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THYROID DYSFUNCTION IN PATIENTS RECEIVING COMBINED TREATMENT FOR BREAST CANCER: A PROSPECTIVE CLINICAL STUDY

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Abstract

Breast cancer is the most common malignancy among women worldwide and remains a leading cause of cancer-related mortality. Combined treatment approaches significantly improve survival but are associated with systemic complications, including endocrine toxicity. The thyroid gland is particularly sensitive to anticancer therapies.

This prospective study aimed to evaluate functional and structural changes of the thyroid gland in patients with breast cancer during combined treatment. A total of 136 patients with stage II–III breast cancer and 23 control patients with stage I disease were included. Thyroid function was assessed by measuring serum levels of TSH, free T4 (fT4), free T3 (fT3), and anti-thyroid peroxidase antibodies (anti-TPO), while ultrasound was used to evaluate structural changes.

The results demonstrated a significant increase in TSH levels and a decrease in fT4 and fT3 concentrations in patients receiving combined therapy compared to controls ($p<0.0001$). The prevalence of hypothyroidism exceeded 60%, with more pronounced changes observed in patients receiving neoadjuvant therapy. Ultrasound examination revealed structural abnormalities in approximately 40% of patients. Clinical symptoms consistent with hypothyroidism were also significantly more frequent in the treatment groups.

In conclusion, thyroid dysfunction is a common manifestation of endocrine toxicity in patients undergoing combined treatment for breast cancer. Routine monitoring of thyroid function and ultrasound evaluation are recommended for early detection and management of these disorders.

Keywords: *breast cancer; thyroid dysfunction; hypothyroidism; chemotherapy; endocrine toxicity; neoadjuvant therapy; thyroid ultrasound; TSH; fT4; fT3; autoimmune thyroiditis*

Introduction

Breast cancer ranks first in the structure of oncological morbidity among women worldwide and remains a leading cause of cancer-related mortality (Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., & Forman, D., 2011; Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., & Jemal, A., 2018). According to international registries, more than 2.3 million new cases are registered annually, and the increasing trend persists (Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., & Forman, D., 2011). In Central Asian countries, including the Republic of Uzbekistan, a steady rise in incidence rates and a shift toward younger patient populations are observed (Early Breast Cancer Trialists' Collaborative Group. 2012).

Modern advances in molecular diagnostics, targeted and hormonal therapy have significantly improved overall and disease-free survival (Harbeck, N., Penault-Llorca, F., Cortes, J., et al. 2019; National Comprehensive Cancer Network (NCCN). 2024). Combined treatment regimens, including surgery, neoadjuvant and adjuvant chemotherapy, radiotherapy, and endocrine therapy, represent the standard management for patients with stage II–III disease (ESMO Guidelines Committee. 2021; Curigliano, G., Cardinale, D., Suter, T., et al. 2012). At the same time, intensification of therapy is accompanied by an increase in systemic complications, which requires expansion of monitoring for associated disorders (Torino, F., Corsello, S.M., & Salvatori, R., 2012).

In recent years, increasing attention has been paid to the problem of endocrine toxicity of anticancer treatment (Faje, A.T., 2016; Illouz, F., Laboureau-Soares, S., Dubois, S., et al., 2014). The thyroid gland is among the target organs sensitive to cytotoxic drugs, targeted agents, and immunomodulatory therapy (Iyer, P.C., Cabanillas, M.E., Waguespack, S.G., et al., 2018). Mechanisms of damage include direct cytotoxic injury to thyrocytes, impairment of peripheral conversion of thyroid hormones, vascular changes, and immune reactions (Brent, G.A., 2012).

Thyroid hormones play a fundamental role in the regulation of energy metabolism, cell proliferation, differentiation, and apoptosis (Biondi, B., & Cooper, D.S., 2008). Disturbances in their secretion may lead to decreased treatment tolerance, reduced quality of life, and the development of asthenic syndrome, which is often mistakenly interpreted as chemotherapy toxicity (Abdel-Rahman, O., ElHalawani, H., & Fouad, M., 2015).

According to various authors, the incidence of subclinical and overt hypothyroidism in oncology patients ranges from 30% to 60%, depending on treatment regimens (Faje, A.T., 2016; Mannavola, D., Coco, P., Vannucchi, G., et al., 2007; de Filette, J., Andreescu, C.E., Cools, F., et al., 2019). A particularly high risk of thyroid dysfunction has been described with the use of targeted agents and combined treatment regimens (Brent, G.A., 2012; Ditsch, N., Liebhardt, S., von Koch, F., et al., 2010). However, data on thyroid status in patients with breast cancer undergoing neoadjuvant and adjuvant chemotherapy remain limited and contradictory (Hegedüs, L., 2004).

In addition to functional changes, structural abnormalities of the thyroid gland detected by ultrasound are also important, including decreased echogenicity, parenchymal heterogeneity, and signs of autoimmune inflammation (Vanderpump, M.P.J., 2011). A comprehensive assessment of hormonal and ultrasound parameters allows for a more accurate determination of the nature and severity of the lesion.

Thus, the study of functional and structural status of the thyroid gland in patients with breast cancer receiving combined treatment represents a relevant scientific and clinical task.

Objective

To evaluate functional and structural changes of the thyroid gland in patients with breast cancer during combined treatment.

Materials and Methods

The study was conducted in a prospective format at a specialized oncology center from November 2023 to January 2025.

The study included 136 patients aged 38 to 68 years (mean age 52.4 ± 6.8 years) with morphologically confirmed stage II–III breast cancer.

The control group consisted of 23 patients (mean age 50.9 ± 5.7 years) with stage

I disease who did not receive aggressive combined therapy.

Patients of the main cohort were divided into two groups:

First group (n=62) – surgical treatment followed by adjuvant chemotherapy.

Second group (n=74) – neoadjuvant chemotherapy followed by surgery and adjuvant therapy.

Inclusion criteria:

1. Age over 18 years
2. Histologically confirmed diagnosis
3. Absence of previously diagnosed thyroid diseases
4. Written informed consent

Exclusion criteria:

1. Previous thyroid surgery
2. Use of thyroid medications before treatment
3. Presence of severe concomitant endocrine pathology

The functional state of the thyroid gland was assessed by determining serum levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), and antibodies to thyroid peroxidase (anti-TPO). The studies were performed using enzyme-linked immunosorbent assay.

The structural state was evaluated using ultrasound with determination of gland volume, echogenicity, parenchymal homogeneity, presence of nodular formations, and signs of autoimmune process.

Statistical analysis was performed using SPSS 16.0. Quantitative indicators are presented as M±SD. Student's t-test was used for group comparison. Differences were considered statistically significant at $p<0.05$.

Results

Group 1 – surgical treatment + adjuvant chemotherapy.

Group 2 – neoadjuvant + adjuvant therapy. Data are presented as mean ± standard deviation.

p – significance of differences between the main groups and the control group.

Table 1. *Thyroid hormonal profile parameters in examined patients (M±SD)*

Parameter	Group 1 (n=62)	Group 2 (n=74)	Control (n=23)	p
TSH (mIU/L)	5.9 ± 1.0	7.2 ± 1.3	3.18 ± 0.48	<0.0001
fT4 (pmol/L)	6.0 ± 0.70	5.4 ± 0.60	8.73 ± 0.63	<0.0001
fT3 (pmol/L)	2.1 ± 0.18	1.7 ± 0.20	4.6 ± 0.25	<0.0001

In patients of both main groups, a statistically significant increase in TSH level and a decrease in concentrations of fT4 and fT3 were revealed compared to the control group ($p<0.0001$). The most pronounced changes were registered in the second group.

Table 2. *Frequency of thyroid functional disorders (%)*

Parameter	Group 1 (n=62)	Group 2 (n=74)	Control (n=23)
Elevated TSH	33.9%	55.4%	8.7%
Decreased fT4	40.3%	62.1%	—
Decreased fT3	38.7%	55.4%	—
Elevated anti-TPO	14.5%	13.5%	4.3%

Comparative analysis demonstrated a statistically significant increase in the frequency of thyroid functional disorders in patients receiving combined therapy compared to the control group ($p<0.05$).

In the second group, an increase in TSH level was registered in 55.4% of patients, which significantly exceeded the indicators of both the first group (33.9%) and the control (8.7%).

A decrease in fT4 was detected in 62.1% of patients in the second group and in 40.3% in the first group, whereas such changes were not observed in the control group ($p<0.05$).

A similar trend was established for fT3: a decrease was registered in 55.4% of patients in the second group and in 38.7% in the first group, with no cases in the control group ($p<0.05$).

The frequency of elevated anti-TPO in the main groups (14.5% and 13.5%) did not differ significantly between them, but exceeded the control group (4.3%), which may indicate a possible immunological component of the detected disorders.

Thus, a significantly higher prevalence of laboratory signs of hypothyroidism was revealed in the second group, confirming the cumulative and dose-dependent nature of the effect of combined anticancer therapy on thyroid function.

Table 3. *Ultrasound characteristics of the thyroid gland (%)*

Parameter	Group 1 (n=62)	Group 2 (n=74)	Control (n=23)	p
Diffuse decrease in echogenicity and heterogeneity	40.3%	40.5%	8.7%	<0.01
Normal echostructure	45.2%	44.6%	87.0%	<0.01

Analysis of ultrasound characteristics of the thyroid gland demonstrated significant differences between the main and control groups.

Diffuse decrease in echogenicity and heterogeneity of the parenchymal structure were detected in 40.3% of patients in the first group and 40.5% in the second group, which is more than four times higher than in the control group (8.7%; p<0.01).

No statistically significant differences were found between the first and second groups for this parameter (p>0.05), indicating a similar frequency of structural changes regardless of the sequence of chemotherapy.

Normal thyroid echostructure was significantly more often observed in the control group (87.0%) compared to the first (45.2%) and second (44.6%) groups (p<0.01).

The obtained data indicate a high prevalence of structural changes of the thyroid gland in patients receiving combined treatment for breast cancer.

Table 4. *Frequency of symptoms (%)*

Symptom	Group 1	Group 2	Control
Fatigue	87.1%	83.8%	26.1%
Dry skin	61.3%	54.1%	13.0%
Drowsiness	54.8%	47.3%	8.7%
Edema	41.9%	35.1%	4.3%
Weight gain	35.5%	33.8%	8.7%

Clinical analysis showed that symptoms characteristic of hypothyroidism were significantly more often observed in patients undergoing combined treatment compared to the control group (p<0.05).

The most pronounced manifestation was general weakness and increased fatigue, observed in more than 80% of patients in both main groups, whereas in the control group this symptom was recorded only in about one quarter of cases.

Dermatological manifestations such as dry skin were registered in more than half of the patients in the main groups, significantly exceeding the control group.

A similar pattern was observed for drowsiness, the frequency of which in the treatment groups exceeded the control values more than fivefold.

Peripheral edema and weight gain were also significantly more frequent in patients receiving anticancer therapy, while in the control group these symptoms were rare.

No statistically significant differences were found between the first and second groups (p>0.05), indicating a similar clinical severity of hypothyroid syndrome regardless of treatment stage.

Thus, clinical data confirm the development of a typical hypothyroid symptom complex in patients undergoing combined treatment for breast cancer.

Discussion

The obtained results indicate the development of persistent thyroid dysfunction in patients undergoing combined treatment for breast cancer. The observed changes are systemic in nature and are confirmed by a combination of laboratory, ultrasound, and clinical data.

An increase in TSH levels combined with a decrease in free thyroxine and triiodothyronine levels indicates the predominance of primary hypothyroidism. More pronounced hormonal changes in the second group suggest a cumulative effect of cytotoxic therapy. It is likely that the sequential use of neoadjuvant and adjuvant therapy increases the load on the hypothalamic-pituitary-thyroid axis, contributing to the exhaustion of compensatory mechanisms.

The absence of significant differences in ultrasound changes between the first and second groups suggests that structural alterations develop at early stages of systemic therapy and persist regardless of treatment sequence. Decreased echogenicity and parenchymal heterogeneity may reflect both dystrophic processes and subclinical inflammation.

The immunological component, reflected by moderate elevation of anti-TPO, does not appear to be dominant; however, its presence in some patients suggests a possible role of immune mechanisms in the pathogenesis.

Clinical symptoms generally correspond to laboratory findings, although their severity does not always directly correlate with hormone levels, highlighting the multifactorial nature of symptoms in oncology patients.

Overall, the results confirm that thyroid dysfunction is a frequent manifestation of endocrine toxicity of combined breast cancer treatment.

Conclusions

1. Patients with breast cancer receiving combined treatment develop significant thyroid dysfunction characterized by increased TSH and decreased fT4 and fT3.
2. The frequency of laboratory signs of hypothyroidism exceeds 60%.
3. Neoadjuvant treatment regimens are associated with more pronounced hormonal changes, suggesting a cumulative and dose-dependent effect.
4. Ultrasound signs of structural thyroid changes are observed in a significant proportion of patients.
5. Clinical manifestations of hypothyroidism are significantly more frequent in treated patients but do not always correspond to laboratory findings.
6. Monitoring of thyroid function and ultrasound assessment should be included in follow-up protocols.
7. Further studies are required to evaluate long-term effects and their impact on treatment outcomes.

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