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Evaluation of the thyroid and hypothyroid function after postoperative radiation therapy among breast cancer patients

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ABSTRACT

Background: The current advances in radiotherapy (RT) have improved the outcome of breast cancer (BC) patients. Despite its therapeutic benefits, the iatrogenic toxicities of RT and its impact on BC survivors are still debated, and further evaluations should be considered. This study aims to assess the rate of subclinical hypothyroidism and hypoparathyroidism among BC patients who were exposed to therapeutic radiation.

Methods: Seventy females undergoing RT for BC were enrolled in this cross-sectional study. Laboratory assessment of thyroid stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) levels was obtained to evaluate thyroid function. The parathyroid function was evaluated by measuring serum levels of Calcium (Ca), Phosphorus (P), and parathyroid hormone (PTH) at baseline, six and 12 months after RT.

Results: The mean age of patients was 54.3 ± 6.4 years. We found no cases of hypothyroidism before radiotherapy. However, nine patients developed hypothyroidism in the six months after radiotherapy (one clinical and eight subclinical, 13% in total), and six patients were identified with hypothyroidism in the 12 months after radiotherapy (one clinical and five subclinical, 8.7% in total). Significant relationships were observed in the hypothyroidism rate at both six months ($p = 0.003$) and 12 months ($p = 0.028$) after RT compared with the baseline. There was no case of hypoparathyroidism before and after RT.

Conclusion: In summary, we found that thyroid and parathyroid dysfunction after RT are relatively common findings among women with BC. It is a treatable source of morbidity in patients undergoing RT. Therefore, routine thyroid function monitoring should be recommended to improve the quality of life in BC survivors.

Keywords: radiotherapy, subclinical hypothyroidism, breast cancer, hypoparathyroidism

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The thyroid gland is the main endocrine organ regulating the metabolism of the body via triiodothyronine (T3) and thyroxine (T4) hormones, which are located between the supraclavicular (SCV) zone, posterior to the sternohyoid and sternothyroid muscles, in the anterior neck. Therefore, RT could potentially be damaging to the thyroid gland among patients who undergo RT in the SCV region, as the thyroid is sensitive to RT. The therapy can induce hypothyroidism, leading to different symptoms like depression and exhaustion, particularly in older women (Darvish et al., 2018; Jereczek-Fossa et al., 2004; Smith et al., 2008). Many studies have reported RT-induced thyroid gland disorders (Bassiri & Utiger, 1974; Beck-Peccoz et al., 1985; Hancock et al., 1995; Jereczek-Fossa et al., 2004). Some studies reported dose limits of 20 Gray as a dangerous dose, resulting in thyroid disorders when all parts of the thyroid tissue are irradiated (Alterio et al., 2007; Emami et al., 1991). However, other studies reported that RT-induced hypothyroidism predominantly occurred in patients who received higher radiation doses (e.g., ≥ 30 Gy; Johansen et al., 2011; Laway et al., 2012). There are some contradictory findings regarding the effects of RT on thyroid function tests. In one study, no significant differences in the level of thyroid hormones were observed before and after RT treatment in BC cases, highlighting the paradox between related studies (Giv et al., 2016). Therefore, it is necessary to evaluate the thyroid gland as an organ at risk in RT among BC patients (Darvish et al., 2018).

In some studies, neck radiation is one of the major predictive factors for the late complications of RT on parathyroid glands in BC patients. The relation between parathyroid hormone (PTH) level and the region of breast radiation is not completely understood. However, some studies reported a strong association between parathyroid adenoma development in relation to RT, which leads to hyperparathyroidism eventually (Rosen et al., 1975; Woll et al., 2012).

Recently, the late side effects of RT in BC have been a major concern among surviving patients. Those with untreated hypothyroidisms are at higher risk for cognitive impairment, weight gain, depression, hypercholesterolemia and loss of consciousness, as well as nephrolithiasis, bone loss, seizures, and arrhythmia in chronic hypoparathyroidisms. Based on these findings, there is a necessity to evaluate the patterns of hypothyroidism and hypoparathyroidism development associated with RT treatment among BC survivors (Park et al., 2022; Pillai et al., 2019; Yao et al., 2022).

Our understanding of radiation-induced thyroid gland dysfunction in BC patients is limited because the thyroid or parathyroid is not commonly recognized as an organ at risk during breast cancer radiotherapy (Hacislamoglu et al., 2019). There is a scarcity of recent studies exploring the updated complications of RT in BC patients. Additionally, the most recent investigations are limited and may not be applicable for certain populations, such as those in Iran. Hence, we decided to evaluate the consequences of RT on hypothyroidism and parathyroid diseases in our region.

METHOD

Study design and participants

Subjects for this study were evaluated from a single-centred oncology-radiotherapy centre in Imam Khomeini Hospital, Ardabil, Iran. Our study population consisted of 70 women randomly enrolled in this cross-sectional study during 2019. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was followed for this observational study (Von Elm et al., 2007). To obtain accurate data, medical records were extracted from the standardized checklists at the time of the survey. The evaluation was performed based on all accessible clinical data. To prevent bias, outlier data and missing findings were extracted from the data.

Women in the final stage of breast cancer, women with hypothyroidism or hypoparathyroidism at the beginning of the study, patients with abnormal albumin levels, and patients who were diagnosed or treated for multiple cancers were excluded from the cross-sectional study.

Measurements and variables

Thyroid and parathyroid Function Measurements – TSH and Free T4 levels – were measured for hypothyroidism, and total calcium (Ca), phosphorus (P), and PTH levels were calculated for hypoparathyroidism in patients with breast cancer who underwent RT. Laboratory evaluation was performed before and after radiotherapy every six months for one year. In our laboratory, the normal range of thyroid function tests is as follows: Thyroid-stimulating hormone (thyrotropin) 0.34–4.25 μ U/ml; Free T4 0.7–1.24 ng/ml; Parathyroid hormone 8–51 pg/ml; Phosphorus 2.5–4.3 mg/dl; and Calcium 8.7–10.2 mg/dl.

Statistical analyses

All statistical analyses were performed using SPSS software (version 24.0; IBM Corporation, Armonk, NY, USA) for Windows. All statistical analyses were two-sided, and Alpha-Error less than 0.05 considered to be significant. Chi-Square test was applied for analysis of categorical variables. The Kruskal-Wallis test was employed to compare the data for the three points of times in follow-up (before RT, at 6 and 12 months after RT).

Ethical considerations

The study was approved by the ethics committee with the IR number ARUMS. REC.1399.025. Patients' information remained confidential. Patients were voluntarily enrolled based on personal consent, and all patients had the right to withdraw from the study at any point.

RESULTS

Initially, a total of 70 women with breast cancer undergoing RT treatment were included in this study. However, after six months, one of the participants was excluded due to brain metastasis. Thus, data analysis was performed based on 69 patients. The mean age of the participating patients was 54.3 ± 0.4 years (ranging from 43 to 69 years).

There were statistically significant differences in the TSH among patients at six and 12 months after radiotherapy ($p = 0.030$). Pairwise comparisons with the post hoc Dunn test

revealed that the serum level of TSH was significantly higher both at 6 months ($p = 0.020$) and 12 months of follow-up ($p = 0.023$) after RT compared to the initial level (Table 1). While we found no statistical difference in TSH level at six months of follow-up in comparison with the 12 months of follow-up.

We found no statistically significant changes in T4 levels at 6 and 12 months of RT.

After six to 12 months of follow-up, there was a statistically significant trend in the rise of PTH over the follow-up times ($p = 0.036$). Pairwise comparisons confirmed that the serum levels of PTH at 6 and 12 months after were higher than the baseline parameters ($p = 0.017$ and $p = 0.040$ respectively). We found no significant difference in the level of Ca and P values at 1-year follow-up ($p = 0.181$ and $p = 0.321$, respectively).

As Table 3 demonstrates, there was one confirmed case of overt hypothyroidism over 6 and 12 months of RT that did not reach statistical significance ($p = 0.469$ and $p = 0.481$, respectively). During 6 months of follow-up, eight (11.8%) breast cancer survivors, and after 12 months, five (7.5%) reported cases developed subclinical hypothyroidism that was found statistically significant ($p = 0.003$ and $p = 0.028$, respectively).

The cumulative incidence of thyroid dysfunction (both subclinical hypothyroidism and clinical hypothyroidism) was 13.0% and 8.7% at 6 and 12 months after RT, respectively, with statistically significant differences compared to the baseline ($p = 0.003$ and $p = 0.028$, respectively). We found no case of hypoparathyroidism over the follow-up period of treatment.

DISCUSSION

Late treatment-related complications of RT, such as thyroid dysfunction, have become increasingly important with the increasing life expectancy among BC patients (Kanyilmaz et al., 2017). The present study aimed to evaluate the patterns of thyroid and parathyroid dysfunction among BC patients undergoing RT. Our single-centre study did not demonstrate any overt hypothyroid or hypoparathyroid dysfunction among our BC patients after RT, but the TSH level showed significant elevation after 6 and 12 months of RT. Therefore, we expected subclinical hypothyroidism as a complication of radiation-induced toxicity. PTH level was observed to increase, but without any specific parathyroid dysfunction cases.

The overall incidence of hypothyroidism in the patients in this study was 13% 6 months after radiotherapy and 8.7%

Table 1

Serum Levels of Thyroid-stimulating and Thyroxine Hormones Before and After Radiotherapy

| Follow up | T4 | P-Value | TSH | P-Value |
|------------------------------|-----------|---------|-----------|---------|
| Before Radiotherapy | 0.98±0.13 | 0.818 | 2.36±0.94 | 0.030 |
| 6 months after radiotherapy | 1.00±0.16 | | 3.26±3.83 | |
| 12 months after radiotherapy | 0.99±0.16 | | 3.57±3.30 | |

Note. T4 = thyroxine; TSH = thyroid-stimulating hormone

Table 2

Serum Levels of Parathormone Hormone, Calcium, and Phosphorus Before and After Radiotherapy

| Follow-up | (PTH) | P-Value | (Ca) | P-Value | (P) | P-Value |
|------------------------------|-------------|---------|-----------|---------|-----------|---------|
| Before Radiotherapy | 35.08±9.46 | 0.036 | 9.47±0.44 | 0.181 | 3.72±0.46 | 0.321 |
| 6 months after radiotherapy | 42.79±19.82 | | 9.59±0.43 | | 3.71±0.50 | |
| 12 months after radiotherapy | 41.83±18.40 | | 9.44±0.37 | | 3.79±0.46 | |

Note. PTH = parathyroid hormone; Ca = calcium; P = phosphorous

Table 3

Frequency of Clinical, Subclinical Hypothyroidism, Total Thyroid Disorders, and Hypoparathyroidism Before and After Radiotherapy

| | Clinical hypothyroidism | | P-Value | Subclinical hypothyroidism | | P-Value | Total thyroid disorders | | P-Value | Hypoparathyroidism | | P-Value |
|------------------------------|-------------------------|------------|---------|----------------------------|------------|---------|-------------------------|-------------|---------|--------------------|-----------|---------|
| | Yes | No | | Yes | No | | Yes | No | | Yes | No | |
| Before Radiotherapy | 0 (0%) | 69 (100%) | Base | 0 (0%) | 69 (100%) | Base | 0 (0.0%) | 69 (0.100%) | Base | 0 (0%) | 69 (100%) | Base |
| 6 months after radiotherapy | 1 (6.1%) | 60 (4.98%) | 469/0 | 8 (8.11%) | 60 (2.88%) | 003.0 | 9 (0.13%) | 60 (0.87%) | 003.0 | 0 (0%) | 69 (100%) | - |
| 12 months after radiotherapy | 1 (6.1%) | 63 (4.98%) | 481/0 | 5 (5.7%) | 63 (6.92%) | 028.0 | 6 (7.8%) | 63 (3.91%) | 028.0 | 0 (0%) | 69 (100%) | - |

12 months later, the majority of which was subclinical. This finding is roughly consistent with the findings of previous studies conducted by Tunio et al. (2015) in Saudi Arabia and Laway et al. (2012) in India. In both studies, the frequency of hypothyroidism after RT in women with BC was reported to be 15% and 16.94%, respectively. It should be noted that the slight variations in the incidence percentage can be attributed to environmental factors or unprovoked patients' demographics such as a contribution of ethnicity or genetic susceptibility, which might have introduced diversity to the TSH value between studies of different areas. Further studies in different locations are highly recommended to derive conclusions and a more precise estimation of the effect of RT-induced thyroid dysfunction among BC patients.

The incidence risk of RT-induced hypothyroidism is much less in comparison with the reported cases in head and neck or lymphoma studies (Bruning et al., 1985; Reinertsen et al., 2009; Smith et al., 2008). However, the frequency is still much higher than expected compared to patients who did not receive RT within their course of treatment (Laway et al., 2012). In our study, one of the most essential factors related to a higher risk of RT-induced hypothyroidism is the smaller size of the thyroid gland attributed to females, as shown in a retrospective study by Alterio et al. (2007). It can put them at increased risk for RT-induced hypothyroidism compared to males. Some data confirm that the presence of thyroid shielding decreases the risk of RT-induced hypothyroidism among patients who receive RT (Tunio et al., 2015).

In our study, TSH level tends to show a slightly increasing pattern after 6 and 12 months following RT compared to the baseline, although we found no statistically significant differences. This contrasts to Tamura et al. (1981) who demonstrated that after 2 years of follow-up, the TSH level increased by 26%, and in long-term evaluation, within 6–12 years after radiation, the percentage increased to 62%. A study conducted by Kanyilmaz et al. (2017) in Turkey detected an incidence of 21% in hypothyroidism as late toxicity developed after curative RT in BC patients, nearly twice as high as our study. In line with our study, the mean age distribution in this study was 53, which is identified as a key factor for radiation-effect sensitivity. To our knowledge, radiation-induced hypothyroidism will be decreased with increasing age due to the reduction of radiosensitivity of the thyroid gland in older patients (Kanyilmaz et al., 2017). Consistent with the previous study, Bruning et al. (1985) showed that 25% of the patients developed hypothyroidism after supraclavicular region radiation. RT field and the dose-volume parameters of the thyroid gland contributed as the most statistically significant predictors for hypothyroidism in their studies. Further evaluation and longer-term follow-up studies are needed to clear up such discrepancies and give practitioners better insight into the lasting complications of RT on the TSH level.

Two distinct studies on BC patients undergoing RT showed that the frequency of hypothyroidism among patients was 4% and 6%, which was lower than the present study (Dahbi et al., 2018; Wolny-Rokicka et al., 2016). This might be attributed to the effect of lower radiation dosage, which would have a

result of a lesser amount of parenchymal thyroid being at risk for injuries and secondary capsular fibrosis (Jereczek-Fossa et al., 2004; Johansen et al., 2011). In line with these findings, Kuten et al. (1996) reported a 40% risk of radiation-induced thyroid damage in patients after head and neck radiation who received 30–45 Gy. However, the risk reached about 27% for those exposed less. So, the tolerance dose of radiation should be determined, which can act as an influential predictive factor for hypothyroidism after RT (Wolny-Rokicka et al., 2016).

The rate of PTH abnormalities after RT is still in debate. In this study, we found no cases of hypo- or hyperparathyroidism. However, the mean level of PTH hormone in patients after RT was significantly higher. There was no difference in serpentine levels of Ca and P in patients before and after RT. Closely following our findings, a study by Holten and Petersen (1988) followed the PTH level after RT and noted an increasing trend of PTH levels within three years of follow-up. The study argued that the development of overgrowth in parathyroid tissue is mainly coming from high-dose RT in patients. This rising trend puts patients at greater risk for hyperparathyroidism in the future (Holten & Petersen, 1988). Moreover, some studies found a correlation between the development of parathyroid adenoma after exposure to ionizing breast radiation and noted an increasing trend of PTH levels over the long-term follow-up (Stephen et al., 2004). Due to the long period of time between radiation exposure and parathyroid abnormalities, it can be inferred that parathyroid screening routinely could be considered in cases with a history of RT (Stephen et al., 2004).

Recent studies suggest that RT leads to dysregulation of vitamin D metabolism. Some reports have identified alteration in the gut microbiota after RT, reduced physical activity, and inadequate intake of vitamin D-rich foods in cancer patients involved in RT-induced Vitamin D deficiency (Huang et al., 2019). Therefore, our data must be interpreted with caution, because the increase in serum PTH levels in our patients may have been secondary to vitamin D deficiency. However, we did not evaluate the serum levels of vitamin D in this study.

Contrary to our study, Aboelnaga and Aboelnaga (2015) demonstrated that levels of PTH and Ca were significantly lower at three weeks and three months after RT in comparison with the levels before radiotherapy. However, their results are contrary to ours in that we saw no differences in serum level of P within the time of follow-up. A possible explanation for these findings might be related to the fact that the accurate detection of PTH abnormalities appears after a long latent period of time following RT (Aboelnaga & Aboelnaga, 2015). In addition, the reduction in the secretion of endogenous PTH can be suppressed by the activity of parathyroid hormone-like peptide (PTHrp) produced by the malignant cells in BC patients (Fierabracci et al., 2001).

Considering these study findings, it is worth noting that despite the introduction of modern radiotherapy techniques, patients still experience side effects, such as hypothyroidism, associated with RT. Since hypothyroidism in both clinical and subclinical forms can cause additional problems in cancer patients, routine thyroid function monitoring should be taken into account.

LIMITATIONS

To the best of our knowledge, this is one of the first papers in Iran discussing the hormonal complications of RT in the neck region among breast cancer patients during 1-year post-radiation. This study, nevertheless, was not without limitations. We were unable to assess the longer-term side-effects of RT, thyroid gland volume, radiation dosage, the effect of other treatments, such as chemotherapy, and correlation of the other underlying disease that could have helped us better understand the outcome of patients after RT. The loss of patients during follow-up and the small sample size might have introduced some bias into the result. In addition, we had no data regarding the existence of autoimmune antibodies, which could have helped in categorizing the severity and underlying cause and of hypothyroidism or hypoparathyroidism.

CLINICAL AND RESEARCH IMPLICATIONS

Our study suggests that patients with BC treated with RT had a long-term elevated risk of hypothyroidism post-RT. On-going monitoring for signs and symptoms of this effect should be considered. It can be inferred that extended studies with different endpoints follow up times and larger sample sizes are recommended. Further studies should consider unmeasured confounding factors, such as obesity, physical activity, and smoking, which can be a better reflection of the additive effect of RT-related long-term complications.

CONCLUSION

The development of subclinical hypothyroidism among our patients was appreciable. In addition, our study showed an increasing pattern in PTH levels among our patients, which needs long-term follow-up of BC patients after RT. Oncologists and nurse practitioners who work in breast cancer settings,

should be alert to the signs and symptoms of hypothyroidism or hypoparathyroidism and monitor the hormonal level imbalances regularly in BC patients after RT.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this research are available upon reasonable request from the corresponding author.

ETHICS

This study was performed according to the principles outlined by the World Medical Association's Declaration of Helsinki on experimentation involving human subjects, as revised in 2000, and has been approved by the ethics committee of the Ardabil University of Medical Sciences.

AUTHOR CONTRIBUTIONS

Niloofar Rahimi: Resources, Software, Farzaneh Mashayekhi: Writing – original draft, Oveis Salehi: Writing – review & editing, Amirreza Khalaji: Writing – original draft, Amir Abbas Kani: Investigation, Resources, Hamed Zandian: Data analysis, Writing – review & editing, Iraj Feizi: Conceptualization, Supervision, Validation.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report and clinical images. Consent has been signed and collected in accordance with the journal's patient consent policy.

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