Thyroid Cancer Markers

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Citation: Bon E.I., Maksimovich N.Ye., Sivitsky D. V. (2025), Thyroid Cancer Markers; *Biomedical and Clinical Research* 4(5)., DOI:10.31579/2834-8486/035

Received: 21 August 2025 | **Accepted:** 06 August 2025 | **Published:** 11 September 2025

Abstract

Thyroid cancer is one of the most common endocrine malignancies. Various biomarkers are used to diagnose and monitor the disease, helping to determine the type of tumor, the stage of the disease, the presence of metastases, and the effectiveness of therapy. This paper reviews the main markers of thyroid cancer, such as thyroglobulin, calcitonin, cancer-embryonic antigen, procalcitonin, TSH, microRNA, as well as genetic markers, including BRAF, RAS, and RET. Particular attention is paid to their diagnostic and prognostic significance. Purpose of the work: to analyze and systematize modern diagnostic, prognostic, and molecular markers of thyroid cancer, including biochemical, hormonal, genetic, and epigenetic indicators, as well as to evaluate their clinical relevance, diagnostic accuracy, and applicability in contemporary medical practice.
Key words: thyroid cancer; biomarkers; thyroglobulin; calcitonin; BRAF; microRNA.

Introduction

Thyroid cancer (TC) is a heterogeneous group of tumors, including papillary, follicular, medullary, and anaplastic variants. Each of these forms has its own molecular mechanisms, biochemical characteristics, and clinical course, which necessitates a differentiated approach to diagnosis and treatment. In recent decades, there has been a steady increase in the incidence of PTC, which is associated not only with improved diagnostic capabilities, such as highly sensitive ultrasound and fine-needle aspiration biopsy, but also with increased exposure to environmental factors, including ecological stress, radiation background, and changes in the hormonal status of the population.The current understanding of the pathogenesis of PTC is based on significant progress in the field of molecular oncology. Recent studies show that tumor formation is associated with the accumulation of both genetic and epigenetic changes: mutations in oncogenes and tumor suppressors, gene rearrangements, DNA methylation abnormalities, changes in microRNA profiles, activation of oncogenic signaling cascades, and dysregulation of cell proliferation and apoptosis. A significant role belongs to disruptions in key signaling pathways, including MAPK/ERK, PI3K/AKT, RET–RAS–BRAF, as well as changes in the expression of genes involved in the metabolism and differentiation of thyrocytes [8, 13].

Particular attention is paid to identifying BRAF V600E mutations and TERT promoter alterations, as these genetic events are associated with a more aggressive disease course, reduced tumor cell differentiation, and an increased risk of metastasis. The combination of these mutations is considered one of the most significant markers of poor prognosis, enhancing tumor oncogenicity through synergistic effects on the cell cycle, replication stress, and the tumor's ability to infiltrate surrounding tissues.An important achievement in modern molecular diagnostics has been the introduction of variable allele fraction (VAF) analysis. The VAF indicator allows for a quantitative assessment of the proportion of cells carrying the mutation, making it possible to evaluate the degree of tumor heterogeneity. A high allelic burden of BRAF or TERT mutations correlates with a more aggressive clinical course, a tendency toward anaplastic transformation, resistance to radioactive iodine therapy, and an increased risk of recurrence. Thus, VAF analysis serves as an important additional tool for risk stratification and personalization of treatment for patients with PTC [1, 9].

1. Thyroglobulin (Tg)

Thyroglobulin is the main biochemical marker of differentiated thyroid cancer, primarily papillary and follicular. It is a high-molecular-weight protein synthesized exclusively by thyroid cells, which makes it a uniquely specific indicator [11,12,13].After total thyroidectomy, the thyroglobulin level should tend toward zero, as there is no normal tissue. An increase in Tg in the postoperative period indicates the presence of residual tissue or tumor recurrence [3, 11].

Dynamic monitoring of Tg is considered particularly important:

- a steadily increasing Tg indicates disease progression,
- a low and stable Tg corresponds to remission.

The Tg level also correlates with the stage of the tumor process, the extent of the lesion, and the presence of metastases in the lymph nodes and distant organs.

The main problem with interpretation is the presence of antibodies to thyroglobulin (anti-Tg), which can distort the test results. In such cases, it is preferable to use mass spectrometry methods or focus on the dynamics of anti-Tg [12].

2. Calcitonin

Calcitonin is a highly specific marker of medullary thyroid carcinoma (MTC) originating from C cells.

Its elevation is observed in primary tumors, as well as in recurrences and metastases. Calcitonin levels are directly proportional to tumor mass, making it a key tool for post-operative monitoring [2, 3, 12].

Special considerations:

- Basal calcitonin levels are an indicator of tumor activity.

- Stimulation tests (pentagastrin, calcium) can be used in cases of questionable values.
- The rate of calcitonin doubling is one of the most reliable prognostic factors:
  1.<6 months → extremely poor prognosis
  2.2 years → favorable course

Calcitonin is also used to detect hereditary forms of MRC (MEN2A, MEN2B), which allows for early preventive thyroidectomy in carriers of RET mutations [2].

3. Carcinoembryonic antigen (CEA)

CEA is used in combination with calcitonin to monitor patients with medullary carcinoma [2, 11]. Although its specificity is lower than that of calcitonin, it is important in the following situations:

- In rapidly progressing medullary carcinoma, CEA often rises faster than calcitonin.
- A discrepancy between CEA and calcitonin levels (CEA↑, calcitonin↓) may indicate a more aggressive and less differentiated tumor.
- The doubling rate of CEA, like calcitonin, is a prognostic factor.

CEA is especially important when metastasis to the liver and lungs is suspected, where its increase correlates with the extent of the lesion.

4. Procalcitonin (PCT)

Procalcitonin is a precursor of calcitonin, which is more stable and less susceptible to fluctuations under the influence of hormonal factors [12].

Unlike calcitonin, which can fluctuate during stress or hypercalcemia, PCT remains stable and can serve as an accurate marker for:

- early diagnosis of MPAH,
- distinguishing tumors from inflammatory processes,
- monitoring postoperative residual disease.

Although PCT does not replace calcitonin, it is useful as an additional marker in complex diagnostic cases, including the presence of antibodies or unstable calcitonin levels [11].

5. Thyroid-stimulating hormone (TSH)

TSH stimulates the proliferation of thyroid cells and the synthesis of thyroid hormones.

For patients with differentiated thyroid cancer after surgery, suppressive therapy with levothyroxine is recommended to suppress TSH. This reduces the risk of recurrence, as residual tumor cells often remain TSH-dependent [5, 8].

Clinical significance:

- High TSH levels are associated with an increased risk of PTC progression.
- The intensity of suppression is selected according to the risk category (according to the ATA).
- Excessive suppression can lead to complications (arrhythmias, osteoporosis), so balance is important.

Thus, TSH is not only a diagnostic marker but also a therapeutic marker that influences the choice of treatment strategy.

6. MicroRNA (miRNA)

MicroRNA are short non-ribosomal regulatory RNAs that control the expression of a large number of genes [8, 13].

They are involved in virtually all processes of oncogenesis:

- apoptosis disruption,
- angiogenesis stimulation,
- invasion and metastasis enhancement,
- regulation of RAS–RAF–MEK, PI3K–AKT, and other signaling pathways.

Dozens of diagnostically significant microRNAs have been identified in PTC:

- miR-221, miR-222 — elevated in papillary carcinoma,
- miR-146b — correlates with aggressiveness,
- miR-21 — involved in apoptosis suppression,
- miR-375 — elevated in medullary carcinoma.

Advantages of microRNAs:

- high stability in blood,
- detectable even in early stages,
- use in multifactorial diagnostic panels.

MicroRNAs are now considered promising targets for therapy and the main source of liquid biopsy in thyroid cancer [7, 10].

Conclusion

The use of biomarkers in papillary thyroid carcinoma (PTC) has transformed modern clinical practice, providing a more precise and individualized approach to diagnosis, monitoring, and prognosis of the disease. In recent years, advances in molecular oncology have demonstrated that PTC is driven by a complex interplay of genetic, epigenetic, and biochemical factors, many of which can now be quantified and utilized as clinically actionable biomarkers. Their integration into standard diagnostic protocols significantly enhances the early detection of malignancy, facilitates risk stratification, and guides the selection of optimal therapeutic strategies for each patient.

Genetic markers such as **BRAF**, **RAS**, **TERT**, and **RET** mutations offer deep insight into the molecular mechanisms underlying tumor initiation and progression. BRAF V600E, the most prevalent mutation in PTC, is strongly associated with increased tumor aggressiveness, invasiveness, and a greater likelihood of recurrence. Mutations in the TERT promoter further amplify malignant potential and, when coexisting with BRAF alterations, create a molecular signature of particularly high-risk disease. RAS mutations, although less aggressive in isolation, contribute important information about tumor differentiation and behavior, especially in follicular-patterned lesions. Meanwhile, RET rearrangements, common in radiation-associated PTC, provide opportunities for targeted treatment with selective RET inhibitors, thus expanding therapeutic options for patients with advanced or refractory disease.

One of the most significant innovations in recent molecular diagnostics is the analysis of **variant allele frequency (VAF)**, which allows quantification of the proportion of tumor cells carrying a specific mutation. Unlike simple qualitative tests that identify the presence or absence of a mutation, VAF analysis reflects tumor heterogeneity, clonal architecture, and the evolutionary dynamics of malignant cells. Higher VAF values have been shown to correlate with increased tumor aggressiveness, metastatic potential, and reduced responsiveness to conventional therapies such as radioactive iodine. As a result, VAF assessment provides an additional dimension of prognostic accuracy and plays a crucial role in defining individualized treatment pathways.Biochemical markers, including **thyroglobulin** in differentiated thyroid carcinoma and **calcitonin** in medullary thyroid cancer, continue to serve as indispensable tools in postoperative surveillance. Thyroglobulin, in particular, remains a highly sensitive indicator of persistent or recurrent disease following thyroidectomy and radioactive iodine ablation. Calcitonin, while specific to C-cell–derived malignancies, offers valuable insights into tumor burden

and progression, especially when interpreted alongside carcinoembryonic antigen (CEA) kinetics. Together, these markers support long-term clinical monitoring and allow for timely detection of biochemical relapse, often preceding radiological findings by months or even years.

A comprehensive and integrated analysis of molecular, biochemical, and genetic biomarkers provides clinicians with far more accurate diagnostic and prognostic information than traditional methods alone. Such multidimensional profiling not only improves treatment outcomes but also enables the development of truly personalized therapeutic regimens. By identifying patients at high risk of progression, tailoring therapeutic intensity, and selecting appropriate targeted agents, biomarker-driven clinical decision-making greatly enhances the effectiveness of contemporary thyroid cancer management.

References

1. Zhang W., Lin S., Wang Z., Zhang W., Xing M. (2024). Coexisting RET/PTC and TERT promoter mutation predict poor prognosis but effective RET and MEK targeting in thyroid cancer. *J Clin Endocrinol Metab*;109(12):3166–3175.
2. Lindsey S.C., Kunii I.S., Germano-Neto F., Sittoni M.Y., Camacho C.P., et all., (2012). Extended RET gene analysis in patients with apparently sporadic medullary thyroid cancer: clinical benefits and cost. *Horm Cancer*;3(4):181–186.
3. Cong R., Ouyang H., Zhou D., Li X., Xia F. (2024). BRAF V600E mutation in thyroid carcinoma: a large-scale study in Han Chinese population. *World J Surg Oncol*.; 22:259.
4. Xing M. (2005). BRAF mutation in thyroid cancer. *Endocr Relat Cancer*;12(2):245–262.
5. Scheffel R.S., de Cristo A.P., Romitti M., Vargas C.V.F., Ceolin L., et all., (2020). The BRAFV600E mutation analysis and risk stratification in papillary thyroid carcinoma. *Arch Endocrinol Metab*;64(6):751–757.
6. Attia A.S., Hussein M., Issa P.P., Elnahla A., Farhoud A., et all., (2022). Association of BRAFV600E mutation with the aggressive behavior of papillary thyroid microcarcinoma: a meta-analysis of 33 studies. *Int J Mol Sci.;*23(24):15626.
7. Bharti J., Gogu P., Pandey S.K., Verma A., Yadav J.P., (2025). BRAF V600E in cancer: exploring structural complexities, mutation profiles, and pathway dysregulation.
8. Forma A., Kłodnicka K., Pająk W., Flieger J., Teresińska B., et all., (2025). Thyroid cancer: epidemiology, classification, risk factors, diagnostic and prognostic markers, and current treatment strategies. *Int J Mol Sci*.;26(11):5173.
9. Fu G., Witterick I., MacMillan C. (2023). Facilitation of definitive cancer diagnosis with quantitative molecular assays of BRAF V600E and TERT promoter variants in patients with thyroid nodules. *JAMA Netw Open*.;6(7): e235000.
10. Guo Y., Hadj-Kakou S., Vitale G. (2024). Advances in targeted therapy and biomarker research in thyroid cancer. *Front Endocrinol*.; 15:1372553.
11. Mian C., Costa G., Carnazza M. et al. (2023). The correlation between biological markers and prognosis in thyroid cancer. *Biomolecules*.;12(12):2826.
12. McIver B., Morris L., Daniels G.H. (2023). Thyroglobulin and calcitonin measurements: pitfalls and future perspectives. *Clin Chim Acta*.; 542:113
13. Nikiforova M.N., Fagin J.A. (2010). Thyroid tumorigenesis and molecular markers in thyroid cancer. *Endocr Rev*.;31(5):620–680.