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Original Research

Radiation-Induced Hypothyroidism in Post-Mastectomy Patients: A Prospective Cohort Study

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Purpose: Our study aims to assess the incidence of radiotherapy-induced hypothyroidism in breast cancer patients and correlate it with the mean dose to the thyroid.

Method: Out of 75 patients, who were treated under 3-dimensional conformal radiotherapy field in field {3D CRT(FiF)} by conventional Radiotherapy to post-modified radical mastectomy (MRM) chest wall, a dosing regimen of 200cGy per fraction for a total 5000cGy at our center in the year 2016, 63 patients were randomized and investigated. All patients were treated by Linear accelerator, varian, with the Eclipse version 13.6 treatment planning system. All information on radiotherapy used for each patient was extracted from the Eclipse treatment planning system. All patients were followed up for 7 years after Radiotherapy. TSH and freeT4 levels were measured. The Chi-square test was used to compare the outcome of the disease in terms of nominal and rank qualitative variables. Student t-test was used to compare in terms of quantitative variables.

Result: After 7 years since the radiotherapy, according to the results, a total of 10 out of 63, {15.87% ($P = 0.008$)} of patients had hypothyroidism, of which 11.11% (7 out of 63) were clinical, and 4.76% (3 out of 63) were subclinical. Dmean > 21 Gy compared with Dmean ≤ 21 Gy was associated with a significantly higher incidence of radiation-induced hypothyroidism (RHT) at 7 years after radiotherapy (3.17% vs. 12.7%, $P<0.001$).

Conclusion: We recommend that the Dmean of the thyroid should be kept lower than 21Gy for post-modified radical mastectomy radiotherapy to decrease the incidence of radiation-induced hypothyroidism. Further investigations in larger cohorts are required to confirm our results.

Introduction

Cancer is listed among the leading causes of mortality and morbidity worldwide, with approximately 19.3 million newly diagnosed cases and 10 million cancer deaths in 2020 [1]. 684996 cases died out of 2.3 million new cases of breast cancer diagnosed in 2020 [1].

Although the majority of breast cancers in the industrialized world are diagnosed in the early stages and the great majority are cured, more than half of the breast cancer patients in low and middle-income countries (LMC's) are diagnosed in late stages (III and IV), with the majority of them dying of metastatic breast cancer.

In India, for every 2 women newly diagnosed with breast cancer, one dies of it as compared to the US where one woman dies for every 5 or 6 newly diagnosed cases [2]. Higher mortality is attributed to presentation at late stages which may be due to lack of awareness, shyness of patients, and social stigma [3].

The treatment of breast cancer has a multidisciplinary approach including surgery followed by radiotherapy, chemotherapy and/or hormonal therapy. Radiotherapy (RT) is an integral component of the multidisciplinary management of breast cancer. External Beam Radiotherapy (EBRT) can be delivered using photon beams at either a Cobalt-60 unit or Linear Accelerator [4].

Radiotherapy plays an important role in the management of patients with breast cancer (BC), ranging from early-stage to advanced and metastatic cases [5].

The relationship between breast cancer and thyroid function has been discussed from different viewpoints ever since Beatson in 1896 noticed the necessity to treat the thyroid gland in advanced breast cancer [6]. Many studies showed that thyroid diseases are common among women with breast cancer [7, 8]. Women with breast cancer were considered to have an increased frequency of hypothyroidism - usually subclinical [9]. The thyroid is the largest endocrine gland of the human body and is responsible for producing free triiodothyronine (fT3) and free thyroxine (fT4) hormones [10]. One of the thyroid disorders is hypothyroidism (HT), which can occur due to various reasons. HT is divided into two categories: clinical and subclinical HT. In clinical HT, Thyroid- Stimulating Hormone (TSH) is high, and fT4 is low, and in subclinical HT, TSH is high, and fT4 is normal. Usually, symptoms such as fatigue, weakness, weight gain, cognitive disorders, swelling, intolerance to cold, muscle pain, anxiety, hearing loss, dry skin, etc., are detected in patients with these disorders [11].

Laboratory tests such as T4 and TSH measurements can be used to detect HT. The TSH level should be between 0.38 and 5.33 mIU/L, and the fT4 level should be between 0.61 and 1.12 ng/ml in normal thyroid.

The thyroid is one of the sensitive organs against ionizing radiation. During Radiotherapy (RT) of the breast and supraclavicular, parts of the thyroid which are near the radiation field, are exposed and make the possibility of abnormalities in the thyroid of breast cancer patients, and cause disorders in its function [11-13].

This study aimed to measure the level of fT4 and TSH as a prospective cohort study in Breast cancer patients treated at Acharya Tulsi Regional Cancer Institute and Research Centre, Sardar Patel Medical College and associate group of hospitals, Bikaner in the year 2016, who had been treated under 3-Dimensional Radiotherapy of the post-MRM chest wall with supraclavicular and axillary nodes. After Demographic and Radiotherapy specifications of patients as mean absorbed dose of thyroid measured by the treatment planning system, and the risk of hypothyroidism after seven years (in the year 2023) of RT was evaluated.

Materials and Methods

Selection criteria

Total of 1252 patients with proven breast Cancer were registered and treated in the year 2016 at our center Acharya Tulsi Regional Cancer Institute and Research Centre, Sardar Patel Medical

College, and associated group of hospitals, Bikaner. In this prospective cohort study, 75 patients with BC who were definitively diagnosed with BC in the year 2016 and treated at ATRCTRI, SPMC were contacted and taken for follow-up. Patients gave their written consent to participate in the study. The designed checklist has no name, and the information was published in general.

Inclusion criteria were definitive diagnosis of primary BC, and consent to participate in the study. Exclusion criteria were the patient's other thyroid diseases or thyroid abnormalities before starting RT, incomplete data recorded in the patient's medical record, history of thyroid disorders in the family, and lack of access to records related to treatment outcome. Totally, out of 75 contacted patients, who were treated under 3-Dimensional conformal radiotherapy (Field-in-field) by conventional RT dosing regimen of 200cGy per fraction for total of 5000cGy at our center in the year 2016, 63 patients were randomised and investigated (Table 1).

Hormone	Mean	SD	Min.	Max.
1.) TSH uIU/ml	1.4	0.9	1.8	5.33
2.) fT4 ng/ml	1.06	0.2	0.69	1.11

Table 1. Before Radiotherapy Thyroid Function Status of the Study Population.

Abbreviations, TSH, thyroid stimulating hormone; fT4, free tetraiodothyronine

Demographic and clinical data

Required data include demographic variables such as age, location of the tumor, ER/PR/HER2Neu status, stage, primary and following used treatment methods such as surgery, chemotherapy, and radiotherapy, extracted from the patient's documents.

Thyroid investigation

All patients were contacted on phone and invited to our center for follow up with informed consent. Asked them about thyroid function by old thyroid investigations, thyroid medication, and clinical signs of hypothyroidism such as fatigue, weakness, weight gain, cognitive disorders, edema, cold intolerance, muscle pain, anxiety, hearing loss, and dry skin. Also, free TSH and T4 tests were done for all patients after calling them to come our centre.

Radiotherapy data

All patients were treated by Linear accelerator, varian, with the eclipse version 13.6 treatment planning system. All information of RT used for each patient was extracted from the eclipse treatment planning system. CT scans of all treated patients were available in the treatment planning system. The software could calculate the absorbed dose of intended organs. To measure the absorbed dose of thyroid, the thyroid of patients contoured in CT scans of patients and calculated by the software.

Statistical analysis

Epi info software version 7.2.5.0 was used to analyze the data. A statistically significant level of less than 5% was considered. The chi-square test was used to compare the outcome of the disease in terms of nominal and rank qualitative variables. Student t-test was used to compare in terms of quantitative variables.

Results

Demographic and Clinical characteristics of patients are presented in Table 2.

Characteristic	Group	No of patients	% of patients
1.) Age (Median age: 50 years)	<30 years	4	6
	31-40 years	10	16
	41-50 years	19	30
	51-60 years	13	21
	61-70 years	11	17
	>70 years	6	10
2.) Stage	IIA	8	13
	IIB	17	27
	IIIA	17	27
	IIIB	2	3
	IIIC	19	30
3.) Quadrant	Central	2	3
	LIQ	7	11
	UIQ	7	11
	LOQ	11	18
	UOQ	36	57
4.) Hormone	ER+/PR+	24	38
receptor	ER+/PR-	7	11
status	ER-/PR+	2	3
	ER-/PR-	30	48
5.) HER 2	HER2+	30	48
Neustatus	HER2-	33	52

Table 2. Demographic and Clinical Characteristics of the Patients.

LIQ, lower inner quadrant; UIQ upper inner quadrant; LOQ lower outer quadrant; UOQ upper outer quadrant; ER/PR, estrogen receptor/progesterone receptor

In 63 breast cancer patients, the median follow-up time study group was 30.5 months. All patients underwent surgical treatment, chemotherapy followed by radiotherapy. The photon energy used in RT of all patients was 6 MV, and the dose of all patients in each session was 200cGy per fraction daily for total of 25 fractions. The total dose was 5000cGy. A total of 63 patients received treatment with 50 Gy which was the target volume the chest wall (after mastectomy), the ipsilateral supra-and infraclavicular fossa, ipsilateral lymph nodes along the internal mammary artery and ipsilateral axilla.

In this prospective cohort study, out of 75 patients included in the training, 63 patients were randomised and investigated. The mean age of the patients was 51.82 ± 12.13 years (28 to 77 years). The median age of patient is 50 years. The majority of the patients are in the 5th decade of life. All patients undergo Modified Radical Mastectomy (MRM), systemic chemotherapy and 3DCRT respectively. Thyroid function Results as TSH and T4 levels were measured and analyzed by Beckman Coulter Unicel Dxl 800 using the sandwich method for antigen detection with chemiluminescence. After 7 years of RT, Mean TSH in patients was 10.9 ± 5.76 uIU/ml (0.9 to 39.8), and the mean of examined fT4 was 0.70 ± 0.13 ng/ml (0.14 to 1.10); (Table 3).

Status	Hormone	Mean	SD	Min.	Max.
Normal (without hypothyroidism)	TSH	3.9	1.1	0.9	5.32

n=53					
	fT4	0.96	0.12	0.64	1.1
Clinical hypothyroidism n=7	TSH	21.4	14.4	6.1	39.8
	fT4	0.24	0.1	0.14	0.59
Subclinical hypothyroidism N=3	TSH	7.4	1.8	5.5	8.9
	fT4	0.91	0.19	0.63	1.08

Table 3. After 7 Years Follow-up of Radiotherapy, the Thyroid Function Status of the Study Population.

Abbreviations-TSH, thyroid stimulating hormone; fT4, free tetraiodothyronine; SD, Standard Deviation

Finally, our results showed that only radiotherapy was associated with a higher incidence of thyroid toxicity. After 7 years since the radiotherapy According to the results, a total of 10 out of 63 {15.87% (P = 0.008)} of patients had HT, of which 7 out of 63 (11.11%) were clinical, and 3 out of 63 (4.76%) were subclinical (Table 3).

The mean volume of thyroid gland before radiation therapy was 1.6 (0.2- 6.9) cc. The mean absorbed dose of thyroid for patients with HT was 24.76 ± 4.51 Gy, while in the group without HT was 20.89 ± 4.55 Gy.

there was a nonlinear relationship between Dmean and the risk of Radiationinduced hypothyroidism. Dmean > 21 Gy was identified as the threshold value for predicting radiation induced hypothyroidism (RHT) (p<0.001). Dmean > 21 Gy compared with Dmean ≤ 21 Gy was associated with a significantly higher incidence of RHT at 7 years after RT (3.17% vs. 12.7%, P<0.001); (Table 4).

Dmean to thyroid	No of patients (Out of 63)	Patients with hypothyroidism
		(clinical +subclinical both)
<21 Gy	20	2
>21 Gy	43	8

Table 4. Patients with Hypothyroidism and Dmean to Thyroid.

Discussion

the survival rate of patients with BCs has increased significantly in recent decades. Therefore, it is essential that the side effects of the treatments, such as HT following RT, be appropriately diagnosed, and treated.

In this historical cohort study, the possibility of HT after RT of breast and supraclavicular was investigated in patients with BC.

Results of the study showed that approximately 15.87% of patients developed HT, seven years after RT, of which approximately one-third were subclinical HT. It can be concluded that HT is due to the effect of radiation absorbed by the thyroid.

Some studies confirm our results. A study done by Akyurek et al. [14] showed that out of 28 patients with BC undergoing RT, 6 (21%) developed HT, which is higher than our results (15.87%).

Another similar study by Kanyilmaz et al. [11] showed a higher rate of HT (21%) compared to the results of the present study. The probable reason for this increase is attributed to a higher amount of radiation to the supraclavicular region and the different follow-up times of the patients.

Tunio et al. [15] showed that 40 patients with BC were divided into two groups. The first group received only breast RT, but the second group received supraclavicular RT. Results showed that 5% of patients in the first group and 15% of patients in the second group developed HT, which is consistent with the findings of our study.

Park et al. [16] investigated the incidence of HT after RT of about 117135 Korean BC patients with a follow-up time of 4 to 8 years. For patients treated with RT the rate of HT at 1, 5, and 8 years were 1.4, 6.2, and 9.3%, respectively, and for patients treated without RT were 1.2, 5.5, and 8.6%, respectively. They concluded that the risk of HT after RT increases after treatment up to 9 years, although they reported a lower rate of HT incidence than ours, which could be due to different demographic and treatment specifications.

Based on the results of these articles, it is predictable that with longer follow-up of patients, a higher rate of HT among the patients of the current study might be seen.

A recent study by Pillai et al. [17] in India confirmed that HT in BC patients was 14.86%.

In another similar study Falstie-Jensen et al. [18] also found that radiation to the thyroid gland increased the risk of HT in BC patients.

A Norwegian study also found that women with BC were twice as likely to develop HT [19]. One of the reasons for the difference in HT prevalence in these patients is the difference in the way HT is assessed.

In some studies, the test result is considered HT, and in others, levothyroxine is prescribed and considered HT.

As opposed to our claims, few studies asserted that HT had been shown to occur not only in patients with BC who have received RT but also happens in patients receiving systemic medications. However, these studies are associated with limitations, such as the small sample size [11].

On the other hand, two studies with a relatively large sample size (more than 1600 women) have shown that the incidence of HT in patients who have survived BC is higher than in the group who did not develop BC [20, 21]. Although the effect of chemotherapy can be attributed to these abnormalities, few studies have examined the effect of chemotherapy on thyroid function. Other results that bolster the idea about the effect of RT aside from chemotherapy on thyroid function, was a relationship between HT and the dose received by the thyroid. It was shown that in both clinical and subclinical HT radiation was higher.

In the present study, it was observed that one of the major factor that could increase the chances of developing HT in patients with BC was the patients’ received mean dose, which increased with growing the dose. Results showed that TSH increased with the mean dose.

Memorial Sloan Kettering Cancer Care (MSKCC) dosimetric planning guidelines for breast intensity- modulated radiotherapy define the mean dose to the thyroid is 20Gy. Zhao et al [22] also found that The 2-year cumulative incidence of radiationinduced HT (RHT) was 26.0% which is higher than our results (15.87%). Patients with Supraclavicular RT (SCRT) had a significantly increased 2-year cumulative incidence of RHT compared with patients without SCRT (31.5% and 11.4%, $p<0.001$). Dmean > 21 Gy was identified as the threshold value for predicting RHT ($p<0.001$). Dmean > 21 Gy compared with Dmean ≤ 21 Gy was associated with a significantly higher incidence of RHT at two years after RT (17.0% vs. 32.2%, $P<0.001$) which is higher than our results (3.17% vs. 12.7%, P<0.001).

The demographic results of this study showed that patients with HT had more underlying disease history with a significant difference, and the relationship between HT and the higher stage was statistically significant. However, few studies have investigated the influence of such parameters on thyroid function with or without the effect of used treatment methods. In this regard, Falstie-Jensen et al. [18] showed that patients with the underlying disease were more likely to develop HT. Therefore, it is further added that having sufficient information about the lifestyle, smoking status, obesity, and physical activity of patients as other factors that may affect the incidence of HT can be accurate conclusions about the effect of radiation on the incidence of thyroid disorders.

It seems that to investigate and control the HT in treated BC patients the effect of underlying disease, as well as chemotherapy, should be investigated more wildly, to determine the exact role of RT on thyroid function.

In conclusion, The survival of breast cancer patients is increasing therefore the incidence of radiation-induced hypothyroidism may be an important factor of the late toxicity. Routine thyroid function monitoring in all breast cancer patients after radiotherapy should be considered for better quality of life of patients. We recommend that the Dmean of the thyroid should be kept lower than 21Gy for postMRM RT for decrease the incidence of radiation-induced hypothyroidism. Further investigations in larger cohorts are required to confirm our results.

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Statement of Transparency and Principals:

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study’s data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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