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Intensity modulated radiation therapy (IMRT) technique for left breast cancer by different numbers of beam fields

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ABSTRACT

Background: Intensity Modulated Radiotherapy (IMRT) can improve radiotherapy (RT) results by improving healthy tissue sparing. Additionally, IMRT provides more consistent dose deliveries and suppresses secondary tumor formation. RT is a principal treatment in breast cancer (BC). ***Aim:*** To evaluate the outcome of the Radiotherapy Plans (RTP) that use IMRT technique to left breast and other organs, including left lung (Lt lung), right lung (Rt lung), heart, and spinal cord. ***Materials and Methods:*** Thirteen patients with left-sided breast carcinoma were treated using IMRT. ***Results:*** The Homogeneity Index (HI) and Conformity Index (CI) showed significant improvement over IMRT-involved plans. All IMRT plans significantly improved CI for 12 patients, where CI <1. Planning target volume (PTV) was under coverage, except for patient No. 6, where CI>1. HI for 13 patients. Mean dose to heart, Lt lung, and Rt lung was (9.966±1.261), (14.388±0.854), and (4.083±0.661) of the prescribed dose, respectively. Cord Max, Dose was (Gy) (20.751±7.384), and Cord Received Max Dose was <45Gy. Mean heart dose was (9.966±1.261) (Gy), and the PTV mean dose was (41.169±0.437) (Gy). Mean dose to lungs for eight patients was <30Gy, except for five patients (No. 1, 2, 5, 12, and 13), which received >30Gy. ***Conclusion:*** The IMRT plans achieved a significant reduction in heart volume and ipsilateral lung exposed to high-dose (≥40.05 Gy). Multi-beam inverse planned IMRT technique might benefit patients with heart diseases, and who are exposed to doses <20 Gy, irrespective of the selected plan. Relative volume of ipsilateral lung or heart receiving high-dose (40.05 Gy) was significantly reduced.

Keywords: *IMRT, breast cancer, Whole breast radiotherapy.*

INTRODUCTION

Radiotherapy intervention consists of three volumes. The first is the Gross Tumor Volume (GTV), which is the gross demonstrable extent and location of the malignant growth. The second volume is called the Clinical Target Volume (CTV), which comprises the GTV and the margin surrounding it. CTV describes the range of pathogenic spread that must be treated. If the tumor has been removed prior to radiotherapy, CTV just can be defined without GTV. It is vital that imaging developments, particularly at a molecular level, specify the extent of CTV. This volume must be effectively treated for achieving a cure.

The third volume is termed the Planning Target Volume (PTV), a geometrical concept that allows uncertainties in planning or delivering treatment. PTV optimizes the precise RT dose delivery to the CTV [1, 2]. RT intervention needs to account for significant inviolate biological structures, referred to as organs at risk (OARs). OARs are healthy tissues that may be affected by RT treatment. On occasion, additional margin paralleling of the PTV around the OAR may prevent healthy tissue from receiving high radiation dose. This provides a low dose volume

for OARs during planning. Moreover, the PTV margin paralleling is applied to healthy organs, such as the spinal cord, lung, and so forth, where even a minimal amount of tissue damage may induce future carcinoma. Modern RT has been improved considerably since the advent of CTV, GTV, and PTV [3].

RTP is vital, and its dose affects outcomes. Additionally, it is reliant on high-quality imaging; thus, development in imaging techniques leads to improved RT outcomes [2, 4]. To control early-stage breast cancer locally, it should be followed by Whole Breast Radiotherapy (WBR). The treatment duration includes 5 weeks of external beam radiotherapy (46–50 Gy), containing 20-25 fractional doses for the whole breast. This is often followed by an additional fractional dose 7–10 of external beam radiotherapy. It has been shown that the IMRT technique useage for whole breast treatment after surgery may improve dose homogeneity together with tumor spread and protect healthy tissue by reducing the dose of OARs [5, 6].

IMRT is a modern external beam technique that can deliver a high conformed dose to cancer and a minimum dose to healthy tissue. However, it can improve dose homogeneity, conformity, as well as prevention of a secondary tumor [7]. In the IMRT treatment technique, the collimation leaves (MLCs) are carefully adjusted according to the shape, size, and location of the tumor. In IMRT several radiation beams are used to focus a higher radiation dose (higher photons energy) on the tumor. This provides a much smaller dose to the surrounding healthy tissue OARs, thereby reduces adverse events. Therefore, IMRT can deliver the same radiation dose to the tumor with minimal side effects as compared to the Three-Dimensional Conformal Radiotherapy (3D -CRT). Further, it is effective when treating tumors generated in proximity to vital organs [8, 9].

This study aimed to evaluate the RTP outcome that uses the IMRT technique to the left breast on healthy tissue, including left lung (Lt lung), right lung (Rt lung), heart, and spinal cord using different beams of X-ray photons. This acted to reduce OARs dose and prevent induced secondary cancer during primary left-sided breast irradiation. The obtained data were compared with the organs' tolerance dose levels at Zhianawa Cancer Center (ZCC) – Kurdistan Region (KR), Iraq. Multi researches in different places as well as various populations, support the idea that there is a relationship between the dose effects of radiotherapy beam with healthy tissue during the radiotherapy process. To authors' best knowledge, this research is the first conducted in this field in the KR.

MATERIALS AND METHODS

Patients

Thirteen patients with early-stage left-sided breast cancer were treated with radiation therapy at Zhianawa Cancer Center (ZCC) using IMRT after breast-conserving surgery. Dose prescriptions for the patients were different according to the cancer stage of each. The present study was conducted following the approval by the Ethical Committee of Hawler Medical University (KR, meeting code: 6, paper code: 8, date: 23/04/2016).

Optima computed tomography CT scanner

Optima CT 580 RT (general electric GE Healthcare-USA) consists of an 80cm big-bore CT-Scanner that is designed for radiotherapy with a flat RT couch. Optima 580 is a 16 slice scanner (it takes 16 slices in one gantry rotation) and can scan with (0.625, 1.25, 2.5, 5, and 10mm) slice thickness. Additionally, it can scan four-dimensional Computed Tomography 4D-CT images and produce helical together with axial scans. The scanner is equipped with a contrast injection system for setup and verification of patient position [9].

Monaco treatment planning system

Monaco is a treatment planning system (TPS) software produced by Elekta for radiotherapy. It has the ability to calculate 3D, IMRT, Volumetric Modulated Arc Therapy (VMAT), Stereotactic Radio Surgery (SRS), and Brachytherapy plans with high accuracy using the Monte Carlo algorithm (the most accurate dose calculation available). Furthermore, it can generate Quality Assurance (QA) plans from the original one to

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check the quality of IMRT and VMAT plans. The Monaco TPS has Segment Shape Optimization for smoothing and clustering segments, and it can optimize beam weights and shapes, which improves plan quality [9, 10]. In ZCC, the Monaco TPS is version 5.00.02 and works on a network of three main high-performance computers (Quad-core Intel Xeon 2.93GHz processor, 24GB DDR3 RAM, 4TB Storage); it is connected with the center's leading network.

Patient Selection

Thirteen patients with early-stage left-sided breast cancer were treated with radiation therapy using IMRT. This study was performed on an Elekta Synergy linac, 2013, from the United Kingdom. The Elekta Synergy linac consists of 3 photon energies (6, 10, and 18MV) and 8 electron energies (4, 6, 8, 10, 12, 15, 18, and 22MeV). The accelerator machine is equipped with Multi-Leaf Collimator (MLC) at the Zhianawa Cancer Center (ZCC), KR, during 2018.

Simulation

All patients underwent Computed Tomography (CT) simulation, which was obtained using a scanner with 16 detector arrays (LightSpeed Xtra; general electric GE Healthcare, Waukesha, WI, USA) while patients were in the supine position on a breast board with both arms above their heads, the elbow support. Marker and tattoos were taken for setting up the patients during the treatment. Scanning was performed in 2.5-mm slices from the clavicle to the mid-abdomen during free-breathing [10].

The ipsilateral whole breast was contoured as the Clinical Target Volume (CTV). The Planning Target Volume (PTV) was constructed by adding 5-mm margins and editing 5-mm of the build-up region from the breast skin surface. Two opposed tangential fields were set up without wedges, and the gantry angles were optimized. Leaf margins of 2 cm were added to the skin side, and leaf margins of 3 mm to the other sides. Each patient's plan was normalized to a reference point at the interface of the breast and pectoralis major muscle at the nipple level. The target volumes were delineated according to the recommendation of ICRU, report No.50. GTV was contoured according to the information from CT-Scanner, MRI, pathology, and oncology reports. PTV was delineated after CTV. Healthy tissues and nearby organs were contoured (spinal cord, Lt lung, Rt lung, heart, and esophagus) as OARs. CTV included tumor volume, as well as Lt lung, Rt lung, heart, and spinal cord tissues as OARs (figure 4). The lungs were automatically delineated on CT scans [11].

The dose was prescribed for all PTVs according to the type, size, and location of the tumor for each patient. Dose prescription and delineation processes were conducted by radiation oncologists at ZCC.

Dose limitation for the OARs is defined as:

D30% was for the Lt lung and Rt lung (equivalent V20%); it is defined as the dose received by 30% of Lt lung and must be <20Gy to avoid pneumonitis.

Moreover, the equivalent dose for the V35% of the heart was D20%. This is defined as a received dose, which is equivalent to 20% of the heart and must be <20 Gy to avoid perica[12, 13].

The prescribed dose by the oncologist was 40.050Gy/ (2.670Gy/fraction), and the number of fractions was 15. These fractions are based on guidelines from the International Commission of Radiation Units and Measurement (ICRU), report 50 and 62 [11].

Comparison of Plans

The provided dose of our plan to 95% of the PTV was 40.05 Gy. The reference point (isocenter) was selected in the middle of the thickest part in the breast at the central axis of each tangent field. The doses were normalized to this reference point. The angles of these fields had to cover all the PTV volumes with 95% to 107% isodose curves in order to avoid the extra doses to the contralateral breast and lung.

Homogeneity Index (HI) (see equation 1) is an objective tool that analyses the uniformity of dose distribution in the target volume. The values of D2% and D98% for PTVs were obtained from DVH. D2% represents the maximum dose that is delivered to 2% of the PTV. Dp is the prescribed dose for PTV, and D98% is the minimum dose calculated for 98%

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of the PTV. The lower the HI, the better the dose homogeneity.

$$HI=(D_{2\%}- D_{98\%})/(D_p) \quad (1)$$

The CI (see equation 2) measures the degree of conformity [14], which is calculated as follows:

CI value indicates the conformity degree of the plan. If CI < 1, the PTV is under coverage. If CI > 1, the normal tissues receive a high dose. Lastly, if CI = 1, in this case, the prescribed dose conforms to the PTV shape.

$$CI=(\text{volume covered by 95\% of the prescribed dose})/(\text{volume of PTV}) \quad (2)$$

IMRT plans

In the present study, IMRT plans were proposed for five fields size beam with gantry 500, 3400, 3000, 1200, and 1800 describing an arc of 1800 on the side of the tumor. In this study, IMRT procedures were used based on five differently spaced fields (gantry from five angles), as well as the volume and location of cancer and OARs [15].

Statistical analysis

Data analysis was carried out via the available statistical package of SPSS-25 (Statistical Packages for Social Sciences- version 25). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The variation significance of different means (quantitative data) was tested through the Paired t-test for the difference of paired observations (or two dependent means). Statistical significance was considered whenever the P-value was equal or less than 0.05.

Table 1. Dose characteristics of the PTV (breast) associated with the IMRT plan, including the mean dose, dose homogeneity, and Conformity Index (CI) in 13 patients.

No. of Patient	Volume (cm3)	Mean Dose (Gy)	D98%	D2%	V95	HI	CI
1	722.265	41.376	34.314	43.234	637.439	0.222694	0.882556
2	529.56	40.911	35.732	43.528	498.925	0.194632	0.94215
3	670.775	40.469	34.53	43.565	614.569	0.225565	0.916207
4	1030.235	41.417	36.531	43.34	913.454	0.169991	0.886646
5	471.275	41.304	37.997	43.418	461.779	0.135339	0.97985
6	673.2	40.992	36.967	43.6	931.894	0.165597	1.384275
7	681.56	40.936	37.074	43.569	649.791	0.162152	0.953388
8	396.925	41.423	38.281	43.414	390.85	0.128149	0.984695
9	1397.025	41.729	39.359	43.591	1391	0.105655	0.995687
10	351.635	41.341	38.425	43.38	347.69	0.123705	0.988781
11	1099.44	41.569	37.221	43.51	889.414	0.157009	0.80897
12	888.95	41.322	36.032	43.627	512.225	0.189614	0.576214
13	479.565	40.91	37.765	43.512	464.667	0.143478	0.968934

RESULTS

IMRT with several beams were compared with each other in relation to conformity, homogeneity, and dose delivered to the OAR. The breast volume had no effect on the conformity index of the treatment since it depended on the volume of PTV, CI = (volume covered by 95% of the prescribed dose)/(volume of PTV). Table 1 indicates a more homogeneous dose distribution in PTV for patient number 9 compared to the others (The lower the HI, the optimal the dose homogeneity).

Dose-Volume Histograms (DVH) refers to the distribution of radiation dose. The X-axis refers to radiation dose, and V% denotes the volume of OARs. The shape and area under the DVH curve were considered to ensure that the target volume was adequately covered with a homogeneous dose, while the dose to critical structures was within acceptable limits. IMRT planning system can calculate the dose in each pixel of the organ outlined to produce a dose volume, figure 1).

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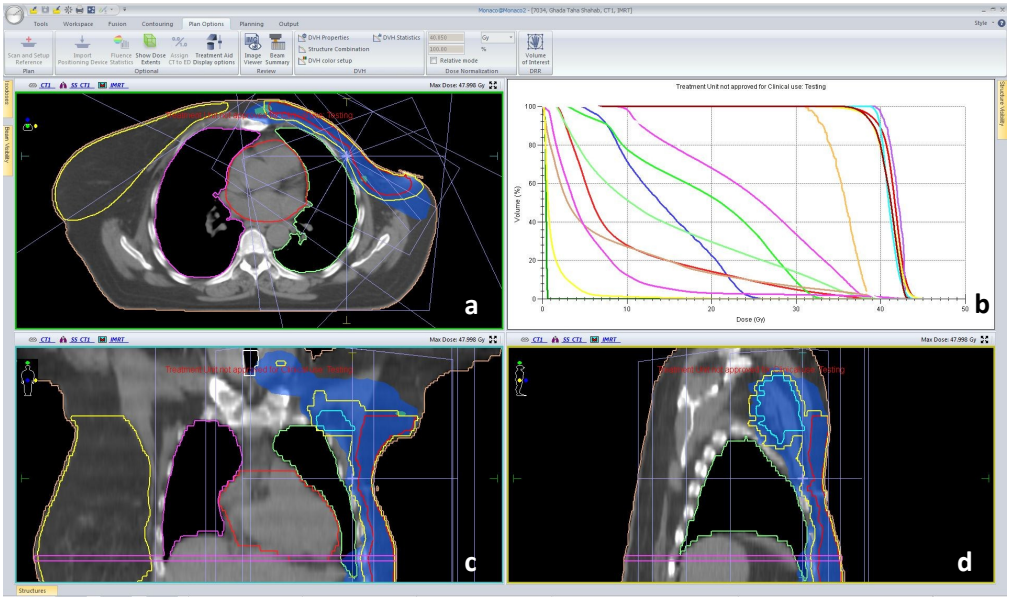


Figure 1. The PTV and OAR are displayed for patient No. 6. Data obtained from table 1, showed **(a)** Shows the eight equi-distant co-planner fields of beams in IMRT planning in left breast with chest wall region of PTV (blue), R Breast and L breast (yellow), and OAR which includes: heart, R ling and L lung (black area), and cord. **(b)** Isodose distribution and DVH of target volume and organs at risk for the IMRT plan which display the radiation dose to tissue volume: target in red color and OAR such as heart in yellow which are used to compare doses for target and OAR. **(c)** Anatomy of structures with distance between the contralateral breast and OAR, the figure is contained right-sided and left-sided breast cancer. **(d)** The cumulative dose-volume for the PTV.

The mean dose to cancer of breast CB calculated by various beam numbers in Lt and Rt sided breasts via the linear model for the 13 patients using the IMRT technique. The mean CB dose was used to predict the risk for radiation-induced malignancy in CB via the linear model (table 2).

Table 2. It shows the Mean± SD for thirteen patients for all OARs.

	Total No. of patients	Mean± SD	(Range)
Cord Max. Dose (Gy)	13	20.751±7.384	(5.514-31.192)
Cord Max. Dose (Gy) > 45	0		
<45	13		
Heart Mean Dose (Gy)	13	9.966±1.261	(7.512-11.956)
Heart Volume>20(%)	13	1.310±0.625	(0.32-2.23)
Heart Volume>(%) >20	0		
<20	13		
Rt Lung Mean Dose (Gy)	13	4.083±0.661	(3.233-5.636)
Rt Lung Volume > (%)	13	0.346±0.740	(0-3.020)
Rt Lung Volume>(%) >30	0		
<30	13		
Lt Lung Mean Dose (Gy)	13	14.388±0.854	(11.479-15.668)
Lt Lung Volume > (%)	13	30.164±2.918	(20.250-33.423)
PTV Volume (cm3)	13	741.984±254.386	(351.635-1397.025)
PTV Mean Dose (Gy)	13	41.169±0.437	(40.236-41.992)
PTV MeanDose(Gy) >45	0		
<45	13		
PTV D98%	13	36.941±1.497	(34.314-39.359)
PTV D2%	13	43.484±0.118	(43.234-43.627)
PTV V95	13	669.515±291.814	(347.690-1391.0)
PTV HI	13	0.163±0.037	(0.106-0.226)
PTV CI	13	0.944±0.174	(0.576-1.384)

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The results of table 2 showed the mean dose Gy to the Rt lung was lower than the mean dose of the Lt lung since the Rt lung was distant from the target (left breast).

The quantitative data obtained from table 2 and figure 2 showed that the mean dose to the heart, Lt lung, and Rt lung for each patient with IMRT plans was (9.966±1.261), (14.388±0.854), and (4.083±0.661) of the prescribed dose, respectively. The spinal cord maximum dose (Gy) was (20.751±7.384), and it was <45Gy. PTV mean dose (Gy) was (41.169±0.437).

According to the findings in table 2 and figure 2, the Mean± SD for heart V20 was (1.310±0.625) that is <30 Gy. The received mean dose volume of the Lt lung was (14.388±0.854) that is <20 Gy, and the received mean dose of the Rt lung was (4.083±0.661) that is <5 Gy. This was since the Rt lung was distant from the target. The mean dose was used to predict the risk for radiation-induced malignancy in breast cancer using the linear accelerator and was based on patients' individual dose-volume histogram DVHs.

Table 3 and figure 3 indicate that the Spinal Cord Max dose was <45 Gy, which concurs with Majumder *et al.* [16]. Lung V20 was <30 Gy. Late-stage fibrosis was associated with V20 with a target of <30% of the lung. PTV volume receives >20 Gy. Furthermore, the DVH parameters, including mean lung dose, were occasionally used. The above results correlate with Xiaoxue and Ouyang [17].

During radiotherapy of Lt Breast cancer, heart segments were exposed to a dose <30 Gy, irrespective of the selected plan. In the course of treatment via the IMRT technique, the mean dose to the bilateral lungs for 8 patients was <30Gy, except for 5 patients (1, 2, 5, 12, and 13) that was >30Gy.

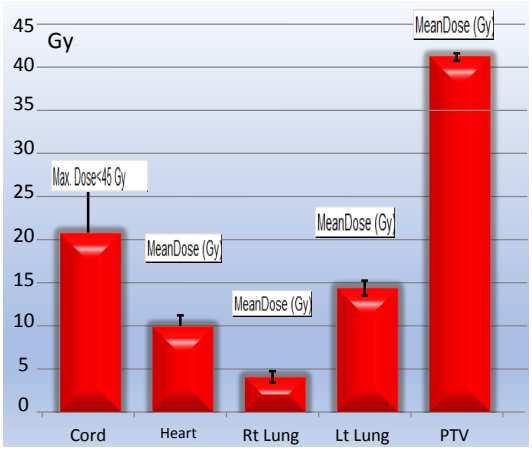


Figure 2. Volume %, the target volume covered % by the x% isodose; the minimal, maximal, and mean target volume dose.

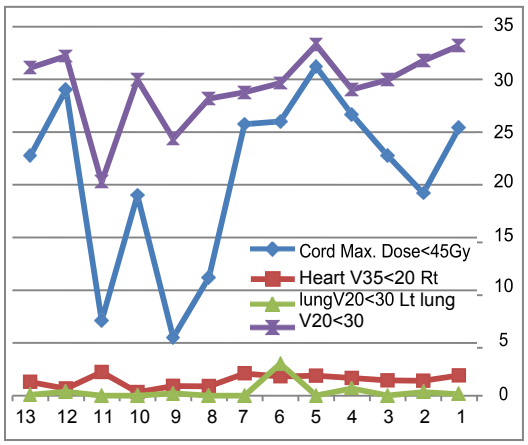


Figure 3. Distribution for low dose volume of healthy tissue in breast cancer irradiation (i.e., Lt -lung, Rt-lung, heart, and spinal cord) according to IMRT plans.

Table 3. Dose comparison to Lt lung, Rt Lung, heart, and Cord; Volume % of the target volume covered by xGy; Dmax and Dmean with IMRT plan for 13 patients.

No. of Patient	Lt-Lung Volume % (V20<30)	RT-Lung Volume % (V20<30)	Heart Volume % (V35<20)	Cord Dose <45Gy)
1	33.2	0.14	1.91	25.398
2	31.75	0.34	1.4	19.198
3	29.94	0.01	1.45	22.771
4	29.04	0.69	1.67	26.646
5	33.27	0.01	1.89	31.192
6	29.63	3.02	1.82	25.999
7	28.77	0	2.1	25.738
8	28.16	0	0.89	11.223
9	24.36	0.21	0.91	5.514
10	29.97	0	0.32	19.002
11	20.25	0	2.23	7.108
12	32.2	0.385	0.67	29.037
13	31.09	0.08	1.29	22.743

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DISCUSSION

The aim of IMRT plans is to generate the homogeneity dose distribution for breast cancer, as well as to achieve a marked decrease in volumes of heart, ipsilateral lung, and spinal cord exposed to high-dose. Cumulative DVHs were assessed according to their target volumes and healthy tissues. Quantitative data were considered from the DVHs and were based on three significant factors: PTV dose, conformity index (CI), and homogeneity index (HI). The $D_{2\%}$ represented the maximum dose delivered to 2% of the PTV for all 13 patients, and D98% was the minimum dose calculated for 98% of the PTV. The prescribed dose received by 95% of the PTV assisted in the evaluation of the dosimetry plans. The dosimetry plan in this study aimed to cover at least 95% of the PTV.

Three major parameters in table 1, PTV dose, CI, and HI, showed significant improvements through IMRT-involved plans. Improved dose homogeneity was achieved through the IMRT technique. Furthermore, the IMRT plans significantly improved CI, which concurs with a study conducted by Woo *et al.* [18]. In table 1, the small amount of HI indicated that a lesser dose exceeded the prescription dose. Therefore, according to the data in table 1, the patient with the minimum HI had better dose uniformity than other patients.

According to table 2 and figure 2, the mean dose of the Rt lung was (4.083±0.661). This revealed that the difference in the mean dose and low dose volume (V20Gy) were significantly lower than the Lt lung (14.388±0.854) in IMRT plans for breast cancer by different numbers of the beam in the left-sided breast. The low amount in the mean dose of the Lt lung was due to its distant position from isotopes axial, which cognates with Popescu *et al.* [19]. Moreover, the V20 for the Lt and Rt lungs, as well as V30 for the heart, showed similarity. Heart maximum dose and volume received <20 Gy, a result that is also identified by Fong *et al.* [20].

Ipsilateral (left) lung mean dose and volume received <20 Gy, and contralateral (Rt) lung mean dose and volume received <5 Gy. This result is consistent with a study conducted by Ayata *et al.* [21].

The main objective of the IMRT plans was to decrease the exposure volume of healthy tissue (i.e., heart, lung, and spinal cord) to radiation when the target received a high RT dose. The parameters for the comparison of the heart (<V30) and ipsilateral lung (<V20) were selected. Any radiation dose may increase the risk of a second malignancy. Although no safe dose limits can be given, the risk may be minimized. In principle, the irradiated volume should be as minimal as possible. The IMRT plans achieved a significant reduction in the volume of heart and ipsilateral lung exposed to high-dose (≥40.05 Gy). In general, the multi-beam inverse planned IMRT technique might benefit patients with heart diseases, and wherever cardiac regions are exposed to doses <20 Gy, irrespective of the selected plan. Heart and lung are the primary organs of concern. In the current research, for the IMRT technique, the relative volume of ipsilateral lung or heart receiving high-dose (40.05Gy) was significantly reduced. With the multi-beam IMRT technique, the relative volume of bilateral lungs and heart receiving even a lower dose (5 Gy) was increased.

CONCLUSION

A plan should ideally produce a steep curve showing that the dose within the PTV is constant; albeit, the dose between 95% - 107% of PTV varies according to the International Commission on Radiation Units and measurements ICRU50.

In a radiotherapy center like Zhianawa Cancer Center (ZCC), where a limited number of RT machines and requirements are available for hundreds of patients in the waiting list, it is necessary to take into consideration the required delivery time, as well as improvement in the target coverage and OARs sparing, when selecting an available treatment method. The dose was prescribed for all PTVs according to the type, size, and location of the tumor for each patient. Dose prescription and delineation process were performed by radiation

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oncologists at ZCC. The RTP outcome that uses IMRT plans for breast cancer may provide a guideline for selecting a possible treatment technique for breast cancer at Zhianawa Cancer Center (ZCC) –Sulaimany-KR-Iraq.

Conflicts of interest*: *Declared none.

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