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# STRATIFICATION OF WELL-DIFFERENTIATED THYROID CANCER BASED ON MOLECULAR GENETIC TESTING: A LITERATURE REVIEW

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## ABSTRACT

***Relevance:*** *Thyroid cancer (TC) is among the most significant malignant diseases of the head and neck, with a steadily growing number of newly diagnosed cases throughout the world. Despite a relatively modest 17th place of TC in the structure of cancer incidence, its treatment in recent decades has seriously worried scientists and physicians due to a very rapid increase in TC incidence among young and middle-aged people. Iodine deficiency decreases immune function, and the effects of ionizing radiation play a role in the development of thyroid cancer. This leads to the development of a stratification system for well-differentiated thyroid cancer (WDTC) at the molecular genetic level. This system is necessary to select patients at risk of progression and to apply aggressive radionuclide therapy and suppressive hormone therapy only to those patients who need it.*

***The study aimed to*** *systematize data from the current literature to assess the need to develop a prognostic stratification of patients with WDTC based on molecular genetic testing.*

***Methods:*** *A literature review of scientific publications was conducted from the PubMed search database from September 2017 to December 2023. Inclusion criteria: publication date from 2017 to present for the main keywords: 'High differentiated thyroid cancer", " prognostic stratification of WDTC based on molecular tests, 'WDTC mutation markers.' Some clinical studies of domestic and foreign specialists were also considered.*

***Results:*** *Based on a meta-review of literature data on prognostic stratification of WDTC patients, the rationale for expanding the panel of genetic markers associated with aggressive forms of WDTC is presented, the importance of gene mutation in the occurrence of disease recurrence, and the choice of adequate treatment is proven.*

***Conclusions:*** *Research efforts are underway to find genetic and pathomorphologic predictors of the prognosis of the disease. Knowledge of molecular and genetic mechanisms of tumorigenesis provides a wide range of opportunities for applying molecular diagnostics in differential diagnosis, prognosis of the course of the disease, and treatment of aggressive forms of tumors.*

***Keywords:*** *well-differentiated thyroid cancer (WDTC), prognostic stratification of WDTC, WDTC mutation markers.*

***Introduction:*** Thyroid cancer (TC) is among the most significant malignant diseases of the head and neck, with a steadily growing number of newly diagnosed cases throughout the world. Despite a relatively modest 17th place of TC in the structure of cancer incidence, its treatment in recent decades has seriously worried scientists and physicians due to a very rapid increase in TC incidence among young and middle-aged people [1]. According to GLOBOCAN 2021, about 500 new TC cases are detected in Kazakhstan yearly, with a crude incidence of 4.2 per 100,000 population. TC is three times more common in women. A gender-standardized incidence worldwide is 6.1 in women and 1.9 in men.

Most cases of TC are associated with nodular goiter. The next most common factors for TC development include hereditary predisposition, lymphadenopathy, voice changes, etc. The most common methods of primary diagnosis of nodular goiter are palpation of the thyroid gland and regional lymph nodes and taking an anamnesis to exclude risk factors for the development of aggressive forms of TC, such as a hereditary predisposition to thyroid cancer, a history of radiation exposure to the head and neck, dysphagia, dysphonia, thyroid neoplasms accidentally detected during positron emission tomography (PET), as well as a history of surgery for thyroid cancer. Laboratory methods are also used to diagnose thyroid cancer: ultrasound, fine-needle aspiration biopsy, pathomorphological examination, molecular genetic testing (MGT), and computed tomography [2].

Well-differentiated thyroid cancer (WDTC) is the most common histological subtype of thyroid cancer and is characterized by a relatively favorable course and high relapse-free and overall survival [3].

The RAI-R study involving 132 patients with malignant thyroid tumors (59 papillary, 24 follicular, 35 Hurthle cell, and 14 anaplastic thyroid carcinomas) identified seven target fusions in samples with no known DNA gene variants. They included commonly reported gene fusions such as CCDC6/RET (PTC1), PRKAR1A/RET (PTC2), or ETV6/NTRK3, as well as gene fusions that are less common in TC (TPM3/NTRK1, EML4/ALK, or EML4/

NTRK3). Notably, most gene fusions were detected in papillary TC (PTC), and MAPK-related changes were less common in Hürthle cell carcinoma (2/35). In 12% of TC carcinoma cases in the RAI-R study with no known DNA gene variants, they detected targeted gene fusions that can be efficiently identified in formaldehyde-fixed tissue. Compounds of these genes can serve as a preclinical justification for introducing specific inhibitors in a personalized treatment regimen for this group of patients to restore iodine delivery and/or take advantage of direct effects on tumor cell viability during disease progression [4-5].

In the Russian clinical study on TC diagnostics and treatment in adults, surgical treatment was most acceptable in patients with low-risk TC, with a tumor size of 1 to 4 cm without extrathyroidal invasion [6].

Methods for molecular diagnostics of thyroid tumors are currently being developed. Most studies focus on molecular genetic research, given that this area is understudied. Scientific research at the molecular genetic level follows several main directions: differential diagnosis of thyroid tumors, prognostic significance of identified mutations in TC, and targeted therapy for aggressive or radioactive iodine-resistant forms of TC [7].

***The study aimed to*** systematize data from the current literature to assess the need to develop a prognostic stratification of patients with WDTC based on molecular genetic testing.

***Materials and Methods:*** A literature review of scientific publications was conducted from the PubMed search database from September 2017 to December 2023. Inclusion criteria: publication date from 2017 to present for the main keywords: 'High differentiated thyroid cancer", " prognostic stratification of WDTC based on molecular studies,' and 'WDTC mutation markers.' Some clinical studies of domestic and foreign specialists were also considered. Fifteen publications were included in the analysis.

***Results:*** The importance of MGT is immense. Still, MGT findings have not yet been included in any TC staging system. In 2015, the American Thyroid Association (ATA) proposed identifying BRAF and TERT mutations. However, a more accurate stratification of the risk of relapse of PTC is required since most patients with a favorable prognosis are overtreated. In contrast, the treatment of patients with aggressive TC types is not substantiated enough.

This disease's clinical outcome is associated with various mutations occurring in the thyroid gland. BRAF V600E is the most common mutation in TC and is associated with a higher risk of relapse. Mutational changes in the TERT promoter are associated with distant metastases and the greatest mortality risk in advanced TC cases. Differentiated thyroid tumors containing RAS mutations without any accompanying changes have an excellent prognosis. Other genetic changes in TC include rearrangements of the NTRK, RET, ALK, BRAF, MET, FGFR, PPARγ, or ROS1 genes, and their relationship with the disease outcome has not yet been sufficiently studied. In children with TC, NTRK fusions are eight times more common than in adults, with a frequency of 18.3% to 25.9% [8].

A study of thyroid tumor frequency showed that 50% of those diagnosed were at the age of 60. Seventy-eight comprehensive studies revealed a significant relationship between the presence of BRAF mutations and metastasis to cervical lymph nodes. Out of 46 studies in Eastern Asia, 24 presented data on metastasis to central lymph nodes, 11 – on metastasis to the lateral lymph nodes, and 10 analyzed a classical/traditional PTC. The Metacum analysis showed no significant association between BRAF and LNM mutations until 2012. After 2012, a significant association began to emerge between BRAF and LNM mutations, which became consistent in 2017 [9].

In Korea, they found specific WDTC variants that influence the type of PTC. Although DTC and PTC are cancer originating from follicular cells, differences still exist between them. The studies show that TC development risk analysis should consider the type of cancer and the patient's personal genotype. Finally, they made a GWAS analysis to reveal DTC in the Korean population and found new susceptibility loci for VAV3, PCNXL2, FHIT, SEPT11, MSRB3, and INSR. Those findings were verified by a cis-eQTL test, an analysis using RNA sequencing data from tumor and normal thyroid tissues. The results obtained could be used to diagnose and choose the treatment tactics for malignant thyroid tumors, which, in turn, will allow us to understand genetic factors in the era of personalized cancer medicine [10].

The study by the National Cancer Institute under the grant for the support of MSK oncological center / main grant (P30 CA008748) and the Bayer AG research grant collected the biggest sample of solid tumors with positive NTRK fusion stained by Pan-Trk immunohistochemistry (IHC). For the first time, this research has described in detail the sensitivity and specificity of a targeted DNA-based next-generation sequencing panel to detect NTRK1-3 fusions. Pan-Trk IHC presented a total sensitivity of 88%; at that, NTRK3 fusions were responsible for the vast majority of false negative results. DNA-based sequencing had a sensitivity of 81%, with most false negative results due to NTRK2 and NTRK3 fusions. DNA-based sequencing specificity exceeded 99%, while IHC specificity largely depended on the examined tumor type. Thus, IHC could potentially exclude NTRK fusion in solid tumors unless IHC sensitivity was not less than 100%. Although, in this study, immunostaining in tumors with NTRK amplification could be attributed to other factors like neuron differentiation,

former studies prove the contrary. Therefore, a positive IHC in such tumors requires further examination using other available tests [11].

There are very few studies on molecular genetic markers. S. Lukyanov et al. assessed microRNA expression in different groups at risk of relapse. The expression of oncogenic miR-221 was found to vary significantly: it was high in the group with a high risk of relapse and lower in the low-risk group. MicroRNA expression levels also varied and were much lower in all risk groups. Therefore, microRNA expression level should be determined at the preoperative stage during fine-needle aspiration biopsy of thyroid nodes [12].

Based on the above, the use of new molecular genetic testing in diagnostics and treatment of thyroid neoplasms provides a more accurate characterization of pathological changes, assessing the nature of pathological changes in the thyroid gland based on the study of genetic mechanisms of carcinogenesis and choosing an optimal personified treatment tactics. Searching for new molecular genetic markers and their combinations is important for assessing the PTC relapse risk.

***Discussion:*** In recent years, several cases of aggressive course of DTC have been described in the literature. Clinical studies are searching for genetic and pathomorphological predictors of disease prognosis. Rapid metastasis of DTC requires the introduction of molecular and histological markers into practice to clarify the degree of aggressiveness of these forms of cancer and find new targets for the development of personalized therapy and diagnostics. This approach will enable oncologists to develop an individual patient management plan, considering the tumor's metastatic potential and the possibility of selecting personalized therapy [13]. This can clarify morphological criteria and increase the likelihood of detecting a mutation, which is an important criterion when choosing treatment methods (prescribing targeted therapy).

The combination therapy with sorafenib and temsirolimus has proven the activity of sorafenib in thyroid carcinoma. The sorafenib and temsirolimus combination is most efficient in RAI-resistant thyroid carcinoma; it delivers impressive patient response rates compared to sorafenib alone. Patients naïve VEGF-targeted treatment, including sorafenib, also demonstrated positive results and long-term disease stabilization. Sorafenib and temsirolimus in RAI-resistant TC deserve further study, especially compared to sorafenib monotherapy. Finally, 1 of 2 study participants with anaplastic TC had a significant response to therapy with sorafenib and temsirolimus, and this particular patient requires further evaluation in future studies [14].

Today, we witness rapid progress in studying molecular mechanisms underlying thyroid gland carcinogenesis. One marker is clearly not enough to diagnose TC. Several biological treatment methods and the identification of key genes shall be applied. E.g., monoclonal antibodies and antibody-drug conjugates shall be prescribed in addition to Tyrosine Kinase Inhibitors [15].

***Conclusion:*** Molecular genetic testing is very necessary today. The presented topic has not yet been sufficiently studied and research on molecular genetic markers is indeed extremely insufficient. Molecular genetic testing can improve TC diagnostics. A well-structured plan will also make it possible to develop treatment options for individual patients with the most aggressive forms of TC. Unfortunately, the use of molecular genetic studies is currently limited due to their high cost and lack of long-term experience of use in clinical practice. Despite this, it is necessary to proceed in this direction and consider all available cases separately to predict treating patients with thyroid tumors.

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**АҢДАТПА**

## МОЛЕКУЛЯРЛЫҚ-ГЕНЕТИКАЛЫҚ ЗЕРТТЕУЛЕР НЕГІЗІНДЕ ЖОҒАРЫ САРАЛАНҒАН ҚАЛҚАНША БЕЗІНІҢ ҚАТЕРЛІ ІСІГІНІҢ СТРАТИФИКАЦИЯСЫ: ӘДЕБИЕТКЕ ШОЛУ

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***Өзектілігі:*** *Қалқанша безінің қатерлі ісігі (ҚБҚІ) - бұл бүкіл әлемде алғаш рет анықталған формалардың саны үнемі өсіп келе жатқан эндокриндік органдардың ең көп таралған қатерлі ауруы. Қалқанша безінің қатерлі ісігінің қатерлі ісік құрылымындағы салыстырмалы түрде қарапайым орнына (17 дәрежелі орын) қарамастан, оны емдеу мәселесі соңғы онжылдықтарда әртүрлі медицина салаларындағы ғалымдар мен дәрігерлерді қатты алаңдатады. Бұл көбінесе жас және орта жастағы адамдар арасындағы аурудың өте тез өсуіне байланысты.*

*ҚБҚ ісігінің дамуында йод тапшылығы, иммундық функцияның төмендеуі, сондай-ақ иондаушы сәулеленудің әсері белгілі рөл атқарады. Бұл молекулалық-генетикалық деңгейде жоғары сараланған ҚБҚІ (ЖСҚБҚІ) стратификация жүйесінің дамуына әкеледі. Мұндай жүйе прогрессия қаупі бар науқастарды таңдау және радионуклидті терапия мен супрессиялық гормондық терапияның агрессивті әдістерін қажет ететін науқастарға ғана қолдану үшін қажет.*

***Зерттеу мақсаты*** *– ЖСҚБҚІ болжамдық маркерлерін анықтау арқылы қазақстандық популяция үшін стратификация жүйесін әзірлеу мақсатында молекулалық-генетикалық зерттеулер негізінде.*

***Әдістері:*** *2017 жылдың қыркүйегі мен 2023 жылдың желтоқсаны аралығында PubMed іздеу базасындағы ғылыми жарияланымдарға әдеби шолу жасалды. Қосу критерийлері: 2017 жылдан бастап қазіргі уақытқа дейін негізгі кілт сөздер бойынша жарияланған күні: «Қалқанша безінің жоғары сараланған қатерлі ісігі», «молекулалық зерттеулерге негізделген ЖСҚБҚІ болжамдық стратификациясы», «ЖСҚБҚІ мутация маркерлері. Сондай-ақ отандық және шетелдік мамандардың кейбір клиникалық зерттеулері қарастырылды.*

***Нәтижелері:*** *ЖСҚБҚІ бар науқастардың болжамды стратификациясының әдеби деректеріне мета-шолу негізінде ЖСҚБҚІ агрессивті формаларымен байланысты генетикалық маркерлер панелін кеңейтудің негіздемесі келтірілген, аурудың қайталануы кезінде гендік мутацияның маңыздылығы және адекватты емдеуді таңдау дәлелденді.*

***Қорытынды:*** *Аурудың болжамының генетикалық және патоморфологиялық болжаушыларын іздеу бағытында ғылыми жұмыстар жүргізілуде. ҚБҚІ пайда болуының молекулалық-генетикалық механизмдерін білу дифференциалды диагностикада, аурудың ағымын болжауда және ҚБҚІ агрессивті формаларын емдеуде молекулалық диагностиканы қолдануға кең мүмкіндіктер береді.*

***Түйінді сөздер:*** *Қалқанша безінің жоғары сараланған қатерлі ісігі, ЖСҚБҚІ болжамды стратификациясы, ЖСҚБҚІ мутациясының маркерлері.*

**ABSTRACT**

## СТРАТИФИКАЦИЯ ВЫСОКОДИФФЕРЕНЦИРОВАННОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ НА ОСНОВАНИИ МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИХ ИССЛЕДОВАНИЙ: ОБЗОР ЛИТЕРАТУРЫ

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***Актуальность:*** *Рак щитовидной железы (РЩЖ) является одним из наиболее значимых злокачественных заболеваний органов головы и шеи, число впервые выявленных случаев РЩЖ ежегодно растёт во всем мире. Несмотря на невысокое место РЩЖ (17е*

*ранговое место) в структуре злокачественных опухолей, его лечение представляет собой серьезную проблему для ученых и врачей в связи с крайне быстрым ростом заболеваемости среди лиц молодого и среднего возраста.*

*Определенная роль в развитии РЩЖ принадлежит йододефициту, снижению иммунной функции, а также действию ионизирующей радиации. Это ведет к разработке системы стратификации высокодифференцированного РЩЖ (ВДРЩЖ) на молекулярно-генетическом уровне. Такая система необходима, чтобы провести отбор пациентов в группы риска прогрессирования и применять агрессивные методы радионуклидной терапии и супрессивной гормонотерапии только тем больным, кому это необходимо.*

***Цель исследования** – систематизировать актуальные литературные данные для оценки необходимости разработки прогностической стратификации пациентов с ВДРЩЖ на основании молекулярно-генетических исследований.*

***Методы:** Был проведен обзор научных публикаций из поисковой базы PubMed за сентябрь 2017 г. по декабрь 2023 г. по ключевым словам: «высокодифференцированный рак щитовидной железы», « прогностическая стратификация ВДРЩЖ на основании молекулярных исследований», «маркеры мутации ВДРЩЖ».*

***Результаты:** На основании мета-обзора литературных данных прогностической стратификации пациентов с ВДРЩЖ приведено обоснование расширения панели генетических маркеров, ассоциированных с агрессивными формами ВДРЩЖ, доказано значение мутации генов при возникновении рецидива заболевания и выборе адекватного лечения.*

***Заключение:** Ведутся научные работы в направлении поиска генетических и патоморфологических предикторов прогноза заболевания. Знание молекулярно-генетических механизмов возникновения РЩЖ дает широкие возможности применения молекулярной диагностики в дифференциальной диагностике, прогнозировании течения заболевания и лечении агрессивных форм РЩЖ.*

***Ключевые слова:** Высокодифференцированный рак щитовидной железы (ВДРЩЖ), прогностическая стратификация ВДРЩЖ, маркеры мутации ВДРЩЖ.*

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