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MORPHOLOGICAL FEATURES OF THYROID DYSFUNCTION DURING COMBINED THERAPY OF BREAST CANCER

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ABSTRACT

Background: Breast cancer treatment is associated with systemic adverse effects, including thyroid dysfunction. **Objective:** To evaluate the impact of combined breast cancer therapy on thyroid function in relation to treatment intensity and tumor biology. **Methods:** A retrospective-prospective study included 136 breast cancer patients (standard therapy, n=62; intensified therapy, n=74) and 23 controls. Thyroid function (TSH, free T3, free T4, anti-TPO) and tumor markers (ER, PR, HER2, Ki-67) were analyzed. **Results:** Both treatment groups showed significant increases in TSH and decreases in free T3 and free T4 compared to controls ($p<0.0001$), consistent with subclinical hypothyroidism. Changes were more pronounced in the intensified therapy group ($p<0.05$). Anti-TPO levels were elevated, suggesting autoimmune involvement. Thyroid dysfunction was more frequent in patients with luminal B subtype and high Ki-67, while no association was found with tumor differentiation. **Conclusion:** Combined therapy for breast cancer is associated with treatment intensity–dependent thyroid dysfunction, influenced by tumor biological characteristics.

KEYWORDS: breast cancer, thyroid dysfunction, hormonal disorders, morphological changes, cytostatic effects.

INTRODUCTION

Breast cancer (BC) is a leading cancer morbidity among women worldwide and remains a major cause of cancer-related mortality.[1,2] According to global epidemiological studies, more than 2 million new cases are registered annually, with an increasing trend in incidence rates, particularly in countries with transition economies.[1] Despite improvements in screening and early diagnosis programs, a significant proportion of patients continue to require complex and long-term treatment.

Modern therapeutic strategies include surgery, polychemotherapy, hormone therapy, targeted therapy, and radiation therapy, which have significantly increased overall and relapse-free survival rates.[3,10] However, the intensification of antitumor treatment is accompanied by the development of systemic complications affecting the cardiovascular, hematological, and endocrine systems.[7,16] The thyroid gland is an organ highly sensitive to cytostatic and hormonal influences. Thyroid hormones regulate energy metabolism, cell proliferation, differentiation, and apoptosis.[5] Impaired synthesis and metabolism can lead to subclinical or overt hypothyroidism, which significantly reduces the patient's quality of life and impairs the tolerability of antitumor therapy.[4,6,15]

According to several studies, the incidence of thyroid dysfunction in cancer patients ranges from 30 to 60% and depends on the type of therapy, its duration, and the individual patient's sensitivity.[7,8,14] Of particular importance is the development of subclinical hypothyroidism, which can remain undiagnosed for a long time but has a negative impact on the body's metabolic and adaptive mechanisms.[4,13] Furthermore, current understanding of the biological heterogeneity of breast cancer suggests that the tumor's molecular profile (luminal A, luminal B, HER2-positive, and other subtypes) determines not only the disease prognosis but also the nature of the body's systemic response to therapy.[9,11] High proliferative activity, assessed by the

Ki-67 index, is associated with a more aggressive course of the disease and the need for more intensive treatment regimens.[14,15] The impact of these factors on thyroid function remains poorly understood.

Therefore, a comprehensive study of the morphofunctional state of the thyroid gland in patients with breast cancer, depending on the nature of therapy and the molecular characteristics of the tumor, is of significant scientific and practical interest.

The aim of this study was to evaluate the effects of various combination therapy regimens for breast cancer on the morphofunctional state of the thyroid gland, taking into account the tumor's molecular subtype and level of proliferative activity.

MATERIALS AND METHODS

The study was retrospective and prospective. It included 136 patients with a morphologically confirmed diagnosis of BC who received combination therapy from 2021 to 2024 in accordance with the standards of the Ministry of Health of the Republic of Uzbekistan.

The patients were divided into two groups:
Group 1 (n=62) — standard combination therapy;
Group 2 (n=74) — more intensive treatment regimens.

The control group consisted of 23 apparently healthy women of comparable age without thyroid pathology.

Inclusion criteria: morphologically verified BC, availability of hormonal and immunohistochemical data.

Exclusion criteria: previously diagnosed thyroid diseases and taking thyroid medications.

Levels of TSH, fT4, fT3, and anti-TPO were determined.

Blood sampling was performed after at least four cycles of chemotherapy or within 30 days of completing combination therapy.

Immunohistochemistry: ER, PR, HER2/neu expression, and the Ki-67 index were assessed. Based on the data obtained, the tumor molecular subtype (luminal A, luminal B, etc.) was determined.

Symptoms of thyroid dysfunction were analyzed: weakness, palpitations, neck discomfort, a "globus sensation" when swallowing, apathy, and increased sweating.

Statistical analysis: Data are presented as mean ± standard deviation. Student's t-test was used to compare quantitative parameters, and the χ^2 test was used for qualitative parameters. Differences were considered significant at $p < 0.05$.

RESULTS

To objectively characterize the functional state of the thyroid gland in breast cancer patients receiving combination therapy, a comparative analysis of key thyroid parameters was conducted. Levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), and thyroid peroxidase antibodies (anti-TPO) as a marker of potential autoimmune activation were assessed. Comparison of the obtained data between the patient groups and the control group allowed us to determine the nature and severity of hormonal changes associated with the treatment. Particular attention was paid to intergroup differences reflecting the impact of the intensity of antitumor treatment on thyroid status.

Table 1: Hormonal indices of thyroid function in the study and control groups.

Study parameters	Grades	Groups of the study			P-value	P-value	P-value
		1-group, n=62	2- group, n=74	control, n=23	control & 1-group	control & 2-group	1st and 2nd group
Age	Range	21-57	25-73	32-61	0,34	0,79	0,572
	Avrg.	46,1+5,3	47,9±6,2	47,5±5,2			
TSH	(Mlu/ml)	5,9±1,0	7,2±1,3	3.18± 0.48	< 0.0001	< 0,0001	0,021
fT4	(ng/ml)	6,0±0,70	5,4±0,60	8.73± 0.63	< 0,0001	< 0,0001	0,019
fT3	(Pg/ml)	2.1 ± 0.18	1.7 ± 0.20	4.6 ± 0.25	< 0,0001	< 0,0001	0,027
anti-TPO	(lu/ml)	33, 1±2,4	37,5+5,1	19,5+5,1	< 0,0001	< 0,0001	0,07

As shown in Table 1, the age of the patients in the compared groups did not differ statistically significantly ($p>0.05$), indicating that the samples were comparable and excluding the influence of age on the identified hormonal changes. Analysis of TSH levels demonstrated a significant increase in this indicator in both study groups compared to the control. In Group 1, the average TSH level was 5.9±1.0 mIU/ml, in Group 2 - 7.2±1.3 mIU/ml, while in the control group it did not exceed 3.18±0.48 mIU/ml. Differences between the control and each of the study groups were highly statistically significant ($p<0.0001$). In addition, a significant difference was found between Groups 1 and 2 ($p=0.021$), indicating increased thyroid stimulating stimulation with more intensive treatment regimens.

fT4 levels were significantly reduced in the study groups. In Group 1, the level was 6.0±0.70 ng/ml, in Group 2 — 5.4±0.60 ng/ml, while in the control group it reached 8.73±0.63 ng/ml. Differences with the control were statistically significant ($p<0.0001$). Intergroup comparison also revealed a significant decrease in fT4 in

Group 2 compared to Group 1 (p=0.019), confirming a more pronounced suppression of thyroid function during intensive therapy. A similar trend was noted when analyzing the level of fT3. In Group 1, the indicator was 2.1±0.18 pg/ml, in Group 2 — 1.7±0.20 pg/ml, while in the control group it was 4.6±0.25 pg/ml. The differences between the control and main groups were highly significant (p<0.0001). A statistically significant difference between Groups 1 and 2 (p=0.027) indicates a progressive decrease in peripheral production of active thyroid hormone with intensification of antitumor therapy. The level of antibodies to thyroid peroxidase (anti-TPO) was significantly higher in patients of both main groups compared to the control (p<0.0001), which may indicate the activation of autoimmune mechanisms of thyroid tissue damage. However, the differences between groups 1 and 2 did not reach statistical significance (p=0.07), which indicates the absence of a significant dependence of autoimmune activity on the intensity of therapy.

Taken together, the obtained data indicate the development of laboratory evidence of subclinical hypothyroidism in breast cancer patients undergoing combination therapy. The increased TSH levels, coupled with a decrease in free T4 and free T3, reflects the compensatory response of the hypothalamic-pituitary system to decreased thyroid hormone production. More pronounced changes in the second group confirm the dose-dependent toxic effects of intensive therapy on thyroid function.

Immunohistochemical changes. To determine a possible relationship between the molecular biological characteristics of breast cancer and the development of thyroid dysfunction, an analysis of the expression of key immunohistochemical (IHC) tumor markers was performed. It is known that the molecular subtype of breast cancer, determined based on the expression of estrogen receptors (ER), progesterone receptors (PR), HER2/neu, and the Ki-67 proliferative activity index, reflects the biological behavior of the tumor, its degree of aggressiveness, and sensitivity to various types of therapy. Given that the intensity of antitumor treatment is largely determined by the molecular profile of the neoplasm, it seems appropriate to evaluate the distribution of IHC markers in the study groups. This allows not only to characterize the sample structure but also to further analyze the possible impact of tumor molecular features on thyroid function. The results of the expression distribution of the main IHC markers in patients of the study groups are presented in Table 2.

Table 2: Characteristics of the expression of IHC markers of breast cancer in patients of the main study groups, n=136.

IHC markers	Groups of the study				Total
	1st group		2nd group		
	abs.	%	abs.	%	
Estrogen, Er	13	20,9	18	24,3	31 22,7%
Progesterone, Pr	11	17,7	12	16,2	23 16,9%
Her2\neu	9	14,5	15	24,2	24 17,6%
Ki-67 >40%	24	38,7	37	50,0	61 44,8%

Analysis of the data in Table 2 demonstrates the distribution of immunohistochemical markers of breast cancer in patients of the main study groups and allows us to evaluate the molecular biological structure of the sample. Expression of ER was detected in 31 patients, which accounted for 22.7% of the total number of observations. In group 1, positive ER expression was recorded in 20.9% of patients, in group 2 - in 24.3%. The obtained indicators indicate a relatively equal distribution of hormone-positive tumors between the groups. Expression of PR was noted in 16.9% of patients in the total sample (17.7% in group 1 and 16.2% in group 2). No significant differences between the groups for this indicator were found, which indicates comparability of the hormonal status of the tumor. Hyperexpression of HER2/neu was determined in 17.6% of patients. Moreover, this marker was more common in Group 2 (24.2%) compared to Group 1 (14.5%), which may reflect a higher prevalence of biologically more aggressive forms of the disease among patients receiving more intensive treatment regimens. Of particular note is the Ki-67 proliferative activity index (PAI) >40%, which was detected in 44.8% of patients in the overall sample. In Group 1, high Ki-67 levels were observed in 38.7% of patients, while in Group 2, they were observed in 50.0%. This fact indicates a higher proportion of tumors with high proliferative activity in Group 2, consistent with a more aggressive biological profile and likely justifying the use of more intensive therapy.

Thus, the data in Table 2 confirm that Group 2 showed a trend toward a higher frequency of HER2-positive tumors and neoplasms with high proliferative activity. This indicates greater biological aggressiveness of tumors in this group and creates the basis for further analysis of the relationship between the molecular characteristics of breast cancer and the severity of thyroid dysfunction.

After assessing the molecular biological characteristics of the tumor, it seems appropriate to analyze the morphological features of breast cancer, in particular the degree of tumor cell differentiation and the histological type of the tumor. Histological grading (G1–G3) is known to reflect the degree of tumor malignancy and

aggressiveness and can also indirectly influence the volume and intensity of therapy.

Furthermore, morphological characteristics of the tumor can potentially determine the severity of the body's systemic response, including endocrine changes. Therefore, a comparative analysis of the distribution of patients by degree of differentiation and histological type of tumor in the study groups was conducted. The results of the morphological characteristics of breast cancer are presented in Table 3.

Table 3: Differentiation of breast cancer tumor cells in study groups 1 and 2, n=136.

IHC markers	Groups of the study				Total
	1st group		2-группа		
	abs.	%	abs.	%	
G grade:					
G1	16	25,8	21	28,4	37 27,2%
G2	27	43,5	29	39,2	56 41,2%
G3	19	30,7	24	32,4	43 31,6%
Tumor hystotype:					
Ductal	37	59,6	42	56,8	79 58,1
Infiltrative	25	40,4	32	43,2	

G-gradation analysis showed (Table 3) that the most common form was a moderately differentiated tumor (G2), which was detected in 41.2% of patients in the overall sample. In group 1, the proportion of G2 was 43.5%, in group 2 - 39.2%. Poorly differentiated tumors (G3) were diagnosed in 31.6% of patients (30.7% in group 1 and 32.4% in group 2). Highly differentiated forms (G1) were less common - in 27.2% of patients (25.8% and 28.4%, respectively). The data obtained indicate relative comparability of the groups in terms of the degree of morphological aggressiveness of the tumor process. No significant differences in the distribution of G-gradation between groups 1 and 2 were found, which allows us to exclude the influence of this factor as the leading cause of intergroup differences in thyroid parameters. An analysis of the histological type revealed that ductal carcinoma was the most common tumor type, accounting for 58.1% of cases (59.6% in Group 1 and 56.8% in Group 2). The infiltrative variant was diagnosed in 41.9% of patients (40.4% and 43.2%, respectively). The distribution of histological types was also comparable between the groups.

Thus, the data in Table 3 demonstrate the homogeneity of the study groups in tumor morphological characteristics. The absence of significant intergroup differences in G-gradation and histotype suggests that the previously identified changes in thyroid status are more related to the molecular characteristics of the tumor and the intensity of therapy than to the morphological differentiation of the tumor.

After assessing the morphological characteristics of the tumor, it seems reasonable to analyze the possible influence of the degree of histological differentiation on the severity of clinical manifestations of thyroid dysfunction. Despite the observed comparability of the G-grading groups, the question of whether tumor morphological aggressiveness may indirectly influence the systemic endocrine changes that occur during combination therapy remains relevant. With this in mind, a comparative analysis of the frequency and severity of clinical symptoms of thyroid dysfunction (palpitations, general weakness, neck discomfort, a "globus sensation" when swallowing, increased sweating, and apathy) was conducted depending on the degree of tumor cell differentiation (G1–G3). The results of this analysis are presented in Table 4.

Table 4: The severity of clinical manifestations of thyroid dysfunction in terms of the histological degree of differentiation of breast cancer cells.

Comparison groups/ Indicators	G1, n=52		G2, n=31		G3, n=53	
	abs	%	abs	%	abs	%
Heartbeat	13	25,0	9	29,0	18	33,9
Neck discomfort	21	40,1	8	25,8	20	37,7
General weakness	44	84,6	27	87,1	45	84,9
Feeling of “lumps when swallowing”	10	19,2	5	16,1	14	26,5
Excessive sweating	7	13,4	2	6,9	9	16,9
Apathy	10	19,2	5	16,1	18	33,9

Analysis of the palpitations symptom showed a gradual increase in its frequency as the tumor differentiation grade decreased: with G1, this symptom was observed in 25.0% of patients, with G2 — in 29.0%, and with G3 — in 33.9%. Despite the identified trend towards an increase in the indicator with more aggressive tumor forms, no statistically significant relationship was established. Discomfort in the neck was recorded in

40.1% of patients with G1, in 25.8% with G2, and in 37.7% with G3. The indicators varied without a clear pattern, indicating the absence of a direct relationship between the degree of differentiation and this symptom. The most common clinical manifestation in all subgroups was general weakness, the frequency of which remained consistently high: 84.6% with G1, 87.1% with G2, and 84.9% with G3. The virtually identical values indicate that this symptom is independent of the morphological aggressiveness of the tumor and is likely associated primarily with the systemic effects of combination therapy. A "lump" sensation when swallowing was noted in 19.2% of patients with G1, 16.1% with G2, and 26.5% with G3. The higher frequency in poorly differentiated tumors may reflect an increase in subjective symptoms with an aggressive course of the disease, but the differences were not significant. Increased sweating was observed in 13.4% of patients with G1, 6.9% with G2, and 16.9% with G3. Similarly, apathy was more frequently recorded in G3 (33.9%) compared to G1 (19.2%) and G2 (16.1%), but no convincing statistical relationship was found.

Thus, analysis of Table 4 revealed no significant correlation between the degree of histological differentiation of the tumor and the severity of clinical manifestations of thyroid dysfunction. These data suggest that the morphological aggressiveness of breast cancer is not the leading factor in the development of thyroid symptoms, while molecular characteristics of the tumor and the intensity of antitumor therapy likely play a more significant role.

Given the lack of a clear correlation between the clinical manifestations of thyroid dysfunction and the degree of histological differentiation of the tumor, it seems appropriate to evaluate the influence of molecular biological characteristics of breast cancer on the severity of endocrine disorders. Current understanding of breast cancer heterogeneity suggests that the molecular subtype and level of Ki-67 largely reflect the biological behavior of the tumor and determine the intensity of therapy. Since the luminal B subtype and high Ki-67 expression are associated with a more aggressive course of the disease and the need for more intensive treatment regimens, it can be hypothesized that they are potentially associated with a higher incidence of thyroid dysfunction.

Therefore, a comparative analysis of the clinical manifestations of thyroid dysfunction was conducted depending on the tumor molecular subtype (Luminal A, Luminal B) and the level of Ki-67 >35% and <35%. The results of this analysis are presented in Table 5.

Table 5: Frequency of clinical manifestations of thyroid dysfunction depending on the molecular subtype of breast cancer and the level of proliferative activity (Ki-67)

Comparison groups/ Indicators	Luminal A n=78		Luminal B n=31		Ki-67>35%		Ki-67<35%	
	abs	%	abs	%	abs	%	abs	%
Heartbeat	21	26.9	19	32.7	25	40.9	15	20.0
Neck discomfort	17	21.8	32	55.2	28	45.9	2115	20.0
General weakness	13	16.7	16	27.6	14	22.9	21	28.0
Feeling of “lumps when swallowing”	68	87.2	51	87.9	43	70.5	15	20.0
Excessive sweating	3	3.8	6	10.3	7	11.5	33	97.3
Apathy	8	10.2	10	17.2	11	18.0	3	2.7

A comparative analysis of luminal subtypes revealed (Table 5) that thyroid symptoms were more frequently recorded in patients with the luminal B variant, characterized by more aggressive biological behavior. Thus, palpitations were noted in 32.7% of patients with the luminal B subtype versus 26.9% with luminal A. Neck discomfort was observed more than twice as often with luminal B (55.2%) compared to luminal A (21.8%), indicating a possible relationship between the biological aggressiveness of the tumor and the severity of subjective endocrine manifestations. A sensation of a “lump” when swallowing and manifestations of apathy were also more frequently recorded in patients with the luminal B subtype (27.6% and 17.2%, respectively) compared to luminal A (16.7% and 10.2%). Excessive sweating was relatively rare; however, its frequency in the luminal B subtype (10.3%) was higher than in the luminal A subtype (3.8%). A separate analysis depending on the level of tumor proliferative activity showed more pronounced thyroid symptoms with Ki-67 >35%. In this subgroup, palpitations were recorded in 40.9% of patients versus 20.0% with Ki-67 <35%. Neck discomfort was noted in 45.9% of patients with high proliferative activity compared to 20.0% with low Ki-67 levels. Indicators of apathy and excessive sweating also tended to increase with high Ki-67 expression. At the same time, the frequency of general weakness remained comparable between subgroups, which may indicate its predominant association with the systemic effect of antitumor therapy, rather than with the molecular subtype of the tumor.

Thus, the data in Table 5 indicate an association between molecular characteristics of breast cancer—in particular, the luminal B subtype and high Ki-67 levels—and a higher incidence of clinical manifestations of thyroid dysfunction. These results support the hypothesis that tumor biological aggressiveness plays a significant role in the development of endocrine disorders in patients receiving combination therapy.

CONCLUSION

Combined breast cancer therapy is associated with the development of subclinical hypothyroidism, with severity depending on treatment intensity. Molecular tumor features, particularly luminal B subtype and high Ki-67, are linked to increased thyroid dysfunction, whereas histological differentiation shows no significant effect. These findings support the need for routine thyroid monitoring in patients undergoing intensive treatment.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2021; 71: 209-249. https://doi.org/10.3322/caac.21660
2. Bray F, Jemal A, Grey N, et al. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol, 2012 Aug; 13(8): 790-801. doi: 10.1016/S1470-2045(12)70211-5. Epub 2012 Jun 1. PMID: 22658655.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. The Lancet, 2011; 379: 432-444Biondi B, Cooper DS. Subclinical hypothyroidism. Lancet, 2008.
4. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest, 2012 Sep; 122(9): 3035-43. doi: 10.1172/JCI60047. Epub 2012 Sep 4. PMID: 22945636; PMCID: PMC3433956.
5. Wartofsky L, Dickey RA. The Evidence for a Narrower Thyrotropin Reference Range Is Compelling. J Clin Endocrinol Metab, 2005 Sep 1; 90(9): 5483–5488.
6. Torino F, Barnabei A, Paragliola R, et al. Thyroid dysfunction as an unintended side effect of anticancer drugs. Thyroid, 2013 Nov; 23(11): 1345-66. doi: 10.1089/thy.2013.0241. Epub 2013 Sep 21. PMID: 23750887.
7. Hartmann K. Thyroid Disorders in the Oncology Patient. J Adv Pract Oncol, 2015 Mar-Apr; 6(2): 99-106. doi: 10.6004/jadpro.2015.6.2.2. Epub 2015 Mar 1. PMID: 26649243; PMCID: PMC4601890.
8. Goldhirsch A, Winer EP, Coates AS, et al. Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013 Sep; 24(9): 2206-23. doi: 10.1093/annonc/mdt303. Epub 2013 Aug 4. PMID: 23917950; PMCID: PMC3755334.
9. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol, 2010 Jun 1; 28(16): 2784-95. doi: 10.1200/JCO.2009.25.6529. PMID: 20404251; PMC2881855.
10. Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update. J Clin Oncol, 2023 Aug 1; 41(22): 3867-3872. doi: 10.1200/JCO.22.02864. Epub 2023 Jun 7. PMID: 37284804.
11. Dowsett M, Nielsen TO, A'Hern R, et al. International Ki-67 in Breast Cancer Working Group. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst. 2011 Nov 16; 103(22): 1656-64. doi: 10.1093/jnci/djr393. PMC3216967.
12. Inwald EC, Klinkhammer-Schalke M, Hofstädter F, et al. Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. Breast Cancer Res Treat, 2013 Jun; 139(2): 539-52. doi: 10.1007/s10549-013-2560-8. PMC3669503.
13. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol, 2020 Feb; 31(2): 171-190. doi:10.1016/j.annonc.2019.10.023. PMID: 31959335; PMCID: PMC8019325.
14. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid®, 2016; 26(10): 1343-1421. doi:10.1089/thy.2016.0229
15. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet, 2012 Mar 24; 379(9821): 1142-54. doi: 10.1016/S0140-6736(11)60276-6. Epub 2012 Jan 23. PMID: 22273398.
16. Burstein HJ. Systemic Therapy for Estrogen Receptor-Positive, HER2-Negative Breast Cancer. N Engl J Med, 2020 Dec 24; 383(26): 2557-2570. doi: 10.1056/NEJMra1307118. PMID: 33369357.