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## CLINICAL ASPECTS OF THYROID DYSFUNCTION DURING COMBINED THERAPY FOR BREAST CANCER

***Azimova Makhbuba Abrorjon qizi*** [1],
***Nasirova Khurshidakhon Kudratullayevna*** [1]

[1] Tashkent Medical Univesity

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**Abstract**

Breast cancer is among the most prevalent cancers affecting women and often necessitates a multifaceted treatment approach. However, combined treatment methods such as chemotherapy and radiotherapy can negatively impact thyroid gland (TG) function, potentially causing hormonal imbalances. These thyroid issues can deteriorate a patient's general health, lower their ability to tolerate treatment, and possibly affect the effectiveness of therapy. In Uzbekistan, this area has not been thoroughly explored, emphasizing the importance of a detailed evaluation of thyroid function in women with BC.

**Keywords:** *breast cancer, chemotherapy, thyroid gland, thyroid dysfunction, anti-TPO antibodies, thyroid hormones, combined therapy*

### Introduction

Breast cancer (BC) remains one of the most prevalent oncological conditions among women globally. According to data from the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (RSSPMCOR) under the Ministry of Health of Uzbekistan, a total of 4,757 new cases of BC were reported in 2024, with 86.7% of these diagnosed at stages II–IV, necessitating intensive multimodal treatment approaches. In recent years, growing attention has been directed toward the effects of anticancer therapies on the endocrine system, particularly the thyroid gland.

Thyroid dysfunction observed in oncology patients may arise as a consequence of therapeutic interventions or may reflect pre-existing, undiagnosed thyroid abnormalities prior to the initiation of cancer treatment. The development of hypothyroidism in this context has the potential to adversely influence the clinical trajectory of BC, diminish patient tolerance to treatment, and negatively impact overall quality of life.

The primary aim of the present study was to evaluate the effects of different combined

treatment modalities for BC on both clinical and laboratory indicators of thyroid gland function.

## Materials and Methods

The study included 136 female patients with histologically confirmed BC treated at RSSPMCOR and its regional branches between 2023 and 2025. Patients' ages ranged from 30 to 73 years (mean 56.3 ± 0.4 years).

Patients were divided into three groups:

- Group 1 (n=52): Stage II BC, treatment consisted of surgery plus 6–8 courses of chemotherapy without neoadjuvant treatment;
- Group 2 (n=64): Stage II–III BC, neoadjuvant and adjuvant chemotherapy;
- Group 3 (control, n = 20): Stage I BC, no chemotherapy.

Previous studies have reported the prevalence of anti-thyroid peroxidase antibodies (anti-TPO) in patients with BC to be approximately 34%, compared to 36% in control populations. Based on an estimated effect size of 0.55, a significance level of 5%, and a statistical power of at least 80%, the minimum required sample size was determined to be 20 participants in the control group and 93 in the experimental (BC) group.

All participants provided written informed consent prior to enrollment, and the study protocol was reviewed and approved by the institutional Ethics Committee.

The research protocol encompassed comprehensive clinical and laboratory evaluations, along with instrumental diagnostic procedures including ultrasound, magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT). Thyroid function was assessed through measurements of serum thyroid-stimulating hormone (TSH), total triiodothyronine (T3), free thyroxine (T4), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), in addition to thyroid ultrasound imaging.

Reference ranges for thyroid hormones were:

- TSH: 0.5–4.5 μIU/mL;
- Total T3: 80–200 pg/mL;
- Free T4: 4–12 ng/mL;
- Anti-TPO levels > 40 IU/mL were considered positive.

### Statistical Analysis

Data were analyzed using SPSS v.19.

Normality was assessed by the Kolmogorov-Smirnov test.

Group comparisons employed Student's t-test for normally distributed data,

Mann-Whitney U test for nonparametric data,

Chi-square and Fisher's exact test for contingency tables.

Statistical significance was set at $p < 0.05$.

## Results

*Clinical manifestations:*

- The most frequently observed symptoms of thyroid dysfunction during the post-chemotherapy period included general weakness (88.9%), palpitations (up to 31.1%), neck discomfort (up to 37.8%), and a sense of a lump during swallowing (up to 26.5%). In contrast, these clinical manifestations were largely absent in the control group.

*Laboratory findings:*

- TSH, T3, and T4 levels were assessed at three time points: prior to the initiation of chemotherapy, one month following its completion, and six months post-treatment. Alterations in thyroid hormone profiles were identified in 78.7% of patients, with subclinical hypothyroidism being the most prevalent abnormality. Additionally, elevated levels of cholesterol and triglycerides were observed, suggesting a potential link between thyroid dysfunction and the development of metabolic syndrome during chemotherapy.
- While no statistically significant difference in TSH levels was observed between the patient and control groups ($p = 0.166$), significant intergroup differences were noted for mean free T4 ($p = 0.001$), total T3 ($p < 0.017$), and anti-thyroid peroxidase antibodies (anti-TPO) ($p = 0.05$). Further analysis using Chi-square and Fisher's exact tests confirmed significant differences between groups for T3 ($p = 0.017$) and anti-TPO ($p = 0.044$), whereas no significant differences

were found for TSH (p = 0.34) or free T4 (p = 0.14).

*Ultrasound and imaging studies:*

Thyroid ultrasound examinations were conducted using 5 MHz convex transducers positioned perpendicular to the midline of the neck, enabling evaluation of the thyroid gland's structure, volume, and dimensions throughout the course of BC chemotherapy. Thyroid volume was calculated using the A. F. Tsyba formula (1990):

$$V = 0.52 \times A \times B \times C \ (sm^3)$$

where:

- *A* represents the length of the thyroid lobe;
- *B* – is the thickness, and
- *C* – is the width measured in the transverse plane.

When indicated, Doppler mapping was employed to assess vascularization and characterize nodular formations.

MRI of the thyroid, using T1-weighted sequences, was performed in 53 patients to detect structural abnormalities. Additionally, PET-CT using 18F-fluorodeoxyglucose (18F-FDG) was employed for disease staging and to evaluate thyroid metabolic activity based on radiotracer uptake.

Patients were instructed to fast for 12 hours prior to receiving an intravenous injection of 18F-FDG at a dose of 200 MBq/m² (total dose ranging from 370 to 420 MBq). Following a 60–90 minute uptake phase, patients were encouraged to consume up to 500 mL of water and to void the bladder in order to reduce background radiotracer activity. A preliminary CT scan was performed to define the anatomical region for PET imaging, and established synchronization protocols were applied for accurate PET-CT data alignment.

*Statistical Analysis of the Material*

The data obtained in the study were statistically analyzed using SPSS version 16.0 (USA). The degree of statistical significance for various comparative parameters was determined accordingly. Parametric data were reported as means ± standard deviations (SD), while non-parametric data were expressed as medians with interquartile ranges (Q1–Q3). Independent samples were analyzed using the Mann–Whitney U-test for non-parametric variables. Categorical variables were evaluated using the Chi-square test and Fisher's exact test. A p-value less than 0.05 was considered indicative of statistical significance. Differences in mean values between groups were assessed using the Student's *t*-test and Fisher's exact test.

To compare long-term (5-year) outcomes of different treatment modalities based on survival stratification, the actuarial life table method – specifically the "Lise-Table method" developed by Cutler S. J. and Ederer F. and endorsed by the Union for International Cancer Control (UICC)—was employed.

Patient survival was further analyzed using the Kaplan–Meier method, applying the formula:

$$s(t)=N\times(1-d_1/n_{10})$$

where *s(t)* represents the survival probability at time *t*, $d_1$ the number of events (deaths) at that time, and $n_{10}$ the number of individuals at risk.

Median durations of disease-free and metastasis-free intervals were determined according to the methodology proposed by D. Collett (1999).

## Discussion

Our study confirms a high prevalence of thyroid dysfunction among BC patients undergoing combined therapeutic regimens. This aligns with previous research linking thyroid disorders – such as nodular hyperplasia, hyperthyroidism, autoimmune thyroiditis, and elevated anti-TPO antibody levels – to breast cancer pathophysiology (Turken O., NarIn Y., DemIrbas S., Onde M. E., Sayan O., KandemIr E. G., 2003; Agarwal D. P., Soni T. P., Sharma O. P., Sharma S., 2007; Giustarini E., Pinchera A., Fierabracci P., Roncella M., Fustaino L., Mammoli C., 2006). Several studies have reported associations between BC and various thyroid-related biomarkers, including anti-TPO, TSH, T3, T4, and estradiol levels (Fierabracci P., Pinchera A., Campani D., Pollina L. E., Giustarini E., Giani C. 2006; Sabitha Suneetha, Mohanty S, Rao P., 2009; Ali A., Mir M. R., Bashir S., Hassan T., Bhat S. A., 2011; Smyth P. P., Shering S. G., Kilbane M. T., Murray M. J., McDermott E. W., Smith D. F., 2017; (Fierabracci P., Pinchera A., Campani D., Pollina L. E., Giustarini E., Giani C., 2006; Sabitha Suneetha, Mohanty S, Rao P., 2009; Ali A., Mir M. R., Bashir S., Hassan T., Bhat S. A., 2011; Smyth P. P., Shering S. G., Kilbane M. T.,

Murray M. J., McDermott E. W., Smith D. F., 2017; Ditsch N., Liebhardt S., Von Koch F., Lenhard M., Vogeser M., Spitzweg C., 2010).

In our cohort, BC patients exhibited significantly elevated anti-TPO (p=0.011) and free T4 (p=0.001) levels compared to controls, while total T3 levels were significantly reduced (p=0.001), and TSH levels were lower but not statistically significant (p=0.166). These findings are consistent with prior literature (Ali A., Mir M. R., Bashir S., Hassan T., Bhat S. A., 2011; Wang G., Chen X-S., Mao Y., Li Y-F., Chen W-G., Shen K-W., 2014; Takatani O., Okumoto T., Kosano H., Nishida M., Hiraide H., Tamakuma S., 1989; Kuijpens J. L., Nyklictek I., Louwman M. W., Weetman T. A., Pop V. J., Coebergh J. W., 2005; Saraiva P., Figueiredo N., Padovani C., Brentani M., Nogueira C., 2005; Rose D. P., Davis T. E., 1979), reinforcing the hypothesis that thyroid dysfunction – potentially driven by autoimmune mechanisms – may influence BC development and progression.

One proposed mechanism involves the estrogen-mimetic action of thyroid hormones and their receptors in modulating cellular proliferation and differentiation (Tosovic A., Bondeson A. G., Bondeson L., Ericsson U. B., Malm J., Manjer J., 2010). Notably, the ratio of free T3 to free T4 has been suggested as a potential tumor biomarker (Ditsch N., Liebhardt S., Von Koch F., Lenhard M., Vogeser M., Spitzweg C., 2010). Some studies have associated elevated free T4 levels with increased BC risk, whereas higher anti-TPO antibody levels may exert a protective effect (Wang G., Chen X-S., Mao Y., Li Y-F., Chen W-G., Shen K-W., 2014; Cengiz O., Bozkurt B., Unal B., Yildirim O., Karabeyoglu M., Eroglu A. 2004; Tosovic A., Becker C., Bondeson A. G., Bondeson L., Ericsson U. B., Malm J., 2012). Additionally, thyroid dysfunction has been reported to correlate with higher tumor grades, suggesting a relationship with malignancy severity (Lemaire M., Baugnet-Mahieu L., 1986).

However, other investigations have failed to identify significant associations between thyroid disorders and BC risk (Michalaki V., Kondi-Pafiti A., Gennatas S., Antoniou A., Primetis H., Gennatas C., 2009; Kuijpens J. L., Nyklictek I., Louwman M. W., Weetman T. A., Pop V. J., Coebergh J. W., 2005). These discrepancies may reflect methodological variability, differences in population characteristics, variability in assay sensitivity, or racial and geographic influences.

An interesting observation from our study was a non-significant trend toward reduced symptoms of thyroid dysfunction in patients receiving prophylactic levothyroxine. Although this finding lacked statistical significance, it suggests a potential benefit that warrants further exploration through randomized controlled trials with larger sample sizes.

In conclusion, the observed associations between thyroid dysfunction and breast cancer highlight the need for comprehensive endocrine assessment in this patient population. Future prospective studies employing standardized methodologies and larger cohorts are essential to clarify the clinical implications and to explore the potential role of thyroid hormone modulation in BC management.

## Conclusions

1. Combined antitumor therapy for BC is associated with a high incidence of thyroid dysfunction, mainly subclinical hypothyroidism, especially in patients receiving neoadjuvant and adjuvant chemotherapy.
2. Common clinical manifestations of post-chemotherapy thyroid dysfunction include general weakness, palpitations, neck discomfort, and difficulty swallowing.
3. Significant hormonal changes involve free T4, total T3, and anti-TPO levels, indicating autoimmune involvement in the pathological process.
4. Ultrasound and radionuclide imaging (PET-CT) reveal structural-functional thyroid alterations correlating with treatment intensity.
5. Preliminary data suggest potential benefits of prophylactic thyroid hormone (levothyroxine) to mitigate thyroid dysfunction symptoms, requiring further randomized trials.
6. Due to the high prevalence and clinical relevance of thyroid dysfunction during BC treatment, routine thyroid status assessment is recommended in oncological patient management protocols.

## Rseferences

Jemal A., Bray F., Center M.M., Ferlay J., Ward E., Forman D. (2011). Global cancer statistics. CA Cancer J Clin; – 61: 69–90.
Shering S. G., Zbar A. P., Moriarty M., Mc Dermott E. W., O'Higgins N.J., Smyth P. P. (1996). Thyroid disorders and breast cancer. Eur J Cancer Prev; – 5: 504–506.
Giani C., Fierabracci P., Bonacci R., Gigliotti A., Campani D., De Negri F. (1996). Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy. J Clin Endocrinol Metab; – 81: 990–994.
Clarke R., Dickson R. B., Brunner N. (1990). The process of malignant progression in human breast cancer. Ann Oncol; – 1: 401–407.
Gogas J., Kouskos E., Tseleni-Balafouta S., Markopoulos C., Revenas K., Gogas G. (2001). Autoimmune thyroid disease in women with breast carcinoma. Eur J Surg Oncol; – 27: 626–630.
Turken O., NarIn Y., DemIrbas S., Onde M. E., Sayan O., KandemIr E. G. (2003). Breast cancer in association with thyroid disorders. Breast Cancer Res; – 5: 110–113.
Perry M., Goldie D. J., Self M. (1978). Thyroid function in patients with breast cancer. Ann R Coll Surg Engl; – 60: 290–293.
Smyth P. P. (2003). The thyroid, iodine and breast cancer. Breast Cancer Res; – 5: 235–238.
Vorherr H. (1978). Thyroid disease in relation to breast cancer. Klin Wochenschr; – 56: 1139–1145.
Saraiva P., Figueiredo N., Padovani C., Brentani M., Nogueira C. (2005). Profile of thyroid hormones in breast cancer patients. Braz J Med Biol Res; – 38: 761–765.
Smyth P. Thyroid disease and breast cancer. J Endocrinol Invest 1993; 16: 396–401.
Agarwal D. P., Soni T. P., Sharma O. P., Sharma S. (2007). Synchronous malignancies of breast and thyroid gland: a case report and review of literature. J Cancer Res Ther; – 3: 172–173.
Fierabracci P., Pinchera A., Campani D., Pollina L. E., Giustarini E., Giani C. (2006). Association between breast cancer and autoimmune thyroid disorders: no increase of lymphocytic infiltrates in breast malignant tissues. J Endocrinol Invest; 29: 248–251.
Giustarini E., Pinchera A., Fierabracci P., Roncella M., Fustaino L., Mammoli C. (2006). Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. Eur J Endocrinol; – 154: 645–649.
Sabitha Suneetha, Mohanty S., Rao P. (2009). Serum anti-TPO levels in benign and malignant breast tumors. Indian J Clin Biochem; – 24: 266–268.
Ali A., Mir M. R., Bashir S., Hassan T., Bhat S. A. (2011). Relationship between the levels of serum thyroid hormones and the risk of breast cancer. J Biol Agric Health; – 1: 56–59.
Smyth P. P., Shering S. G., Kilbane M. T., Murray M. J., McDermott E. W., Smith D. F. (2017). Serum thyroid peroxidase autoantibodies, thyroid volume, and outcome in breast carcinoma. J Clin Endocrinol Metab 1998; – 83: 2711–2716. Motie/Taheri/Noorian 8628 Biomed Res – Vol. 28. – Issue 20.
Ditsch N., Liebhardt S., Von Koch F., Lenhard M., Vogeser M., Spitzweg C. (2010). Thyroid function in breast cancer patients. Anticancer Res; – 30: 1713–1717.
Michalaki V., Kondi-Pafiti A., Gennatas S., Antoniou A., Primetis H., Gennatas C. (2009). Breast cancer in association with thyroid disorders. J Buon; – 14: 425–428.
Wang G., Chen X-S., Mao Y., Li Y-F., Chen W-G., Shen K-W. (2014). Patients with breast cancer have a higher level of serum free thyroxine (T4) compared with those with benign breast diseases. Tumor; – 34: 366–369.
Takatani O., Okumoto T., Kosano H., Nishida M., Hiraide H., Tamakuma S. (1989). Relationship between the levels of serum thyroid hormones or estrogen status and the risk of breast cancer genesis in Japanese women. Cancer Res; – 49: 3109–3112.
Kuijpens J. L., Nyklictek I., Louwman M. W., Weetman T. A., Pop V. J., Coebergh J. W. (2005). Hypothyroidism might be related to breast cancer in post-menopausal women. Thyroid; – 15: 1253–1259.

Saraiva P., Figueiredo N., Padovani C., Brentani M., Nogueira C. (2005). Profile of thyroid hormones in breast cancer patients. Brazil Med Biol Res; – 38: 761–765.
Rose D. P., Davis T. E. (1979). Plasma triiodothyronine concentrations in breast cancer. Cancer; – 43: 1434–1438.
Tosovic A., Bondeson A. G., Bondeson L., Ericsson U. B., Malm J., Manjer J. (2010). Prospectively measured triiodothyronine levels are positively associated with breast cancer risk in postmenopausal women. Breast Cancer Res; – 12: 33.
Cengiz O., Bozkurt B., Unal B., Yildirim O., Karabeyoglu M., Eroglu A. (2004). The relationship between prognostic factors of breast cancer and thyroid disorders in Turkish women. J Surg Oncol; – 87: 19–25.
Tosovic A., Becker C., Bondeson A. G., Bondeson L., Ericsson U. B., Malm J. (2012). Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to breast cancer risk. Int J Cancer; – 131: 2126–2133.
Lemaire M., Baugnet-Mahieu L. (1986). Thyroid function in women with breast cancer. Eur J Cancer Clin Oncol; – 22: 301–307.

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Contact: azimovamakhbuba@gmail.com; hursh77@mail.ru