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PROGNOSTIC SIGNIFICANCE OF GENETIC TUMOR MARKERS IN THYROID NEOPLASMS: LITERATURE REVIEW

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Abstract

Background. This review examines recent advances in the identification of molecular markers using next-generation sequencing and microarrays. The potential for using these tumor markers to differentiate the most common sporadic forms of thyroid cancer is presented and compared. Public databases with datasets obtained from high-throughput experiments are a valuable source of information that helps tumor marker research in general, including the identification of molecular signatures of thyroid tumors.

The aim of this review is to analyze well-established tests with a special emphasis on the effective role of new potential thyroid tumor markers based on modern data on the molecular genetic mechanisms involved in the tumor process.

Search strategy. To conduct the study, articles in the public domain were analyzed using the following databases and specialized search engines for scientific publications: PubMed, Web of Science, Scopus, Google Scholar, Cochrane Library. Inclusion criteria: publications with a high level of evidence (level A and B), including meta-analyses, systematic reviews and cross-sectional studies. Short reports and advertising articles were excluded.

Results and conclusions. The literature review is devoted to the problem of prognostic significance of genetic tumor markers of thyroid gland tumors. Various types of tumor markers of thyroid gland tumors are presented, including tumor markers of benign neoplasms. The significance of tumor markers of thyroid gland tumors is substantiated.

Key words: *thyroid tumor markers, markers, thyroid tumor, diagnostic value of thyroid markers.*

Резюме

ПРОГНОСТИЧЕСКАЯ ЗНАЧИМОСТЬ ГЕНЕТИЧЕСКИХ ОНКОМАРКЕРОВ НОВООБРАЗОВАНИЙ ЩИТОВИДНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность. Настоящий обзор рассматривает последние достижения в области идентификации молекулярных маркеров посредством секвенирования нового поколения и использования микрочипов. Представлены и сопоставлены возможности применения данных онкомаркеров для дифференциации наиболее распространённых спорадических форм рака щитовидной железы. Публичные базы данных с наборами данных,

полученными в результате высокопроизводительных экспериментов, являются ценным источником информации, которая помогает исследованиям онкомаркеров в целом, включая выявление молекулярных признаков опухолей щитовидной железы.

Целью обзора является анализ хорошо зарекомендовавших себя тестов с особым акцентом на эффективную роль новых потенциальных онкомаркеров щитовидной железы, основанных на современных данных о молекулярно-генетических механизмах, вовлечённых в опухолевый процесс.

Стратегия поиска. Для проведения исследования были проанализированы статьи, находящиеся в открытом доступе, с использованием следующих баз данных и специализированных поисковых систем научных публикаций: PubMed, Web of Science, Scopus, Google Scholar, Cochrane Library. Критерии включения: публикации с высоким уровнем доказательности (уровень А и В), включающие мета-анализы, систематические обзоры и поперечные исследования. Исключены короткие отчёты, рекламные статьи.

Результаты и выводы. Литературный обзор посвящен проблеме прогностической значимости генетических онкомаркеров опухолей щитовидной железы. Представлены различные виды онкомаркеров опухолей щитовидной железы, в том числе и онкомаркеры доброкачественных новообразований. Обоснована значимость онкомаркеров опухолей щитовидной железы.

Ключевые слова: *маркеры опухолей щитовидной железы, маркеры, опухоль щитовидной железы, диагностическая ценность маркеров щитовидной железы*

Түйіндеме

ҚАЛҚАНША БЕЗІНІҢ ІСІКТЕРІНІҢ ГЕНЕТИКАЛЫҚ МАРКЕРЛЕРІНІҢ БОЛЖАМДЫ МАҢЫЗДЫЛЫҒЫ: ӘДЕБИЕТТЕРГЕ ШОЛУ

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Сәйкестік. Сәйкестік. Бұл шолуда келесі ұрпақ секвенциясы мен микромассивтерді пайдалана отырып, молекулалық маркерлерді анықтаудағы соңғы жетістіктер талқыланады. Қалқанша безінің ең жиі кездесетін спорадикалық ісіктерін ажырату үшін осы биомаркерлерді пайдалану мүмкіндігі ұсынылған және салыстырылған. Жоғары өнімді эксперименттерден алынған деректер жиыны бар жалпыға қолжетімді дерекқорлар жалпы биомаркерді зерттеуге, соның ішінде қалқанша безінің ісіктерінің молекулалық белгілерін анықтауға көмектесетін құнды ақпарат көзі болып табылады.

Мақсат. Бұл шолудың мақсаты қалқанша безінің ісіктерінің пайда болуына ықпал ететін молекулалық-генетикалық оқиғалар туралы соңғы білімге негізделген жаңа әлеуетті қалқанша безінің биомаркерлерінің тиімді рөліне ерекше назар аудара отырып, жақсы қалыптасқан сынақтарды қарастыру болып табылады.

Іздеу стратегиясы. Зерттеуді жүргізу үшін ашық қолжетімді мақалалар PubMed, Web of Science, Scopus, Google Scholar, Cochrane Library сияқты дерекқорлар мен ғылыми жарияланымдарды іздеуге арналған мамандандырылған іздеу жүйелерін пайдалана отырып талданды. Іріктеу критерийлері: жоғары дәлелдеме деңгейіндегі (А және В деңгейі) жарияланымдар, соның ішінде мета-талдаулар, жүйелі шолулар және көлденең зерттеулер. Қысқаша есептер мен жарнамалық мақалалар алынып тасталды.

Нәтижелер мен қорытындылар. Әдебиеттерге шолу қалқанша безі ісіктерінің генетикалық ісік маркерлерінің болжамдық маңыздылығы мәселесіне арналған. Қалқанша безінің ісіктері үшін ісік маркерлерінің әртүрлі түрлері ұсынылған, соның ішінде қатерсіз ісіктердің ісік маркерлері. Қалқанша безінің ісіктері үшін ісік маркерлерінің маңыздылығы дәлелденді.

Түйінді сөздер: *қалқанша безі ісіктерінің маркерлері, маркерлер, қалқанша безінің ісігі, қалқанша безінің маркерлерінің диагностикалық мәні.*

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Introduction

Thyroid tumors are a heterogeneous group of diseases that include both well-differentiated and benign neoplasms, such as goiter nodules, and malignant neoplasms, including differentiated cancers of follicular origin, as well as poorly differentiated, undifferentiated, medullary and anaplastic forms of cancer, all of which arise as thyroid nodules. Thyroid malignancies account for approximately 2% of all cancer cases worldwide [12].

Radiation is an environmental factor that increases the risk of developing thyroid cancer. There are many actual and potential situations involving exposure to both external and internal radiation. [50]. The Chernobyl nuclear power plant accident on April 26, 1986, resulted in significant radioactive contamination of Belarus, Ukraine, and western Russia. As a result of the release of large amounts of radionuclides from the damaged reactor, there was an increase in the incidence of thyroid cancer among people exposed to radiation in childhood and adolescence. This phenomenon was first recorded in Belarus, then in Ukraine and Russia. Studies have confirmed an increased risk of thyroid disease caused by exposure to iodine-131. The main medical consequence of the accident was an increase in the incidence of thyroid cancer among the affected population [13]

Territory of Semipalatinsk Nuclear Test Site (NTS) is one of the most well-known locations associated with a sharp increase in radiation-induced diseases, primarily related to exposure to radioactive iodine isotopes [32]. The interaction of factors leads to a significant increase in the frequency of thyroid neoplasms, the risk of which continues to exceed the national average and is observed to this day [1].

Given that thyroid cancer includes a wide spectrum of neoplasms that differ in molecular and histological characteristics, as well as in clinical course, there is a need to develop reliable tumor markers for accurate diagnosis and treatment. Such tumor markers are also important for preoperative classification of thyroid nodules, about 15–30% of which remain diagnostically indeterminate based on fine-needle aspiration (FNA) biopsy results [45,22].

biomarkers may include genetic materials, proteins, chemical modifications, and other molecular characteristics that can be measured based on clinical, pathological, radiological, and other data. In recent years, the rapid development of high-throughput technologies has facilitated the identification of many new thyroid cancer tumor markers. These markers not only facilitate accurate diagnosis and, in some cases, early detection of the disease, but also provide important information for clinical decision-making in patients with thyroid cancer. This review provides a comprehensive analysis of current advances in the study of genetic and epigenetic changes, as well as protein expression, considered as thyroid tumor tumor markers.

The aim of this review is to analyze well-established tests with a special emphasis on the effective role of new potential thyroid tumor markers based on modern data on the molecular genetic mechanisms involved in the tumor process.

Search strategy. The study analyzed full-text publications in English and Russian devoted to the prognostic significance of genetic tumor markers of thyroid tumors. The search was conducted in the following databases: PubMed, Web of Science, CyberLeninka, Google Scholar, using relevant keywords. Publications for the period from 2013 to 2023, mainly foreign and in English. In the process of analysis, sources from more recent years, such as 2009, 2011 and 2012, were used, as they contain key information necessary for the study. These works provide the basic theoretical framework, conceptual approaches, comparative data and evidence that contribute to a comprehensive understanding of the topic under consideration. The search identified over 114 publications, of which 62 met the inclusion criteria: level A and B evidence publications, including meta-analyses, systematic reviews, cohort and cross-sectional studies. Short reports, publications of low methodological quality, and conference proceedings were excluded.

Results and conclusions: Thyroid cancers account for approximately 2% of all cancer cases worldwide. In 2016, there were an estimated 238,000 new cases of thyroid cancer and 43,000 deaths. The standardized incidence rates were 2.2 per 100,000 in men and 4.4 per 100,000 in women [12].

Over the past decades, there has been a steady increase in the incidence of thyroid cancer worldwide. According to the European Network of Cancer Registries, incidence rates in women were approximately three times higher than in men (9.3 and 3.1 cases per 100,000 person-years, respectively). These rates vary by country, with the highest values reported in Lithuania, Italy, Austria, Croatia, and Luxembourg per 100,000 people. At the same time, the estimated mortality rates from thyroid cancer remain low (0.7 and 0.5 cases per 100,000 person-years for women and men, respectively), and show smaller regional and temporal variations [16].

The increase in incidence is almost entirely due to the increase in differentiated thyroid cancer (DTC), particularly papillary thyroid cancer (PTC), while the incidence of

follicular (FT), anaplastic (APTC), and medullary thyroid cancer (MTC) has remained relatively stable over the past 30 years. Increased use of imaging techniques, biopsy procedures (eg, fine-needle aspiration), and improved access to health care have facilitated the detection of small, subclinical forms of PTC. There is growing support for more conservative, risk-based thyroid cancer management strategies, including active surveillance [4,5].

The use of molecular diagnostics has advanced significantly over the past 10-15 years: a number of previous generation tests remain relevant, but many of them are being replaced by next generation sequencing (NGS) platforms. generation Recent studies have shown that detection of mutations in BRAF, RAS, RET/PTC, and PAX8/ PPARγ genes in clinical fine needle aspiration (FNA) specimens improves the diagnostic accuracy of FNA cytology. However, current diagnostic tests still show insufficient sensitivity and specificity [58].

RAS mutations play a significant role in thyroid tumorigenesis, but their diagnostic value remains limited when used alone. New studies suggest that when combined with other markers, they may improve prognostic value and stability of clinical management, especially in the non-surgical approach to benign nodules and cancers with an excellent prognosis. [57] RAS mutation testing has been proposed to clarify such cases, but the presence of non-invasive follicular thyroid tumors, which often contain RAS mutations and have a benign course, reduces their specificity [41]. The presence of RAS mutation in benign nodules suggests conservative treatment, and RAS mutations should be considered in combination with other genetic alterations for clinical significance [33].

The diagnostic and prognostic significance of RAS mutations remains uncertain because they are found not only in thyroid cancer but also in benign follicular adenomas (FA). RAS mutations are predominantly found in tumors of follicular cell origin, such as FA, follicular thyroid cancer (FTC), and follicular variant of papillary thyroid cancer (FVPTC), which are difficult to differentiate as benign or malignant based on cytology alone. Therefore, preoperative FNAB of these tumors often yields an indeterminate cytological diagnosis [42].

Molecular diagnostics using FNA with somatic mutation analysis improves diagnostic accuracy in follicular thyroid lesions, increasing sensitivity to 80% compared to FNA. Although BRAF mutations indicate malignancy in all cases, RAS mutations are associated with cancer in only 19–57% of cases [15, 29,48].

The identification of the BRAF V600E mutation in papillary thyroid carcinoma (PTC) in 2003 was one of the first molecular discoveries linking a specific genetic variant to the histological picture of the disease. The BRAF V600E mutation is a highly specific but insensitive marker for thyroid cancer, especially in the case of indeterminate thyroid nodules (ITNs). thyroid nodules), where the presence of BRAF V600E is detected in less than 10% of molecularly tested aspirates [26]. This has stimulated research into the development of mutation panels that could improve the sensitivity of tests (SN - test sensitivity) for more efficient detection of malignant nodes. One of the first such studies was a prospective multi-institutional study that assessed BRAF V600E, BRAF K601E mutations, NRAS, KRAS, HRAS gene codons, as well as RET/PTC 1/3 rearrangements and PAX/ PPARγ fusions [39]. This panel demonstrated high specificity: 97% of mutation-positive nodes were histologically malignant, but the sensitivity was only 62%, since not all malignant neoplasms contained variants or fusions detected by this panel [14].

Currently, various molecular markers are used to improve diagnostic accuracy in cases of indeterminate or suspicious cytology tests and to detect mutations in clinical fine-needle aspiration specimens of thyroid nodules. In addition to BRAF mutation, detection of mutations in the RAS, RET/PTC, and PAX8/ PPARγ genes also facilitates the diagnosis of thyroid cancer [51]. However, nodules with non-atypical indeterminate cytology are considered to have a 20% to 30% risk of malignancy, whereas only 5%–15% of nodules with follicular lesion of indeterminate significance are found to be malignant in the postoperative period. Moreover, 70%–85% of cytologically indeterminate nodules that are resected are found to be benign, which retrospectively imposes an undue burden of risk and cost on the patient. In this regard, the search for reliable preoperative molecular tumor markers has become a priority task [44,45]. Up to 70% of thyroid cancer cases contain at least one known genetic mutation.

Ideally, detection of genomic mutations can be used to characterize indeterminate nodules and prevent or minimize unnecessary surgery. Point mutations in one of three genes - NRAS, KRAS, and HRAS - are currently the second most common genetic alterations in thyroid cancer, second only to mutations in the BRAF gene [36, 31].

Another molecular marker is the chimeric oncogene PAX8-PPARγ, which is formed as a result of a balanced translocation between chromosome 2 (exons 7, 8 or 9) and chromosome 3 (exon 1), in which PAX8 (paired-box transcription factor 8, 2q13) and the PPARγ gene (peroxisome proliferator -activated receptor, 3p25) are combined. PAX8-PPARγ gene rearrangements are found in 30–35% of follicular thyroid carcinomas (FTC). Tumors with such rearrangements are characterized by a solid growth pattern and are associated with vascular invasion. However, PAX8-PPARγ rearrangements are also found in 2–10% of follicular adenomas, which limits their differential diagnostic value as independent markers [2].

The role of molecular diagnostics in determining benign and malignant diagnosis

Molecular testing has become an important clinical tool for assessing the risk of malignancy in patients with indeterminate thyroid nodules. It has the potential to bias the risk of malignancy by providing clinicians with accurate data to guide decisions on conservative observation or surgical intervention [46]. In the United States, three molecular tests are most commonly used: Afirma GSC, ThyGeNEXT / ThyraMIR, and Thyroseq v3 (TSv3). These platforms use different approaches to gene mutation and fusion analysis, providing clinicians with information on the likelihood of malignancy.

Afirma GSC uses next-generation RNA sequencing to analyze the transcriptome and uses machine learning algorithms to assess risk. The multi-platform ThyGeNEXT / ThyraMIR test combines targeted mutation sequencing and microRNA classification for more accurate risk stratification. TSv3 examines mutations, gene fusions, and expression

changes, assessing changes in 112 genes associated with thyroid cancer. Each of these tests provides accurate data to help physicians make informed decisions about the management of thyroid nodules [54].

The multiplatform test underwent analytical validation and clinical evaluation in a retrospective, blinded, multicenter study. In 19% of the cases in this study, unanimous histopathological conclusions could not be reached, and these cases were excluded from the analysis. In a sample of patients with indeterminate thyroid nodules (n=197) with a disease prevalence of 30%, test results were categorized by malignancy risk as positive, moderate, or negative. Moderate risk was identified in 28% of patients, and the malignancy rate in this group matched the baseline cancer prevalence (30%). Patients with confirmed malignant histology were classified as true positive, and those with benign histology as true negative. This supported the overall sensitivity and specificity of the test. However, data from patients with moderate risk were not included in the calculations of positive and negative predictive values [54,22].

Adjusted for histological subtypes, the assay demonstrated 95% sensitivity and 90% specificity. Negative results excluded disease with a 97% negative predictive value, and positive results excluded high-risk malignancies with a 75% positive predictive value. The updated next-generation sequencing panel improved the detection of strong driver mutations by 8%, including the most common BRAF V600E and telomerase reverse transcriptase mutations. Paired microRNA analysis for the diagnosis of medullary thyroid cancer demonstrated 100% accuracy [10, 17].

An update to the test including miR-21 and microRNA expression related interplay (MPTXv2) showed a significant reduction in the proportion of patients with intermediate risk and an improvement in positive predictive value to 96% and negative predictive value to 99%. Independent studies of the test's performance have not yet been conducted, but an analysis of pediatric tumors showed a sensitivity of 70% and a specificity of 96% [17,18].

According to recent studies and clinical data, the BRAF mutation serves not only as a diagnostic marker but also as a prognostic indicator. The MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) and PI3K/Akt (phosphatidylinositol 3-kinase/protein kinase Akt) signaling pathways play an essential role in transduction systems involving ligands, transmembrane receptors, and cytoplasmic second messengers, which act on the cell nucleus to regulate gene expression associated with critical cellular processes such as growth, proliferation, and apoptosis. Mutations or aberrant expression of genes encoding proteins in these pathways (RET, RAS, BRAF, PI3K, PTEN, AKT) are observed in thyroid cancer originating from follicular cells [30, 23].

In follicular cell-derived tumors, RAS mutations are most commonly detected in follicular adenomas, follicular thyroid carcinoma (FTC), and follicular variant papillary thyroid cancer (FVPPC), which are challenging to classify as benign or malignant based on cytology alone. Detection of RAS mutations is particularly clinically relevant for this group: in a recent study of 67 nodules with RAS mutations, cytology showed malignancy in 3% of cases, benignity in 3%, and indeterminate results in 94% [21].

In a study by Nikiforov et al., an analysis of biopsy samples with indeterminate cytology showed that RAS mutation was the most frequent (72%), followed by BRAF (21%), PAX8-PPAR (6%), and RET/PTC (1%) mutations [43]. The likelihood of malignancy in cases with RAS mutation was 85%, consistent with other studies reporting rates between 74% and 88% [36, 40, 61].

RET/PTC mutations are found in around 20% of adult patients with sporadic papillary thyroid carcinoma. Although these mutations can be identified using reverse transcription-quantitative polymerase chain reaction (RT-qPCR), this technique is seldom applied in clinical practice due to challenges in standardization. The reported prevalence of RET/PTC mutations varies widely across studies, which can be attributed to differences in detection sensitivity, as well as geographic diversity and genetic heterogeneity [59, 34]. Thus, radiation-induced RET and NTRK1 rearrangements in post-Chernobyl papillary thyroid carcinomas have important phenotypic and clinical implications [34,37].

The distribution of RET/PTC rearrangements within a tumor can also be heterogeneous, ranging from clonal RET/PTC mutations present in only a small fraction of tumor cells to non-clonal RET/PTC mutations. This heterogeneity complicates the diagnosis and characterization of papillary thyroid carcinomas [34,39]. RET/PTC can be detected in cytological specimens using RT- qPCR, which is uncommon in clinical practice and difficult to standardize. Clinical studies have shown the presence of RET/PTC in 30-50% of papillary carcinomas detected in fine-needle aspiration cytological specimens, but this assay is complex and effective only in combination with other markers [44,45].

The role of molecular genetic testing in predicting the prognosis of thyroid cancer

Molecular genetic testing serves as an important tool for assessing patient prognosis by identifying specific mutations present in thyroid cancer. Certain genetic mutations are linked to increased tumor aggressiveness, lymph node metastasis, dedifferentiation, and a diminished response to radioactive iodine treatment. The primary mutational mechanisms involved in thyroid cancer development include point mutations in the BRAF, RAS, TERT, RET, and TP53 genes, along with gene fusions such as RET/PTC, PAX8/PPARγ, and NTRK. [24]. The importance of molecular genetic testing for thyroid tissues, performed both preoperatively and postoperatively, is steadily increasing. By classifying genetic mutations in thyroid cancer into types like BRAF-like, RAS-like, and non-BRAF-non-RAS-like, it becomes possible to better evaluate the risk of complications, such as the spread beyond the thyroid or lymph node involvement [39, 4]. For example, a retrospective analysis by Tang et al found a statistically significantly higher frequency of T4 tumors and N1b lymph node metastasis in tumors with BRAF-like mutations (22%) compared with other classes (≤6%) among other aggressive tumor characteristics [55].

In 2020, the panel was expanded to 593 genes, enabling XA to detect 905 variants and 235 gene fusions. The results of the Afirma XA classifier provide significant prognostic information; for instance, nodules with a molecular profile distinct from RAS and BRAF mutations

have a lower risk of lymph node metastasis and spread beyond the thyroid [27]. A large retrospective study conducted by Hu and colleagues showed that 44% of Bethesda III/IV nodules and the majority of Bethesda V/VI nodules (87%) contained at least one genomic variant or fusion, which may help improve individualized therapeutic decisions [25,5, 4].

A study by Korean scientists determines the relationship between age and the risk of recurrence in patients with papillary thyroid cancer (PTC) who have been identified as having the BRAFV600E mutation. The study indicated that younger patients (under 35 years) with a positive BRAFV600E result face a considerably higher risk of recurrence than older patients (over 55 years). At the same time, in patients with BRAFV600E-negative PTC, age did not significantly affect the risk of recurrence. These results highlight the importance of considering both age and BRAFV600E mutation status when developing individualized treatment strategies and surveillance plans for patients with PTC [47].

Research indicates that genetic alterations, notably BRAF V600E and TERT mutations, are commonly found in thyroid nodules with suspicious cytology (Bethesda VI) and are linked to aggressive disease progression [30, 38]. In a study conducted by Labourier and colleagues, the BRAF V600E mutation was identified in 70-75% of such cases, while TERT mutations were present in 11% [30]. Patients with these mutations tend to have a higher likelihood of extrathyroidal tumor spread, lymph node metastasis, and a greater risk of recurrence [38].

Molecular tests, such as TSv3, provide a more accurate evaluation of thyroid cancer risk in patients with indeterminate cytology. Skaugen et al., for example, demonstrated that TSv3 has high sensitivity and specificity in detecting malignant nodules categorized as Bethesda V [52]. Moreover, TSv3 results allow for stratifying patients according to molecular risk, improving disease prognosis and aiding in optimal treatment planning.

The study by Hescot and colleagues highlighted that the molecular profile identified through TSv3 can effectively predict disease outcomes in patients with poorly differentiated thyroid cancer [23]. Patients with high-risk molecular profiles, such as TERT and TP53 mutations, were more prone to distant metastasis and had worse survival rates.

Molecular genetic markers play a key role in the development of diagnostic panels aimed at improving sensitivity, specificity, and positive and negative predictive values [19]. The positive predictive value (PPV) shows how many patients actually have the disease if the test detects it, and the negative predictive value (NPV) indicates how many patients have benign changes with a negative test result [53]. Panels that include mutations of genes such as BRAF, KRAS, HRAS, and others show high PPV and specificity, which can reduce the need for surgical interventions in cases of low risk of malignancy [43, 60].

The use of panels based on genetic mutations and rearrangements, such as ThyroSeq, increases the accuracy of diagnosis of malignant and benign lesions [35,8]. These panels are particularly effective in the case of indeterminate cytological test results, such as changes of undetermined significance (CUS) and follicular indeterminate changes (FUC). For example, the use of a 7-gene panel can significantly reduce the risk of malignancy and recommend less aggressive surgical interventions [21,49].

In addition, panels based on microRNA analysis are promising, which allow differentiation between benign and malignant tumors with high accuracy [28,7]. Commercial products such as RosettaGX Reveal ™ and ThyraMIR ™ offer high NPV and sensitivity rates, making them important tools in clinical practice, especially in pediatrics and when cytology results are inconclusive [3].

It is important to note that there are currently no standardized guidelines for making management decisions based on the detection of most genetic alterations found in thyroid nodules, regardless of cytological category. In case of indeterminate nodules, the main focus is on diagnosing their benign or malignant nature [6]. The prognostic value of molecular alterations in thyroid nodules and their impact on cytological diagnosis still requires further study in prospective multicenter studies [62]. In addition, the performance of molecular tests is usually assessed without taking into account other clinically relevant factors, such as family history of thyroid cancer, hereditary syndromes, radiation exposure, and ultrasound data. One promising area of research is the identification of aggressive forms of thyroid cancer that may be candidates for systemic targeted therapy, including in the neoadjuvant setting [14].

Conclusions

In summary, In the modern era of molecular analysis, genetic markers have emerged as effective tools for assessing the growth and progression of thyroid tumors. Molecular biomarkers not only aid in classifying tumor subtypes and predicting disease outcomes but also hold promise for the development of molecular therapies targeting cancers resistant to conventional treatments. The identification of specific genetic alterations and mechanisms underlying thyroid cancer development is anticipated to lead to more personalized treatment approaches for patients with advanced and recurrent forms of the disease. Utilizing molecular testing to identify therapeutic targets could carry significant clinical implications. Understanding molecular mutations, gene fusions, and expression profiles, especially in the most aggressive forms of thyroid cancer, is likely to further drive the discovery and development of new drugs globally. Despite the molecular changes identified, the precise role of molecular biomarkers in the formation of different thyroid tumor subtypes remains incompletely understood.

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Literature:

1. *Дроздович В., Шонфельд С., Акимжанов К., Алдынгуров Д., Лэнд С.Е., др.* Поведение и структура потребления продуктов питания населения, подвергшегося в 1949-1962 годах воздействию радиоактивных осадков Семипалатинского ядерного

полигона в Казахстане. Радиационная экология и биофизика. 2011. Март, 50(1):91-103.

2. *Казубская Т.П., Козлова В.М., Кондратьева Т.Т., и др.* Фолликулярно-клеточный (папиллярный и фолликулярный) рак щитовидной железы, генетическая обусловленность и молекулярные маркеры диагностики. Архив патологии. 2014. 76(5):3-12.

3. *Якушина В.Д., Лернер Л.В., Казубская Т.П., Кондратьева Т.Т., Субраманиан С., Лавров А.В.* Молекулярно-генетическая структура фолликулярно-клеточного рака щитовидной железы. Клиническая и экспериментальная тиреоидология. 2016. 12(2):55-64.

4. *Ali S.Z., Siperstein A., Sadow P.M., Golding A.C., Kennedy G.C., Kloos R.T., Ladenson P.W.* Extending expressed RNA genomics from surgical decision making for cytologically indeterminate thyroid nodules to targeting therapies for metastatic thyroid cancer. Cancer Cytopathol. 2019. Т. 127, № 6. С. 362-369.

5. *Angell T.E., Wirth L.J., Cabanillas M.E., Shindo M.L., Cibas E.S., Babiarz J.E., Hao Y., Kim S.Y., Walsh P.S., Huang J., Kloos R. T., Kennedy G. C., Waguespack S.G.* Analytical and Clinical Validation of Expressed Variants and Fusions From the Whole Transcriptome of Thyroid FNA Samples. Front Endocrinol (Lausanne). 2019. Т.10. С. 612.

6. *Beaudenon-Huibregtse S., Alexander E.K., Guttler R.B., Hershman J.M., Babu V., Blevins T.C., Moore P., Andruss B., Labourier E.* Centralized molecular testing for oncogenic gene mutations complements the local cytopathologic diagnosis of thyroid nodules. Thyroid. 2014, 24, 1479–1487.

7. *Benjamin H., Schnitzer-Perlman T., Shtabsky A. et al.* Analytical validity of a microRNA-based assay for diagnosing indeterminate thyroid FNA smears from routinely prepared cytology slides. Cancer Cytopathol. 2016. doi: 10.1002/cncy.21731.

8. *Buryk M.A., Monaco S.E., Witchel S.F. et al.* Preoperative cytology with molecular analysis to help guide surgery for pediatric thyroid nodules. Int J Pediatr Otorhinolaryngol. 2013. 77(10):1697-1700. doi: 10.1016/j.ijporl.2013.07.029

9. Cancer Genome Atlas Research N. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014. Т. 159, № 3. С. 676-90.

10. *Ciarletto A.M., Narick C., Malchoff C.D., Massoll N.A., Labourier E., Haugh K., Mireskandari A., Finkelstein S.D., Kumar G.* Analytical and clinical validation of pairwise microRNA expression analysis to identify medullary thyroid cancer in thyroid fine-needle aspiration samples. Cancer cytopathology. 2021. Т. 129, № 3. С. 239-249.

11. *Ciampi R., Romei C., Pieruzzi L. et al.* Classical point mutations of RET, BRAF and RAS oncogenes are not shared in papillary and medullary thyroid cancer occurring simultaneously in the same gland. J Endocrinol Invest. 2017. 40(1):55-62. doi: 10.1007/s40618-016-0526-5.

12. *de Morais Fernandes F.C.G., de Souza D.L.B., Curado M.P., de Souza T.A., de Almeida Medeiros A., Barbosa I.R.* Incidence and mortality from thyroid cancer in Latin America. Trop Med Int Health. 2021. 26(7):800-809. doi:10.1111/tmi.13585 1.

13. *Drozdovitch V.* Radiation exposure to the thyroid after the Chernobyl accident. Frontiers in endocrinology. 2021. Т. 11. С. 569041 3.

14. *Duan H., Liu X., Ren X., Zhang H., Wu H., Liang Z.* Mutation profiles of follicular thyroid tumors by targeted sequencing. Diagn. Pathol. 2019,14, 39.

15. *Eszlinger M., Piana S., Moll A. et al.* Molecular testing of thyroid fine-needle aspirations improves pre-surgical diagnosis and supports the histologic identification of minimally invasive follicular thyroid carcinomas. Thyroid 2015. 25: 401–409.

16. *Filetti S., Durante C., Hartl D. et al.* Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019. 30(12):1856-1883. doi:10.1093/annonc/mdz400

17. *Finkelstein S.D., Sistrunk J.W., Malchoff C., Thompson D.V., Kumar G., Timmaraju V.A., Repko B., Mireskandari A., Evoy-Goodman L.A., Massoll N.A.* A retrospective evaluation of the diagnostic performance of an interdependent pairwise MicroRNA expression analysis with a mutation panel in indeterminate thyroid nodules. Thyroid. 2022. Т. 32, № 11. С. 1362-1371.

18. *Franco A.T., Labourier E., Ablordeppey K.K., Surrey L.F., Mostoufi-Moab S., Isaza A., Adzick N.S., Kazahaya K., Kumar G., Bauer A.J.* miRNA expression can classify pediatric thyroid lesions and increases the diagnostic yield of mutation testing. Pediatric Blood & Cancer. 2020. Т. 67, № 6. С. e28276.

19. *Giordano T.J.; Beaudenon-Huibregtse S.; Shinde R., Langfield L., Vinco M., Laosinchai-Wolf W., Labourier E.* Molecular testing for oncogenic gene mutations in thyroid lesions: A case-control validation study in 413 postsurgical specimens.Hum. Pathol 2014,45, 1339–1347

20. *Gupta N., Dasyam A., Carty S.E. et al.* RAS mutations in thyroid FNA specimens are highly predictive of predominantly low risk follicular- pattern cancers. J Clin Endocrinol Metab. 2013;98:E914–E922. doi: 10.1210/jc.2012-3396.

21. Gupta N., Dasyam A.K., Carty S.E., et al. RAS mutations in thyroid FNA specimens are highly predictive of predominantly low-risk follicular-pattern cancers. J Clin Endocrinol Metab. 2013;98(5). doi: 10.1210/jc.2012-3396.

22. *Jackson S., Kumar G., Banizs A. B., Toney N., Silverman J. F., Narick C. M., Finkelstein S. D.* Incremental utility of expanded mutation panel when used in combination with microRNA classification in indeterminate thyroid nodules. Diagnostic cytopathology. 2020. Т. 48, № 1. С. 43-52.

23. *Hescot S., Al Ghuzlan A., Henry T., Sheikh-Alard H., Lamartina L., Borget I., Hadoux J., Baudin E., Dupuy C., Nikitski A.V., Nikiforov Y. E., Schlumberger M., Nikiforova M. N., Leboulleux S.* Prognostic of recurrence and survival in poorly differentiated thyroid cancer. Endocr Relat Cancer. 2022. Т. 29, № 11. С. 625-634.

24. *Hlozek J., Pekova B., Rotnagl J., Holy R., Astl J.* Genetic Changes in Thyroid Cancers and the Importance of Their Preoperative Detection in Relation to the General Treatment and Determination of the Extent of Surgical Intervention-A Review. Biomedicines. 2022. Т. 10, № 7.

25. *Hu M.I., Waguespack S.G., Dosiou C., Ladenson P.W., Livhits M.J., Wirth L. J., Sadow P. M., Krane J.F., et al.* Afirma Genomic Sequencing Classifier and Xpression Atlas Molecular Findings in Consecutive Bethesda III-VI Thyroid Nodules J Clin Endocrinol Metab. 2021. Т. 106, № 8. С. 2198-2207.

26. *Hu M.I., Waguespack S.G., Dosiou C., Ladenson P.W., Livhits M.J., et al.* Afirma genomic sequencing classifier and Xpression atlas molecular findings in consecutive Bethesda III-VI thyroid nodules. The Journal of Clinical Endocrinology & Metabolism. 2021. Т. 106, № 8. – С. 2198-2207.

27. *Krane J.F., Cibas E.S., Endo M., Marqusee E., Hu M.I., Nasr C.E., Waguespack S., Wirth L.J., Kloos R.T. The* Afirma Xpression Atlas for thyroid nodules and thyroid cancer metastases: Insights to inform clinical decision-making from a fine-needle aspiration sample. Cancer Cytpathol. 2020. Т. 128, № 7. С. 452-459.

28. *Keutgen X.M., Filicori F., Crowley M.J. et al.* A panel of four miRNAs accurately differentiates malignant from benign indeterminate thyroid lesions on fine needle aspiration. Clin Cancer Res. 2012.18(7):2032-2038. doi: 10.1158/1078-0432.CCR-11-2487

29. *Krane J.F., Cibas E.S., Alexander E.K., Paschke R., Eszlinger M.* Molecular analysis of residual ThinPrep material from thyroid FNAs increases diagnostic sensitivity. Cancer Cytopathol 2015;123: 356–361.

30. *Labourier E., Fahey T.J.* Preoperative molecular testing in thyroid nodules with Bethesda VI cytology: Clinical experience and review of the literature. Diagn Cytopathol. 2021. Т. 49, № 4. С. E175-E180.

31. *Liu S., Gao A., Zhang B., Zhang Z., et al.* Assessment of molecular testing in fine-needle aspiration biopsy samples: An experience in a Chinese population. Exp. Mol. Pathol.2014,97, 292–297

32. *Maeda S. et al.* Accuracy of thyroid cancer diagnosis and surgery in patients with thyroid cancer may be affected by the Semipalatinsk Nuclear Test Site: A collaboration between Nagasaki (Japan) and Semipalatinsk (Kazakhstan) medical centers. Acta medica Nagasakiensia. 2021. Т. 64. №. 3. С. 77-80

33. *Marotta V., Bifulco M., Vitale M.* Significance of RAS Mutations in Thyroid Benign Nodules and Non-Medullary Thyroid Cancer.Cancers 2021, 13, 3785. https://doi.org/10.3390/cancers13153785

34. *Milosevic Z., Pesic M., Stankovic T. et al.* Targeting RAS-MAPK-ERK and PI3K-AKT-mTOR signal transduction pathways to chemosensitize anaplastic thyroid carcinoma. Transl Res. 2014 Nov. 164(5):411-23. doi: 10.1016/j.trsl.2014.06.005.

35. *Monaco S.E., Pantanowitz L., Khalbuss W.E. et al.* Cytomorphological and molecular genetic findings in pediatric thyroid fine-needle aspiration. Cancer Cytopathol. 2012.120(5):342-350. doi: 10.1002/cncy.21199.

36. *Moses W., Weng J., Sansano I. et al.* Molecular testing for somatic mutations improves the accuracy of thyroid fine-needle aspiration biopsy. World J Surg. 2010. 34:2589–2594. doi: 10.1007/s00268- 010-0720-0.

37. *Nagayama Y., Mishima H.* Heterogenous nature of gene expression patterns in BRAF-like papillary thyroid carcinomas with BRAF(V600E). Endocrine. 2019 Dec. 66(3):607-613. doi: 10.1007/ s12020-019-02063-z

38. *Niciporuka R., Nazarovs J., Ozolins A., Narbuts Z., Miklasevics E., Gardovskis J.* Can We Predict Differentiated Thyroid Cancer Behavior? Role of Genetic and Molecular Markers. Medicina (Kaunas). 2021. Т. 57, № 10. P.52-59.

39. *Nikiforov Y.E., Steward D.L., Robinson-Smith T.M., Haugen B.R., et al.* Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. The Journal of Clinical Endocrinology & Metabolism. 2009. Т. 94, № 6. С. 2092-2098.

40. *Nikiforov Y.E., Ohori N.P., Hodak S.P. et al.* Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: A prospective analysis of 1056 FNA samples. J Clin Endocrinol Metab. 2011. 96:3390–3397. doi: 10.1210/jc.2011–1469.

41. *Nikiforov Y.E., Carty S.E., Chiosea, S.I., Coyne C.; DuvvuriU.; Ferris, et al.* Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. Cancer 2014, 120, 3627–3634

42. *Nikiforov Y.E., Seethala R.R.* RAS mutations in thyroid nodules: Molecular diagnostics and clinical implications. Surgery, 2016. 160(1), 77-88. https://doi.org/10.1016/j.surg.2016.04.054

43. *Nikiforov Y.E., Carty S.E., Chiosea S.I. et al.* Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. Cancer. 2014. 120(23):3627-3634. doi: 10.1002/cncr.29038.

44. *Ohori N.P., Singhal R., Nikiforova M.N. et al.* BRAF mutation detection in indeterminate thyroid cytology specimens: underlying cytologic, molecular, and pathologic characteristics of papillary thyroid carcinoma. Cancer (Cancer Cytopathol). 2013. 121: 197-205

45. *Onenerk A.M., Pusztaszeri M.P., Canberk S., Faquin W.C.* Triage of the indeterminate thyroid aspirate: What are the options for the practicing cytopathologist? Cancer Cytopathol. 2017. Т. 125, № S6. С. 477-485.

46. *Ohori N.P., Schoedel K.E.* Variability in the atypia of undetermined significance/follicular lesion of undetermined significance diagnosis in the Bethesda System for Reporting Thyroid Cytopathology: sources and recommendations. Acta Cytol. 2011. 55:492-498.

47. *Park J., An S., Kim K., Bae J.S., Kim J.S.* BRAFV600E Positivity-Dependent Effect of Age on Papillary Thyroid Cancer Recurrence Risk. Cancers (Basel). 2023 Nov 13. 15(22):5395. doi: 10.3390/cancers15225395. PMID: 38001654. PMCID: PMC10670702.

48. *Paschke R., Cantara S., Crescenzi A., Jarzab B., Musholt T., Sobrinho Simoes M.* European Thyroid Association Guidelines regarding Thyroid Nodule Molecular Fine-Needle Aspiration Cytology Diagnostics. European Thyroid Journal, 2017. 6(3), 115-129. Retrieved Oct 29, 2024, https://doi.org/10.1159/000468519]

49. *Puzziello A., Guerra A., Murino A. et al.* Benign thyroid nodules with RAS mutation grow faster. Clin Endocrinol (Oxf). 2016. 84(5):736-740. doi: 10.1111/cen.12875

50. *Saenko V., Mitsutake N.* Radiation-Related Thyroid Cancer. Endocr Rev. 2024. 45(1):1-29. doi:10.1210/endrev/bnad0222.

51. *Shen X., Liu R., Xing M.* A six-genotype genetic prognostic model for papillary thyroid cancer. Endocr. Relat. Cancer. 2017, 24, 41–52.

52. *Skaugen J.M., Taneja C. et al.* Performance of a Multigene Genomic Classifier in Thyroid Nodules with

Suspicious for Malignancy Cytology. Thyroid. 2022. T. 32, № 12. C. 1500-1508.

53. *Song Y.S., Won J.K., Yoo S.K. Jung K.C. et al.* Comprehensive Transcriptomic and Genomic Profiling of Subtypes of Follicular Variant of Papillary Thyroid Carcinoma.Thyroid. 2018. 28, 1468–1478.]

54. *Steward D.L., Carty S.E., Sippel R.S., Yang S.P., Sosa J.A., Sipos J.A. et al.* Performance of a multigene genomic classifier in thyroid nodules with indeterminate cytology: a prospective blinded multicenter study. JAMA oncology. 2019. T. 5, № 2. C. 204-212.

55. *Tang A.L., Kloos R.T., Aunins B., Holm T.M., Roth M.Y. et al*. Pathologic Features Associated With Molecular Subtypes of Well-Differentiated Thyroid Cancer. Endocr Pract. 2021. T. 27, № 3. C. 206-211.

56.*Xing M.* Molecular pathogenesis and mechanisms of thyroid cancer. Nat Rev Cancer. 2013. 13:184-199.

57. *Xing M.* Clinical utility of RAS mutations in thyroid cancer: a blurred picture now emerging clearer. BMC Med. 2016 Jan 27. 14:12. doi: 10.1186/s12916-016-0559-9. PMID: 26817707; PMCID: PMC4730731

58.*Yan Liu, Leslie Cope, Wenyue Sun, Yongchun Wang et al.* DNA Copy Number Variations Characterize Benign and Malignant Thyroid Tumors, The Journal of Clinical Endocrinology & Metabolism, Volume 98, Issue 3, 01.03.2013, pp. E558–E566

59. *Yarchoan M., LiVolsi V.A., Brose M.S.* BRAF Mutation and Thyroid Cancer Recurrence. J Clin Oncol. 2015. 33(1):7–8. doi: 10.1200/JCO.2014.59.3657.

60. *Yip L., Wharry L.I., Armstrong M.J. et al.* A clinical algorithm for fine-needle aspiration molecular testing effectively guides the appropriate extent of initial thyroidectomy. Ann Surg. 2014;260(1):163-168. doi: 10.1097/SLA.0000000000000215

61. *Yoo S.K., Lee S., Kim S.J., Jee H.G., Kim B.A.* Comprehensive Analysis of the Transcriptional and Mutational Landscape of Follicular and Papillary Thyroid Cancers. PLoS Genet. 2016. T.12, № 8. C. e1006239.
2014. 76(5):3 12.

62. *Zhao L., Dias-Santagata D., Sadow P.M., Faquin W.C.* Cytological, molecular, and clinical features of noninvasive follicular thyroid neoplasm with papillary-like nuclear features versus invasive forms of follicular variant of papillary thyroid carcinoma. Cancer Cytopathol. 2017, 125, 323–331.

References: [1-3]

1. Drozdovitch V., Schonfeld S., Akimzhanov K., Aldyngurov D., Land C.E., Luckyanov N., Mabuchi K., Potischman N., Schwerin M.J., Semenova Y., Tokaeva A., Zhumadilov Z., Bouville A., Simon S.L. Povedenie i struktura potrebleniya produktov pitaniya naseleniya, podvergshegosya v 1949-1962 godakh vozdeistviyu radioaktivnykh osadkov Semipalatinskogo yadernogo poligona v Kazakhstane. [Behavior and food consumption pattern of the population exposed in 1949-1962 to fallout from Semipalatinsk nuclear test site in Kazakhstan]. *Radiatsionnaya ekologiya i biofizika* [Radiat Environ Biophys]. 2011 Mar. 50(1):91-103

2. Yakushina V.D., Lerner L.V., Kazubskaya T.P., Kondrat'ieva T.T., Subramanian S.-., Lavrov A.V. Molekulyarno-geneticheskaya struktura follikulyarno-kletochnogo raka shchitovidnoi zhelezy [Molecular genetics of follicular cell thyroid carcinoma]. *Klinicheskaya i eksperimental'naya tireoidologiya* [Clinical and experimental thyroidology]. 2016. 12(2):55-64. [In Russian] https://doi.org/10.14341/ket2016255-64

3.Kazubskaya T.P., Kozlova V.M., Kondrat'eva T.T. et al. Follikulyarno-kletochnyi (papillyarnyi i follikulyarnyi) rak shchitovidnoi zhelezy, geneticheskaya obuslovlennost' i molekulyarnye markery diagnostiki [Follicular cell (papillary and follicular) thyroid carcinoma, genetic inheritance, and molecular diagnostic markers]. *Arkhiv patologii* [Russian Journal of Archive of Pathology]. 2014. 76(5):3-12. [InRussian].

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