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RADIOIODINE-RESISTANT DIFFERENTIATED THYROID CANCER: CLINICOPATHOLOGICAL CHARACTERISTICS, MOLECULAR GENETIC ALTERATIONS. REVIEW.

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Abstract

Introduction. Thyroid cancer is one of the most common endocrine malignancies. Radioactive iodine I^{131} is the baseline drug in the therapy of patients with differentiated thyroid cancer (DTC); however, 5% to 15% of DTC and 50% of metastatic DTC are not amenable to radioactive iodine I^{131} therapy. Some patients suffer from recurrent disease after complex treatment. Recurrent disease is often resistant to radioiodine and shows a poor response to radioactive iodine therapy.

The aim. To analyze the publications devoted to the problems of radioiodine-resistant thyroid cancer and their clinicopathological and molecular-genetic characteristics.

Search strategy. The literature search was performed in the electronic databases Web of Science Core Collection, Scopus, Google Scholar over the past 5 years: from 2018 to 2023. *Inclusion criteria* were systematic reviews, original articles. *Exclusion criteria* were articles of poor methodological quality, duplication, missing or incomplete data in articles, case reports, letters, editorials, and expert opinions. 135 articles were found, of which 88 were selected for analysis.

Results of the research. According to the material studied, special attention is now paid to the presence of driver mutations, such as telomerase reverse transcriptase promoter mutations TERT, BRAF V600E, NRAS, which show an aggressive genetic pattern; they can also be used for patient risk stratification when determining radioiodine resistance in patients. In addition, histological examination of the tumor is also one of the most important predictors of DTC prognosis.

Conclusion. Based on the analysis of publications, we can conclude that significant progress has been made over the past decades in understanding the molecular mechanisms that cause the malignant evolution of DTC and the development of radioiodine resistance. Given the relationship between molecular and histological heterogeneity, the selection of tumor samples for molecular genetic analysis should be based on the results of histological evaluation of the entire tumor. Comprehensive molecular genetic analysis, as well as histological characteristics of the tumor, will subsequently play an important role in stratifying patients and determining further patient management tactics.

Keywords: *Well-differentiated thyroid cancer, Radioactive iodine therapy, Radioiodine resistance, BRAF V600E, TERTp, NRAS.*

Резюме

РАДИОЙОДРЕЗИСТЕНТНЫЙ ДИФФЕРЕНЦИРОВАННЫЙ РАК ЩИТОВИДНОЙ ЖЕЛЕЗЫ: КЛИНИКО-ПАТОЛОГИЧЕСКИЕ ХАРАКТЕРИСТИКИ, МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИЕ АЛЬТЕРАЦИИ. ОБЗОР ЛИТЕРАТУРЫ.

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Введение. Рак щитовидной железы является одним из наиболее распространенных злокачественных новообразований эндокринной системы. Радиоактивный йод I^{131} является базисным препаратом в терапии пациентов с дифференцированным раком щитовидной железы (ДРЩЖ); однако от 5% до 15% дифференцированных раков щитовидной железы и 50% метастатических ДРЩЖ не поддаются лечению радиоактивным йодом I^{131}. Некоторые пациенты страдают от рецидивов заболеваний после комплексного лечения. Рецидивирующее заболевание часто оказывается устойчивым к радиоактивному йоду и показывает низкий ответ на радиойодтерапию.

Цель. Проанализировать публикации, посвященные проблемам радиойодрезистентного рака щитовидной железы и их клинико-патологическим и молекулярно-генетическим характеристикам.

Стратегия поиска. Поиск литературы был осуществлен в электронных базах Web of Science Core Collection, Scopus, Google Scholar за последние 5 лет: с 2018 по 2023 годы. *Критериями включения* являлись систематические обзоры, оригинальные статьи. *Критериями исключения* являлись статьи низкого методологического качества, случаи дублирования, отсутствия или неполные данные в статьях, отчеты о клинических случаях, письма, редакционные статьи и мнения экспертов. Были найдены 135 статей, из них 88 были выбраны для анализа.

Результаты исследования. Согласно изученному материалу, на сегодняшний день особое внимание уделяется наличию драйверных мутации, таких как мутации промотора обратной транскриптазы теломеразы TERT, BRAF ^{V600E}, NRAS, которые демонстрируют агрессивную генетическую картину, они также могут быть включены для стратификации риска пациентов в определении радиорезистентности у пациентов. Более того, гистологическое исследование опухоли также является одним из ключевых предикторов прогноза ДРЩЖ.

Выводы. Исходя из анализа публикаций, можно сделать вывод, что за последние несколько десятилетий достигнут значительный прогресс в понимании молекулярных механизмов, вызывающих злокачественную эволюцию ДРЩЖ и развитию радиойодрезистентности. Учитывая связь между молекулярной и гистологической гетерогенностью, отбор образцов опухоли для молекулярно-генетического анализа должен основываться на результатах гистологической оценки всей опухоли. Комплексный молекулярно-генетический анализ, а также гистологическая характеристика опухоли в последующем будет играть важную роль в стратификации пациентов и определения дальнейшей тактики ведения пациента.

Ключевые слова: *Высокодифференцированный рак щитовидной железы, Радиойодтерапия, Радиойодрезистентность, BRAF V600E, TERT, NRAS.*

Түйіндеме

РАДИОЙОДҚА ТӨЗІМДІ ҚАЛҚАНША БЕЗІНІҢ САРАЛАНҒАН ОБЫРЫ: КЛИНИКО-ПАТОЛОГИЯЛЫҚ СИПАТТАМАЛАРЫ, МОЛЕКУЛЯРЛЫҚ-ГЕНЕТИКАЛЫҚ АЛЬТЕРАЦИЯЛАРЫ. ӘДЕБИ ШОЛУ.

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Кіріспе. Қалқанша безінің қатерлі ісігі - эндокриндік жүйенің ең көп таралған қатерлі ісіктерінің бірі. Радиоактивті йод I^{131} қалқанша безінің сараланған обыры (ҚБСО) бар науқастарды емдеудегі негізгі препарат болып табылады, алайда, қалқанша безінің сараланған обырының 5%-15% дейін және 50% метастаздық ҚБСО I^{131} радиоактивті йодпен емдеуге төзімді болып келеді. Кейбір науқастар кешенді емдеуден кейінгі рецидивтерден зардап шегеді. Қайталанатын ауру жиі радиойодқа төзімді болып келеді және радиойодты терапияға нашар жауап береді.

Мақсаты. Радиойодқа төзімді қалқанша безінің қатерлі ісігі мәселелеріне және олардың клинико-патологиялық және молекулалық-генетикалық сипаттамаларына арналған жарияланымдарды талдау.

Іздеу стратегиясы. Әдебиеттерді іздеу Web of Science Core Collection, Scopus, Google Scholar электронды базаларында соңғы 5 жылдың ішіндегі: 2018 жыл мен 2023 жылдар аралығында жүргізілді. *Қосылу критерийлеріне* жүйелі шолулар, түпнұсқа мақалалар енгізілді. *Алып тастау критерийлеріне* әдістемелік сапасы төмен мақалалар, мақалалардағы деректердің қайталануы, жетіспейтін немесе толық емес деректері, жағдайлық есептер, хаттар, редакциялық мақалалар және сараптамалық қорытындылар кірді. 135 мақала табылып, оның 88-і талдауға іріктеліп алынды.

Зерттеу нәтижелері. Зерттеу нәтижесі гистологиялық, Ki-67 LI экспрессиясының иммуногистохимиялық (ИГХ) зерттеулерін жүргізу радиойодқа төзімді қалқанша безінің сараланған қатерлі ісігінде маңызды болжамы болып табылатынын көрсетті. Сондай-ақ BRAFV600E/TERTp, BRAFV600E/NRAS драйверлік мутацияларының қатар кездесуі агрессивті клинико-патологиялық сипаттамалармен және радиойодқа төзімділіктің пайда болуымен байланысты болуы мүмкін, бұл өз кезегінде емдеу тактикасын анықтауда маңызды болып табылады.

Қорытынды. Қорытындылай келе, радиойодқа төзімді қалқанша безінің қатерлі ісігінің клинико-патологиялық және молекулалық сипаттамаларын анықтау үшін гистологиялық, Ki-67 LI экспрессиясының иммуногистохимиялық (ИГХ) зерттеулерін жүргізу, сондай-ақ TERTp, BRAFV600E, NRAS мутацияларына молекулалық-генетикалық зерттеу жүргізу қажет. Бұл көрсеткіштерді одан әрі зерттеу өзекті мәселе болып табылады және қосымша зерттеулерді қажет етеді.

Түйінді сөздер. *«жоғары сараланған қалқанша безінің қатерлі ісігі», «радиойодты терапия», «радиойодқа төзімділік», «BRAFV600E», «TERT», «NRAS».*

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Introduction

In recent decades, thyroid cancer (TC) has become a serious public health problem [60]. In terms of growth rate, thyroid cancer outpaces other malignant neoplasms. This trend is not solely attributed to a rise in the number of patients affected by this condition, but also to advancements in diagnostic tools that facilitate the early identification of malignant growths and follicular abnormalities [6]. According to the latest global malignant neoplasm statistics from the International Agency for Research on Cancer (GLOBOCAN 2020), thyroid cancer is the ninth most common malignancy worldwide and its incidence continues to increase, with 586,000 new cases reported in 2020. To date, the highest incidence rates are found in North America, Australia/New Zealand, East Asia and Southern Europe in both sexes, and in Micronesia/Polynesia and South America are often found in females [60].

According to the figures of the Oncological Service of the Republic of Kazakhstan for 2022, thyroid cancer is included in the list of the ten most frequent localizations of cancer in women in 2022. Thyroid cancer moved up from 11th to 9th place, which shows the growth of this disease among women compared to men. The structure of oncopathological incidence in the Republic of Kazakhstan by gender in 2022 is presented in Figure 1 (Figure 1).

The increase in the incidence of malignant neoplasms for 2022 was recorded for all nosologies in general, including malignant neoplasm of the thyroid gland increased from 3.4 to 4.3, that is roughly +26.5%.

Well differentiated thyroid cancer (WDTC), which has a favorable course, is usually treated surgically, i.e. complete thyroidectomy followed by radioiodine therapy and thyroid hormones that suppress thyroid hormone levels.

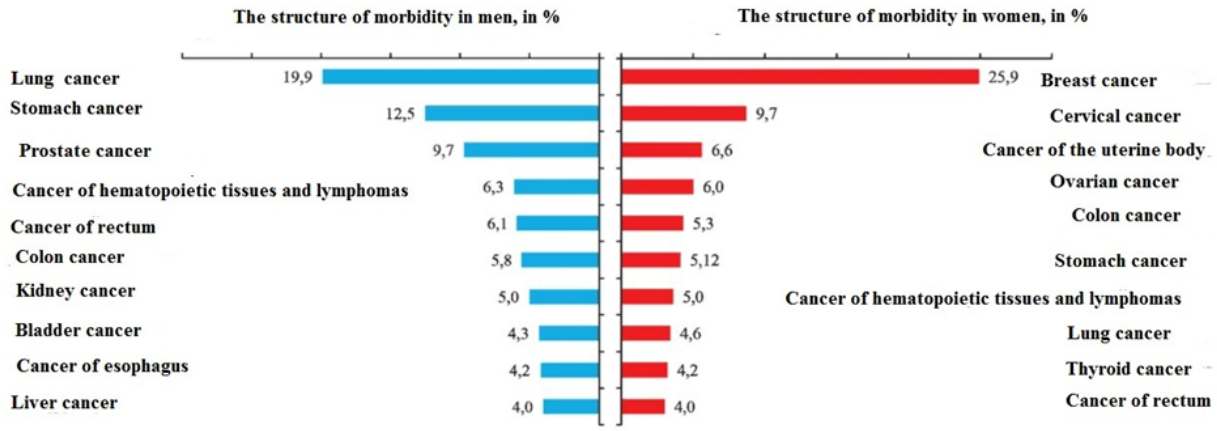

Figure 1. Structure of oncopathological morbidity in the Republic of Kazakhstan by sex in 2022.
(Taken from the report of the Kazakh Research Institute of Oncology and Radiology: "Indicators of the Oncology Service of the Republic of Kazakhstan for 2022" translated from Russian into English.)

Radioactive iodine I^{131} is the baseline drug in the therapy of patients with differentiated thyroid cancer (DTC). Nevertheless, 5% to 15% of differentiated thyroid cancer and 50% of metastatic DTC are not amenable to I^{131} treatment. Some patients suffer from recurrent disease after significant treatment. This kind of disease is often resistant to radioiodine and shows a poor response to Radioactive iodine therapy.

Although most of the patients with WDTC have no evidence of disease with appropriate early treatment, recurrence develops in 20-40% of patients. During tumor progression, Radioactive iodine therapy is the first line of treatment. However, up to 5% of thyroid cancer metastases may lose the ability to concentrate iodine and this is called radioiodine resistance disease (RRD); this phenomenon is responsible for a large number of thyroid cancer-related deaths [3].

The aim: To analyze publications devoted to the problems of radioiodine-resistant thyroid cancer and their clinicopathological and molecular-genetic characteristics.

Search strategy. The literature search was performed in the electronic databases PubMed, WoS, Scopus, Google Scholar over the past 5 years: from 2018 to 2023. Several sources do not fall into the specified depth, but were accepted for analysis because they contain conceptual information. *Inclusion criteria* were systematic reviews, original articles, literature reviews of peer-reviewed publications. *Exclusion criteria* were articles of poor methodological quality, duplication, missing or incomplete data in articles, case reports, letters, editorials, and expert opinions. From the remaining articles, a plan was formed to write a literature review according to the following sequence: «Radioactive iodine therapy», «The problem of occurrence of radioiodine-resistant well-differentiated thyroid cancer», «Clinicopathological characteristics of radioiodine-resistant thyroid cancer», «Molecular genetic alterations in radioiodine-resistant thyroid cancer». The search was performed by keywords like "well-differentiated thyroid cancer," "Radioactive iodine therapy," " radioiodine resistance," "BRAF V600E," "TERT," and "NRAS." According to the topic, depth of research and keywords, 135 articles were found, of which 88 were selected for review. The source selection algorithm is presented in Figure 2.

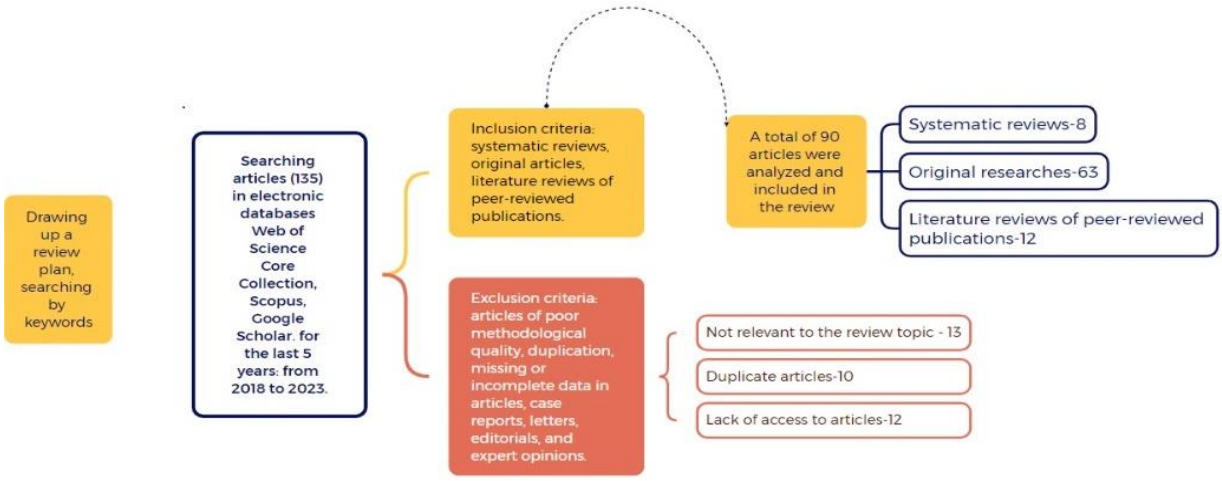

Figure 2. Article selection algorithm.

Results of the study.

Radioactive iodine therapy.

Treatment with radioiodine therapy is based on the selective accumulation of radioactive iodine I131 in thyroid cells or tumor tissue of differentiated thyroid cancer. Radioactive iodine has a damaging effect on β-particles resulting from the decay of I131 [8,13]. In order to monitor the localization of the isotope within the body, whole-body

planar scintigraphy or single photon emission computed tomography uses y-rays [10]. The radiopharmaceutical used for RAI is an isotonic solution of Na I^{131}, pH about 6-7, or as capsules with Na I^{131} lyophilisate. I^{131} almost 100% is resorbed from the gastrointestinal tract, thyroid tissue is capable of accumulating up to 80% of orally administrated activity, depending on its functional state [49]. Iodine, in the form of various compound forms, can penetrate through the intestine into the bloodstream, ultimately being transported to the thyroid tissue via the blood current [5]. Radioiodine therapy is made possible by the selective uptake of iodine by thyroid cells, resulting in a concentration of I^{131} in the thyroid gland that is significantly higher than in the blood [86]. This selective uptake is facilitated by the sodium iodide symporter. It is a membrane glycoprotein that actively transports I131 from the blood into the follicular epithelium of the thyroid gland [5,37].

Radioiodine therapy allows you to destroy the remnants of thyroid tissue and possible areas of residual tumor that accumulate radioiodine. This treatment has a positive effect on metastases of differentiated thyroid cancer. The use of specialized treatment reduces the risk of relapse and improves long-term results of therapy [6,42].

Radioiodine ablation is a postoperative course aimed at destroying residual thyroid tissue. Use as adjuvant therapy makes it possible to identify distant metastatic foci in the early stages [10].

Recommendations for the use of radioiodine therapy are based on an assessment of the postoperative risk of relapse and persistence of the disease. Also, according to these recommendations, patients can be constantly monitored [32,87]. For this, oncologists are based on the recommendations of various world societies. Recommendations provided by the European Society of Medical Oncology (ESMO; 2019), National Comprehensive Cancer Network (NCCN; 2022), Society of Nuclear Medicine and Molecular Imaging/European Association of Nuclear Medicine (SNMMI/EANM; 2022). and Society of Nuclear Medicine and Molecular Imaging/European Association of Nuclear Medicine (SNMMI/EANM; 2022) [33].

It is important to note that there are several options for using radioactive iodine in the treatment of differentiated thyroid cancer. Radioiodine ablation and radioiodine therapy are used as treatment for residual disease. In addition, radioiodine therapy is used to destroy distant metastases and for persistent thyroid disease [27]. These treatment options differ in the amount of therapeutic activity of I131 [11].

Papillary thyroid cancer and follicular thyroid cancer are collectively characterized as differentiated thyroid cancer. These histological types of cancer account for more than 90% of all malignant neoplasms of the thyroid gland [31]. Most cases of thyroid cancer are successfully treated with thyroidectomy, selective radioiodine therapy, and thyroid hormone suppression therapy. When these types of treatments are used in combination, they help patients have a good prognosis for their disease in the future [8].

The incidence of distant metastases at diagnosis is known to be less than 5% in thyroid cancer. Relapses account for approximately 15% of cases during the course of the disease. It should be noted that relapses or metastases can lead to death from thyroid cancer [68]. In these cases, radioactive iodine I^{131} (RAI) is the standard initial therapy for recurrent or metastatic thyroid cancer. Patients treated with radioiodine therapy and whose whole body scintigraphy was negative after therapy showed improved survival rates. The 10-year survival rate and quality of life of such patients reached 92%. However, for some patients, radioiodine therapy is not effective. It is expressed by a decrease in iodine absorption by thyroid cells. It should be noted that the 10-year survival rate in patients resistant to radioiodine therapy decreases to 10–29% [61].

The problem of radioiodine resistance in well-differentiated thyroid cancer.

Most patients with differentiated thyroid cancer (DTC) are successfully treated with surgery and radioactive iodine. However, some patients with thyroid cancer may experience less favorable treatment outcomes. In these situations, individual treatment approaches are used [46,11]. Postoperative radioactive iodine therapy is used to remove residual thyroid issue [5], eliminate suspected micrometastases or known advanced disease [75].

Radioiodine therapy is based on the expression of the sodium iodide symporter (NIS). This transmembrane protein is located on the plasma membrane of both normal and tumor epithelial cells of the thyroid gland. The NIS transports two sodium ions and one iodine ion into the cytosol. The iodide is then processed by iodine in the thyroid cells [34]. The above glycoprotein may affect the effectiveness of radioiodine treatment. Thus, the sodium iodide symporter may play a significant role in the development of radioiodine resistance. On the one hand, some patients experience remission after one or more courses of radioiodine therapy; on the other hand, other patients develop radioiodine resistance. This is because some patients may have multiple or macrometastases, along with less differentiated tumor status. In this situation, the disease may have a worse prognosis [77,23].

The process of dedifferentiation involves the reduction or disappearance of NIS expression. During the course, the direction of the transmembrane protein changes to the plasma membrane, where NIS functions optimally. This change leads to a decrease in the ability of thyroid cells to absorb iodine [16,19].

A long term study showed that the 10 and 15 year survival rates of patients without any radioiodine administration were much lower than those of patients receiving radioiodine. It should be taken into account that some patients develop radioiodine resistance even with the most appropriate administration of RAI [73]. This significantly worsens the prognosis: the life expectancy of patients with radioiodine refractory differentiated thyroid cancer is 2.5-3.5 years from the moment of diagnosis [43]. Although DTC is often curable by surgery, with or without radioiodine therapy, approximately two-thirds of patients with relapse or metastases develop radioiodine-resistant DTC, which usually has a poor prognosis [86] The most frequent forms of refractory thyroid cancer in RAI (RAIR-DTC) are PTC, followed by low-differentiated thyroid carcinoma [41]. Despite the fact that PTC has an indolent character and good prognosis in some patients with PTC (5–10%) develops aggressive metastatic disease and resistance

to radioiodine therapy [52]. There are some aggressive subtypes of thyroid cancer. These include tall cell, columnar cell, diffuse sclerosing and spinous nail variants. These variants were associated with higher rates of extrathyroidal spread, multifocality, nodal and distant metastases. Moreover, they are more likely to relapse and are resistant to radioiodine therapy [53,65,66].

Currently, the following criteria are generally used to define tumor radioiodine resistance [19,72]:

- Absence or a progressive decline in radioactive iodine uptake during a whole-body scan after treatment;
- Absence of radioiodine uptake in primary regional recurrence or distant metastases without radioiodine uptake during whole body scan after treatment;
- Structural tumor progression 12-16 months after radioactive iodine therapy despite the presence of iodine in the post-therapy scan;
- Presence of tumor in patients who have received radioiodine therapy with an activity of 600 millicuries (mCi)/22.2 gigabecquerel (GBq) or more, but without evidence of remission;
- Inconsistency between I131and 18F-FDG accumulation, i.e. there is a negative result on SPECT/CT with radioactive iodine, while a positive result on PET-CT with 18F-FDG.

The presence of the above criteria predicts the likelihood of a tumor being resistant to radioiodine therapy and should be used together for tumor risk stratification in resistance assessment [57]. However, today special attention is paid to the presence of driver mutations, such as pTERT, BRAF V600E, NRAS. These types of mutations demonstrate an aggressive genetic pattern. They can also be used in patient risk stratification to determine treatment tactics [10, 39].

Clinicopathological characteristics of radioiodine-resistant thyroid cancer.

The clinicopathological characteristics of thyroid cancer are based on the international histological classification of cancer, which is presented by the World Health Organization ang updated [12,13]. Until now, pathohistologists relied on the 2017 classifications when making a thyroid diagnosis [85,87]. Still, it should be emphasized that in 2022, the World Health Organization (WHO) released the latest updated fifth edition of the histological classification of thyroid neoplasms in 2022 [38].

The classification system divides thyroid cancer of follicular origin into four categories. The main histological variants are differentiated thyroid cancer, including predominantly papillary thyroid cancer and follicular thyroid cancer. There is also oncocytic cancer; high-grade carcinomas, including poorly differentiated thyroid cancer and anaplastic thyroid cancer [7].

Modern histological classification is developed on the basis of clinical histopathology and molecular pathogenesis. Most encapsulated or confined thyroid tumors with a predominant follicular growth pattern exhibit a RAS-like molecular profile [37]. Conversely, most thyroid tumors with BRAF V600E-like thyroid cancer and RAS-like thyroid cancer may acquire additional genetic alterations. Subsequently, these histological types can progress to high-grade malignant neoplasms [20].

Currently, histological examination of the tumor is an important predictor of prognosis. In cases where there are Hurthle cells and low-grade thyroid cancer, there is a higher likelihood of developing radioiodine resistance. It should also be noted that histological variants of tumor cells in patients with primary lesions and metastases may become less differentiated during treatment with I131 [47].

In addition, it has been discovered that the classic and follicular variants of papillary thyroid cancer are less aggressive histological subtypes. Conversely, high-cell variant of papillary thyroid cancer, sclerosing diffuse papillary thyroid cancer, hobnail variant, Hurthle cell variant papillary thyroid cancer, and poorly differentiated thyroid cancer are considered such as high-risk histological groups [47]. Therefore, it can be stated that histological subtypes of thyroid cancer are predictors in determining radioiodine resistance [18].

Oncocytic cell tumors are a unique category of thyroid tumors at the genetic and genomic levels. In clinical settings, oncocytic cell carcinomas tend not to absorb radioiodine and often spread to lymph nodes. They also have a higher likelihood of developing into anaplastic thyroid cancer compared to other thyroid cancer types, with some cases showing elevated overall mortality and morbidity rates [58].

Updated World Health Organization (WHO) classification provides a clearer comprehension of the cell origins, pathological characteristics (histopathology), molecular categorization and biological behavior of thyroid cancer [14,17].

Molecular and genetic alterations in radioiodresistant thyroid cancer.

To date, a number of main factors for the development of refractory thyroid cancer in RAI have been identified. These include the presence of mutations of the BRAF, PTEN, APC, DICER1, MNG, NRAS, KRAS, TERT family, etc. This can also include exposure to ionizing radiation, hereditary syndromes (Gardner), Cowden, multiple endocrine neoplasia types 2A and 2B, etc.) [47,76]. Mutations or rearrangements of certain genes as well as abnormal expression of molecules in certain signaling pathways are common causes of worsening of DTC.

Over the past few decades, significant progress has been made in understanding the molecular mechanisms causing the malignant evolution of DTC and the transition to resistance to RAI. Iodine can accumulate specifically in thyroid tissue under physiological conditions, which is attributed to sodium iodide symporter (NIS)-mediated iodine uptake localized in the basolateral cell membrane [82,25,84]. One of the hallmarks of dedifferentiation is impaired Na/I symporter (NIS) function [5,55,74]. RAI penetrates the cells through the NIS and emits beta particles that destroy the follicular cell [53].

Unfortunately, some patients experience an initial or gradual loss of iodine uptake and even a decrease in plasma membrane sodium iodide symporter expression. This process indicates a dedifferentiation status known as radioiodine-resistant differentiated thyroid cancer (RAIR-DTC) [67,46]. Radioiodine-resistant cancer cells arise from loss of thyroid differentiation, including iodine uptake and organization. This loss of differentiation is associated with the level of mitogen-activated protein kinase (MAPK) activation. High levels of

such activation are observed in tumors with BRAF (B-raf proto-oncogene) mutations or RAS mutations [48].

The MAPK signaling pathway is often constantly activated across various histological subtypes. The key proteins and major players in this pathway include RAS, RAF, MEK, and ERK, which participate in various cellular processes such as differentiation, proliferation, and apoptosis [59,40]. Thyroid cancer often becomes RAI-R by co-opting RAF and RAS signaling, thereby suppressing NIS and RAI uptake [71]. Genetic and epigenetic changes in the above signaling pathways due to acquired point mutations, chromosomal rearrangements, or aberrant gene mutations underlie decreased NIS signaling. In turn, they are a central factor in the refractoriness of RAI [54,80].

Gene alterations in DTC include point mutations, gene translocations, chimeric fusions, gene amplifications and deletions [50]. In addition, a comprehensive molecular analysis of the primary tumor under the guidance of histological analysis may help to better stratify patients to determine treatment tactics. Given the relationship between molecular and histological heterogeneity, tumor sampling for molecular analysis should be based on a thorough histological evaluation of the entire tumor [22,24].

The clinical significance of BRAFV600E is directly related to the fact that its presence unequivocally indicates the malignant nature of a thyroid neoplasm [1,69]. The BRAFV600E mutation in PTC is strictly specific, with an incidence of 40-70% [29,79]. Also, BRAFV600E correlates with a more aggressive phenotype and higher clinical tumor stage [70,56].

Rumyantsev P.O., Nikiforovich P.A. and co-authors [9] in their study indicated that BRAF V600E has prognostic value, increasing the probability of relapse of PTC. It is reported that the presence of BRAFV600E mutation is a prognostically unfavorable factor increasing the probability of tumor foci resistance to radioactive iodine therapy, which should be taken into account when choosing the tactics of patient management [62]. It should also be noted that in 2015 the clinical guidelines of the American Thyroid Association (ATA) described BRAFV600E and TERT mutations as unfavorable factors of clinical prognosis. Mutations of the TERT promoter are involved in the suppression of slc5a5 mRNA in RAIR-DTC. It is suggested that TERTmutations, reduce NIS protein expression and its location in cell membranes. The expression of slc5a5 mRNA has a greater association with DTC aggressiveness and prognostic features than NIS protein expression detected by immunohistochemical analysis [62].

Liu X., Qu S. et al. [45] conducted a study to detect the prevalence of TERT promoter mutation (C228T and C250T) and determined its association with BRAFV600E mutation. The authors examined postoperative paraffin blocks of thyroid tumors: of which 44 cases were benign tumors, 22 cases of classical follicular cancer and 408 cases of papillary cancer from five regions in China. The result showed that no TERT p mutation was found in any of the 44 benign tumors. C228 mutation was much more common than C250 T mutation in both PTC and FTC. The C228T mutation was found in 9.6% of cases (39 of 408) of PTCs and C250T was found in 1.7% (7 of 408) of PTC. Together, the two mutations were found in 11.3% (46 of 408) of PTC. In follicular thyroid cancer, C228T was found in 31.8% (7 of 22) and C250T in 4.6% (1 of 22) of samples, and together they were found in 36.4% (8 of 22) of PTC. The authors of this study concluded that, in general, TERT p. mutations were associated with aggressive clinicopathological characteristics of PTC [21]. Also, the results illustrated that the coexistence of BRAF and TERT mutations were associated with aggressive clinical and pathological behavior of PTC [42]. Molecular analyses provide useful information on the role of predicting the occurrence of radioiodine-resistant PTC [47].

Liu X, Bishop J. *et al.* [44] investigated the effects of BRAF V600E or TERT promoter mutations and their coexistence on the clinicopathological outcomes of PTC from 421 thyroid tissue samples: of these, 85 were benign opxcholes, 257 PTC, and 79 FTC. Two mutations were detected in 11 of 12 (91,7%) thyroid cancer cell lines. The C228T mutation was found in 0 of 85 (0,0%) benign thyroid tumors, in 30 of 257 (11,7%) PTC, in 9 of 79 (11,4%) FTC, in 3 of 8 (37,5%) PTC, and in 23 of 54 (42,6%.). The C250T mutation was absent in the PTC sample but was detected in two FTC cell lines, as well as two anaplastic thyroid cancer (ATC) cell lines. Both two TERT promoter mutations found to be exclusive of each other in both thyroid cancer cell lines and tumor samples. Altogether, they were identified in 11 of 79 (13.9%) FTC, 25 of 54 (46,3%) ATC and 7 of 7 (100%) ATC samples. The TERT promoter mutations was not observed in 16 MTC samples. In three cases, PTC and ATC were located in the same thyroid gland, and in each case both PTC and ATC contained the C228T mutation. In their study, the authors concluded that a large proportion of PTC samples positive for TERT promoter mutations contained the BRAF V600E mutation. This means that it is possible that BRAFV600E mutations, together with TERTp, are associated with greater aggressiveness of thyroid cancer. Possible mechanisms for the connection between genetic mutations and the development of radioiodine resistance were also discovered. However, it is worth noting that a connection between these two types of mutations could not be established [29].

The significance of BRAF, TERT p and RAS mutations as prognostic biomarkers has been evaluated in a number of studies [63]. BRAF mutations are associated with markers of clinical aggressiveness (larger tumors, older age, extra-thyroidal spread and LNM) and poor clinical outcome, although the latter association depends on additional clinicopathological features [70]. BRAF mutations are also associated with decreased expression of the sodium iodide symporter, a crucial determinant of response to radioiodine therapy [57]. Although few data are currently available on the clinical significance of TERT p mutations, current publications report an association between the presence of this mutation and clinically aggressive disease, including resistance to radioiodine [81]. Analysis of molecular markers including BRAFV600E and the p-TERT, C228T and C250T mutations have been proposed as reliable prognostic biomarkers and have been reported to be associated with aggressive clinical and pathological characteristics, making the study of these biomarkers a new area of cancer research [24].

However, the coexistence of TERT promoter mutation and BRAFV600E have a marked synergistic effect on the aggressiveness of PTC, including increased tumor

recurrence, high patient mortality and resistance to radioiodine therapy, while either mutation individually has been reported to show less significant effects. In adult patients (>55 years), the disease tends to progress more rapidly and the tumor behaves more aggressively than in younger individuals [89].

Huang M, Yan C. and co-authors [35] conducted a study in northwest China, where 483 patients were included. Of these, 435 (90.1%) patients with PTC had BRAF V600E mutation, 419 patients had BRAF V600E mutation alone and 16 patients had double mutations. Forty-eight patients had triple negative mutations. The authors concluded that the prevalence of the BRAF V600E mutation was higher in northwest China. The authors also note that the coexistence of the BRAF V600E and TERT p mutations was significantly correlated with lymph node metastases and multifocality. Patients with these mutations are more likely to have distant metastases and tumor relapses. The presence of a double mutation results in tumor spread beyond the thyroid gland and may result in disease-related death [35].

RAS mutation is a classical activator of the MAPK pathway and the photocatidylinositol-3-kinase (PI3K) pathway. RAS genes including NRAS, HRAS and KRAS are called proto-oncogenes. RAS mutation is closely associated with distant metastasis and other clinical adverse reactions of thyroid cancer. Among them, mutation in NRAS codon 61 is the most common, in addition to HRAS codon 61, KRAS codon 12/13, KRAS codon 61 and other mutations. RAS mutation has been found to coexist with BRAF mutation and RET/PTC rearrangement, especially in advanced stages of papillary TC, and it is an important factor for unfavourable prognosis [36].

Leila Shobab, Cristiane Gomes-Lima et al. retrospectively analyzed the data of patients with CRC followed up during 2013-2017 in two centers. Patients were considered refractory to radioiodine according to the American Thyroid Association guidelines. The control group was comparable in gender and age and had either regression or stabilization of disease (according to response evaluation criteria for solid tumors) at follow-up for at least three years after initial therapy. The molecular profiles of a subset of patients with radioiodine resistance were reviewed. Molecular profiling data in the radioiodine resistance subgroup showed that 50% of patients had mutations in the RAS/RAF pathway. The authors also noted that among patients with metastatic differentiated thyroid cancer, patients with radioiodine resistance had similar histopathological and clinical characteristics to patients with avid thyroid cancer. The risk of radioiodine refractoriness increases at age ≥46 years and decreases in Caucasian race [30].

Conclusion. Based on the analysis of publications, we can conclude that significant progress has been made over the past decades in understanding the molecular mechanisms that cause the malignant evolution of DTC and the development of radioiodine resistance. Given the relationship between molecular and histological heterogeneity, the selection of tumor samples for molecular genetic analysis should be based on the results of histological evaluation of the entire tumor. Comprehensive molecular genetic analysis, as well as histological characteristics of the tumor, will subsequently play an important role in stratifying patients and determining further patient management tactics.

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