Estimation of the Thyroid Secondary Cancer Risk on the Patient of Standard Breast External Beam Radiotherapy

Abstract

Background: The purpose of this study was to estimate the secondary cancer risk of thyroid in standard radiotherapy methods which are commonly used for breast cancer patients. **Methods:** A total of 64 breast cancer patients (their age range was around 50 years old) who referred to Seyed-Al-Shohada hospital (Isfahan, Iran) were included in this study. The radiotherapy of the mentioned patients was performed using 6-MV photon beams. Dose measurements were also done using thermoluminescent dosimeters. Calculation of the risk of developing secondary cancer in thyroid was done using the Biological Effects of Ionizing Radiation Committee VII and recommended quantity of the International Radiation Protection Commission, excess relative risk. **Results:** The mean radiation dose to thyroid for the tangential beams, tangential field with supraclavicular (SC) field, and also a tangential field with SC field in modified radical mastectomy (MRM) were 0.883 ± 0.472, 1.512 ± 0.365, and 1.587 ± 0.37, respectively. The risk of developing secondary thyroid cancer over a period of 5 years after breast cancer therapy in the tangential, tangential with a SC field, and also tangential beam with SC field in MRM were 9.974 ± 4.318, 17.891 ± 0.365, and 18.783 ± 4.384, respectively. The mean of the measured thyroid doses in patients treated with tangent fields was significantly lower than the patients under the irradiation of the tangent fields with SC field ($P < 0.001$). **Conclusions:** Using radiation protection equipment is suggested for breast cancer patients who treated with the studied radiotherapy methods.

Keywords: *Breast cancer, second cancer risk, thyroid, TLD, radiotherapy*

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Introduction

Breast cancer is one of the most common malignancies, which are more prevalent in the developing countries.[1] The annual rate of incidence of breast cancer risk is approximately 1 million worldwide.[1-3] Radiation therapy is one of the most common approaches to treat breast cancer treatment.[4] In external radiation therapy, healthy tissue outside the radiation field is inevitably exposed to out of field radiation. The imposed dose in this region is called peripheral dose (PD).[5,6] The PD sources are leakage and scattered radiation from the linac head and scattered radiation from the irradiated volume of patient.[7,8] The goal of the treatment planning process is to deliver prescribed dose to the target volume and to limit the organ at risk dose.[9,10] The absorbed dose of out of field tissues is not respected in treatment planning because of the limitation of treatment planning

systems (TPS) in the calculation of the accurate dose in out of field region and also the lack of tomographic images of this region in routine imaging prescription. The ability of several TPS inaccurate dose calculation is limited to 3 cm out of field region.[11] Therefore, the estimation of the risk of developing secondary cancers after radiotherapy was the goal of several studies.[12] The risk of developing secondary cancer in patients who undergone radiation therapy has long been known.[8] Several studies have shown that women with breast cancer have an additional risk for other cancers such as thyroid cancer.[12-14] Many studies evaluated the risk of secondary cancer in radiotherapy of breast cancer patients and also a great variety can be seen in their methodology (measurement[15] or calculation[16]), dosimetry mediums (phantom[17,18] or patient[19]), dosimeters (thermoluminescent dosimeter [TLD], metal-oxide-semiconductor field-effect transistor or other types),[13,17,20] treatment techniques (standard or complex),[17,18] type

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of treatment machines, reported quantity (medium dose, equivalent dose, and skin dose),[20-22] and the risk models (International Radiation Protection Commission [ICRP] or biological effects of ionizing radiation [BEIR]).[18,23]

The results of many studies have indicated that this risk cannot be ignored.[15] A number of studies demonstrated different radiation dose for thyroid in the mentioned patients who were treated with different methods. The results of an *in vivo* study on 23 patients, who underwent breast radiotherapy using tangential and supraclavicular (SC) fields, shown the thyroid dose were 2 and 8% of the prescribed dose, respectively.[13] In another study, the skin entrance dose (SED) of thyroid following breast radiotherapy was 7% of the prescribed dose for SC field, which was more than thyroid's tolerance.[17] In another study on 69 patients, the mean reported thyroid doses were 3.7% of the delivered dose measured by the TLD. The results of this study indicate a significant risk of thyroid cancer after breast radiotherapy and the need for thyroid protection especially for young patients.[21] Thyroid absorbed dose in out of breast radiotherapy fields depends on the field size and distance from field border. Therefore, thyroid dose differs in radiotherapy with different treatment plans and treatment machines. The purpose of this study was to measure the absorbed dose of thyroid and estimate the risk of its secondary cancer in breast cancer patients who treated with different radiotherapy techniques including the following: tangential beams, tangential with SC fields, and also a tangential field with SC field in modified radical mastectomy (MRM), using 6-MV photon beams of an ELECTA linear accelerator.

Materials and Methods

A total of 64 breast cancer patients who referred to Seyed-Al-Shohada Hospital (Isfahan, Iran) were included in this study. The TiGRT (Linatech company) TPS was used to design the treatment plans. The planning target volume and the organs at risk were specified by a radiation oncologist. The prescribed dose of tumor for each patient was 50 Gy in 25 fractions. The standard treatment plans of the selected patients classified in two groups as follows: (1) whole breast irradiation with two tangential field techniques (Tan) and (2) two tangential field plus two SC lymph node fields technique (Tan + SCL). About 64 evaluated patients, 29 patients with mean age of 42.34 ± 6.48 were treated with Tan plan, 35 patients with a mean age of 43.94 ± 5.63 and also 34 mastectomy patients a mean age of 42.18 ± 5.52 were treated with Tan + SCL plan. Summary of the treatment plans characteristics is shown in Table 1. The selected patients were chosen according to the following criteria: the patients younger than 50 were selected for the study, because of the longer lifespan of younger patients.[24-26] Considering the high dependence of PD on the distance from the radiation field,[22] another criterion for patient selection was the distance between the thyroid and the irradiated breast, which was determined using

computed tomographic images of the patients. The distance between the upper limit of the breast and the lower limit of the thyroid gland was measured as the thyroid distance from the breast. Dose measurements were performed using LiF Thermoluminescence dosimeters LiF (TLD-100). Kry has reported that TLD-100 is well suited for measuring out-of-field dose at 6 MV.[27] TLDs were read out using a SOLARO-2A Model TLD reader (NE company) according to the protocol suggested by manufacturer. TLDs were calibrated with 6-MV beams of ELECTA linac. The thyroid dose measurements were performed for each patient at three locations specified by a radiation oncologist. According to the Schneider *et al.*, the average dose can be considered as an average thyroid dose.[23] Therefore, three TLDs were located in the middle of the two right and left lobes and in the middle of the thyroid. The average of these three dose values was considered as thyroid dose for risk calculation.

To calculate the radiation-induced second thyroid cancer, the BEIR committee cancer incidence model was used. The BEIR VII model provides organ-specific parameters for each sex and includes a parameter relating cancer incidence risk with age at exposure and attained age. Equation (1) is the BEIR VII model for both excess relative risk (ERR) and excess absolute risk. In this equation, D is radiation absorbed dose; β_S, γ, and η are organ-specific parameters for each sex; e is age at exposure; $e^* = (e - 30)/10$ for $e < 30$ and 0 for $e > 30$ years; and a is the attained age.

The thyroid-specific parameters of the model (β_S, γ, and η) are presented in Table 2.

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

The ERR of secondary thyroid cancer for 5, 10, and 15 years after breast radiotherapy was calculated using the

Table 1: Summary of the treatment plans characteristics used for breast radiotherapy of evaluated patients

Treatment planning	Field size	Angle of gantry (degree)	Prescribed dose (cGy)
Tan			
Middle field	20.7×15.3	292.9	2500
Lateral field	20.1×15.5	121.8	2500
Tan + SCL			
Middle field	16.8×11.8	49	2500
Lateral field	17.4×11.2	220.3	2500
Anterior field	14.6×5.8	3.9	3750
Posterior field	14.6×7.0	183.9	1250

SCL – Supraclavicular lymph node

Table 2: Thyroid-specific parameters of biological effected of ionizing radiation committee VII risk model (1)

Location of cancer	γ	β_M	β_F	η
Thyroid	−0.3	0.45	0.27	−2.8

measured average dose values of thyroid in each breast treatment plans and equation.[1]

Statistical analysis in this study was performed using SPSS (ver 20) software. The statistical tests selection was performed based on the type of our variables and their probable dependence. The one-way ANOVA test was applied on age-related data and thyroid doses in three different thyroid lobes. The *post hoc* test (Tukey HSD) was used to compare the average dose values of three different lobes of the thyroid. To find any dependency of mean thyroid dose on the side of the irradiated breast, the independent *t*-test is used.

Results

Table 3 indicates the mean thyroid doses in the evaluated patients who were included in this study. Table 3 also illustrates the results of the thyroid dose measurements for the mastectomy patients.

Table 3, compares the measured radiation dose for thyroid among left and right breast cancer patients. The percentage of patients with right breast cancer with Tan and Tan+SCL plans were 58.6% and 62.9%, respectively. The number of mastectomy patients with right and left breast cancer was equal in this study.

Table 4, indicates the dependent Variable: Relationship of mean measured dose of thyroid and treatment plan (Tan or Tan+SCL or MRM) (Tukey HSD).

The results of average thyroid dose values against the distance of thyroid from SC field, is illustrated in Figure 1. Because of the field size dependence of PD, the thyroid dose values of irradiated patients with 10×10 cm^2 equivalent field size, are shown in this Figure 2.

Figure 3 shows the ERR data of developing secondary thyroid cancer following breast cancer radiotherapy with different treatments.

Discussion

The aim of this study was to measure thyroid doses and to estimate the risk of developing secondary cancers of the thyroid after breast cancer radiation therapy. The thyroid is a radiosensitive organ, and there are a lot of evidence for the incidence of radiation-induced cancer in radiotherapy patients. According to the Radiation Therapy Oncology Group report, to reduce thyroid damage, the maximum thyroid dose should be kept below 3% of the prescribed dose.[15,17] For this reason, our study aimed to evaluate the thyroid risk in breast cancer patients who underwent radiotherapy in Seyed-Al-Shohada Hospital at Isfahan.

Many studies have been conducted on the incidence of thyroid secondary cancer in breast cancer when is treated with radiation. Among several studies aimed to measure the thyroid dose during breast cancer radiotherapy, those with
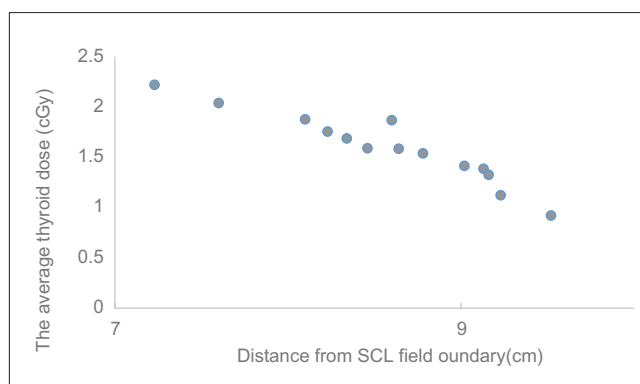

Figure 1: Thyroid dose as a function of the distance of thyroid from the supraclavicular field edge in breast radiotherapy with 200 cGy fraction size
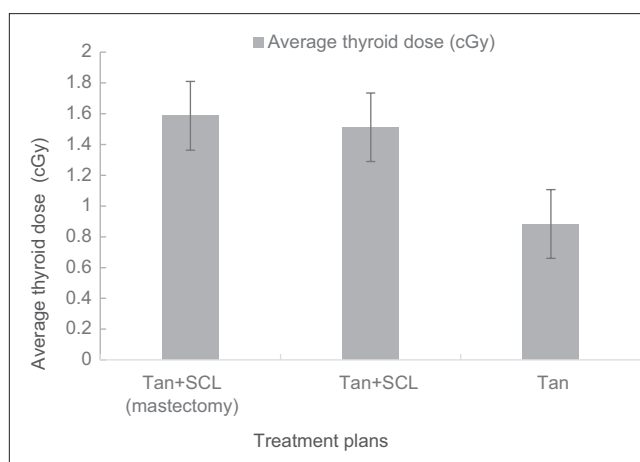

Figure 2: Mean thyroid dose (cGy) from breast radiotherapy (in one 200 cGy fraction) with different techniques
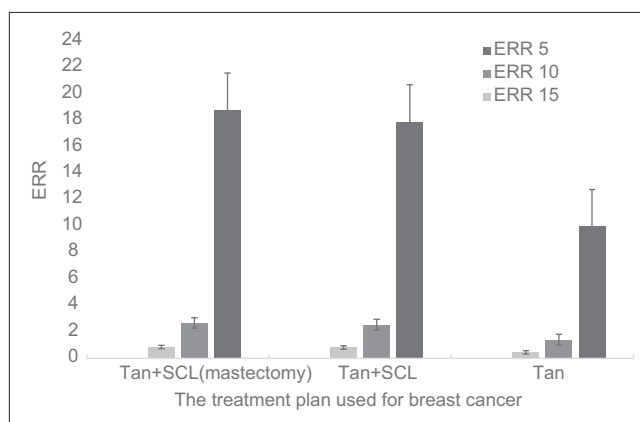

Figure 3: Excess relative risk of secondary thyroid cancer following breast radiation therapy with different plans

approximately similar treatment plans and methodology were selected for comparison. Vlachopoulou *et al.* reported thyroid dose, using metal-oxide-semiconductor field-effect transistor, 8% ± 2% and 2% ± 0.8% of the prescribed dose, following three-dimensional conformal radiotherapy of breast with and without SCL field, respectively. The relevant risk of secondary thyroid cancer of obtained

Table 3: Comparison of thyroid dose values between left and right breast radiotherapy

Treatment plan	The side of the treated breast	The range of thyroid doses	Thyroid mean dose±SD	*P*
Tan fields	Right	0.286-1.506	0.85±0.337	0.549
	Left	0.39-1.526	0.93±0.369	
Tan + SCL fields	Right	0.566-2.22	1.542±0.39	0.536
	Left	0.985-2.038	1.462±0.328	
Tan + SCL fields (mastectomy)	Right	0.886-2.26	1.629±0.336	0.524
	Left	0.701-2.25	1.546±0.407	

SCL – Supraclavicular lymph node; SD – Standard deviation

thyroid dose is calculated using the ICRP 103 risk model 1% and 0.3%, respectively.[13] Farhood *et al.* reported SED 7% of the prescribed dose in one fraction in patients undergoing breast treating with Tan and SC plans using TLD.[17] In another study, the mean reported thyroid dose in 69 patients undergoing radiation therapy for breast cancer using TLD was 3.7% of the prescribed dose, which is consistent with 3.02% measured in our study.[21] In a study by Donovan *et al.*, thyroid dose in an anthropomorphic phantom under breast radiotherapy with Tan plan using TLD was reported 0.3% of the delivered dose against 1.76% measured in our study.[16] Our findings verify the dependency of the thyroid dose on the distance of the thyroid from the field edge. The highest and lowest thyroid dose values were measured 3.17 cGy in SC field and 0.29 cGy in Tan field, respectively. The major contribution of SCL fields in thyroid dose is due to the less distance of the thyroid to SC field edge. The dose near the field edge is found higher [Figure 2] which may be due to the penumbra of the primary beam,[28] the steep variation of thyroid dose with distance from the field edge is related to rapid attenuation of scattered radiation within the patient.[29] By performing one-way ANOVA on age-related data and thyroid doses in three different thyroid lobes, we concluded that the mean age of the patients was the same in three evaluated groups ($P = 0.394$). The average dose values of three different lobes of the thyroid were significantly different between three groups ($P < 0.001$). The results of the *post hoc* test (Tukey HSD) show that the mean measured dose of thyroid in patients treated with Tan plan was significantly lower than in patients undergoing Tan + SCL plans ($P < 0.001$) which is in confirmation with Vlachopoulou *et al.* finding.[13] The proximity of the thyroid to the SC fields and high dependency of PD to distance from field edge could be the cause of this difference. Comparison of the average thyroid dose in patients undergoing breast-saving and mastectomy surgery against who had treated with the same Tan + SCL plan, does not show any significant difference ($P = 0.667$).

Independent *t*-test results indicate that the measured mean thyroid dose is independent on the side of the irradiated breast ($P = 0.53$). According to BEIR VII and ICRP reports, the radiation-induced secondary cancer more likely incidence during <10 years after radiotherapy.

Table 4: Comparision of mean measured dose of thyroid among subjects group

Group (I)	Group (J)	Mean difference (I−J)	*P*
Tan	Supra	−0.6295	0.001
	MRM	−0.7045	0.001
Supra	Tan	0.6295	0.001
	MRM	−0.0749	0.667

SCL – Supraclavicular lymph node; MRM – Modified radical mastectomy

Conclusions

In this study, the imposed dose of thyroid and the risk of its secondary cancer in breast cancer patients who treated with tangential beams, tangential with SC field, and also tangential field with SC field in MRM plans were evaluated.

Based on the results of this study, to reduce the risk of secondary thyroid cancer in a patient treated with radiotherapy technique for breast cancer, protection of the thyroid gland is necessary.

Conflicts of interest

There are no conflicts of interest.

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