the skin surface. The planning Target Volume (PTV) comprised the CTV with a 7mm circumferential margin to allow for daily set-up variations and account for setup uncertainties and respiratory motion, and was also retracted 5mm from the skin surface.

The involved OARs including contra-lateral breast, entire heart, left and right lung, LAD, LCx, RV, LV, spinal cord, oesophagus and liver were delineated by the treating physician. For RT planning two tangential beams were used with a matched posterior border to avoid divergence. The total dose prescribed was 60Gy, with 2.0 Gy per fraction per day (50 Gy in 2 Gy/fraction in 25 fractions to whole breast, 10 Gy in 2 Gy/5 fractions to tumor bed) according to the ICRU report number 83[10-11].

The aim of the treatment plan was to achieve at least 95% of the planning target volume receiving 47.5 Gy (95% of 50.0 Gy), and the ipsilateral lung volume receiving 20 Gy or more ($V20 \geq 10\%$), while keeping the contralateral lung below a mean dose of 5 Gy. In all patients, Varian linear accelerator fitted with Multi Leaf Collimator (MLCi) was used to treat the breast with 6-MV photon energy beam. The boost was applied with electron energy. Electron energy was selected to allow the 85–90% isodose line to encompass target. Dose volume histograms (DVH) were reviewed for all the patients. Maximum, minimum, and mean doses (D_{max} , D_{min} , and D_{mean}) to heart, LAD, LCx, RV, and LV were calculated from the cumulative Histogram Dose Volume (DVH).

Analysis statistics

Both analyses and results were performed using JAMOVI Statistical Software, online version, and a statistical significance level of 0.05 was used ($p < 0.05$).

Results:-

A total of 38 patients were included in our study ;all of them had undergone breast conserving surgery followed by adjuvant RT.We divided them into two equal groups .Nineteen patients had right-sided breast cancer and nineteen had a left-sided one.

In patients with right-sided breast cancer, the mean age was 52 years (37–76 years). In 13 of the patients (59,09%), the tumor size was ≤ 2 cm (T1), and in nine of them (40,91%), it was between two and five cm (T2). In 11 of the patients (57,89%), the tumor was in the inner quadrant, and in eight of them (42,11%) in the external quadrant [Table 1]. None of the patients had lymph node involvement or distant metastasis. Moreover, six of the patients (31,58 %) received chemotherapy (4 cycles in six patients, 6 cycles in five patients). In the patients with left-sided Breast Cancer, the mean age was 55 years (40–72). In 10 of the patients (62,50%), the tumor size was ≤ 2 cm (T1), and in six of them (37,50%), it was between two and five cm (T2). In nine of the patients (47,37%), the tumor was located in the inner quadrant, and in other 10 of them (52,63%), in the external quadrant. None of the patients had lymph node involvement or distant metastasis. Moreover, 12 patients (63,16%) were treated with chemotherapy (4 cycles in nine patients and 6 cycles in four patients) [Table 1].

The doses calculated after RT planning in patients with right and left sided breast cancer are represented below [Table 2]. All Dmean, Dmax and Dmin values on LAD, LCx, RV, LV and heart of the patients with left-sided breast cancer were significantly higher than the values of the patients with right-sided cancer ($P < 0.0001$). The mean V5 of the LV was 20.32% (7.95–42.80). The mean V25 of the LV was 7.31% (0.91–18.34). The mean V5 in the bilateral ventricles was 27.69% (4.64–29.81). The mean V25 in the bilateral ventricles was 8.72% (0.88–16.45).

Discussion:-

Breast cancer is the primary cause of cancer mortality after lung cancer and the most common cancer among women .A number of randomized controlled clinical trials have shown that breast conserving surgery combined with post-operative radiation therapy(PORT) has the same curative effect as the Halsted radical mastectomy. Port has been shown improvement of long-term survival and significant reduction of local relapse but in the other hand major toxicities to the organs at risk(OARs) : heart,the lung and a risk of secondary breast cancer were found [12-13]. Latest update for Early Breast Cancer Trial Writers Cooperation Group demonstrates radiation therapy was associated with excessive cardiac mortality disease. However, many of the studies included in a review involved older treatment techniques, which probably delivered a higher dose to the heart than seen in modern radiotherapy clinics .The cardiovascular complications induced by radiation as a main radiotherapy-related late toxicity[14]. This is a new concern since new research suggest that arteries are particularly susceptible to radiation.The injury of coronary artery induced by radiation is consistent with coronary atherosclerosis due to additional factors [15-16]. Clinical studies have demonstrated that the incidence of coronary artery disease in patients is up to 85%, it closely related to the radiation dose, location, time, and other factors[17-18-19].In our study, we used the regimen that were routinely used in breast cancer patients and determined our cardiac dose rates, according to the dose and plan used for right and left-side breast RT, and tried to evaluate the effect of these doses on coronary disease risk.Aznar MC et al.In their study[19], included women in the age ranging from 36 to 76 years, with median age 58.5 years, at the time of treatment.Chung et al, in their study, included women with a median age of 50 (25–74) years. In our study, the mean age of the patients with right-sided breast cancer was 52 (37–76) years and of those with the left-sided breast cancer was 55 (40–72) years. In the last decade it has been a strong focus on reducing the radiation dose to the heart in order to minimise the risk of side effects with the help of advanced imaging and treatment techniques[20].The highest radiation doses are likely to be the anterior portion of the heart ,including the left anterior descending coronary artery(LAD) especially in left-sided breast RT .This is a concern since new studies suggest those arteries are particularly sensitive to radiation and the cardiovascular mortality tends to increase after RT[21-22].According to the Quantitative Analyses of Normal Tissue Effects in the Institution, National Surgical Adjuvant Breast and Bowel Project, and Radiation Therapy Oncology protocols, heart mean dose is < 26 Gy, < 4 Gy, and < 32 Gy, respectively. In our study, the cardiac morbidity or the cardiovascular mortality was not examined since it was not a follow-up study.The RACE collaboration reported a dose response relationship between the heart disease risk and mean dose [23]. Compared with the women with estimated heart doses < 5 Gy, the relative risks of heart disease in women with estimated doses 5 to 14 Gy and > 15 Gy were 15% and 108% higher, respectively. The Danish Breast Cancer Cooperative Group recommends that the volume of heart receiving more than 40 Gy be kept below 5%, as well as the volume receiving more than 20 Gy be kept under 10%. Although it is generally accepted that a dose of 40 Gy or more of radiation can lead to heart disease, McGale and Darby have shown evidence of an increased risk of

radiation-induced heart disease at doses below 5 Gy [24-25]. In our study, the mean doses for heart of patients with a left-sided breast cancer was 4.80 ± 1.23 Gy, and the maximum dose was 50.45 ± 2.96 Gy. For hearts of patients with a right-sided breast cancer, the mean of dose was 2.03 ± 0.45 Gy, and maximum dose was 7.49 ± 8.61 Gy, suggesting a reasonable estimated lower dose on heart compared with the heart of patients with left-sided breast cancer for the relative risk of heart. To adequately predict the cardiac risks of modern radiation techniques, the determination of a relationship between cardiac doses and long-term morbidity and mortality is necessary [26-27]. In our study, the long-term effects of RT and heart disorders should be investigated in future. Hoening et al., retrospectively reviewed the incidence of cardiovascular disease in 10-year survivors of breast cancer, treated from 1970 through 1986 [28-29]. Although the risk of cardiovascular disease increased with increasing estimated mean heart doses, the risk was decreased with more modern treatment techniques. More recently, Nilsson et al. demonstrated with the coronary angiography that the location and severity of coronary artery stenosis correlates with the expected regions of high-dose radiation, especially for left-sided radiation or inclusion of the internal mammary nodes [28]. Correa et al., conducted a study on 14 patients, 13 with left and one with right-sided breast cancer, which had stress tests and underwent cardiac catheterization. In this study, in 11 of the 13 patients, the LAD was affected. In eight of these 11 patients, a single vessel was affected, in one patient, both LADs and the LCx were diseased, and in one other patient, three main coronary vessels were diseased. On the other hand, 1 patient had LCx and right coronary stenosis without evidence of LAD disease [30]. In our study, not only the mean and maximum doses of RT on heart of left-sided breast cancer were higher than the right-sided cancer, but also the mean, maximum and minimum doses on LAD, LCx, and both ventricles of left-sided cancer were also significantly higher than left-sided cancers, suggesting a possibility of tendency for heart diseases as well as LAD and LCx diseases. Taylor et al. did a study to describe hot-spot areas for radiation and classify RT as high or low risk [31]. In their study, the mean doses received by Swedish women treated for left-sided breast cancer in the 1990s were 3.0 ± 0.5 Gy to the heart and 12.0 ± 2.3 Gy to the LAD (including 1 cm margin). These differences with the literature could be caused by differences in treatment techniques or more likely in contouring strategy: These results also indicate that a very low dose to LAD seems to be associated with a very low dose to the heart for breast tumors in different sides. To provide additional information, we suggest that LAD should be contoured as a risk organ along with the whole heart and used prospectively for optimization of RT plan. If it is not possible to contour both structures owing to limited time, the LAD should be preferred as an organ at risk. Handbook recommendation for breast RT is as follows: LV and combined bilateral ventricle limits: $V5 \leq 10\%$ and $V25 \leq 5\%$. The American Society for Radiation Oncology (ASTRO) Consensus Statement dose constraints for 3D-CRT Accelerated Partial Breast Irradiation (JROBP 2009) reports as follows: heart $V5 < 5\%$ for right-sided tumors and $< 40\%$ for left-sided tumors [31]. In this study, the mean $V5$ of the LV was 20.32% (7.95–42.80). The mean $V25$ of the LV was 7.31% (0.91–18.34) and consistent with the recommendations. The mean $V5$ in the bilateral ventricles was 27.69% (4.64–29.81). The mean $V25$ in the bilateral ventricles was 8.72% (0.88–16.45). These limits were found higher than the recommendations, which can increase the risk of cardiac complications. According to the guidelines, to minimize cardiac side effects, the left ventricular dose should be $V5 \leq 10\%$, the bilateral ventricular dose $V25 \leq 5\%$, and the whole heart dose < 4 Gy. For this purpose, a study reported that deep inspiration breath hold plans proved large reductions of dose to the heart. $V20$ of the heart is reduced from 7.8% to 2.3%, $V40$ from 3.4% to 0.3% and mean dose from 5.2 to 2.7 Gy [32]. This technique (deep inspiration breath hold respiratory gating) may be used to minimize dose to heart. Our estimates will be useful to improve radiotherapy practice and to better management of radiation-related heart diseases.

Conclusion:-

Adjuvant radiotherapy for breast cancer patients can lead to cardiac morbidity and mortality after treatment due to excessive heart irradiation. In our experience we suggest that the whole heart substructures and especially the LAD in the left-sided breast cancers must be contoured with precision as organ at risk, if necessary, deep inspiration breath hold respiratory gating and modern techniques are highly recommended to reduce radiation-related heart diseases.

What is already known on this Topic

Multiple follow-up studies have shown that delivery of radiation breast or chest-wall results in delayed cardiac morbidities ranging from ischemic heart disease (IHD) to acute coronary syndromes and finally congestive cardiac failure.

Table 1:- Patients' characteristics.

	Right-sided Breast Cancer n (%)	Left-sided Breast Cancer n (%)
Breast conservation surgery	19 (100%)	19 (100%)
Mean age (years)	52 (37–76)	55 (40–72)
T stage	T1 13 (59,09%)	10 (62,50%)
	T2 9 (40,91%)	6 (37,50%)
N stage	N0 19 (100%)	19(100%)
M stage	M0 19 (100%)	19 (100%)
Tumor location	Outer quadrant 8 (42,11%)	10 (52,36%)
	Inner quadrant 11 (57,89%)	9 (47,37%)
Tumor size	≤ 2 cm 13 (95,09%)	10 (62,50%)
	2–5 cm 9 (40,91%)	6 (37,50%)
Chemotherapy	Yes 6 (31,58 %)	12 (63,16%)
	No 13 (68,42%)	7 (36,84%)
Number of chemotherapy cycles	4 6 (54,55%)	9 (69,23%)
	6 5(45,45%)	4 (30,77%)

Table 2:- The dosimetric parameters (Dmean : mean dose ;Dmax :maximum dose ;Dmin :minimum dose) of left anterior descending coronary artery (LAD), left circumflex coronary artery (LCx), right ventricle (RV), left ventricle (LV) and heart depending on the side of the tumor.All values are given as mean + standard deviation (range).

	Dosimetric parameters	Right-sided Breast Cancer	Left-sided Breast Cancer	<i>P value</i>
Heart	Dmean			< 0.0001
	Dmax	120.33 ± 19.05 (97.3– 189.2)	396.56 ± 131.73 (158.5–588.7)	

		634.48 ± 751.55 (277–3759.5)	5032.44 ± 331.02 (4134.3–5992.9)	
LAD	Dmean Dmax Dmin	97.57 ± 10.26 (73.8–114) 111.87 ± 16.15 (78.8–145) 83.12 ± 9.31 (63.7–100.1)	2402.48 ± 838.39 (1020–3783) 4752.83 ± 498.46 (3700–5703.8) 222.59 ± 76.42 (95–471)	< 0.0001
LCx	Dmean Dmax Dmin	84.99 ± 9.09 (63.8–100.8) 96.27 ± 11.33 (75.6–116.3) 74.59 ± 8.57 (54.5–92.1)	170.55 ± 45.36 (85.8–260.2) 203.49 ± 55.9 (112–353.9) 137.63 ± 38.59 (69.7–235.5)	< 0.0001
RV	Dmean Dmax Dmin	130.18 ± 24.92 (110.8–224.2) 464.76 ± 517.55 (221.2–2619) 75.51 ± 7.81 (58.8–90.5)	563.65 ± 221.78 (140.9–875.6) 4576.55 ± 1077.66 (460.1–6149.3) 103.41 ± 28.67 (49.3–184.9)	< 0.0001
LV	Dmean Dmax Dmin	81.71 ± 7.9 (60.9–96.5) 149.13 ± 43.75 (85.1–264.2)	536.8 ± 193.24 (230–1018.1) 4822.6 ± 362.4 (3964.4–5835.4)	< 0.0001

		65.75 ± 7.02 (47.1–80.2)	105.49 ± 26.64 (52.2–184.2)	
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What this study adds

This study evaluated RT doses to the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCx), right ventricle (RV), left ventricle (LV), and heart in patients who underwent right and left sided breast conservative surgery and determine whether these doses constituted a risk for ischemic heart disease.

Conflicts of Interest

The authors declare they have no conflict of interest.

Authors Contribution

All the authors contributed in this study.

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