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Assessment of Radiation-induced Secondary Cancer Risks in Breast Cancer Patients Treated with 3D Conformal Radiotherapy

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ABSTRACT

Introduction: In this survey, radiation-induced secondary cancer risks (SCRs) have been assessed in irradiated organs following three-dimensional conformal radiation therapy (3D-CRT) of breast cancer using the Biological Effects of Ionizing Radiation (BEIR) VII models.

Material and Methods: Sixty patients with left-sided breast cancer, who were treated with a total breast dose of 50 Gy in 2 Gy fractions were chosen for this study. Differential dose volume histograms (dDVHs) were retrieved, and values of mean organs dose were computed. Second cancer risks for the heart, ipsilateral lung, liver, thyroid, and contralateral were estimated using both excess relative risk (ERR) and excess absolute risks (EAR) models as proposed by the BEIR VII committee of the U.S National Academy of Sciences.

Results: The mean organ dose values of these 60 patients were 6.8, 15.9, 3.7, 4.5, and 1.5 Gy in the thyroid, ipsilateral lung, contralateral breast, heart, and liver, respectively. Based on the BEIR VII models, ERR was estimated to be 21.2, 5.0, 1.6, and 1.4 Gy^{-1} for the ipsilateral lung, thyroid, heart, and liver, respectively. In addition, excess absolute risks for cancer incidence were calculated as 105, 45.8, 15.8, and 4.35 Gy^{-1} for these organs, respectively.

Conclusion: In this survey, SCRs were quantitatively measured for various organs of breast cancer patients who received 3D-CRT. We observed that 3D-CRT treatment was associated with a relatively high SCR in the lung.

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Introduction

Breast cancer is one of the most common malignancies in women around the world [1]. Over the last two decades, postoperative radiotherapy has been incrementally used as an adjuvant treatment for early breast cancer. Furthermore, it has been proved to be effective in decreasing loco-regional recurrence and overall survival rates [2-6]. However, it is worth noting that in patients who receive radiotherapy (RT), parts of the tissue volume can receive high radiation doses. Among all possible side effects of RT, the increased risk of secondary cancer by scattered radiation fields from the primary cancer radiotherapy is significant [7-12].

The risk of second cancer following radiotherapy is clinically important for patient care and treatment efficacy. Due to poor lifestyle choices and genetic predisposition, patients undergoing RT may be subjected to a high risk of second cancer. Many studies imply that the risk of post-radiotherapy secondary cancer is negligible and difficult to statistically detect [13]. However, with extensive follow-up of long-term cancer survivors, these risks are being identified in various radiation epidemiological analyses [14-19].

A number of international organizations such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [*20*], the International Commission on Radiological Protection (ICRP) [21], the National Council on Radiation Protection and Measurement (NCRP) [22], and the American Association of Physicists in Medicine (AAPM) [23], as well as several large-scale studies have reviewed the available data concerning SCR after radiotherapy.

The National Academy of Sciences (NAS) established the Committee on Biological Effects of ionizing radiation (BEIR Committee), which provided reports on the risk of secondary cancer in the years 1956-2007. One of the committee's reports attributed the risk of secondary cancer to parameters such as radiation dose, and the age of the irradiated patient and introduced models for excess relative risk (ERR) and excess absolute risk (EAR) and predictive methods for reporting [24].

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In the treatment of breast cancer with the 3D-CRT technique, due to the divergence of the beams and the photon scattered radiation fields, some adjacent organs receive significant doses of radiation, and thus, may be sites for therapy-induced secondary cancers. For breast radiotherapy, the key organs for risk assessment include the contralateral breast, heart, thyroid, ipsilateral lung, and liver. Therefore, calculating the absorbed dose by these organs and the SCR in adjacent organs during RT of breast cancer is clinically imperative for patient follow-up and treatment efficacy. The aim of this survey was to evaluate the SCR in radiation-sensitive organs under RT for breast cancer by the 3D-CRT technique and using the BEIR IIV radiobiology models. These models provide parameters for specific organs for both sexes and the attained age at the time of risk assessment.

Materials and Methods

Computed tomography (CT) and treatment techniques

This cross-sectional study was carried out among 60 patients with left-sided breast cancer, who were treated with the 3D-CRT technique at Imam Khomeini Medical Center Hospital-based Cancer Registry (IMHCR) between 2014 and 2018. Most patients were within the age group of 33-55 years, and only three patients exceeded the age of 60 years. All the patients underwent a CT simulation scan for treatment planning purposes (General Electric Inc., Light speed). The slice thickness was 5 mm, and all patients were in the supine position with the help of a breast board for arm positioning above the head. The CT images were used to identify targets for treatment and for reporting dose to normal non-targeted organs and tissues. Computed tomography datasets were transferred in DICOM format to the treatment planning system (TPS) for localization of targets and organs at risk (OARs). All OARs such as the heart, contralateral breast, thyroid, liver, and ipsilateral lung, as well as the planning target volume (PTV), were contoured by a radiation oncologist.

The plans and CT-based dose calculations were performed on PCRT-3D v6.0.2 (Técnicas Radiofísicas, Zaragoza, Spain) TPS, using a superposition (SP) algorithm according to the standard clinical practice. All dose calculations were performed with a 6-MV X-ray linear accelerator machine (Elekta Compact 6 MV, China) at the prescription dose of 50-60 Gy in 25-30 fractions.

The treatment technique consisted of two tangential wedged fields, from both medial and lateral sides and anterior-posterior supra-clavicle fields. The planning aimed at corroborating the 95% isodose level to the PTV, while the maximum dose, based on the ICRU recommendations, should be limited to 107%. Conformity, optimal target coverage, homogeneity, and OARs' dose limits (as small as possible, without compromising target coverage or conformity) were incorporated into the optimization and evaluation of all plans. An example of the plans is presented in Figure 1, which shows a patient's treatment plan using the 3D-CRT technique. Afterwards, the DVHs were retrieved for all the OARs and the PTV. An example of the DVH curves for the PTV and OARs is shown in Figure 2. In our study, both thyroid lobes were considered as defining the thyroid organ.

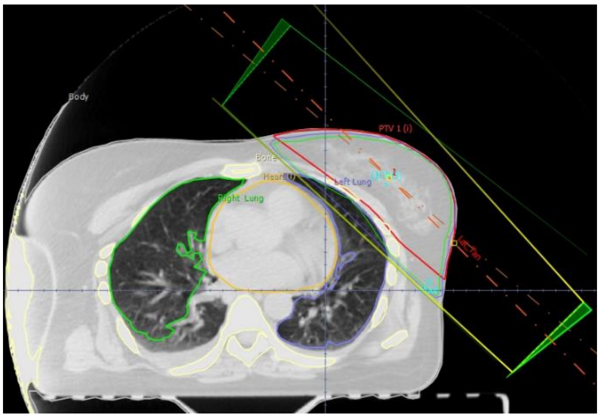

Figure.1. Axial view of a 3D-CRT breast radiation treatment plan; isodose distributions for a typical patient in tangential wedge beam plan

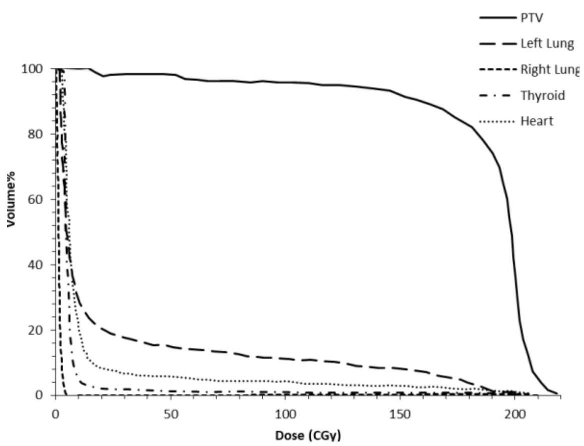

Figure 2. An example of dose volume histogram (DVH) curves for planning target volume and organs at risk of a patient for breast cancer treatment

Organs' median doses

After treatment design for each patient, the mean doses to the liver, ipsilateral lung, thyroid, heart, and contralateral breast were calculated for the 3D-CRT, based on the DVH curves. The median doses were obtained directly from the treatment planning system.

Secondary cancer risk model

Equation 1 is the BEIR committee recommended model for both excess relative risk (ERR) and excess absolute risk (EAR) [25]:

$$\mathrm{ERR}(D.s.e.a) \text{ and } \mathrm{EAR}(D.s.e.a) = \beta_s\, D \exp(\gamma e^*)\left({}^{a}/_{60}\right)^{\eta} \qquad (1)$$

where D represents the mean organ dose, (in Gy); β_S, γ, and η are model parameters; e is the age at exposure time; $e^* = (e - 30)/10$ for $e < 30$ and 0 for $e > 30$ years; and a is the attained age.

Table1. Parameters of risk incidence models in BEIR VII[a]

Cancer	ERR model				EAR model			
	β_M	β_F	γ	η	β_M	β_F	γ	η
Liver	0.32	0.32	-0.3	-1.4	2.2	1	-0.41	4.1
Lung	0.32	1.4	-0.3	-1.4	2.3	3.4	-0.41	5.2
Breast	Not used				See text			
Other solid	0.27	0.45	-0.3	-2.8	6.2	4.8	-0.41	2.8
Thyroid	0.53	1.05	-0.3	0	Not used			

[a]From Table Twelve–Two (National Research Council 2006).

Table 1 shows the values for these parameters, which are set according to the patient's gender and body organs [12].

In this study, we concentrated on estimating the incidence of cancer in the 30 to 80 years age group (reflecting the typical age distribution of breast cancer incidence in both Europe and the U.S.).

The models of the BEIR VII Committee, as shown in Table 1, give the risk of breast cancer only in terms of EAR. In contrast, the risk model for the thyroid is given in terms of only the ERS. Regarding thyroid cancer, the model introduced by this committee differs slightly from Equation 1. The committee offers the model to calculate the relative risk of thyroid cancer as follows:

$$\mathrm{ERR(D.s.e.a)} = \beta_s \,\mathrm{D} \exp[\gamma(^{e-30}/_{10})](^{a}/_{60})^{\eta} \qquad (2)$$

where in contrast to Equation 1, the ERR always declines exponentially for all ages as exposure age increases. This equation is based on the outcomes obtained from thyroid cancer-affected patients under the age of 15 years.

Building upon the data published in the BEIR VII report, the risk of secondary cancer was estimated using only an EAR model. This report offers the absolute risk of breast cancer as:

$$\mathrm{EAR(D.s.e.a)} = \beta_s \,\mathrm{D} \exp\left[\gamma\left(^{e-50}/_{10}\right)\right]\left(^{a}/_{50}\right)^{\eta} \qquad (3)$$

where β = 9.9 and γ= -0.51 are considered. Also, if the patient's age is less than 50 years old (a<50), η = 3.5 and for ages greater than 50 years (a≥50) η = 1.1 is considered.

In summary, doses and cancer risks were assessed for the thyroid, ipsilateral lung, contralateral breast, liver, and heart using risk models proposed in the BEIR VII report.

Results

Measured organ doses

The absorbed dose in various sensitive organs (OARs) was estimated in 60 patients undergoing 3D-CRT for breast cancer. These values were obtained using the DVH curve for each organ. In addition, the mean age of the patients in this survey was 44 years, which is considered to be the lower age for this disease among women.

Table 2 shows the range of mean dose as calculated for patients undergoing 3D-CRT treatment of breast cancer for the OARs. For the ipsilateral lung, 3D-CRT resulted in the highest mean dose (16.0 Gy). The mean doses for other susceptible organs such as the heart, thyroid, contralateral breast, and liver were 4.51, 6.85, 3.73 and 1.54 Gy, respectively. Liver mean dose was significantly lower compared to other organs. The mean values of organ dose in Table 2 are the average values obtained from the 60 patient cohort.

Calculation of secondary cancer risk

The risk of secondary cancers in radiotherapy treatment was obtained using the BEIR VII risk models, which was primarily based upon the observed cancer incidence rates in the Japanese Atomic Bomb Survivor cohort [24]. Accordingly, the ERR and EAR values were obtained using the mathematical equations for these two models from the BEIR VII report. In the following sections, we examine both the ERR and EAR of secondary cancer following 3D-CRT treatment of breast cancer.

Excess relative risk (ERR)

As indicated, ERR and EAR depend on parameters such as age at exposure, dose, and gender of the patient. To investigate these values, we considered a range of attained age from 30 to 80 years.

The presented equation for most solid tumors has a limitation for the amount of ERR on the age at exposure over the age of 30 years. Practically, the equation will be eliminated for ages above 30 years. This limitation does not exist for the thyroid. According to this equation, the ERR value decreases exponentially with an increase in the age at exposure. As shown in Equation 1, the risk is proportional to the dose; thus, according to the BEIR VII models, the dimension for this quantity is Gy^{-1}. The ERR rate for different organs caused by breast cancer therapy is displayed in Table 3. The data are for a patient who was 38 years old at the time of exposure and in all patients for all measured organs.

Table.2. Average absorbed doses (Gy) in various organs at risk for 60 patients in the treatment of breast cancer using 3D-CRT technique

Organ at risk	Mean Dose (Gy) ± SD*		
	This study	Yasser Abo-Madyan et al. [29]	Grantzau et al. [30]
Contralateral Breast	3.73± 0.48	0.51	_
Ipsilateral Lung	15.99±4.29	7.40	8.40
Thyroid	6.85±10.30	_	_
Heart	4.51±2.99	_	_
Liver	1.54±3.24	_	_

*SD, standard deviation.

Table.3. Excess relative risk and excess absolute risk of all measured organs for one patient (38-year old) and all patients

Organ	ERR (Gy^{-1})		EAR (Gy^{-1})	
	[a]One patient	All patient	[a]One patient	All patient
Contralateral Breast	-	-	14.11	16.41±5.83
Ipsilateral Lung	26.45	21.23±7.03[b]	51.36	95.96±5.78
Thyroid	3.14	5.01±3.97	-	-
Heart	2.86	1.58±1.56	25.23	23.26±2.65
Liver	0.48	1.36±0.98	1.22	6.81±3.45

[a] Exposure age =38, attained age =58
[b] SD, standard deviation.

As illustrated in Table 3, the highest risk of secondary cancer associated with 3D-CRT for breast cancer treatment was related to the ipsilateral lung. The next highest organ at risk was the thyroid, with the heart and liver displaying the lowest risk of secondary cancer. In order to compare the relative risk of different organs, we obtained the average of different data and gathered them in Table 3. The results indicated that the ERR model predicted the relative risk of breast radiation in crucial organs such as the ipsilateral lung, thyroid, heart, and liver as 21.2, 5.01, 1.58, and 1.36 Gy^{-1}, respectively. The risk of secondary ipsilateral lung cancer was higher than the risk of secondary thyroid, heart, and liver cancer by a factor of 423, 1343, and 1561, respectively.

Excess absolute risk (EAR)

The EAR was calculated based on the BEIR VII model equations and the mean dose obtained from patients' DVHs. The EAR rate for the various organs examined in this project was acquired using equations 1 and 3.

Excess absolute risk values for age at exposure for a patient aged 38 years at the time of treatment and for all patients within the age range of 27 to 78 years are presented in Table 3. To compare the relative risk of different organs among all patients, we obtained the average of different data. Also, in this method, the highest relative risk in breast cancer treatment that can lead to secondary cancers was related to the ipsilateral lung. The EAR model predicted that the average excess risks of ipsilateral lung, heart, contralateral breast, and liver cancer were 95.96, 23.26, 16.41 and 6.81 Gy^{-1}, respectively. The risk of secondary ipsilateral lung cancer was higher than the risk of secondary heart, contralateral breast, and liver cancers by a factor of 415, 584, and 1140, respectively, based on the excess risk value. The EAR and ERR data showed the strong age dependency of secondary cancer risk according to the BEIR VII model.

Discussion

The BEIR VII radiobiological model, with the introduction of the two EAR and ERR methods, examines the SCR following radiation exposure [9]. In this study, we evaluated the SCR of radiation-sensitive organs in 3D-CRT breast treatment using the BEIR VII models. The analysis of the data by the BEIR VII models showed that the SCR increased with the use of radiotherapy.

The age of cancer incidence is of great importance for radiotherapy-treated patients [26]. Today, younger patients are presenting with breast, stomach, and esophagus cancers in clinics. In this study, the mean age of female breast cancer patients was 44 years (Figure 1). We observed that the risk of secondary cancer declines as the exposure age increases using either of the ERR and EAR methods, which is consistent with the studies reported by Donvon et al. They found an increased risk of breast cancer in younger individuals [25]. Also, other studies have shown that the risk of recurrence in the younger age group was higher than that for older women [21, 27, 28]. Tercilla, Krasin, and Lawn-Tsao measured dose in the contralateral breast among 15 patients treated with ^{60}Co gamma rays using TLD dosimetry, which ranged from 3.2 to 6.5 Gy in patients receiving a total prescribed dose of 50 Gy to the involved breast [29]. However, in our study the mean dose of contralateral breast in patients with a total dose of 50 Gy was 3.73 Gy. We expect this difference can be attributed to the techniques and machines used.

Studies with more advanced techniques, such as CRT and IMRT, reduced the dose of the opposite breast up to 10-20%, although it still received about 3 to 6% of the 50 Gy total dose that cannot be ignored. Usually, IMRT causes a 20% reduction in doses relative to the CRT [29].

Table 2 shows our estimates of mean dose in radiosensitive organs around the breast tissue delivered cumulatively during breast radiotherapy. According to the data presented in Table 2, the ipsilateral lung has the highest organ dose among the measured organs. The ipsilateral lung dose was about 428%, 233%, 1038%, and 354% higher than those reported for the contralateral breast, thyroid, liver, and heart, respectively. These results revealed that the ipsilateral lung is at higher risk for secondary cancer. This is due to the presence of a significant part of the ipsilateral lung in the tangential fields in the treatment plan. Notably, an increased incidence of heart damage and pulmonary fibrosis has been reported among patients undergoing RT, and the lung is at a greater risk of receiving peripheral dose from breast treatments [25, 30].

Also, a large part of the lung peak is in the supraclavicular field, which will greatly influence the increase in lung dose. Furthermore, the dose received by the thyroid was subject to much fluctuation among the patient cohort. This depends somewhat on the thyroid volume in different patients, but the main reason for the difference in this data is related to the supraclavicular field, which is selected according to the physician's opinion. Therefore, different volumes of the thyroid may be exposed to radiation that causes a change in thyroid doses.

Similar to our study, a study by Abo-Madyan et al. was conducted on the risk of secondary cancer of lung and breast following breast cancer treatment, which examined the SCR [31]. Our results indicated that the mean doses to the ipsilateral lung and contralateral breast in 3D-CRT treatment were 16.0 and 3.73 Gy, respectively, while Yasser Abo-Madyan et al.reported that the largest of these values were 7.40 and 0.51 Gy, respectively. In another study, the lung mean dose was reported at 8.40 Gy, which was much less than the lung dose in our study [32].

In line with other studies, our findings indicated an increased risk of ipsilateral lung cancer among patients who received RT [2, 16, 33]. The analysis of data showed the ERR for ipsilateral lung cancer was higher than for other organs in the 3D-CRT treatment, and thus, radiation-induced cancer risk is significantly higher for this organ (Table 3). The risk ratio for the ipsilateral lung was about 423%, 1343% and 1561% higher than those reported for the thyroid, heart, and liver, respectively.

Over the years, several experimental studies have investigated the increased risk of thyroid cancer among survivors of the atomic bomb explosions in Japan and among patients who received RT [34-39]. Generally, studies found an increased risk of thyroid cancer in the younger age group. Also, the current results showed a relationship between the risk of thyroid cancer and RT for breast cancer patients. Nevertheless, no significant relationship was observed [36, 40-42].

The ERR value for the liver is very negligible in comparison to that for the ipsilateral lung, and consequently, the SCR for liver cancer using the 3D-CRT breast radiotherapy is also very low (Table 3). Therefore, in treatment planning, the priorities of the physician and the therapeutic team should be focused on the ipsilateral lung, thyroid, heart, and liver, respectively. It has been well established that organs away from target volumes, such as the liver, are at a lower risk for cancer [25, 43]. Furthermore, Kim et al. measured the SCR based on the organ’s distance from the target volume [44], whose results were consistent with the findings of this study.

The risk of recurrence in older women was less than that for the younger age group, and the risk of secondary cancers was found to decrease with increasing age at exposure by the ERR method. Also, it was determined that the risk of secondary cancer with the EAR method for the ipsilateral lung was higher than for other organs, and the risk ratio for the ipsilateral lung was about 415%, 584% and 1140% higher than those reported for the heart, contralateral breast, and liver, respectively. Along with this, the probability of secondary cancers in the heart is 150% higher than the contralateral breast, and the lowest risk has been reported for the liver.

During left-sided breast cancer RT, a part of the heart frequently receives a considerable dose, in particular when the internal mammary lymph nodes (IMNs) are included in the treatment plan. The use of RT for left-sided breast cancer is usually linked to an increase in cardiac complications. When the treatment aims the inclusion of the IMNs, the elimination of cardiac injury risk will be unlikely using the present RT techniques. As it is known, the risk of secondary cancer decreases with increasing the age at exposure by the EAR method, and with increasing attained age, the EAR rate also upsurges exponentially.

In conclusion, RT for breast cancer is associated with the increased risk of secondary cancers of the OARs, and the highest level of risk was found to be related to ipsilateral lung cancer.

The results indicated that the risk value is critically dependent on the organ dose, location of OARs relative to the primary cancer site, and the age at exposure. Nonetheless, SCR is generally linked to the exposed dose and non-negligible uncertainties, namely uncertainty in the model parameter and uncertainty in the dose-response curve.

Recently, scholars are advised not to choose among several dose-response models solely based on the experimental data [24]. This implies that large intrinsic uncertainties in the risk estimation might be present. Despite development in RT techniques during the last decade, few studies have estimated SCR using new treatment techniques, and the SCR of these methods remains uncertain [45, 46]. All of these indicate that further research is needed for determining SCR. Once sufficient data is gathered, future treatment plans may be assessed based not only on DVH-derived conventional factors, but also on the SCR evaluations.

Conclusion

It can be stated that in the 3D-CRT technique of breast cancer, the SCR for the ipsilateral lung is higher than for other normal, non-targeted organs. After the ipsilateral lung, the heart has the next highest risk, followed by the thyroid, contralateral breast, and liver with substantially lower secondary cancer risks. Therefore, caution should be exercised in the treatment planning of breast cancer patients to minimize the absorbed dose to adjacent organs as much as possible by choosing proper field sizes and techniques to avoid excess dose to those organs, which could decrease the risk of induced cancer in the future.

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