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Research Article

Radiotherapy-Induced Structural and Functional Changes in the Thyroid Gland

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Abstract

Background: Despite their specific functional hazards, radiotherapy induced thyroid disorders remain under-evaluated, even though, various types of irradiation caused either benign and malignant changes of the thyroid gland have been mentioned in this study.

Aim: To report the current status concerning the hazards of various types of irradiation on the detection of different thyroid abnormalities either benign and/or malignant changes.

Materials and Methods: This is a retrospective clinical study on 40 cancer patients received irradiation between July 2011 and July 2016. 14 (35%) males and 26 (65%) females, their age range (33-80y, mean ± SD=56.5 ± 11.8). After the completion of treatment, all patients were seen at 6 weeks then every 4–6 months for first 5 years. Due to the study, full thyroid gland assessment was performed (clinical examination, lab investigations, thyroid U.S and biopsy for malignant thyroid.

Results: After full clinical and anatomical assessment of the thyroid gland abnormalities in all 40 cancer patients

received a variable doses of radiotherapy, we found that 40% of the patients showed multinodular goiter, 22.5% showed thyroiditis and 37.5% showed differentiated cancer thyroid (25% papillary,12.5% follicular cancer) proved later by biopsy from the gland. The incidence of malignant thyroid diseases increased significantly among the older patients received high radiation doses(>50Gy) over long post-therapy follow up.

Conclusion: Various thyroid gland disorders may result after radiation exposure. There are a Little literatures report the true incidence, causes and risk factors of these disorders. Patients age and high radiation dose(>50Gy) has an account for the occurrence of malignant thyroid diseases.

Keywords: Radiotherapy; Benign and malignant structural changes; Thyroid gland

1. Introduction

The thyroid gland has two sided lobes linked by a central lobe called isthmus which is positioned at the lower neck. The thyroid gland secretes and stores thyroid hormones that are necessary in regulating growth, metabolism, reproduction and other physiological processes [1]. Thyroid gland considers one of the organs mostly produce clinically/subclinically abnormalities after therapeutic external radiation [2]. Radiation hazards induced thyroid abnormalities were first registered in thyrotoxic patients administered radiotherapy in 1920s [3]. Later, radioactive iodine (RAI) was used in patients with cardiac diseases to decrease their metabolic rate (BMR) [4, 5]. The initial reports on hypothyroidism after receiving radiotherapy on neck region were detected since 1960s, [6, 7]. About 20-30% of patients with lymphomas, and head and neck cancers (HNCs) affected by RT-induced thyroid disturbances, after receiving curative radiotherapy to the neck region and with approximately half of these events occurring within the first 5 years after treatment [8-10]. The thyroid gland receives a significant dose of radiation (10–80 Gy) after RT to head and neck region as the whole gland or large part of it is cited in or around the target organ which leads to abnormal hypothyroidism, Graves'disease, and hyperparathyroidism [11]. Repeated curative or accidental radiation of the thyroid gland raises the incidence of thyroid tumors. Two-thirds of benign tumors occurring after external beam irradiation, and the other one third are malignant, mostly well-differentiated, and rarely advanced cancers (90% are papillary type) [12]. These tumors do not differ clinically from accidentally occurring thyroid cancers [13, 14]. They are often followed or associated with benign adenomas. The risk of secondary thyroid malignancy increases up to 15- to 53- fold versus non-irradiated population [15]. In this study, we summarize the current status concerning the hazards of different types of irradiation on the development of benign, malignant structural and functional diseases of the thyroid. Through a retrospective analysis on 40 cancer patients with different primaries treated with different doses of radiotherapy in which clinical assessment and anatomical imaging tools were performed for clinical evaluation of the thyroid gland associated with histopathological examinations for suspected malignancies in the thyroid gland.

2. Design and Methodology

2.1 Nature of the study

- This is a clinical study on 40 cancer patients received either curative or incidental radiation at our Department between July 2011 and July 2016, the data collected retrospectively.
- The aim of the paper was to report the current status concerning the hazards of different types of irradiation on the development of different thyroid abnormalities either benign and/or malignant changes.

2.1.1 Eligibility: After taking the Ethical Review Committee approval and informed consent from each patient before participation in the study, only 40 cancer patients met the following eligibility criteria were selected carefully: (1) Histologically proven primary cancer with no other evidence of distant metastases at the thyroid gland (2) who were euthyroid clinically(with normal hormonal profiles) preceding irradiation to the neck region. Patients with a past history of any thyroid problems or on any thyroid therapy were excluded. Normal TFT, were defined as; (TSH) ≤4. 2 mIU/L; (FT4) 12.5-22 pmol/L and (T3) between 3.1 and 5.5 pmol/L.

2.1.2 Radiation therapy

***2.1.2.1 For breast cancer*:** All women were treated with 3DCRTH in which the target volume included the breast (after BCS) or the chest wall (after MRM), the ipsilateral supra-and infra-clavicular fossa, ipsilateral lymph nodes along the internal mammary artery and ipsilateral axilla (as indicated in every individual case). The RT planning was based on transverse CT scans covering the region of mammary area. CT slice thickness and pitch was 0.5 cm. The clinical target volume, both lungs and the heart, but not the thyroid gland were routinely delineated in the planning CT images. The breast/chest wall should receive a total dose of 60/50 Gy, and the regional lymph nodes 46-50 Gy, using photon energy 6-15 Mev on linac. Median absorbed dose in the thyroid gland after breast cancer irradiation is 30 Gy.

***2.1.2.2 For lymphomas*:** The extent of radiation therapy ranged from treatment one or more of the involved fields included the thyroid region. The radiation doses were depended using either 2DRTH or 3DRTH with the protection of midline structures using either lead blocks or MLC but inevitable considerable dose (ranging from 35Gy to 40Gy) to the thyroid occurred.

***2.1.2.3 For naso/hypopharynx and MUO with cervical lymph nodes*:** patients were treated with 3DRTH over 2 Gy daily fractions. Most patients were treated at 2Gy per fraction for 33-35 fractions (according to stage and bulky lymph node existence). Elective nodal regions in the neck were generally treated to 46-54 Gy. Because planning objectives to reduce the thyroid dose were not used for most patients, many patients received large, unavoidable radiation doses to the thyroid, with significant portions of the gland receiving ≤50 Gy. Median absorbed dose in the thyroid gland after head & neck irradiation is 42Gy.

***2.1.2.4 Thyroid function assessment*:** After the completion of treatment, all patients were seen at 6 weeks, then every 4–6 months for first 5 years. For the purpose of the study, each follow-up included a detailed history with neck examination., FT3 (free triiodothyronine), FT4 (free thyroxin), TSH, TG (thyroglobulin), and thyroid antibodies (anti-TG, antimicrosomal, and antiperoxidase) were performed annually after the completion of radiation therapy. Thyroid U/S and/or thyroid scan was performed for the patients with palpable nodular swelling regardless of clinical symptoms even FNAC (Fine Needle Aspiration Cytology) was needed in some cases to exclude malignancy. Based on the last follow-up, patients were then grouped in three (a) euthyroidism (normal TFTs) in multinodular goiter and (b) hypothyroidism (high level of TSH and/or low FT3/FT4 or receiving thyroid replacement therapy) in thyroiditis and (c) differentiated cancer thyroid (papillary and follicular cancer thyroid) proved histologically.

2.1.3 Statistical analysis

SPSS version for windows version 16 was used for all date entry and analysis. The data were gathered in a retrospective manner. Chi square test was used to test for significance in case of two variables. ANOVA test was

used for multiple variables analysis. For all P-values <0.05 were selected as significant.

2.1.3.1 Patients characteristics: 40 patients were included in this retrospective analysis, 14(35%) males and 26(65% females, their age range (33-80y, mean ± SD=56.5 ± 11.8), their primary cancer were breast, lymphomas, naso/hypopharynx and metastases of unknown origin) with the majority of the patients have breast cancer representing (40%). The radiation doses are showed in (Table 1) as given by each patient, with the majority of the patients (62.5%) received <50Gy among cancer breast.

Personal Characteristics		
Age: (years)		
• mean ± SD	56.5 ± 11.8	
• range	33-80 y	
Sex	**n**	**%**
male	14/40	35
female	26/40	65
Primary cancer	**n**	**%**
Breast	16/40	40
HD	8/40	20
NHL	2/40	5
Naso/hypopharnyx	10/40	25
MUO	4/40	10
Thyroid Diseases	**n**	**%**
Multinodular goiter (MNG)	16/40	40
Thyroditis	9/40	22.5
Papillary c	10/40	25
Follicular c	5/40	12.5
Radiation dose (Gy)	**n.**	**%**
Breast/Chest wall (10-80 Gy)		
<50Gy	10/16	62.5
>50Gy	6/16	37.5
Hodgkin's disease (20-35Gy)		
<30Gy	5/10	50
≥30Gy	3/10	30
Non Hodgkin’s Lymphoma (24-30Gy)	2/10	20
Naso/hypopharynx		
High risk (66-81Gy)	5/10	50
low risk (44-50Gy)	5/10	50

Metastases of unknown origin (59-70Gy)		
60Gy	2/4	50
70Gy	2/4	50

Descriptive test

Table 1: Demographic characteristics.

3. Results

After full clinical and anatomical assessment of the thyroid gland abnormalities in all 40 cancer patients received a variable doses of radiotherapy referred to the Clinical Oncology and Nuclear Medicine Department, we found that 40% of the patients had multinodular goiter proved by thyroid U/S with normal hormonal profile, 22.5% showed thyroiditis presented by hypothyroid symptoms confirmed by low T3 and T4,elevated TSH and Anti-thyroid Antibodies and 37.5% showed differentiated cancer thyroid (25% papillary,12.5% follicular cancer) assessed initially by U/S proved later by Fine Needle Aspiration Cytology from the gland(FNAC). To evaluate the predictors for these benign and malignant structural changes in the thyroid gland induced by radiotherapy, those changes were assessed in related to patient gender, age, pathology of primary cancer, radiation doses (Gy) and post-therapy follow up (m/ys).

3.1 Patients gender

65% of the patients were females with 46.1% of them showed multinodular goiter with normal thyroid function on thyroid U.S, there is no statistical difference between male and female in the occurrence of benign and malignant structural thyroid diseases (P-value>0.05).

3.2 Patients age

Patients are divided into two groups according to their ages (cut off age=56ys), older patients with papillary cancer thyroid showed a significant difference as compared to the younger group (P-value=0.004), while the other benign structural thyroid diseases showed no significance between the both groups.

3.3 Primary tumor pathology

The evidence of benign and malignant structural changes in the thyroid gland showed no statistical significance among the patients with different primaries (P-value>0.05).

3.4 Radiation doses (Gy)

Patients who received less than 50 Gy of the radiotherapy showed a significant increase in the incidence of multinodularity in the thyroid gland, while the patients who received more than 50Gy, the incidence of malignant thyroid diseases (papillary or follicular type) was significantly high.

3.5 Post-therapy follow up(m/ys)

The incidence of nodular goiter of the thyroid gland in cancer patients showed a significant increase over follow up time as well as in patients with papillary cancer thyroid (P-value<0.05).

Gender	**Male**	**Female**	**P-value**
n/total	14/40	26/40	
MNG	4	12	0.278
Thyroiditis	4	5	0.5

Thyroid cancer	**n=15/40**		
Papillary c thyroid	5	5	0.251
-Follicular c thyroid	1	4	0.452

MNG: multinodular goiter; * Statistical significant difference (P< 0.05)

Table 2: Incidence of thyroid diseases induced by radiotherapy vs, patients gender.

Age	**<56ys**	**≥56ys**	**P-value**
n/total	19/40	21/40	-
MNG	8	8	0.796
Thyroiditis	5	4	0.583
Thyroid cancer	**n=15/40**		
Papillary c thyroid	2	8	*0.04
Follicular c thyroid	4	1	0.12

* Statistical significant difference (P< 0.05)

Table 3: Incidence of thyroid diseases vs, patients age.

Primary tumor	**Breast c**	**lymphoma**	**Naso/hypopharynx**	**MUO**	**P-value**
n/total	16/40	10/40	10/40	4/40	
MNG	8	4	3	1	0.716
Thyroiditis	2	4	2	1	0.462
Thyroid cancer	**n=15/40**				
Papillary c thyroid	5	1	3	1	0.670
Follicular c thyroid	1	1	2	1	0.660

ANOVA test; * Statistical significant difference (P< 0.05)

Table 4: Incidence of thyroid diseases vs, primary tumor pathology.

Primary tumor	**≤50Gy**	**>50Gy**	**P-value**
n/total	25/40	15/40	-
MNG	15	1	*0.001
Thyroiditis	8	1	0.063
Thyroid cancer	**n=15/40**		
Papillary c thyroid	1	9	*0.000
Follicular c thyroid	1	4	*0.036

* Statistical significant difference (P< 0.05)

Table 5: Incidence of thyroid diseases vs. radiation dose (Gy).

Primary Tumor	6-18ms	2-5ys	P-value
n/total	-	-	-
MNG	13	3	*0.018
Thyroiditis	7	2	0.216
Thyroid cancer	**n=15/40**		
Papillary c thyroid	1	9	*0.000
Follicular c thyroid	3	2	1.00

* Statistical significant difference (P< 0.05)

Table 6: Incidence of thyroid diseases vs. post-therapy follow up (m/ys).

4. Discussion

Numerous thyroid disorders may develop after irradiation to the low neck, using fields that include all or part of the gland. They may include simple goiter, multinodular goiter, thyroiditis, hypothyroidism, Grave's disease, even may include radiotherapy-induced thyroid cancer. There is a Little data about the true impact of the hazards of various radiation types on the development of benign, malignant structural and functional diseases of the thyroid. In our study, the incidence of RT-induced hypothyroidism (22.5%) is similar with other relevant literature (20–30%) [9], while Tunio et al, reported only 15% of hypothyroidism in cancer patients after receiving radiotherapy, which is much lesser than reported in relevant studies [16-18]. Structural and functional thyroid diseases are the main categories of thyroid disease, which include tumor growth and nodularity, as well as simple goiter (simple enlargement of the thyroid gland) while, hypo/hyperthyroidism as well as thyroiditis are the main functional diseases. Thyroid cancer is relatively rare [19]. In our study, out of 77.5% of the studied population, 40% expressed nodular goiter that consisting with other relevant studies reported approximately (30-40%) examined with ultrasound [20-22], while (15/40) of irradiated patients expressed thyroid malignancy, in consisting with Steven, et al study that showed nearly the same number of patients but with reported 6 out of 44 patients had papillary or follicular cancers [23].

In this study, we analyzed different risk factors such as sex, age, primary tumor location, radiation dose and follow up duration. Diaz et al, reported that the gland with small volume had a high incidence for development of post-RT thyroid hazards [24]. Furthermore, Alterio et al. verified that women's thyroid glands were less influenced by radiation hazards as they have smaller volume than men's [9]. We found that female sex was associated with a high incidence of thyroid disorders (26/44) compared with male sex (14/40) with no significant correlation among them in the development of post-RT benign and malignant structural thyroid changes (P-value>0.05). However, when we grouped the patients according to age above and below 56 years, we found that older age was a significant risk factor for post-RT malignant changes (P-value=0.004). The increased efficacy of RT in elder patients who have a decline in sodium iodine symporter activity or maybe there is something intrinsic to either the cancer or the treatment may explain the greater incidence of malignancy in this group (≥56years) [25]. However, the effect of age has been disproved by many researchers [26-28]. The difference of our study from others could be that age was analyzed in two groups (<56ys and ≥56ys). The effects of primary tumor site RT on the thyroid gland (e.g. carcinomas of

naso/hypopharynx) could be significant, because it is located in very proximity to the target of irradiation [29-30]. Conversely, some studies found no association between incidence of thyroid dysfunction and primary tumor site irradiation as in our study [9, 31, 32]. The significant effect of radiation dose on the risk of post-RT thyroid changes was also reported in some studies [27, 33-34], Our result show that if the mean radiation dose received by the thyroid was less than 50 Gy, it is a significant risk factor for post-RT nodular thyroid changes and this risk starts after 20 Gy (P-value=0.001). On the other hand, if the mean radiation dose received by the thyroid was more than 50Gy, it is a significant risk factor for post-RT malignant thyroid changes (P-value<0.05) Conversely, with other literature [23, 27, 35, 36]. The time to development of thyroid changes had not been conclusively defined. Prospective trials have been conducted in an attempt to answer this question [37, 38]. In our study, The incidence of nodularity as well as malignant changes at the thyroid gland showed a significant increase over follow up time (P-value<0.05).

5. Conclusion

Numerous thyroid disorders may develop following irradiation to the thyroid gland. Patients age older than 56ys and high radiation dose (>50Gy) play an important role in the occurrence of structural thyroid changes. Therefore, thyroid functional imaging (Neck U/S, thyroid scan) should be checked on a regular basis every 6 months for the first 5 years after RT and annually thereafter in all patients who receive more than 50 Gy to the thyroid, regardless of clinical symptoms. Further prospective studies with large sample size are warranted in order to understand better the dose-effect and to reduce the incidence of radiotherapy-induced thyroid dysfunction.

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