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Original article

RADIOTHERAPY- INDUCED THYROID DYSFUNCTION

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Abstract

Aim: The aim of this paper was to evaluate the effects of radiotherapy on thyroid function in breast cancer patients, comparing those treated only on the chest wall with those who also received supraclavicular (SCV) nodal irradiation.

Material and Methods: A total of 100 women with breast cancer treated with radiotherapy were analyzed. Blood samples were taken before radiotherapy and evaluated by measuring serum thyroid stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) levels. None of the women were on thyroid substitution therapy. Thyroid function, including TSH, fT3 and fT4 levels, was monitored in patients every 6 months after the completion of radiation.

Results: The results revealed a significant impact on thyroid function, particularly an increased incidence of hypothyroidism in the SCV irradiation group. The study reported that after six months of radiotherapy, 35% of patients developed hypothyroidism, and this percentage decreased to 27% after twelve months. This suggests that while many patients may experience immediate thyroid dysfunction following radiotherapy, some may recover over time, though a substantial portion remains affected.

Conclusions: The data presented highlight a concerning trend of increased hypothyroidism among breast cancer patients undergoing radiotherapy, particularly those receiving SCV irradiation. The study's findings indicate that a substantial proportion of patients may experience lasting thyroid dysfunction, necessitating vigilant monitoring and management.

Keywords: breast cancer, radiotherapy, thyroid disorder, supraclavicular nodal irradiation

Introduction

The relationship between breast cancer and thyroid function has been discussed from different viewpoints ever since Beatson in 1896 noticed necessity to treat thyroid gland in advanced breast cancer[1]. Many studies have shown that thyroid diseases are common among women with breast cancer [2]. Supraclavicular (SCV) nodal irradiation is recommended in the majority of node-positive breast cancer (BC) patients as part of adjuvant radiation therapy (RT) to the chest wall or breast. Radiation exposure to a part of the thyroid is unavoidable in BC patients receiving adjuvant radiotherapy that includes ipsilateral SCV nodal irradiation. Practices such as delineating the thyroid, spinal cord and utilizing three-dimensional conformal (3DC) RT planning in BC nodal irradiation are being increasingly performed, while practices such as utilizing conventional SCV or full-nodal irradiation fields are decreasing. Even though some dosimetric data on 3DCRT planning of SCV irradiation showed better target coverage, they also indicated that increased radiation doses were being absorbed by the thyroid [3]. Several reports examined post-treatment hypothyroidism in breast cancer (BC) [4-7]. Joensuu *et al*. demonstrated that an immunoassay of 80 patients (21%) treated with post-mastectomy radiation showed evidence of hypothyroidism [7]. Further, in their retrospective study of 200 BC patients, Bruning *et al.* found that the prevalence of hypothyroidism was significantly greater in patients who had received regional nodal irradiation compared to those who received radiation to the chest wall or breast alone[5]. The tolerance level of thyroid tissues to radiation is poorly defined but, theoretically, the development of radiation-induced hypothyroidism is primarily related to vascular damage and less viable tissue that is not able to produce thyroid hormone post-radiation. This largely depends on the volume of the thyroid gland receiving high radiation doses [8]. The risk of developing post-radiation hypothyroidism is not remarkably high (15%-18%)[7,3,9].

Hypothyroidism has a significant impact on the quality of life and over the past two decades, BC patients have shown dramatic improvements in their long-term survival. Thus, it is of interest to explore the effects of radiation exposure on the thyroid glands of BC patients, and further studies are needed to evaluate the dose-effect relationship between RT and long-term thyroid toxicity following regional nodal irradiation.

Aim

In this paper, we aimed to evaluate the response of the thyroid gland to radiation by assessing thyroid function among breast cancer patients before irradiation and at regular intervals thereafter.

Materials and methods

This non-randomized, prospective study included 100 women with breast cancer treated with radiotherapy in the Radiotherapy Department at the University Clinical Center of Kosovo in the period between September 2022 and September 2023. The study was conducted by a single physician in a period of 2 years, during which thyroid function was assessed in 35 women who received radiotherapy to the breast after breast-conserving surgery (BCS) or mastectomy (control group) and in 65 women who underwent irradiation of regional lymph nodes and the breast or scar- (SC-RT group). In the SC-RT group, a part of the thyroid gland was irradiated. It was documented using contouring the thyroid gland for all patients were irradiated on supraclavicular area. Each treatment plan consisted of dose volume histograms (DVHs) in which distribution of isodoses in the critical organs was described, and additionally, distribution of isodoses in thyroid gland for the SC-RT group was shown.

Patients received radiation doses of 50 Gy in 2 Gy daily fractions to either the breast or chest wall and regional nodes.

Inclusion criteria:

1. Adult female patients with pathologically proven invasive BC.
2. Patients treated surgically either by modified radical mastectomy (MRM) or breast conservation surgery (BCS).
3. Patients treated with adjuvant radiation with three fields of RT, but only when the target volume included the breast after BCS or the chest wall after MRM, as well as the ipsilateral regional lymph nodes.

Exclusion criteria:

1. Patients with abnormal thyroid glands or abnormal thyroid nodules were excluded from this study.
2. Metastatic patients.

Blood samples were drawn before radiotherapy and evaluated by measuring the serum thyroid stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) levels. None of the women were on thyroid substitution therapy. Thyroid function, including TSH, fT3 and fT4 levels, was monitored in patients every 6 months after the completion of radiation.

Serum TSH, T3 and T4 levels were measured by the electro-chemiluminescence immunoassay method using commercial kits. The reference values in our hospital for these. Parameters are: TSH - normal range: 0.3 - 4.2 mIU/ ml, fT4 normal range: 12.0–22.0 pmol/l and fT3 normal range: 3.1 - 6.8pmol/l. Although hypothyroidism can be divided into clinical and subclinical classifications, we defined hypothyroidism as a TSH value greater than the maximum value of laboratory range, regardless of symptoms.

Target delineation and treatment planning

1. The scan images were exported to the treatment planning system for target delineation and computer dosimetric planning.
2. The following volumes were included and routinely delineated on CT slides: the breast, chest wall, SCV, axilla, lungs, heart, and spinal cord. The thyroid gland was contoured for the purpose of this study.
3. The total radiation dose delivered to the chest wall or breast was 50 Gy in 25 fractions (2 Gy/fraction) followed by ± additional tumor bed boost of 10 Gy/5 fractions using photons or 6-12 MeV electrons. The total prescribed radiation dose to the ipsilateral SCV was 50 Gy.

Results

Among the 100 breast cancer patients, the median follow-up time was 325.0 days in the control group and 400.0 days in the SC-RT group.

Sixty-five patients received treatment with 50 Gy. The target volume included the breast (after BCS) or the chest wall (after mastectomy), the ipsilateral supra-and infraclavicular fossa, ipsilateral lymph nodes along the internal mammary artery and ipsilateral axilla. Thirty-five patients received 50 Gy irradiation to the whole breast (WBI) and 10 Gy as a boost to a tumor bed after BCS.

Table 1 shows the baseline values of thyroid parameters in both groups. Before treatment, similar values of TSH, fT3 and fT4 were observed in the SC-RT group and in the control group (Table 1).

Table 1. Baseline values of thyroid parameters in both groups

Variable	Group	Statistical Parameter mean ± SD	
bRT – TSH (µIU/ml)	SC-RT	2.11 ± 1.3	t=0.6
	Control	2.28 ± 1.2	p=0.52
bRT - fT3 (pmol/l)	SC-RT	4.31 ± 1.1	t=0.076
	Control	4.30 ± 0.8	p=0.9
bRT - fT4 (pmol/l)	SC-RT	14.39 ± 3.5	t=0.4
	Control	14.68 ± 3.4	p=0.7

t (Student t-test)

After 6 months of therapy, TSH hormone values did not differ significantly between the two groups (p=0.81), while fT3 and fT4 values were significantly lower in the SC-RT group (p=0.0038 and p=0.048, respectively). The median fT3 was 3.99 pmol/L in the SC-RT group, and 4.49 pmol/L in the control group.

After 12 months of therapy, TSH was significantly higher in the SC-RT group (mean=3.96 ± 2.2, median=3.23 µIU/ml) compared to controls (mean= 2.77 ± 0.9µIU/ml, median=2.97 µIU/ml), p=0.024). Significantly lower values in the SC-RT group were obtained for fT3 (3.87 ± 1.5 *vs.* 4.50 ± 0.9 pmol/l, p=0.027), and no significantly lower values for fT4 (14.31 ± 2.6 *vs.* 15.04 ± 1.8 pmol/l, p=0.15)(Table 2) (Figure 1, 2, 3, 4).

Table 2. Baseline values of thyroid parameters in both groups after 6 and 12 months

Variable	Groups	Statistical Parameter		p-value
		mean ± SD	min – max median (IQR)	
6mRT - TSH (µIU/ml)	SC-RT	4.11 ± 5.2	2.7 (1.47 - 5.32)	Z=0.2
	Control	3.34 ± 2.7	2.48 (1.64 - 4.2)	p=0.8
6mRT - fT3 (pmol/l)	SC-RT	3.69 ± 1.2	3.99 (2.92 - 4.6)	Z=2.9
	Control	4.62 ± 1.3	4.49 (3.99 - 5.12)	**p=0.0038
6mRT - fT4 (pmol/l)	SC-RT	14.34 ± 10.7	14.35 (12.86 - 15.69)	Z=1.98
	Control	15.23 ± 4.0	15.1 (13.05 - 18.6)	*p=0.048
12mRT - TSH (µIU/ml)	SC-RT	3.96 ± 2.2	3.23 (2.46 - 5.86)	Z=2.25
	Control	2.77 ± 0.9	2.97 (2.1 - 3.22)	*p=0.024
12mRT - fT3 (pmol/l)	SC-RT	3.87 ± 1.5	1.1 - 6.87	t=2.25
	Control	4.50 ± 0.9	32 - 6.11	*p=0.027
12mRT - fT4 (pmol/l)	SC-RT	14.31 ± 2.6	10.2 - 20.0	t=1.46
	Control	15.04 ± 1.8	12.46 - 19.3	p=0.15

t (Student t-test); Z(Mann-Whitney U test), *sig p<0.05, **sig p<0.01

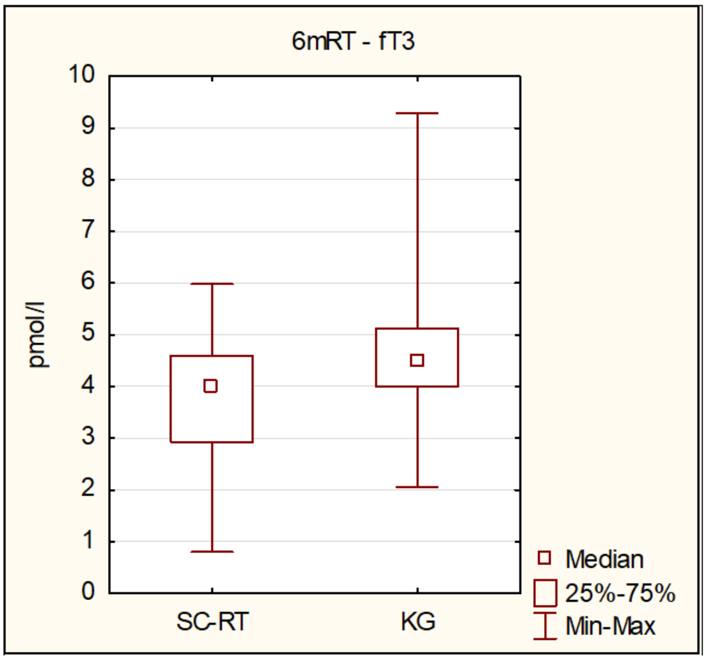

Fig. 1. Comparison of fT3 values between the two groups after 6 months

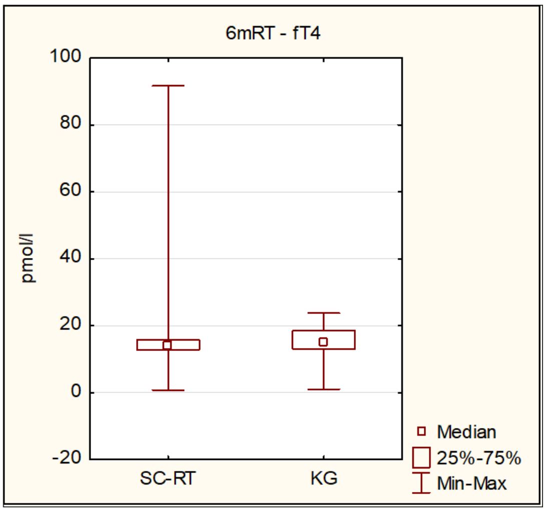

Fig. 2. Comparison of fT4 values between the two groups after 6 months

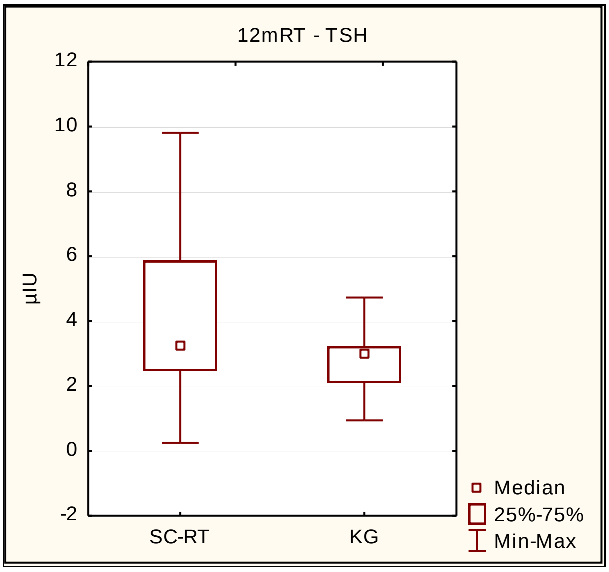

Fig. 3. Comparison of TSH values between the two groups after 12 months

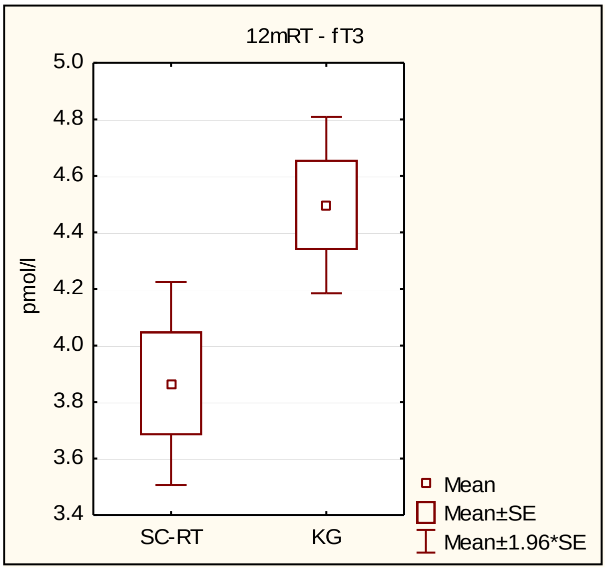

Fig. 4. Comparison of fT3 values between the two groups after 12 months

After 6 months of radiotherapy, hypothyroidism was reported in 35% of patients, and after 12 months in 27% of patients. The difference in the percentage of hypothyroidism between 6 and 12 months of radiotherapy was not statistically significant (p=0.32) (Table 3).

Table 3. Percentage of hypothyroidism after 6 and 12 months

Hypothyroidism	After 6 months	After 12 months
Yes	35(35%)	27(27%)
No	65(65%)	72(72%)
no data		1(1%)

McNermar Chi-square =0.97 p=0.32

Analysis of hypothyroidism values

This study investigated the impact of radiotherapy on thyroid function in breast cancer patients and revealed several significant findings regarding hypothyroidism. A deeper analysis of these values can enhance our understanding of the relationship between radiation exposure and thyroid dysfunction.

The results obtained showed that 35% of patients developed hypothyroidism after six months of radiotherapy, while this figure decreased to 27% after twelve months. This suggests that while many patients may experience immediate thyroid dysfunction following radiotherapy, some may recover over time, though a substantial portion remains affected. The difference in hypothyroidism rates between the two time points was not statistically significant (p=0.32). This indicates that while the initial incidence of hypothyroidism is high, the long-term outcomes do not show a significant decrease in prevalence after one year. This emphasizes the need for ongoing monitoring and management of thyroid function in these patients.

At six months, the mean TSH level in the SC-RT group was 4.11 µIU/ml, while in the control group; it was 3.34 µIU/ml. At twelve months, TSH levels in the SC-RT group rose significantly to 3.96 µIU/ml compared to 2.77 µIU/ml in the control group (p=0.024). This increase indicates that patients receiving SCV irradiation experienced greater stimulation of the thyroid gland, possibly due to tissue damage and impaired hormone production.

The mean fT3 level at six months was significantly lower in the SC-RT group (3.69 pmol/l) compared to the control group (4.62 pmol/l, p=0.0038). At twelve months, the values remained lower in the SC-RT group (3.87 pmol/l) compared to the control group (4.50 pmol/l, p=0.027). This suggests that radiation may impair the thyroid's ability to produce adequate levels of fT3, which is critical for metabolic regulation. Similar trends were observed for fT4 levels, which were lower in the SC-RT group compared to controls at both time points. After six months, the mean fT4 was 14.34 pmol/l in the SC-RT group *versus* 15.23 pmol/l in the control group (p=0.048), while after twelve months, it was 14.31 pmol/l *versus* 15.04 pmol/l (p=0.15). The initial significant difference that diminished over time suggests that the impact of radiation on fT4 may stabilize, but it still indicates impaired thyroid function.

Discussion

The rising incidence of breast cancer in Kosovo, particularly the notable increase in cases post-pandemic, aligns with trends observed in various international studies. The 400 new breast cancer cases reported in 2023 highlight a concerning escalation, which echoes findings from studies conducted in other regions that have documented similar trends in breast cancer incidence. For instance, the study by Smith *et al.* [4] reported an increasing risk of breast cancer among older populations, potentially related to improved detection methods and changing risk factors.

Breast cancer has been consistently recognized as the most common cancer among women, both in Kosovo and globally. This finding is consistent with reports from countries like South Korea, where Park *et al.* [2] found a high prevalence of breast cancer among women receiving radiation therapy as in our study group. The demographics of breast cancer patients in Kosovo, characterized by a younger median age, may be a reflection of lifestyle factors and genetic predispositions that require further investigation.

Additionally, the observed impact of radiation therapy on thyroid function, as documented in the study on hypothyroidism following radiotherapy, underlined the complexities of cancer treatment. The significant increase in hypothyroidism in patients receiving supraclavicular nodal irradiation (SC RT) is particularly relevant when compared to findings from Joensuu and Viikari [7], who also highlighted a correlation between radiation exposure and thyroid dysfunction. In our study, after 6 months of radiotherapy, TSH levels were significantly higher in patients undergoing SC RT treatment compared to controls, aligning with the findings of Bruning *et al*. [5] that emphasized the risk of thyroid disorders in breast cancer patients receiving regional nodal irradiation.

While the study's results indicated a 35% incidence of hypothyroidism at six months post-radiotherapy, other studies have reported varying prevalence rates, with some noting a range from 15% to 30%. This discrepancy may be attributed to differences in study designs, populations, and treatment protocols. For example, Reinertsen *et al.* [6] observed thyroid dysfunction in women post-multimodal treatment, suggesting that various treatment regimens can exacerbate thyroid-related issues.

The findings underscore the need for comprehensive screening programs in Kosovo to address rising breast cancer incidence and the importance of monitoring thyroid function in patients undergoing radiotherapy. The growing evidence of thyroid complications post-treatment necessitates the establishment of preventive strategies and follow-up protocols to enhance patient quality of life and optimize cancer care. Future research should focus on elucidating the dose-response relationship of radiation exposure on thyroid function and the long-term consequences for breast cancer survivors.

Conclusion

The data presented highlight a concerning trend of increased hypothyroidism among breast cancer patients undergoing radiotherapy, particularly those receiving SCV irradiation. The study's findings indicate that a substantial proportion of patients may experience lasting thyroid dysfunction, necessitating vigilant monitoring and management. Given the implications for patient quality of life and overall health, it is crucial to develop protocols that include regular thyroid function assessments and appropriate interventions for those affected. Future research should focus on establishing guidelines for dose limits to the thyroid gland during radiotherapy and exploring additional protective measures to mitigate the risk of hypothyroidism in breast cancer patients.

Conflict of interest. None declared.

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