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Comparative Study of Cardiac Radiation Dose With Different Types of Surgery in Breast Cancer Patients

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Abstract

Background: It has been demonstrated that radiation therapy lowers both the death rate from breast cancer and its recurrence. Precise calculation of the radiation dose is crucial for treating the target site as well as protecting vital organs like the heart since large doses of radiation therapy significantly increase patient morbidity and death.

Objective: To compare the mean heart dose of radiation in breast cancer patients between breast-conserving surgery versus mastectomy, between different radiotherapy doses and fractionation schedules, and between right and left breast cancer irradiation.

Patients and Methods: This is a cross-sectional descriptive retrospective comparative study that was conducted in Baghdad Radiotherapy Center from January 2018 to June 2018, carried on 174 breast cancer patients of different age groups selected randomly and their mean heart dose data collected from their files and database in Baghdad Radiotherapy Center.

Results: The overall average of the mean dose was 372 cGy (range from 76.4 to 716.2). The greatest difference in the mean heart dose was between (BCS) patients who received 5000 cGy with regional nodal irradiation and (BCS) patients who received 4005 cGy also with regional nodal irradiation (difference in the mean is 639.8, the P – value <0.001). Regarding the side of breast cancer, the greatest difference in mean heart dose was seen between left and right breast cancer patients who did the same type of surgery (MRM) and received the same dose of radiotherapy (4256 cGy) (difference in the mean is 565cGy and the P – value <0.001). No statistically significant difference in the mean dose between breast-conserving surgery and mastectomy was recorded.

Conclusion: The mean heart dose of radiotherapy is significantly increased in left-sided breast cancer irradiation as compared to the right side. A dose of 5000 cGy has the greatest effect on the dose received by the heart, especially in left breast cancer. The type of surgery whether breast-conserving surgery or mastectomy did not affect the mean dose received by the heart.

Keywords: Breast cancer, cardiac radiation dose, breast cancer surgery, breast cancer treatment.

Introduction

A modified radical mastectomy typically includes an axillary node dissection in addition to the removal of the entire breast, nipple, and areola (1). Following breast-conserving surgery (BCS), adjuvant whole-breast radiotherapy (RT) is usual and has been demonstrated to decrease the incidence of local recurrence among all subgroups of women (2). Given that multiple single trials have demonstrated a survival benefit for post-mastectomy radiation therapy (RT), women who are at high risk of local recurrence (T3–T4, > 4 positive lymph nodes, and excision margin < 1 mm) should be routinely administered RT following mastectomy (3). The standard modern technique for definitive radiation therapy for early-stage breast cancer is three-dimensional radiation therapy (3D CRT) with appropriate compensation using an intensity-modulated radiation therapy (IMRT) or field-in-field technique to provide a homogeneous dose to the breast tissue. It was shown that all breast tissue should be included in these fields, which should be collimated to run parallel to the chest wall. Angles of the gantry, collimation, and Cerrobend blocks or the multileaf collimator (MLC) are the greatest ways to treat breast tissue without damaging the heart or lungs. Wedges are a compensatory tool used by some centers (4). Breath-hold is a technique that is being used more frequently for patients with left-sided breast cancer. It involves the patient taking a deep breath and holding it for a brief period (30 to 1 minute). This technique allows the heart to be moved away from the chest wall, which frequently results in better cardiac sparing and better breast/chest wall coverage (5). The internal organs at Cerrobend blocks or the multileaf collimator (MLC) are the greatest ways to treat breast tissue without damaging the heart or lungs. The heart and lungs are at risk (OAR; treatment is limited to the left side). Within the START and FAST-Forward studies, dose limitations for the heart and lung have been established (6). The use of dose-volume histogram (DVH) criteria to assess treatment plans is still being studied. The mean cardiac dosage and the risk of cardiac events have a linear, no-threshold relationship, which is supported by population-based data. This suggests that the cardiac dose should be kept as low as is practical (7). For women with tumors in the left breast, the estimated mean doses of radiation to the heart were 6.6 Gy on average, 2.9 Gy for those with tumors in the right breast, and 4.9 Gy overall. For every 1 Gy increase in the mean radiation dose administered to the heart (95% CI, 2.9 to 14.5; P<0.001), the rate of major coronary events increased by 7.4%. (7, 8). There is less evidence of cardiac toxicity from more recent trials that used methods to restrict exposure to normal cardiac and pulmonary tissues (9). Pericarditis was the most frequent symptom, and it became a serious issue when extensive areas of the heart, or the pericardium, were exposed to doses greater than 40 Gy (10). Very few incidences of coronary artery disease that could be linked to radiation were found in the initial research. But radiation-induced heart disease (RIHD) is the umbrella term for a variety of conditions that can be brought on by radiation exposure; these conditions include arrhythmias, pericarditis, cardiomyopathy, coronary artery disease, pericardial effusions or constriction, and valvular illness (11). It can impact any one of the heart's anatomical structures. Pericarditis with effusion in the pericardium has been reported, either in conjunction with or apart from constrictive pericarditis. Due to fibrosis and macroangiopathy in the myocardium, cardiomyopathy may develop, which will ultimately result in heart failure. Radiation therapy to the arteries may hasten atherosclerosis and result in carotid and coronary artery disease, which raises the risk of ischemic stroke and IHD, respectively (12, 13). The EBCTCG meta-analyses and the early randomized radiation trials demonstrated a decline in breast cancer deaths that was offset by an increase in cardiovascular mortality (14). Compared to right-sided breast cancer, left-sided breast cancer has been linked to a greater mortality rate from IHD (14, 6, 15). The purpose of this study was to examine the mean cardiac dose of radiation from two distinct types of breast cancer operations, namely mastectomy and breast-conserving surgery, as well as the various radiation dosages utilized in the treatment of breast cancer and the distinction between radiation treatment for left and right breast cancer.

Patients and Methods

This is a cross-sectional retrospective descriptive comparative study that was conducted in Baghdad Radiotherapy Center from January 2018 to June 2018, carried on 174 breast cancer patients of different age groups, and their data was collected from their files and database in Baghdad Radiotherapy Center. The patients enrolled in this study have already been diagnosed with breast cancer and received radiotherapy in our center, the majority of patients were females 170 and only 4 males, their ages ranged from 18 to 77 years old with a mean age of 47.5 years. All the data are obtained from the patient file database in our center and the radiation data from the MOSAIQ system for the mean heart radiation dose for each patient. The patients in this study underwent full staging to exclude secondary metastasis before starting the treatment and then managed by neoadjuvant chemotherapy at the start or surgery either breast-conserving surgery or with modified radical mastectomy both with axillary lymph node sampling or dissection, then followed by adjuvant chemotherapy if indicated for each case with or without hormonal treatment, and radiotherapy is given for them according to their indication to the chest wall with or without axillary irradiation.

Patients excluded from the study are those with:

- Recurrent disease
- Bilateral disease
- Those with bolus used

Those with boost to tumor bed (if the patient has boost then the heart dose is taken with the boost dose). The 174 patients are divided into two groups:

Breast-conserving surgery: 81 patients further divided into two different radiation doses and two different sides (right and left):

- 5000 cGy includes 50 patients subdivided into: the right side with lymph node irradiation 18, without lymph node irradiation 10, and the left side with lymph node irradiation 9, without lymph node irradiation 13.
- 4005 cGy includes 31 patients subdivided into: the right side with lymph node irradiation 12, without lymph node irradiation 6, and the

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left side with lymph node irradiation 7, without lymph node irradiation 6.

Modified radical mastectomy and axillary dissection: 93 patients further divided into two radiation doses and two different sides (right and left):

- 4256 cGy include 50 patients, all with lymphatic irradiation subdivided into: right side 20 and left side 30.

- 4005 cGy includes 43 patients, all with lymphatic irradiation, also subdivided into right side 23 and left side 20.

Concerning the distribution of the patients in the study, (46.5%) of patients did BCS, and (53.5%) did MRM. For the sides of breast cancer, they were almost equally distributed between the right and left sides (51%) and (49%), respectively.

Statistical Analysis

All the data was analyzed using the Statistical Package for Social Sciences (SPSS) version 16, and all the quantitative variables were presented as mean and standard deviation, while qualitative variables were presented as frequency and percentages. One Way ANOVA test is used to evaluate the statistical difference and compare different groups. A P-value <0.05 was considered significant.

Results

Demographical data

In this study, 174 breast cancer patients were included, with their ages ranging from (18 to 77) years. The highest incidence of breast cancer was seen in the 6th decade (50 – 59) years, and their percentage (29.3%) was followed by the 5th and 7th decades equally (23.5%). whereas the lowest incidence is seen in young patients (3rd decade), as shown in Figure (1).

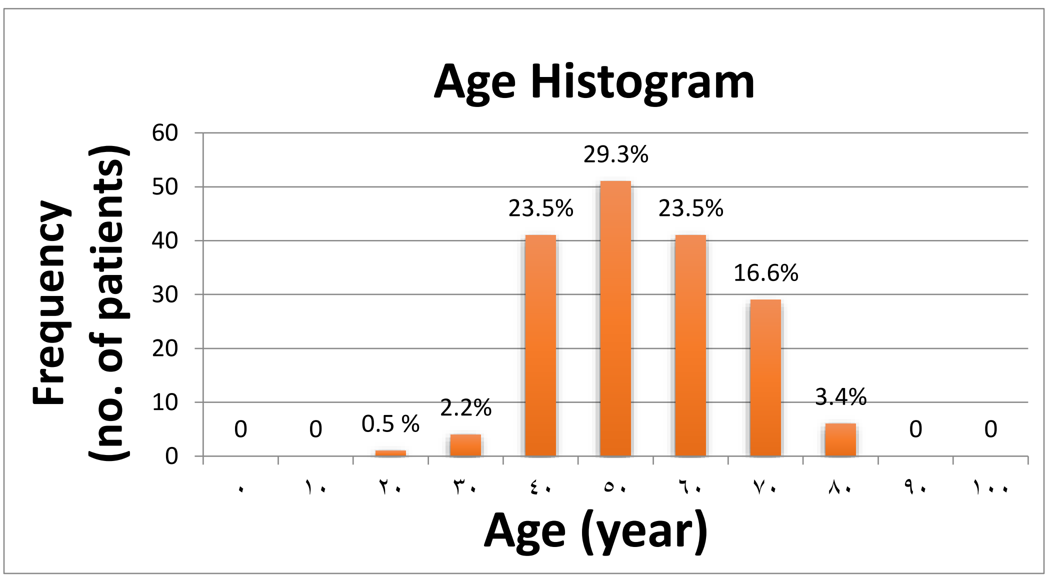

Figure (1): Age distribution in the studied breast cancer patients.

Regarding the staging of breast cancer and according to the most commonly used staging system, the American Joint Committee on Cancer (AJCC) we found that the most frequent stage regardless of the type of

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surgery was stage IIIA (T2N2M0) making about (19%) of our patients studied to be followed by stage IIIB (T2N3M0) about (15%). only a few patients (3%) had non-invasive disease (DCIS). About (30%) of patients had early breast cancer, while the remaining had advanced disease. further details can be seen in Figure (2).

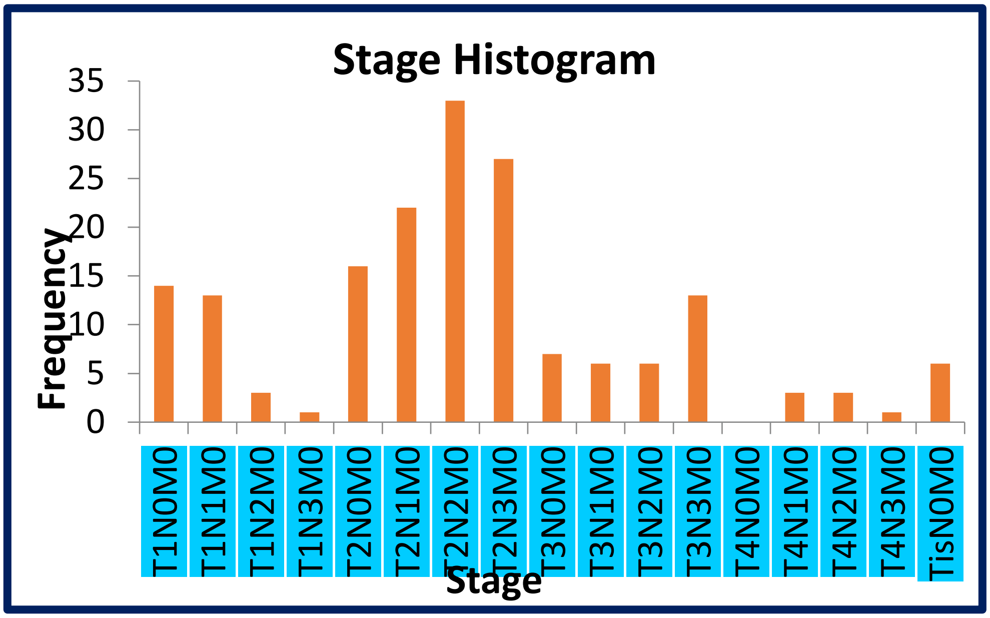

Figure (2): Stage distribution in breast cancer patients in our data collected.

Heart mean dose data

This study involved two main groups of breast cancer patients: those with breast-conserving surgery (BCS) and modified radical mastectomy (MRM); each group is further subdivided according to the dose of radiotherapy, whether regional nodal irradiation given or not and also according to the sidedness of breast cancer (right and left). The mean heart dose was calculated and compared between the different groups. In Table (1) below we see that patients with left-sided breast cancer who underwent breast-conserving surgery (BCS) and received a dose of 5000 cGy with nodal irradiation have the highest mean heart dose (716 cGy) with standard deviation (± SD 275) and confidence interval of the mean (C.I. 211), followed by patients with left-sided disease with modified radical mastectomy (MRM) who received 4256 cGy with nodal irradiation in which the mean heart dose was (658 cGy) with (± SD 199 and C.I. of mean 74). The lowest mean heart dose was seen in patients with right-sided breast cancer who did (MRM) and received a dose of 4005 cGy with nodal irradiation (mean heart dose 76 cGy with ± SD 27 and C.I. of mean 17). The overall average of the mean dose was 372 cGy (range from 76 to 716). The average mean heart dose on the left side was 627 cGy (range from 551 to 716). While the average mean heart of the right side was 117 cGy (range from 76 to 158).

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Table (1): different study groups with mean heart doses and standard deviation. BCS: breast-conserving surgery, MRM: modified radical mastectomy, YES: means L.N. irradiation, NO: without L.N. irradiation, all MRM received L.N. irradiation, RT: right, LT: left.

Column	Number of patients	Mean dose(cGy)	Std. Dev.	C.I. of Mean
BCS-4005-Yes-RT	12	76	27	17
BCS-5000-Yes-LT	9	716	275	211
BCS-5000-No-LT	13	620	262	158
MRM-4005-RT	23	130	131	56
MRM-4005-LT	20	653	231	108
MRM-4256-RT	20	93	30	14
MRM-4256-LT	30	658	199	74

* BCS: breast-conserving surgery, MRM: modified radical mastectomy, YES: means L.N. irradiation, NO: without L.N. irradiation, all MRM received L.N. irradiation, RT: right, LT: left.

The one-way analysis of the variance (one-way ANOVA) was used for testing the difference in the values of the mean heart dose and its significance, which shows that the differences in the mean values among the study groups are greater than would be expected by chance. There is a statistically significant difference (P = <0.001). Power of performed test with alpha = 0.050: 1.000. All Pairwise Multiple Comparison Procedures (Tukey Test) were used for testing the difference in the mean heart dose and its significance by comparing each group with the others and the comparison of each effective possible factor such as the type of surgery, side of breast cancer, radiotherapy dose and the lymph node irradiation. In the table (table 2) below, the test shows the greatest difference in the mean heart dose was between (BCS) patients who received 5000 cGy with nodal irradiation and (BCS) patients who received 4005 cGy also with nodal irradiation (difference in the mean is 639 cGy, the P – value <0.001). Regarding the side of breast cancer, the greatest difference in mean heart dose was seen between left and right breast cancer patients who did the same type of surgery (MRM) and received the same dose of radiotherapy (4256 cGy) (difference in the mean is 565 cGy and the P – value <0.001). The difference in the mean dose between breast-conserving surgery and mastectomy was not significant.

Table 2: Comparison of mean heart dose for different study groups and its significance.

Comparison	Difference of Means(cGy)	number	P value	P<0.050
BCS-5000-Yes vs. BCS-4005-Yes	639	12	<0.001	Yes
BCS-5000-Yes vs. BCS-4005-No-	557	12	<0.001	Yes
MRM-4256-LT vs. MRM-4256-RT	565	12	<0.001	Yes
MRM-4256-LT vs. MRM-4005-RT	528	12	<0.001	Yes
MRM-4005-LT vs. MRM-4005-RT	523	12	<0.001	Yes
MRM-4005-LT vs. BCS-4005-No-RT	495	12	<0.001	Yes
MRM-4005-LT vs. BCS-4005-No-LT	102	12	0.983	Do Not Test
BCS-5000-No- vs. BCS-5000-Yes	503	12	<0.001	Yes
BCS-5000-No- vs. BCS-4005-No-	461	12	<0.001	Yes
BCS-4005-Yes vs. BCS-4005-No-	408	12	0.001	Yes
BCS-4005-No-LT vs. MRM-4005-RT	421	12	<0.001	Yes
BCS-4005-No-RT vs. MRM-4005-RT	28	12	1.000	Do Not Test

* BCS: breast-conserving surgery, MRM: modified radical mastectomy, YES: means L.N. irradiation, NO: without L.N. irradiation, all MRM received L.N. irradiation, RT: right, LT: left.

A result of the "Do Not Test" occurs for a comparison when no significant difference is found between two means that enclose that comparison. Also, not testing the enclosed means is a procedural rule, and a result of the Do Not Test should be treated as if there is no significant difference between the means, even though one may appear to exist.

Discussion

Increasing age is an important established risk factor for breast cancer development. In this study, 174 breast cancer patients were included with their ages ranging from (18 to 77) years, the highest incidence of breast cancer seen in the 6th decade (50 – 59) years and their percentage (29.3%) followed by the 5th and 7th decades equally (23.5%) (18). In this study, the lowest incidence was seen in young patients (3rd decade), similar to many epidemiological data, which state that sporadic breast cancer is relatively uncommon among women younger than 40 years but increases significantly thereafter (19). Due to increased screening, the majority of patients present with early-stage breast cancer, which was inconsistent with the results of this study in which the most frequent stage, regardless of the type of surgery, was stage IIIA (T2N2M0), making about (19%) of our patients studied to be followed by stage IIIB (T2N3M0) about (15%) and only about (30%) of patients had early breast cancer, while the remaining had advanced disease. The distribution of the patients in the study, (46.5%) of patients did BCS and (53.5%) did MRM, and for the doses of radiotherapy, those who received doses of (5000 cGY, 4260 cGY) were (28.8%) for each, and (42.5%) of patients received a dose of (4005 cGY). For the sides of breast cancer, they were equally distributed between the

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right and left sides (51%) and (49%), respectively. The majority of patients received lymph node irradiation (80%), and those who did not (20%) according to the stage of the disease. All the doses and fractionations of radiotherapy used in our study were the standard doses and fractionations used in many centers worldwide after publications of the randomized trials (16, 17, 18). LAD is considered to be a more important vessel at risk due to its implication in the pathogenesis of ischemic heart disease. Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray, with no apparent threshold. The increase started within the first 5 years after radiotherapy and continues for at least 20 years after radiotherapy. In this study, the overall average mean dose of the heart was 372 cGy (3.7Gy) (range from 76 cGy to 716 cGy), and this is considered acceptable as compared with a population-based case-control study conducted in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark. Individual patient information was obtained from hospital records. For each woman, the mean radiation doses to the whole heart and the left anterior descending coronary artery were estimated from her radiotherapy chart. The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72) (20). In our study we see that patients with left sided breast cancer who underwent breast conserving surgery (BCS) and received a dose of 5000 cGy with nodal irradiation have the highest mean heart dose (716) with standard deviation (± SD 275) and confidence interval of mean (C.I. 211), followed by patients with left sided disease with modified radical mastectomy (MRM) who received 4256 cGy with nodal irradiation in which the mean heart dose was (658) with (± SD 199 and C.I. of mean 74). the greatest difference in the mean heart dose was between (BCS) patients who received 5000 cGy with nodal irradiation and (BCS) patients who received 4005 cGy also with nodal irradiation (difference in the mean is 639 , the P – value <0.001) these findings are consistent with the results of prospective randomized trial conducted in Egypt at Kasr AL-ainy center of clinical oncology and nuclear medicine (NEMROCK) to assess cardiac toxicity in left sided breast cancer patients with different fractionations in two arms ; one arm using conventional fractionation (5000 cGy / 25fx / 5wks) and the other arm using hypofractionation (4256 cGy / 16fx / 3 ½ wks) 5 years after 3D conformal radiotherapy using the same planning technique that is used in our center (the breast or chest wall was treated isocentrically using 2 tangential beams with selective multileaf blocking to protect the organs at risk "heart and lung") and the volume of the heart that received 40Gy (V40) was not allowed to exceed 30% . The results showed that cardiac dysfunction developed more in the conventional arm and concluded that hypo-fractionated radiotherapy decreased cardiac toxicity though not statistically significant (21). There are possible factors that have led to the high mean dose of the heart in left-sided breast irradiation in our study: if the distance of the heart from the chest wall is too small for some women, it was not the breath hold or respiratory gating technique or those who require internal mammary irradiation, in which the mean dose may be around 10 Gy as confirmed in many studies in which cardiac dose and toxicity increased with internal mammary nodal irradiation. (22). In comparison between the right and left breast cancer mean heart dose, our study showed that the average mean dose on the right side was 1.1 Gy (range from 0.7 to 1.5), and The average mean heart dose on the left side was 6.2 Gy (range from 5.5 to 7.1) which was also consistent with the population-based data which state that The mean cardiac dose from irradiation of left-sided breast cancer can be two or three times that for a right-sided breast cancer, and the Current mean doses of radiation to the heart from radiotherapy for breast cancer are typically about 1 or 2Gy for the disease of the right breast and 6.6 for the left side and the risk of cardiovascular events was greater with left breast cancer radiotherapy when compared with the right. (23,24). In our study, there was no statistically significant difference in mean heart dose between patients who underwent breast-conserving surgery and mastectomy, which was incomparable with a study evaluating cardiac radiation exposure in patients after mastectomy and after breast-conserving surgery, which showed that the mean heart dose after BCS was 141 cGy (SD 61.8) and 234 cGy (107.5) after mastectomy indicating that the type of surgery affects the heart dose of radiotherapy (25,26).

Conclusion

The mean dose of radiotherapy received by the heart is greatly affected by the side of breast cancer, with a dose two to three times more in left-sided treatment. The mean heart dose was highest in a dose of 5000 cGy compared to the other doses. In addition, the type of surgery has no significant effect on the mean heart dose.

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Recommendations

The use of new techniques such as breath holding deep inspiration technique and advanced planning systems such as IMRT in left-sided breast cancer radiotherapy especially if pre-existing cardiac disease is present or in young patients with long life expectancy is recommended to keep the mean heart dose as low as possible. In addition, the introduction of intraoperative IORT in selected cases of breast cancer may be beneficial in decreasing the heart dose.

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Ethical Clearance: Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024SAK860).

Conflict of Interest: Non

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دراسة مقارنة للجرعة الإشعاعية القلبية بأنواع مختلفة من العمليات الجراحية لمرضى سرطان الثدي

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الملخص

خلفية الدراسة: لقد ثبت أن العلاج الإشعاعي يقلل من عودة سرطان الثدي وكذلك الحد من وفيات سرطان الثدي. إن جرعة الإشعاع مهم ان يتم حسابها بدقة لكل من الموقع المراد معالجته وكذلك لحماية الأعضاء الحيوية مثل القلب حيث يكون له تأثير كبير على المرضى والوفيات على المرضى إذا تلقوا جرعة عالية من العلاج الإشعاعي.
اهداف الدراسة: للمقارنة بين متوسط جرعة القلب من الإشعاع لدى مرضى سرطان الثدي بين ما يلي: جراحة الحفاظ على الثدي واستئصال الثدي، وجرعات العلاج الإشعاعي المختلفة وجداول التجزئة وكذلك بين جهة اليمين واليسار عند العلاج الشعاعي لسرطان الثدي.
المرضى والطرائق: هذه دراسة مقارنة وصفية مقطعية أجريت في بغداد مركز للعلاج الإشعاعي في الفترة من يناير ٢٠١٨ إلى يونيو ٢٠١٨، ونفذت على ١٧٤ مريضا بسرطان الثدي من مختلف الفئات العمرية حيث ان بيانات جرعة القلب التي تم جمعها من ملفاتهم ومن قاعدة بياناتهم في مركز العلاج الإشعاعي في بغداد. ينقسم المرضى إلى مجموعتين: جراحة الحفاظ على الثدي واستئصال الثدي الجذري المعدل. كل مجموعة يتم تقسيمها إضافيا حسب جرعة العلاج الإشعاعي وجهة سرطان الثدي المصابة.
النتائج: كان المتوسط العام لجرعة القلب من الاشعاع ٣٧٢ cGy (يتراوح من ٧٦,٤ إلى ٧١٦,٢). أكبر فارق في متوسط جرعة القلب كان بين مرضى (جراحة الحفاظ على الثدي) الذين تلقوا ٥٠٠٠ cGy مع اشعاع العقد اللمفاوية ومرضى (جراحة الحفاظ على الثدي) الذين تلقوا ٤٠٠٥ cGy أيضا مع الإشعاع للعقد اللمفاوية (الفرق في المتوسط هو ٦٣٩,٨، P - القيمة <٠,٠٠١).
فيما يتعلق بجانب سرطان الثدي، فإن أكبر فارق في متوسط الجرعة المستلمة بين مرضى سرطان الثدي جانبي اليسار واليمين الذين قاموا بنفس النوع من الجراحة (استئصال الثدي الجذري المعدل) وتلقوا نفس الجرعة من العلاج الإشعاعي (٤٢٥٦ cGy) (الاختلاف في المتوسط هو ٥٦٥cGy و P - القيمة <٠,٠٠١).
لا يوجد فروق ذات دلالة إحصائية في معدل جرعة القلب من الاشعاع بين جراحة الحفاظ على الثدي واستئصال الثدي.
الاستنتاجات: ان معدل جرعة القلب من العلاج الإشعاعي زادت بشكل ملحوظ في تشعيع الجانب الايسر لسرطان الثدي بالمقارنة مع الجانب الأيمن. جرعة من ٥٠٠٠ cGy له التأثير الاكبر على الجرعة التي يتلقاها القلب خاصة في سرطان الثدي الأيسر. لا يؤثر نوع الجراحة، سواء كانت جراحة الحفاظ على الثدي أو استئصال الثدي، على معدل الجرعة التي يتلقاها القلب.
الكلمات المفتاحية: سرطان الثدي، جرعة الإشعاع القلبي، جراحة سرطان الثدي، علاج سرطان الثدي.
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