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Second Cancer Risk Evaluation from Breast Radiotherapy Using Dose-Response Models

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THIS study aimed to evaluate the radiation-induced second cancer risks in normal tissues after the treatment of breast cancer with three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) plans for 10 breast cancer patients. The 3DCRT and IMRT plans were evaluated and compared with several dosimetric parameters for Planning Target Volume (PTV) and the Organs at Risk (OARs). The Organ Equivalent Dose (OED) was calculated based on linear, linear-exponential, and plateau dose-response models. The Second cancer risks were evaluated by Excess absolute risk (EAR) for OARs. For breast, PTV dose coverage parameters were significantly improved in IMRT compared to 3DCRT. The ipsilateral lung V30Gy % and V20Gy % were significantly decreased with IMRT. However, The IMRT plans were shown significant increases ($p<0.05$) in the mean doses D_{mean} to OARs. Compared with the 3DCRT, the IMRT plans increase OED in OARs based on the linear, plateau, and linear-exponential models. The second cancer risk with IMRT increased by 2.5 -3.5fold, 3.3-4fold, 3-7fold, and 4.6-5.3fold for contralateral lung, contralateral breast, esophagus, and stomach based on dose-response model applied. Conclusion: IMRT technique demonstrated a clear advantage in dose coverage, conformity, and homogeneity over 3DCRT and was superior in terms of OAR-sparing. The Second cancer risk in normal tissues based on the EAR model after IMRT is higher than 3DCRT. Advanced radiotherapy techniques as IMRT for breast cancer treatment must be evaluated based on secondary cancer risks when treating young patients.

Keywords: Three-Dimensional Conformal Radiotherapy (3DCRT); Intensity Modulated Radiotherapy (IMRT); Second cancer risk; Breast cancer; Organ Equivalent Dose (OED).

Introduction

Breast cancer is one of the most common cancers in the world. The present technological progress in the early diagnosis and treatment of cancer patients has led to a higher number of cancer patients with long-term survivors[1] Progressive treatment of early stage breast cancer strategies has improved the survival of patients who have breast conserving surgery[2]. After surgery, patients normally undergo radiotherapy for the whole breast[3]. This method decreases local cancer recurrence by one-half to two-thirds and reduces the risk of death by around one-sixth due to breast cancer[4]. There is an increased risk of second malignancies in patients undergoing radiation therapy due to radiation within the treatment field and dispersion away from the treatment field[5]. Although the risk of secondary cancer induction for patients treated with radiotherapy is minimal, particularly among younger patients, this remains an important concern[6]. In women among> 10-year survivors, the probability of developing second cancer elevated significantly in women who were treated with radiotherapy at the age of 45 years or less [7]. The quality of life and long-term survival of these breast cancer patients, minimizing the radiation dose to normal tissues with maintaining tumor control becomes very important[8]. Several treatment modalities have been used to treat breast cancer using a conventional linear accelerator. Patients may be treated with (3DCRT) or (IMRT) or volumetric modulation radiotherapy. Previous comparative studies have shown that the chance of secondary

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cancer induction with the IMRT plan is higher than with the 3DCRT plan. The IMRT involves more beams, and therefore a larger volume of normal tissue is irradiated with a low dose of radiation that requires a longer treatment time with a higher number of monitor units (MU) are used, and consequently, the integral dose may increase in normal tissues[9]. The OED definition has recently been established and used to estimate the secondary risk from three-dimensional dose distributions[10]. The cancer risks at low doses are linear with dose, and the OED is the average organ dose. However, at doses more than 2 Gy, cell sterilization effects are present. So cancer risks incidence rates are not necessarily a linear function of the dose, and OED is different from the mean organ dose because the cell sterilization effects at high doses [10]. In a previous study by Abo-Madyan, et al. [1] They estimated the cumulative excess absolute risks (EAR) to contralateral breast , ipsilateral , contralateral lungs based on linear , linear-exponential and plateau models. They considered all patients at the age of 30 years, and second cancer risk was estimated at attained age of 70 years with absolute EAR0 for breast and lung. Estimate second cancer risk to anther normal organs after breast cancer treatment became very important. The aim of this study was to calculate and compare second cancer risk for ipsilateral, contralateral lung, contralateral breast, liver, esophagus, stomach, and thyroid after 3DCRT and IMRT for breast cancer using the concept of the OED for three dose-response models linear, linear-exponential and plateau model.

Materials and Methods

Computed tomography (CT) and treatment techniques

In this study, ten female breast cancer patients were retrospectively selected. The patients were 5 with right breast cancer and 5 with left breast cancer. The patients' age was from 32-57 years in our study. A CT simulator Somatom definition AS 20 VA48A (Siemens Healthcare) was used to acquire CT images for radiotherapy planning with 3 mm slice thickness. The patients were positioned on breast board in a supine position with both arms above the head. To reduce any skin folds that may increase the skin reaction, the patient's head turned to the contralateral side. In order to delineate the clinical borders of breast tissue, radiopaque fiducial wires are positioned on the patient skin before the CT scan. Patients' breast PTVs and OARs (ipsilateral lung, contralateral lung, heart, contralateral breast, liver, esophagus, stomach, and thyroid) were contoured using Elekta Monaco SIM (version 5.11.02). To eliminate most of the buildup area for the DVH analysis. The PTV was delineated with 5 mm skin extraction. Two plans were built for each of the 10 patients the 3DCRT plan with tangential wedged beams and IMRT Plan with multi-beams from 7-9 beams. The treatment planning system (TPS) Monaco (version 5.11.02 Elekta, CMS software, St. Louis, USA) was used for 3DCRT, and IMRT plans design and dose calculation. For IMRT plans, the dose calculation was done with a Monte Carlo calculation algorithm but collapsed cone algorithm was used in 3DCRT plans. The 6 MV beam energy of Elekta Synergy linear accelerator with agility head MLC160 leaves was used as a treatment machine and plans calculation in our study. The prescription dose for breast PTV was 50 Gy in 25 fractions, and the plans were normalized to produce at least 95% of PTV volume covered with 95%of the prescribed dose. The DVH of the PTV and organs at risk of the 3DCRT and IMRT plans were generated and dose parameters compared. The PTV dose coverage was evaluated based on the comparison of dosimetric parameters (D95 %, D2 %) where Dn is the minimum dose in Gy delivered to n% of the PTV volume also V105% the parentage of PTV volume that receives 105 percent of prescription dose. The minimum dose (D_{min} Gy), maximum dose (D_{max} Gy), and means dose (D_{Mean} Gy) are compared for the PTV. The homogeneity of dose within PTV has been evaluated by using homogeneity index (HI) as defined by[11].

$$HI = \frac{D_{5\%}}{D_{95\%}} \quad (1)$$

Where $D_{5\%,}$ and $D_{95\%}$represent the dose to 5% and 95% of the PTV volume respectively. When HI equal one that indicate high dose homogeneity in the PTV. The degree of the prescribed dose conformality in the target has been evaluated by the conformation number (CN) [12]. This number has been described as follows.

$$CN = \left(\frac{TV_{RI}}{TV}\right) \times \left(\frac{TV_{RI}}{V_{RI}}\right) \quad (2)$$

Where TV_{RI} is the volume of the PTV covered by the reference isodose, TV is PTV volume, and V_{RI} is the reference isodose volume. The reference isodose used in this study was isodose 95%of the prescription dose. The dosimetric parameters from the DVH for the ipsilateral lung ($V_{30Gy\ \%}$,

$V_{20Gy\ \%}$ and $V_{5Gy\ \%}$) which is the percentage of the Ipsilateral lung volume that receiving 30 Gy, 20 Gy and 5 Gy respectively. Also, the mean dose D_{Mean} (Gy) has been compared in 3DCRT and IMRT plans. The mean organ dose D_{Mean} (Gy) for contralateral lung, thyroid, liver, heart, esophagus and stomach has been evaluated in the two plans sets. The statistical analysis was performed with paired student's t-test to assess whether the means of two plans were statistically significant ;if P-Value was ≤0.05, then the dosimetric parameter considered statistically significant between two plans.

The Organ Equivalent Dose (OED) and Excess absolute risk (EAR) calculations

Second cancer risk after radiotherapy treatment is normally represented with EAR per 10,000 persons per years per Gy. EAR refers to the absolute difference in cancer rates between persons exposed to a radiation dose and those not exposed to a radiation dose above the natural dose exposure. The EAR was calculated as follows [1]

$$EAR = EAR_0 \times OED \quad (3)$$

EAR_0 represented the initial slope of the dose-response curve at a low dose and included population-related parameters, such as age at exposure (agex), sex (s) and attained age (agea). The EAR of developing a second cancer in one of the investigated organs was calculated as follows:

Where β′ was the initial slope for the dose-response relationship of second cancer induction, γ_e and γ_a were the age-modifying factors. All parameters for EAR calculation are listed in Table 1. The OEDs for OARs (ipsilateral lung, contralateral lung, heart, contralateral breast, liver, stomach, and thyroid) were calculated from differential DVH bases up on the linear, linear-exponential and plateau dose–response models[10], [13]. In this study the patiens's age at exposure (agex) was from 32-57years and attained age was 70 years. The linear model assuming that the dose-response is directly proportional to organ absorbed dose. The linear $OED_{T,linear}$ for an organ T was calculated as follows:

$$EAR = OED\beta' exp[\gamma_e(agex - 30) + \gamma_a \ln(agea/70)] \quad (4)$$

Considering the possibility of cell killing effect increased exponentially with organ absorbed dose which would reduce the induction of cancer because the death of mutated cells. The linear-exponential model $OED_{linear\text{-}exp}$ for an organ calculated as follows:

For a plateau model which basd on the fact that the dose-response initially increases linearly with dose until a threshold dose at which the dose-responseand risk reach to a plateu due to sterilization of cell at higher doses and full repair of normal tissues in a fractionated scheme. The plateau model $OED_{plateau}$ for an organ calculated as follows:

$$OED_{T,linear} = \frac{1}{V_T}\sum_i \{DVH(D_i).D_i\} \quad (5)$$

Where $DVH(D_i)$ is the volume of organ receiving dose D_i and the summation runs over all voxels of organ(T)with volumeV_T. The model parameters α and δ were estimated from a combined fit to the JapaneseA-bomb and Hodgkin cohorts by Zwahlen et al. [13]

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$$OED_{T,linear-exp} = \frac{1}{V_T}\sum_i \{DVH(D_i).D_i.e^{-\alpha D_i}\} \quad (6)$$

$$\alpha = 0.044Gy^{-1}$$

Results

The PTV dose coverage parameters at 3DCRT and IMRT Plans are indicated in **(Table 2)**. In the ten patients, the PTV dose coverage parameters were better in IMRT plans when compared with 3DCRT plans. There were significant differences in $D_{95}(\%), D_2(\%), D_{min}(Gy), D_{Mean}(Gy)$, and V105% (P<0.5) between 3DCRT and IMRT plans. A higher significance difference (p=0.000095) was observed in D_{min}(Gy) between 3DCRT and IMRT .This is due to lower PTV dose coverage with the 3DCRT technique, and the D_{min} is minimum dose point dose in the PTV. Also, the CN mean values were (0.58±0.074) and (0.77±0.078) for 3DCRT and IMRT, respectively. The homogeneity index IH among 3DCRT and IMRT (1.08±0.021, 1.07±0.017, p = 0.022). So, the dose conformality and homogeneity in the PTV was improved with IMRT in comparison with 3DCRT. The numbers of MU per fraction have higher values in IMRT and increased by 124 % compared with 3DCRT plans.

$$OED_{T,plateau} = \frac{1}{V_T}\sum_i \{DVH(D_i).(1 - e^{-\delta D_i})/\delta\}; \quad (7)$$

$$\delta = 0.139Gy^{-1}$$

The dose statistics to OARs for3DCRT and IMRT plans are tabulated in **Table 3**. The V_{30Gy} %, V_{20Gy} %for Ipsilateral lung improved with the IMRT plan compared with 3DCRT, but the volumes receiving low dose (V_{5Gy} %) increased with IMRT Plans. The mean doses D_{Mean}(Gy) in

the normal tissues contralateral lung, contralateral breast, thyroid, liver, heart, and esophagus were significantly increased with IMRT plans. Figure1shows the isodose curves and beams arrangement for 3DCRT and IMRT for patient case in our study. The isodose distributions of low dose cover large volumes of normal tissues with IMRT plan compared with 3DCRT as shown in (figure1). The cumulative DVHs for one of an investigated case in our study for 3DCRT and IMRT has shown in (figure2). The 3DCRT plans results were displayed as solid lines, and the IMRT plans results were displayed as dashed lines. The DVHs for OARs were shown increase the percentage of volumes of tissues in low dose region and decrease in high dose region with IMRT compared to 3DCRT.

Table 4. shows the mean values of OED and standard deviation (Mean ±SD) in organs of interest for 3DCRT and IMRT plans using the linear, plateau, or linear-exponential dose–response model. Figure 3 demonstrates the mean values OED for normal tissues for 3DCRT and IMRT with the three dose-response models. The OED in Ipsilateral lung has no significant difference between 3DCRT and IMRT plans for linear or linear-exponential dose–response model, but significantly increased with the plateau model in IMRT plans. Compared with the 3DCRT plans the IMRT plans increases OED in the contralateral lung, contralateral breast, thyroid, liver, esophagus and stomach with the three dose-response models. This increase in OED was statically significant ($p < 0.05$).

TABLE 1. The Excess absolute risk (EAR) calculation parameters from Sechnider et al., 2011[14].

organ	β_init	γe	γa
Lung	8	0.002	4.23
Breast	8.2	-0.037	1.7
Liver	2.4	-0.021	3.6
Thyroid	o.4	-0.046	0.6
Esophgus	3.2	-0.021	1.9
Stomach	5.2	-0.002	1.9

TABLE 2.The PTV Mean values of dose-volume parameters comparison for 3DCRT and IMRT Plans.

DVH parameters	3DCRT (Mean ±SD)	IMRT (Mean ±SD)	P-Value
D_{95}(%)	96.5±1.2	97.2±1.2	0.02164532
D_2(%)	106.2±0.74	105.5±0.93	0.056
D_{min}(Gy)	12.85±11.73	31.4±7.3	0.000095
D_{max}(Gy)	54.35±1.34	54.5±1.35	0.2455
D_{Mean}(Gy)	50.93±1.34	51.02±1.3	0.22
V105%	7.2±4.1	4.2±3.2	0.067
CN	0.58±0.074	0.77±0.078	0.00036
HI	1.08±0.021	1.07±0.017	0.022
MU per fraction	303±75	679±118	0.0013

SD: Standard deviation, PTV: Planning Target Volume.

TABLE 3. The dose–volume parameters and mean doses comparison in OARs for 3DCRT and IMRT Plans.

OARs	DVH parameters	3DCRT (Mean ±SE)	IMRT (Mean ±SE)	P-Value
Ipsilateral Lung	V_{30Gy} %	14.7 ± 2	8.6 ± 3.9	0.000094
	V_{20Gy} %	18.12 ± 2.1	15.9 ± 3.5	0.0072
	V_{5Gy} %	37.8 ± 3.1	56.2 ± 12.2	0.000098
	D_{Mean}(Gy)	10.68 ± 0.7	10.13 ± 1.27	0.053
Contralateral Lung	$V_{5Gy\%}$	0.1 ± 0.35	19.1 ± 23.05	0.01
	D_{Mean}(Gy)	0.96 ± 0.3	3.2 ± 1.8	0.0013
Contralateral Breast	D_{Mean}(Gy)	0.61 ± 0.16	2.5 ± 1.2	0.00023
Thyroid	D_{Mean}(Gy)	0.61 ± 0.2	0.72 ±0.3	0.133
Liver	D_{Mean}(Gy)	2.3 ± 1.9	4.6 ± 3.6	0.0028
Heart	D_{Mean}(Gy)	7.6 ± 2.3	4.1 ± 3.6	0.0029
Esophagus	D_{Mean}(Gy)	1.53 ± 0.6	3.9 ± 0.14	0.016
Stomach	D_{Mean}(Gy)	4.01 ± 1	4.2 ± 1.2	0.48

SD: Standard deviation.

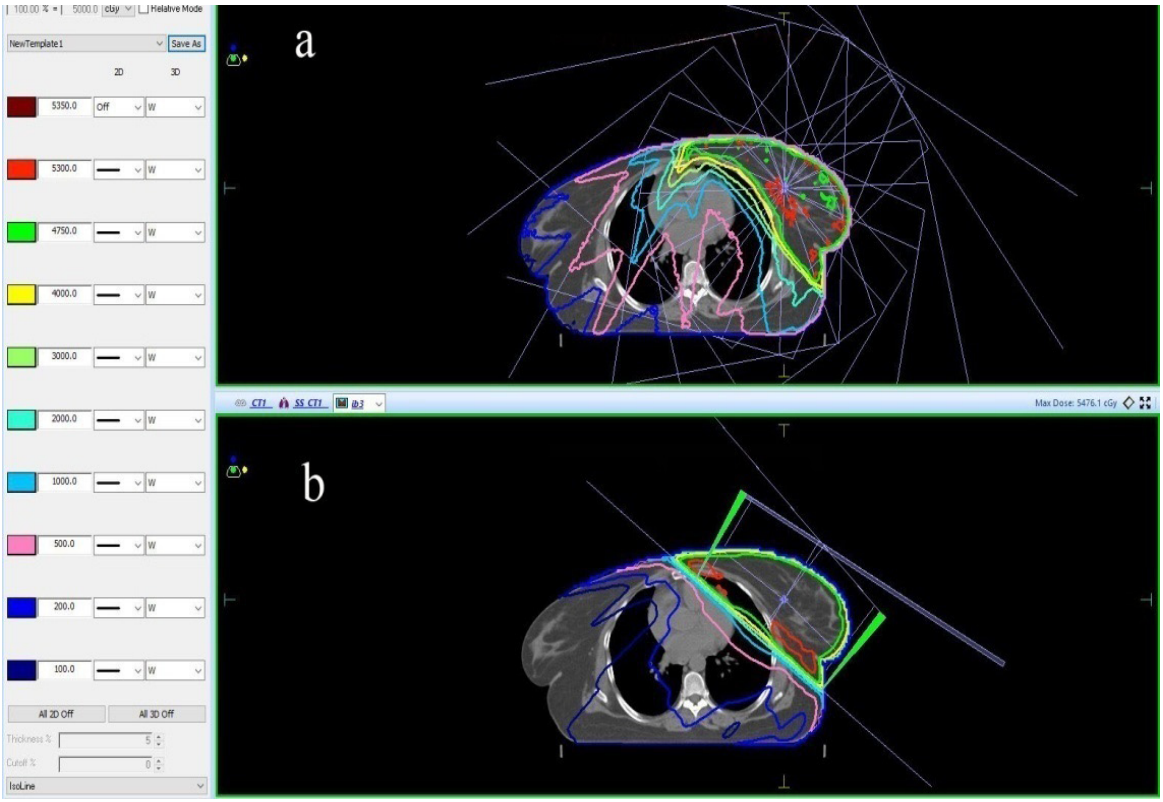

Fig.1. The beams arrangements and isodoses distributions on transverse CT planning. (a) for IMRT plan. (b) for 3DCRT plan.

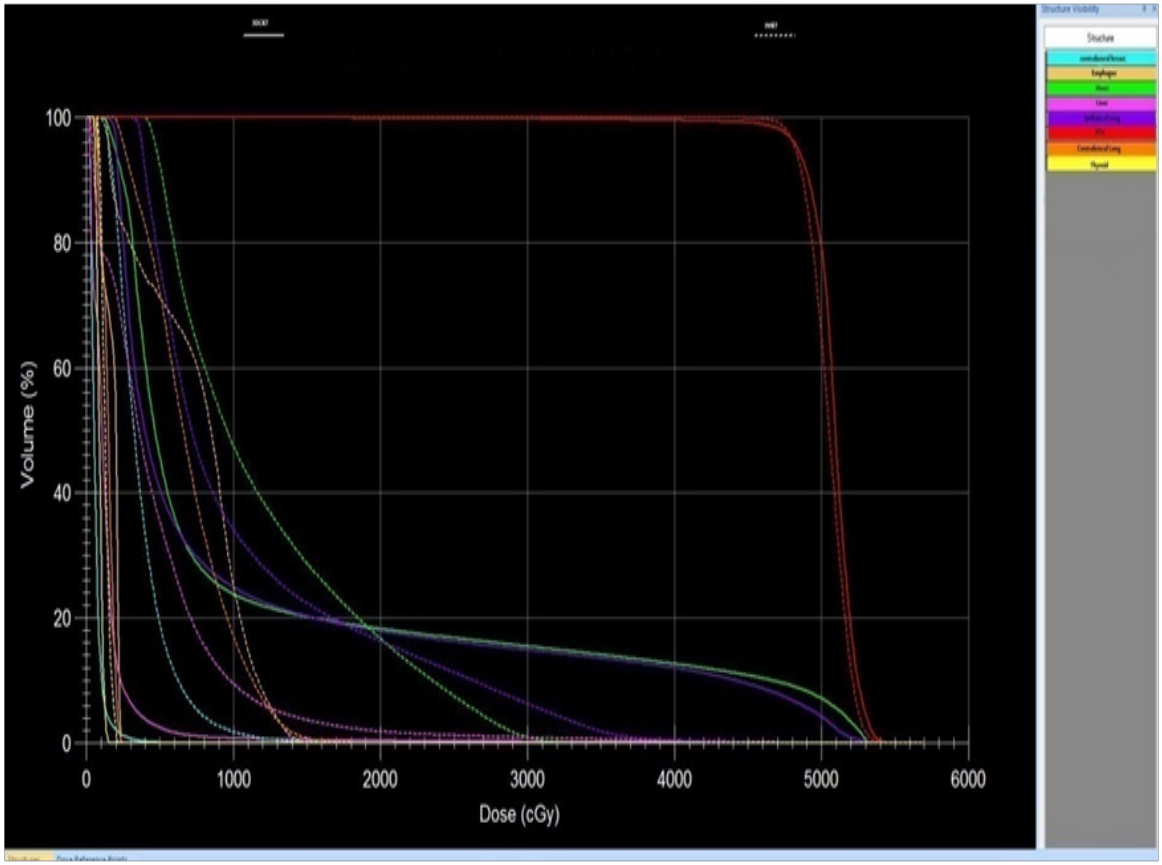

Fig. 2. The cumulative DVHs of the representative patient for PTV, Contralateral breast, Esophagus ,Heart, Liver, Ipsilateral Lung ,contralateral lung and Thyroid for 3DCRT plan (Solid line) and IMRT plan (Dashed line).

The excess absolute risk EAR per 10,000 persons per year per Gy mean values and standard deviation (Mean ±SD) for normal tissues is given in Table 5. Also, the EAR for the linear, plateau and linear-exponential dose–response model between 3DCRT and IMRT is demonstrated in (figure 4). The EAR of the ipsilateral lung was increased by 1.4%, 21.4%, and 10.4% for linear, plateau, and linear-exponential dose–response model, respectively, with IMRT plans in comparison with 3DCRT. Compared with 3DCRT, the IMR Plans have been shown increase of EAR in the contralateral lung by 3.4,2.5 and 3.5fold in linear, plateau, and linear-exponential dose–response model, respectively. The second cancer risk in the contralateral breast was increased from3.3to4 fold in IMRT plans according to three dose–response model estimations.

Using the linear dose–response model, the EAR in thyroid was increased by 50% in IMRT, but for plateau and linear-exponential model increased by 41.7% in comparison with the 3DCRT technique. The EARs to the esophagus were significantly higher for IMRT ($P < 0.05$), increasing the risks by 3.7, 2.7, and 3-fold over 3DCRT by applied linear, plateau, and linear-exponential dose–response model respectively. Also, the EAR for the stomach significantly increased with IMRT compared with EAR at the 3DCRT technique according to dose–response model used. The second cancer risk evaluated by EAR and based on the linear, plateau, and linear-exponential dose–response model was significantly higher ($P < 0.05$) in IMRT than 3DCRT for the contralateral lung, contralateral breast liver, thyroid, esophagus, and stomach. Also, the IMRT significantly increases second cancer risk in Ipsilateral Lung when the plateau dose-response model is applied.

Discussion

Based on our understanding of the carcinogenic effects of ionizingradiation at least a portion of these is likely to be caused by radiation exposure. After breast cancer surgery,

radiotherapy can dramatically reduce local recurrence rates and increase a patient's survival rates. However, radiotherapy has late effects on healthy tissues in the treatment area, such as secondary cancer. Robust and risk assessment is important to maximize radiotherapy effect for breast cancer patients while minimizing the risk of radiation-induced secondary malignancies. In this study, 3DCRT and IMRT techniques for the treatment of breast cancer were evaluated based on the dose coverage of the breast PTV and dose to OARs. Also, the second cancer risk was evaluated by EAR based on the linear, plateau and linear-exponential dose–response model between the two techniques. In general, the comparison of dose coverage parameters in PTV was significantly improved ($P< 0.05$) with the IMRT technique. In the present study, statistically significant improvement was shown in CN with IMRT plans compared to 3DCRT plans (0.58±0.074 vs. 0.77±0.078, $p =0.00036$). Also, the HI has been shown better value with IMRT plans1.07±0.017 vs 1.08±0.021 in 3DCRT with $p = 0.022$. The results of this study have been shown that the IMRT improved dose conformality and homogeneity, which improve cosmetic results and reduce late treatment- toxicity to the breast [15].

TABLE 4. The mean values of Organ Equivalent dose OED (Gy) (mean ± standard deviation) with 3DCRT and IMRT for the organs of interest for Linear, Plateau and Linear-exponenential dose-response model.

OARs	Model	3DCRT (Mean ±SD)	IMRT (Mean ±SD)	P-Value
Ipsilateral Lung	Linear	10.39 ± 0.86	10.55 ± 1.4	0.3607
	Plateau	3.46 ± 0.33	4.2 ± 1.48	0.00043
	Linear -exponential	3.87 ± 0.59	4.25 ± 1.48	0.272
Contralateral Lung	Linear	0.94 ± 0.37	3.35 ± 1.79	0.00081
	Plateau	0.85 ± 0.32	2.46 ± 1.02	0.00026
	Linear -exponential	0.88 ± 0.34	2.7 ± 1.2	0.00035
Contralateral Breast	Linear	0.69 ± 0.31	2.73 ± 0.83	0.00026
	Plateau	0.62 ± 0.26	2.12 ± 0.52	0.0000126
	Linear -exponential	0.64 ± 0.28	2.05 ± 0.76	0.000163
Thyroid	Linear	0.56 ± 0.23	0.82 ± 0.2	0.000757
	Plateau	0.53 ± 0.21	0.77 ± 0.18	0.000873
	Linear -exponential	0.54 ± 0.22	0.82 ± 0.22	0.000774
Liver	Linear	2.47 ± 1.96	5.31 ± 3.45	0.0019
	Plateau	1.2 ± 0.66	2.83 ± 1.33	0.00026
	Linear -exponential	1.25 ± 0.7	3.22 ± 1.59	0.000774
Esophagus	Linear	1.38 ± 0.21	5.14 ± 1.3	0.031
	Plateau	1.24 ± 0.12	3.36 ± 0.76	0.015
	Linear -exponential	1.29 ± 0.3	3.81 ± 0.99	0.018
Stomach	Linear	0.59 ± 0.2	3.18 ± 1.4	0.00012
	Plateau	0.57 ± 0.1	2.55 ± 1.7	0.00033
	Linear -exponential	0.57 ± 0.1	2.75 ± 1.2	0.000143

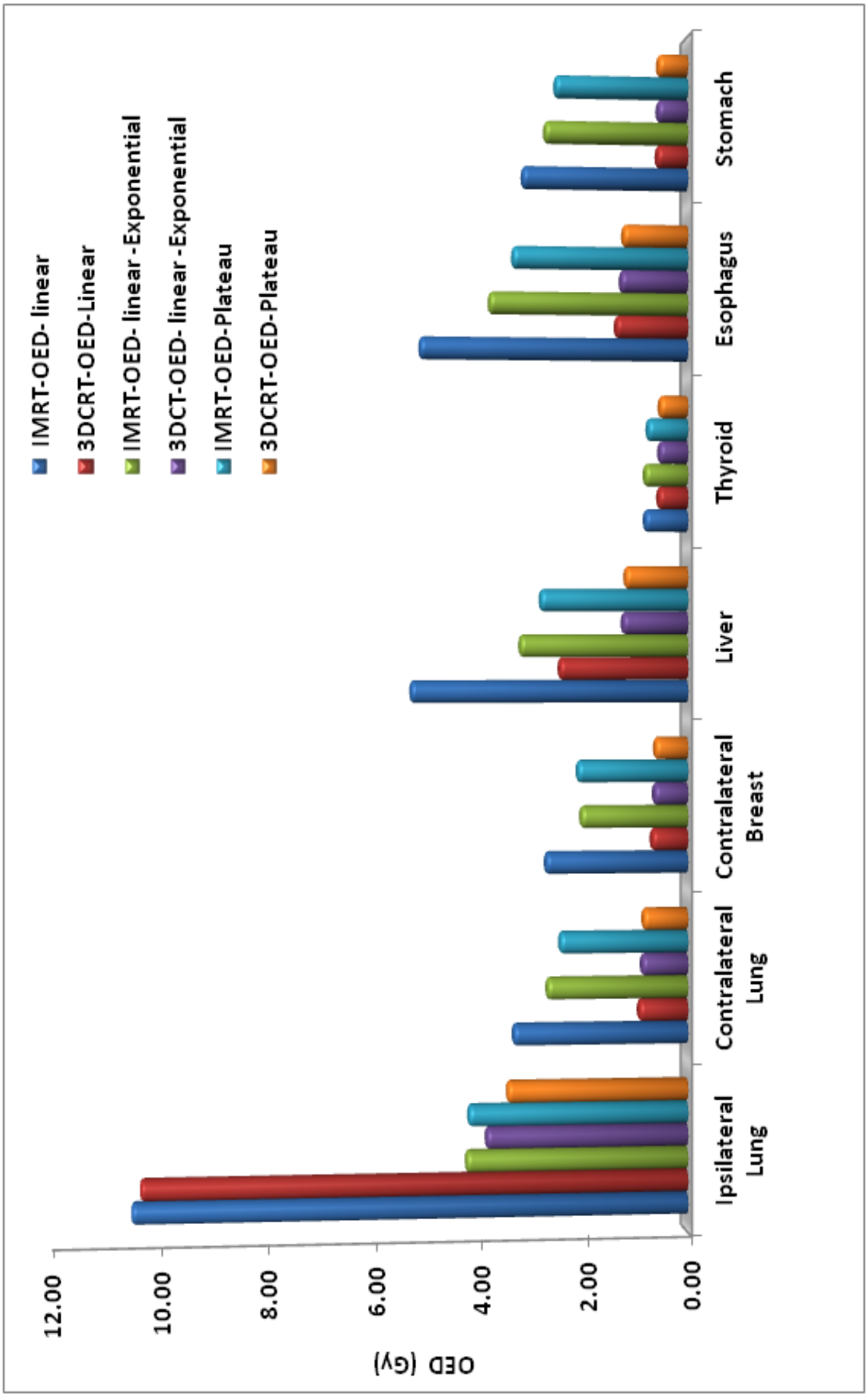

Fig. 3. The organ equivalent doses (OED) for normal tissues (Ipsilateral Lung, Contralateral Lung, Contralateral Breast, Liver, Thyroid, Esophagus, and Stomach) with (3DCRT) and (IMRT) techniques using linear, plateau, and linear-exponential dose–response model.

TABLE 5. The excess absolute risk EAR per 10,000 persons per year per Gy (mean ± standard deviation) with 3DCRT and IMRT for the organs of interest for Linear, Plateau and Linear-exponenential dose-response model.

OARs	Model	3DCRT (Mean ±SD)	IMRT (Mean ±SD)	P-Value
Ipsilateral Lung	Linear	85.6 ± 7.8	86.8 ± 9.3	0.4
	Plateau	28.5 ± 3	34.6 ± 4	0.0004
	Linear -exponential	31.8 ± 4.8	35.1 ± 12.4	0.264
Contralateral Lung	Linear	7.7 ± 3.1	27.7 ± 15	0.0009
	Plateau	7 ± 2.7	20.3 ± 8.6	0.003
	Linear -exponential	7.3 ± 2.8	22.3 ± 10.1	0.0004
Contralateral Breast	Linear	3.4 ± 1.6	13.7 ± 6.1	0.0002
	Plateau	3.1 ± 1.3	10.6 ± 4.1	0.0002
	Linear -exponential	3.2 ± 1.4	10.7 ± 5.6	0.0008
Thyroid	Linear	0.12 ± 0.07	0.18 ± 0.06	0.0011
	Plateau	0.12 ± 0.07	0.17 ± 0.06	0.0013
	Linear -exponential	0.12 ± 0.1	0.17 ± 0.1	0.0011
Liver	Linear	4.2 ± 3.3	9.6 ± 6.5	0.0027
	Plateau	2.1 ± 1.1	5.8 ± 2.6	0.0027
	Linear -exponential	2.2 ± 1.1	5.8 ± 3.1	0.0007
Esophagus	Linear	0.86 ± 0.1	3.18 ± 1.1	0.04
	Plateau	0.77 ± 0.2	2.09 ± 0.51	0.045
	Linear -exponential	0.8 ± 0.13	2.37 ± 0.4	0.046
Stomach	Linear	0.3 ± 0.03	1.59 ± 0.4	0.002
	Plateau	0.28 ± 0.01	1.28 ± 0.6	0.0001
	Linear -exponential	0.29 ± 0.02	1.38 ± 0.7	0.0007

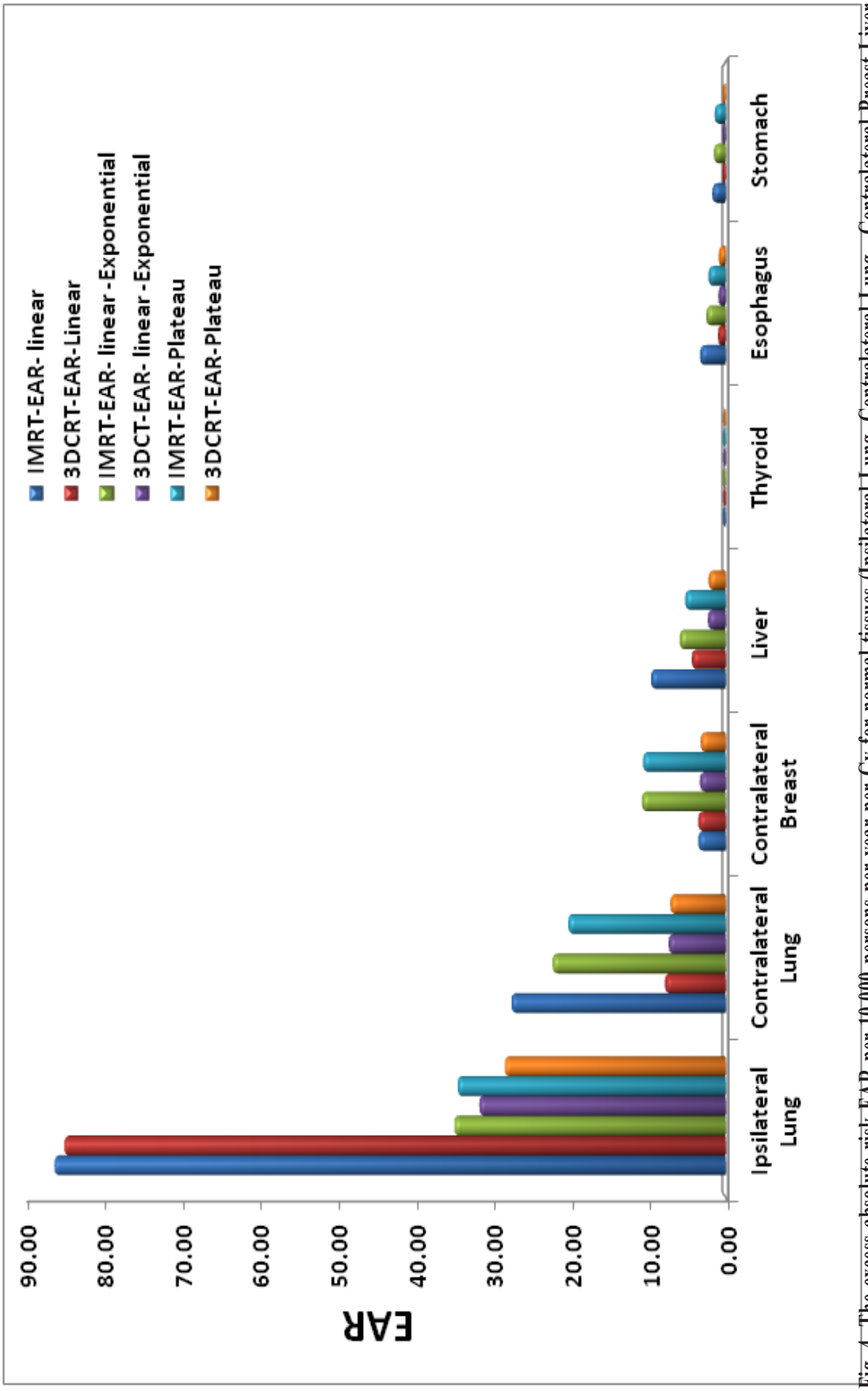

Fig. 4. The excess absolute risk EAR per 10,000 persons per year per Gy for normal tissues (Ipsilateral Lung ,Contralateral Lung , Contralateral Breast Liver Thyroid Esophagus and Stomach) with (3DCRT) and (IMRT) techniques using linear, plateau, and linear-exponential dose–response model.

The beam MUs per fraction were higher in IMRT compared with 3DCRT that increase treatment time, and the scatter doses in normal tissues during beam modulation. The IMRT plans were shown 2.3 times increase in beam MUs relative to 3DCRT plans in our study. The V_{20Gy} % of Ipsilateral lung significantly improved with IMRT plans in comparison to 3DCRT. S. Moorthy et al. compared IMRT and 3DCRT for the chest wall. In their results, the IMRT was produced better OARs sparing like Lung V20, the heart (mean dose and V30), and LAD (left anterior descending artery) mean and maximum dose.[16]. Similar results were observed in this study for Ipsilateral lung V20 and the mean dose to the heart. However, in the current study, IMRT plans significantly increases the mean dose and the volume exposed low dose in healthy tissues (Contralateral Lung, Contralateral Breast, Thyroid, Liver, Esophagus, and Stomach).Al-Rahbi et al. found that inverse planned intensity modulated radiotherapy (IP-IMRT) plans increased the total MUs, thereby increasing the volume of normal tissues exposed to the very low dose [17]

In the present study, the OED based on dose–response models were used to estimate secondary cancer risk for organs in high and low dose area. There is uncertainty in the shape of the radiation dose-response curve for doses greater than 2Gy[13]. Because cell killing and sterilization of already mutated cells can become more important at higher doses so estimating second cancer risk is imprecise when the linear model was used. In this study the results show that OED based on the three models significantly higher with IMRT than 3DCRT.The higher OED was observed in ipsilateral Lung that because it is close to the target. The EAR of Ipsilateral lung was increased by 1.4%, 21.4% ,and 10.4% for linear, plateau and linear-exponential dose–response model respectively, with IMR plans in comparison with 3DCRT.

The results of EAR show a small difference between linear, plateau, and linear –exponential dose-response model, but Zhang et al., has reported higher difference in the ipsilateral lung[18] This confirms the fact that at doses higher than 5Gy, the linear model deviates from the other two models [10]. In present study, the second cancer risk with IMRT increased by2.5 -3.5fold, 3.3-4fold, 3-7fold, and 4.6-5.3fold for contralateral lung, contralateral breast, esophagus, and stomach based on dose-response model applied compared with 3DCRT. So secondary cancer risk in all normal tissues in this study was increased with multifield IMRT as observed by Hall et al. [19]

The reason for this is that a larger volume of normal tissues is being exposed at lower doses due to the use of multiple beams and the high number of monitor units used in IMRT[20].

The present study dose calculation was done on treatment planning systems that are commercially available. As a result, there may be inaccuracies in the estimates of dose corresponding to deficiencies in each calculation algorithm. For both in-field and out-of-field dose calculations, Monte Carlo is known as the most accurate dose calculation algorithm, as reported by Howell, Rebecca M., et al.[21]. The XVMCMonte Carlo dose calculation algorithm was used for IMRT plan dose calculation in this study. This could therefore improve the accuracy in dose calculations and second cancer risk estimate in normal tissues. Fleckenstein, Jens, et al. concluded that the XVMC Monte Carlo algorithm in combination with the virtual energy fluence model, as implemented in MONACO TPS, is capable of predicting the dose distribution accurately over the whole range of human tissue densities even for highly modulated VMAT treatment arcs[22]. However, Collapsed Cone algorithm was used with 3DCRT wedged fields. This dose calculation algorithm was allowed in the Monaco TPS for 3DCRT planning with a pencil beam algorithm. In this technique, the Collapsed Cone algorithm was used, which is an effective algorithm and well reported[23].

Ruben et al. quantified the effect of IMRT on secondary cancer risk when treating different tumor sites. They were documented findings that are closely comparable to our estimates in the case of the breast cancer with four-field IMRT and 3DCRT with physical wedges. In their assessment, was depending on linear, exponential, and plateau risk models. The risk was higher for four-field IMRT at 1.1% compared with 0.8% for 3DCRT with physical wedges[24] Abo-Madyan, Yasser, et al. got a similar risk estimate to our study[1] They found that the cumulative EAR of (ipsilateral lung + contralateral lung + contralateral breast) were increased by 82 ± 96%, 71 ± 82% with the linear model, 3 ± 14%, 123 ± 78%, 113 ± 61% for the plateau model and2 ± 15%, 131 ± 85%, 123 ± 66% for the linear-exponential risk model with tangential intensity modulated radiotherapy (t-IMRT), multibeam intensity modulated radiotherapy (m-IMRT),

and volumetric modulated arc therapy (VMAT) respectively compared to 3DCRT. They concluded that the second cancer risk after 3D-CRT or t-IMRT is lower than for m-IMRT or VMAT by about 34% for the linear model and 50% for the linear-exponential, and plateau models, respectively[1] In another study Zhang, Quanbin, et al. 6-field IMRT and VMAT compared with 3DCRT with physical wedges(W-TF)a significantly increased the cumulative EAR [18]

In addition to radiotherapy, the second cancer risk in cancer survivors patients may increase due to patients lifestyle, genetic susceptibility, and chemotherapy treatment[25]. There are about 17-19% cancer survivors patients have second cancer development after primary cancer treatment[26]. From the total treatment options for cancer patients, about 5% of second malignancies are related to radiotherapy. The well examples of solid tumors induced by radiation were observed in Japanese atomic bomb survivors, which have breast cancer incidence with a higher rate in women exposed to radiation when they were examined fluoroscopically for tuberculosis or irradiated for treatment of lymphomas or benign tumors[27]. However, some studies have reported the lack of cancer risk to the contralateral breast after radiotherapy with the conventional technique for breast cancer [28]. Grantzau and Overgaard decided on their studies of a meta-analysis of 762,468 breast cancer patients the radiotherapy increased the relative risk (RR) of second cancers for non-breast cancer organs with a RR of 1.22 (95% CI, 1.06–1.41) at five or more years after the treatment[29]. Also, after five years, lung RR 1.39 (95% CI1.28–1.51), esophagus RR 1.53 (95% CI 1.01–2.31), and second sarcomas RR 2.53 (95% CI 1.74–3.70). By the time the relative risk was increased. It was higher at 15 years or more after the breast cancer diagnosis, for second lung RR 1.66 (95% CI 1.36–2.01) and second esophagus cancer RR 2.17 (95% CI 1.11–4.25). However, second thyroid cancer has no significant association with breast radiotherapy [29].

Because of the short time span of its therapeutic availability, there are currently no clinical reviews focusing on second cancer induction after IMRT. Also, there is controversy about the carcinogenic risks of IMRT in comparison to 3DCRT. Based on this study, the IMRT plans with a multibeam were improved PTV dose converge and homogeneity compared with 3DCRT. The IMR plans produce better OARs sparing (Ipsilateral Lung and heart) compared with 3DCRT Plans. However, The IMRT raises the second cancer risk in normal tissues; this is due to high volumes of normal tissues exposed to low doses, higher numbers of MUs, and radiation scattered from the treatment head of linear accelerator during the beam's modulation. The second cancer risk estimated with the linear, plateau, and linear-exponential dose–response model has a higher difference between the three models at higher organ OED. While at low organ OED the second cancer risk estimated with linear, plateau, and linear-exponential dose–response model has a small difference.

Conclusion

Three-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT) afforded accepted dose coverage of PTV. However, the IMRT technique demonstrated a clear advantage in breast PTV dose coverage, conformity, and homogeneity over 3DCRT. IMRT was superior to 3DCRT in terms of OAR-sparing of ipsilateral lung and heart, which in high dose region. Also, IMRT techniques were increased the volumes of low does and the mean dose in normal tissues compared with 3DCRT. The second cancer risk in normal tissues based on the EAR model after IMRT is higher than 3DCRT. Advanced radiotherapy techniques as IMRT for breast cancer treatment must evaluate based on secondary cancer risks when treating young patients.

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تقييم خطر الإصابة بالسرطان الثانى من العلاج الإشعاعى للثدى بإستخدام نماذج الإستجابة للجرعة

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هدفت هذه الدراسة إلى تقييم مخاطر الاصابة بالسرطان الثانى الذى يسببها الإشعاع في الأنسجة الطبيعية بعد علاج سرطان الثدي بالعلاج الإشعاعى ثلاثى الابعاد 3DCRT والعلاج الإشعاعى المعدل الشدة IMRT،وذلك لـ ١٠ مرضى مصابيين بسرطان الثدى، تم تقييم خطط العلاج الإشعاعى ثلاثى الابعاد 3DCRTوالعلاج الإشعاعى المعدل الشدة IMRT ومقارنتها بالعديد من المعاملات الدوزمترية لحجم الهدف المخطط (PTV) والأعضاء المعرضة للخطر (OARs)، تم حساب الجرعة المكافئة للأعضاء (OED) بناءً على نماذج الاستجابة للجرعة الخطية والخطية الأسية والهضبة،ثم تم تقييم مخاطر الاصابة بالسرطان الثاني من خلال نموذج الخطر المطلق الزائد (EAR) للأعضاء المعرضة للخطر (OARs)، اظهرت النتائج انه بالنسبة للثدي ، تم تحسين عوامل تغطية الجرعة لحجم الهدف المخطط (PTV) من الثدى بشكل ملحوظ بإستخدم العلاج الإشعاعى المعدل الشدة IMRT مقارنة بالعلاج الإشعاعى ثلاثى الابعاد، كما انخفضت النسبة المئوية لحجم الرئة المجاورة المغطى بـ ٣٠ جراى و ٢٠جراى ($\%V_{30Gy}$ % and V_{20Gy}) بشكل ملحوظ بإستخدام تقنية العلاج الإشعاعى المعدل الشدة ، بالمقارنة بخطط العلاج الإشعاعى ثلاثى الابعاد، ومع ذلك، أظهرت خطط العلاج الإشعاعى المعدل الشدة زيادات ملحوظة ($p<0.05$) فى قييم الجرعة المتوسطة فى الانسجة السليمة ،مقارنة بالعلاج الإشعاعى ثلاثى الابعاد، وايضا قد زادت الجرعة المكافئة للأعضاء OED مع خطط العلاج الإشعاعى المعدل الشدة بناء على نماذج الاستجابة للجرعة الخطية والهضبة والخطية الأسية ايضا، كما زاد خطر الإصابة بالسرطان الثاني عند إستخدام العلاج الإشعاعى المعدل الشدة بمقدار ٢,٥ - ٣,٥ ضعف، و ٣,٣ - ٤ أضعاف ، و ٣ - ٧ أضعاف ، و ٤,٦ - ٥,٥ ضعف في الرئة المقابلة ، والثدي المقابل ، والمريء ، والمعدة بناءً على نموذج الإستجابة للجرعة المستخدم .

الخلاصة: تقنية العلاج الإشعاعى المعدل الشدة أظهرت نتائج افضل عن تقنية العلاج الإشعاعى ثلاثى الابعاد من حيث تغطية وتجانس الجرعة للورم وتقليل الجرعة الإشعاعية على الانسجة السليمة المحيطة بالورم،بينما خطر الإصابة بالسرطان الثانى فى الانسجة السليمة اعلى عند إستخدام العلاج الإشعاعى المعدل الشدة من العلاج الإشعاعى ثلاثى الابعاد، يجب تقييم تقنيات العلاج الإشعاعى المتقدمة مثل العلاج الاشعاعى المعدل الشدة بناء على تقدير خطرالإصابة بالسرطان الثانى وخصوصاعندما يتم علاج المرضى صغار السن.