Original Article

The Measurement of Thyroid Absorbed dose by Gafchromic™ EBT2 Film and Changes in Thyroid Hormone Levels Following Radiotherapy in Patients with Breast Cancer

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Abstract

Background: Radiotherapy is a main method for the treatment of breast cancer. This study aimed to measure the absorbed dose of thyroid gland using Gafchromic EBT2 film during breast cancer radiotherapy. In addition, the relationship between the absorbed dose and thyroid hormone levels was evaluated. **Methods:** Forty-six breast cancer patients, with the age ranged between 25 and 35 years, undergoing external radiotherapy were studied. The patients were treated with 6 and 18 MV X-ray beams, and the absorbed thyroid dose was measured by EBT2 film. Thyroid hormone levels, thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxin (T4), were measured before and after the radiotherapy. Pearson's, Spearman's, and Chi-square tests were performed to evaluate the correlation between the thyroid dose and hormone levels. **Results:** The mean thyroid dose was 26 ± 9.45 cGy with the range of 7.85–48.35 cGy. There were not any significant differences at thyroid hormone levels between preradiotherapy and postradiotherapy ($P > 0.05$). There was a significant relationship between increased thyroid absorbed dose and changes in TSH and T4 levels ($P < 0.05$), but it was not significant in T3 level ($P = 0.1$). **Conclusion:** Regarding the results, the thyroid absorbed dose can have an effect on its function. Therefore, the thyroid gland should be considered as an organ at risk in breast cancer radiotherapy.

Keywords: *Breast cancer, Gafchromic film, radiotherapy, thyroid gland*

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Introduction

Breast cancer is one of the most common types of cancer among women worldwide.[1,2] There are some methods for the treatment of breast cancer, including surgery, radiotherapy, chemotherapy, and hormone therapy.[1,3,4] Given the long-term advantages, radiotherapy has been assessed as the primary treatment modality in most clinics for breast cancer.[1,2,5] In this modality, ionizing radiation can destroy the cancerous cells or change the genes to terminate cellular growth.[6]

Although technological advances have led to major improvements in the radiation therapy of breast cancer, adverse effects such as increased exposure to ionizing radiation have been reported during the process of treatment of benign and malignant tumors.[4,7]

Radiation dose measurements of out-of-field organs, including lung, heart, ipsilateral breast and thyroid as organ at risk (OARs), during breast radiotherapy are crucial.[7,8] Thyroid is one of the OARs during breast cancer radiotherapy; therefore, the probability of malignancies in this organ increases the following radiotherapy.[9-11]

Several studies have shown that there are some dosimetric devices for measuring radiotherapy doses.[11-13] Gafchromic™ films have lots of advantages, and they are widely used in radiotherapy, for example, to verify treatment planning systems and evaluate two-dimensional absorbed dose maps.[13-15]

In a study, Kourinou *et al*.[11] investigated the scattered out-of-field dose in some OARs such as thyroid, lungs, and breast during head-and-neck radiotherapy with thermoluminescent dosimeter (TLD). In another study by Lee *et al*.,[7] the secondary cancer risk of breast cancer radiotherapy in some OARs including thyroid, brain, and

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eyes were evaluated by TLD dosimeter and also compared in different radiotherapy techniques.

Subclinical thyroid disease is defined by high or low serum concentrations of thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxin (T4), and they have a quite wide range due to analytical and biological variation in human; therefore, the assessment of hormone changes during radiation and subsequent to it, is very important.[16]

Due to the lack of studies on the thyroid absorbed dose by EBT2 films as a high sensitivity dosimeter, the current study aimed to measure the thyroid absorbed dose using EBT2 films during radiotherapy and to evaluate subsequent thyroid function in 46 breast cancer patients.

Materials and Methods

Gafchromic™ EBT2 film, irradiation, and calibration process

In the present study, Gafchromic™ EBT2 (International Specialty Products, Wayne, NJ, USA) film with dimensions of 8 × 10 inch was used. EBT2 films have several advantages compared to the previous ones, including better spatial resolution, energy and dose rate independence, density close to soft tissue or water, and less sensitivity to room light.[17-19] Furthermore, they do not need the conventional chemical processing and can be shaped to any phantoms.[18]

This type of film includes an active layer (30 µm), a thin topcoat (5 µm), and polyester substrate (175 µm). Furthermore, the coated layers are overlaminated with 50 µm polyester and a pressure-sensitive adhesive.[20]

The films were exposed using 6 MV X-rays from Varian linac 2100EX (Varian Medical Systems, Palo Alto, CA, USA). For the calibration process of the films, they were positioned at the depth of maximum absorbed dose in the slab phantom (PTW, Freiburg, Germany). Ten 30 cm × 30 × 1 cm acrylic sheets were set underneath the films.[21] Irradiation was done using 10 cm × 10 cm field at a source to surface distance of 100 cm. In addition, to validate the data obtained by a film, a farmer type 30,013 ionization chamber with sensitive volume of 0.6 cc (PTW, Freiburg, Germany) was used at the same condition of the film irradiation. All measurements were performed following the American Association of Physicists in Medicine Task Group-55 reports.[22]

Scanning and analysis of the films

To obtain the calibration curve, the film pieces were irritated with different dose levels as follows: 25, 50, 100, 150, 200, 250, and 300 cGy to plot the calibration curve.

The films were cut into pieces of dimensions 2 cm × 3 cm and marked to indicate the film orientation. Furthermore, to evaluate the statistical error, three pieces of the film were randomly used for each radiation dose. Three unexposed film pieces were used to obtain the background fog.

The irradiated films were scanned with the Microtek 9800XL scanner (Microtek Inc. Santa Fe Spring, CA, USA) 48 h after irradiation, to stabilize the color, in the landscape mode.[23] All of the films were scanned with a 127-dpi spatial resolution in transmission scan mode in three colors, 48 bit RGB, and images were stored in Tagged Image File Format.

The scanned images were entered into ImageJ software (National Institutes of Health, Bethesda, Maryland), and the pixel values of the images were measured. About 2016 pixels (6 mm × 21 mm), located in the center of the films, were selected, and the mean value was calculated. Finally, the calibration (dose-response) curve of films was obtained based on the proposed method by Devic.[23]

Patient selection and treatment planning

Forty-six consecutive women with breast cancer (T1b-T3 stages and node-positive) undergoing breast-conserving surgery were incorporated in this study from February to December 2018. The average age of patients was 32 years (25–35 years), and the majority of the cohort (37 patients; 80.4%) had left-sided breast cancer. The patients were referred to Reza Radiation Oncology Center (Mashhad, Iran). The images for planning were obtained by a computed tomography (CT) scanner (Siemens Somatom Plus16; Siemens Healthineers, Munich, Germany) in the standard supine position during free breathing.

Radiation sensitive organs including lungs, spinal cord, larynx, heart, and thyroid gland, the gross tumor volume (GTV) and clinical tumor volume (CTV) were contoured by a radiation oncologist on the CT images. The planning target volume (PTV) was contoured regarding the borders proposed by the guidelines of the Radiation Therapy Oncology Group (RTOG) on the CT slices.[24] RT Dose PLAN treatment planning system (Math Resolutions, Columbia, USA) was used for three-dimensional conformal radiotherapy planning of patients.

In our study, all of the patients underwent partial breast surgery; therefore, there was no GTV, and the whole breast considered as CTV. The PTV consisted of the CTV plus a 5-mm margin to consider breathing motion and treatment setup uncertainties, and the borders of the PTV were chosen regarding the borders proposed by the guidelines of the RTOG.[24]

The 50 Gy prescribed dose was delivered to the patients in 25 fractions. The patients were irradiated by 6 and 18 MV X-rays using Varian Clinac 2100EX linear accelerator.

Two opposed tangential fields (medial and lateral) were planned to encompass the breast. Furthermore, two supraclavicular fields (anterior and posterior) were used to deliver the prescribed dose to the level I-II and supraclavicular lymph nodes [Figure 1]. Different weighing of the anterior and posterior fields was used to attain higher homogeneity and conformity. Wedges (15°) were used to

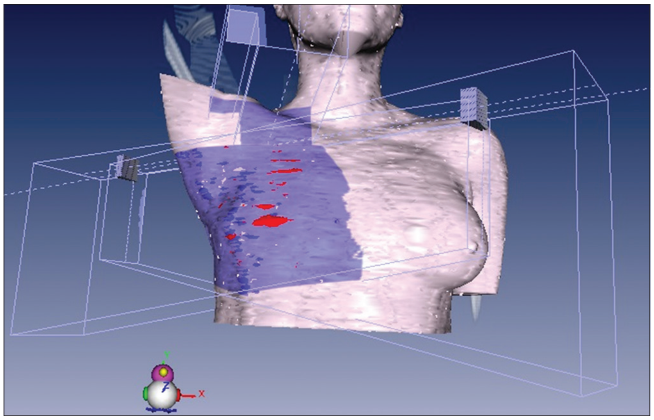

Figure 1: Two opposed tangential and supraclavicular fields used in three-dimensional conformal radiotherapy of breast

improve the dose homogeneity. Dose-volume histograms were assessed to control the PTV coverage and OARs dosimetric parameters of each plan.

Thyroid surface absorbed dose measurement

The thyroid region for each patient was marked based on the CT images by an oncologist. The EBT2 film pieces were placed at three or four different positions (based on the thyroid size) on the neck for measuring thyroid surface absorbed dose. The scanned image of exposed film pieces was entered into ImageJ software to obtain the absorbed dose regarding the obtained calibration curve.

Evaluation of thyroid function

Thyroid function before and after radiotherapy (3 months later) was evaluated by measuring TSH, T3, and T4 levels in 46 patients. Due to differences in laboratory ranges of the hormones, the relative values were calculated for statistical analyses and comparisons.

Statistical analysis

The correlation between the variables was evaluated using Pearson's test, Spearman's test, and *t*-test with version 11.5 of SPSS software (SPSS Inc., Chicago, Illinois, US). Furthermore, Chi-square test was performed to determine the significant of the correlations. $P < 0.05$ was considered as statistically significant.

Results

The mean thyroid volume was 10.2 cm^3 (9.5–10.5). After obtaining the films' calibration curve from optical density data of red channel of scanned images, thyroid gland absorbed dose was calculated. Figure 2 shows the thyroid mean absorbed dose of each patient in one treatment session. The mean thyroid absorbed dose was 26 ± 9.45 cGy with the range of 7.85–48.35 cGy. Furthermore, it is notable that the thyroid gland surface absorbed dose in 67% of patients was 20–40 cGy.

The mean levels of thyroid hormones before radiotherapy were as follows: TSH = 2.35 ± 1 µIU/mL (0.3–6.32), T3 = 1.35 ± 0.44 ng/mL (0.45–2.38), and T4 = 9.6 ± 1.7 µg/dL (3.9–12.3), and the same values after radiotherapy were as follows: TSH = 2.27 ± 0.91 µIU/mL (0.3–4.6), T3 = 1.36 ± 0.41 ng/mL (0.31–2.11), and T4 = 9.7 ± 2.1 µg/dL (1.57–12.5). According to obtained *P* value data from Chi-square test (0.686 for TSH, 0.152 for T3, and 0.146 for T4), there is not any correlation between the thyroid hormone levels before and after radiotherapy.

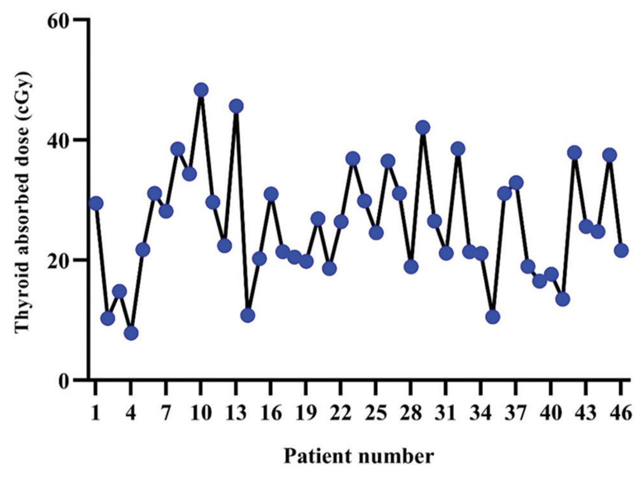

Figure 2: Mean absorbed dose of thyroid of 46 studied patients in one-session treatment

After radiotherapy, the mean level of TSH decreased, and the highest variation was 5.83 µIU/m, but the mean levels of T3 and T4 increased, and the maximum variations were 0.79 ng/mL and 7.86 µg/dL, respectively. Table 1 indicates the variations of the hormone levels in all patients.

There was a significant correlation between the absorbed dose and TSH ($P = 0.03$) and T4 ($P = 0.02$) levels. However, there was no significant correlation between the absorbed dose and the change of T3 level ($P = 0.1$).

Discussion

Since in radiotherapy techniques, peripheral radiation can damage the out-of-field organs, the minimization of radiation-induced damages is a major concern in treatment planning.[8]

One of the OARs during breast radiotherapy is thyroid gland.[7,11] Thyroid cancer can occur after radiation incidence or during diagnostic and therapeutic procedures;[8,25] therefore, the study of the dose received by this organ is an important issue.

In this study, we measured the thyroid absorbed dose, during radiotherapy, by EBT2 film in patients with breast cancer. Furthermore, thyroid hormone levels (TSH, T3, and T4) were compared before and after the radiotherapy.

Our results showed that the mean thyroid absorbed dose was 26 ± 9.45 cGy. Lee *et al*.[7] and Momeni *et al*.[26] measured the thyroid secondary cancer risk after breast cancer radiotherapy. In their researches, the mean thyroid absorbed dose was 5 cGy–1.3 cGy, respectively, obtained

Table 1: The variation of the thyroid hormone levels thyroid-stimulating hormone, triiodothyronine, and thyroxin before and after 3-month radiotherapy

Patient	TSH (µIU/mL)	T3 (ng/mL)	T4 (µg/dL)	Patient	TSH (µIU/mL)	T3 (ng/mL)	T4 (µg/dL)
1	−0.19	0.102	0.91	24	1.37	0.01	−1.75
2	0.94	−0.62	−5.6	25	0.02	0.07	−1.24
3	0.07	−0.51	−3.56	26	1.44	−0.04	0.35
4	0.8	0.09	−1.62	27	0.3	−0.65	0.13
5	0.07	0.13	−2.09	28	−0.06	0.33	−0.8
6	−2.15	−0.73	−2.27	29	0.62	0.2	1.42
7	0.37	0.46	1.45	30	−0.06	0.19	0.71
8	5.83	0.38	−0.83	31	−0.23	−0.29	−0.87
9	0.03	0.29	−0.73	32	0.8	0.08	−1.69
10	2.15	0.24	0.7	33	0.28	−0.09	1.85
11	0.19	−0.79	0.68	34	−0.27	−0.18	1.17
12	−0.25	0.14	−0.8	35	−0.26	0.32	−1.53
13	0.69	0.49	2.4	36	0.23	−0.14	1.47
14	0	0.09	1	37	0.02	0.4	0.9
15	−0.6	−0.1	−0.8	38	−0.43	−0.39	1.3
16	0.6	0.66	−0.9	39	−0.19	−0.13	−1.32
17	0.06	0.02	0.66	40	0.04	0.14	−2.5
18	−0.43	−0.25	−0.6	41	−0.45	−0.13	−0.5
19	−0.09	−0.14	−1.52	42	−0.52	0.3	4.66
20	−0.24	−0.25	−1.15	43	−0.15	−0.17	0.78
21	−0.15	0.06	−0.55	44	−0.53	−0.11	3.04
22	−1.03	−0.56	−2.47	45	−1.45	−0.16	1.33
23	−1.49	0.07	0.18	46	−0.44	0.54	7.86

TSH=Thyroid-stimulating hormone

by TLD dosimeter. The different results may have resulted from variations in dosimeter, treatment planning system, and thyroid volume.

The obtained absorbed dose values of thyroid in our study were in the range from 7.85 to 48.35 cGy. This variation can result from different tumor volume, the distance of the tissues from the radiation field, the positions of the dosimeters, and different thyroid volumes.

After radiotherapy, the mean TSH decreased, while the mean T4 and T3 experienced an increase; however, this variation was not significant in comparison with measured levels before radiotherapy. In line with the finding of this study, Alterio *et al*.[16] reported a slight statistically significant for TSH variation ($P = 0.049$) but no variation for T3 and T4 values before and after radiotherapy among 14 patients.

Radiotherapy is a powerful inducer of inflammatory changes in endothelial cells.[27] It can lead to some metabolic effects and systemic inflammation which can cause the development of an inflammatory phenotype of the plaque,[28] which is the result of the local effects of the irradiation inducing arterial pathophysiology.[29] Soon after the process of radiotherapy, inflammatory diseases involving the thyroiditis may be caused. Thyroid hormones T3 and T4 increase and TSH decrease. Moreover, in this situation, T4 level increases more than the T3.[29]

There was a significant correlation between the absorbed dose and the TSH and T4 levels. Yoden *et al*.[30] showed that there is a risk for hypothyroidism (high level of TSH and/or low level of T3 and/or T4) when thyroid received dose is ≥30 Gy, and also this risk is possible for thyroid dose ranges between 10 and 30 Gy. Other studies have reported that the relative risk of hypothyroidism is 40% for patients receiving 30–45 Gy and 12%–27% for those receiving less[31,32] in patients treated for Hodgkin's disease. In our study, the mean total thyroid absorbed dose (at 25 sessions) was 6.5 ± 2.36 Gy; therefore, there is a potential risk of hypothyroidism.

Tunio *et al*.[33] evaluated the dose distribution at the thyroid gland during breast cancer patients treated by supraclavicular radiotherapy technique. They expressed that the risk of hypothyroidism depends on the thyroid gland volume and follow-up duration and can be minimized using thyroid shield.

One of the limitations in our study was the short period thyroid hormones investigation after radiotherapy.

It is not entirely clear, the relationship between the absorbed dose values and thyroid hormones. Furthermore, considering the effect of different treatment techniques on thyroid dose values, the results of this study are not expandable to other treatment planning. Therefore, it is suggested that additional researches should be carried out with various treatment techniques to determine the correlation of absorbed dose, secondary cancer risks, and hormone level variations at thyroid gland during varying periods.

Conclusion

In the current study, the thyroid absorbed dose and variation of thyroid hormones attributable to breast irradiation were evaluated for 46 breast cancer patients. Our finding showed that there was a significant relationship between the increased thyroid absorbed dose, which measured using EBT2 films, and changes in TSH and T4 levels. Therefore, the thyroid gland should be considered as OARs in all breast cancer radiotherapies.

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None.

Conflicts of interest

There are no conflicts of interest.

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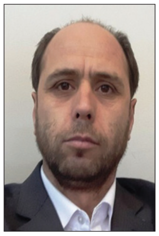

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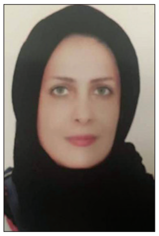

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