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CLINICAL AND MORPHOLOGICAL FEATURES AND UNSOLVED ISSUES IN DIAGNOSIS OF AGGRESSIVE FORMS OF PAPILLARY THYROID CARCINOMA

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КЛИНИКО-МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ И НЕРАЗРЕШЕННЫЕ ПРОБЛЕМЫ ДИАГНОСТИКИ АГРЕССИВНЫХ ВАРИАНТОВ ПАПИЛЛЯРНОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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Differentiated thyroid cancer (DTC) is a disease with a favorable clinical course and high survival rate compared to other epithelial tumors. The majority of DTC (up to 85 %) is represented by various subtypes of papillary thyroid cancer (PTC). Aggressive forms of PTC characterized by early lymphogenous and hematogenous metastasis, low avidity to radioiodine therapy (RIT), low relapse-free survival rates and high mortality rate compared to other types of PTC occur among them. Preoperative diagnosis of PTC is based on the results of ultrasound (US) examination and fine-needle aspiration biopsy (FNA) with cytological examination of the as-

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pirate. At the same time, the capabilities of cytological examination in determining the histological type of PTC are limited and it does not allow to predict its aggressiveness and plan adequate treatment. Molecular genetic tests of the tumor cytological and morphological material are effective in prognosis of aggressiveness of PTC due to the determination of specific mutations in the BRAF, TERT, RAS genes and the quantitative expression of oncogenic and tumor suppressive microRNAs. Some of these indicators are already used in the morphological classification of tumors of the endocrine system.
At the same time, there are contradictory data concerning the connection of the molecular genetic portrait of PTC, the clinical manifestations of its aggressiveness (extrathyroidal invasion, early metastasis, and radioiodine resistance) and its pathomorphological structure. We tried to summarize and analyze the literature data regarding the diagnosis of aggressive variants of PTC.
Keywords. Aggressive variants, papillary thyroid carcinoma, molecular genetic test, microRNA, BRAF mutation.

Дифференцированный рак щитовидной железы (ДРЩЖ) является заболеванием, благоприятным по клиническому течению и выживаемости, в сравнении с другими опухолями человека. Большая часть ДРЩЖ (до 85 %) представлена различными вариантами папиллярного рака щитовидной железы (ПРЩЖ), среди них встречаются агрессивные формы ПРЩЖ, которые характеризуются ранним лимфогенным и гематогенным метастазированием, резистентностью к радиойодтерапии (РЙТ), а также низкими показателями безрецидивной выживаемости с высокими показателями летальности по сравнению с другими вариантами ПРЩЖ. Дооперационная диагностика ПРЩЖ основана на результатах ультразвукового исследования (УЗИ) и тонкоигольной аспирационной биопсии (ТАБ) с цитологическим исследованием аспирата. При этом возможности цитологического исследования в определении гистологического типа ПРЩЖ ограничены, что не позволяет спрогнозировать его агрессивность и адекватно планировать лечебную тактику. Одним из перспективных методов, показавших свою эффективность в прогнозировании агрессивности ПРЩЖ, является молекулярно-генетическое исследование клеточного материала опухоли с определением специфических мутаций в генах BRAF, TERT, RAS и количественная оценка онкогенных и онкосупрессорных микроРНК. Некоторые из этих показателей уже используются в морфологической классификации опухолей эндокринной системы. При этом в литературе имеются противоречивые данные о взаимосвязи молекулярно-генетического портрета ПРЩЖ с клиническими проявлениями его агрессивности (экстратиреоидный рост опухоли, раннее метастазирование и радиойодрезистентность) и его патоморфологической структурой. Проводится анализ литературных данных, касающихся диагностики агрессивных вариантов ПРЩЖ.
Ключевые слова. Агрессивные варианты, папиллярный рак щитовидной железы, молекулярно-генетическое исследование, микроРНК, мутация BRAF.

INTRODUCTION

This review used scientific publications from PubMed and eLibrary. Filters were used in the search procedure, namely, date of publication from 2013 to the present; keywords papillary thyroid cancer, aggressive variants, molecular genetic studies, microRNA, mRNA, papillary thyroid microcarcinoma, papillary thyroid carcinoma, hobnail variant, diffuse sclerosing variant, tall cell variant, columnar cell variant, solid variant, BRAF, RET, RET/PTC, KRAS, NRAS, HRAS, and TERT; search queries for diagnostics of aggressive variants of papillary thyroid cancer; molecular testing of thyroid nodules; and diagnosis and management of thyroid nodules.

Differentiated thyroid cancer (DTC) is a heterogeneous group of epithelial tumors with a favorable course and prognosis and high survival rates [1].

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer characterized by relatively low aggressiveness with a high 10-year disease-free survival rate [2]. Most PTC patients experience a slow course of the tumor process and most often treatment ends with recovery after surgery, even in the presence of metastatic lesions of the lymph nodes [3; 4]. Survival rates in DTC patients are high, which is associated with distant metastases in a small proportion of patients and local recurrence with invasive tumor growth. The proportion of patients exceeding the 10-year survival threshold remains at 85 % [4–6].

In patients with a confirmed cytological diagnosis of DTC, surgical treatment of the primary tumor is indicated to the extent determined by preoperative and intraoperative examination (hemithyroidectomy, thyroidectomy, cervical lymphadenectomy of levels 2–6). Radioactive iodine therapy (RIT) is prescribed after surgery based on postoperative stratification of the risk of tumor persistence and recurrence. If radioiodine refractoriness develops, targeted therapy is advised. Moreover, external beam radiation therapy is recommended as palliative treatment in patients with unresectable metastases and metastases that do not accumulate radioactive iodine [7].

Standard preoperative diagnostic methods, such as ultrasound (US) and fine-needle aspiration biopsy (FNAB) of thyroid nodules with cytological examination of the biopsy material, cannot determine the presence of an aggressive subtype of PTC in the patient examined. Cytological diagnostics has significant limitations and is inappropriate for stratifying the risk of malignancy and predicting whether a patient has an aggressive subtype of PTC [8–10]. Despite clear pathological criteria for diagnosing these tumors, there is currently no consensus among pathologists who can accurately determine the aggressiveness of a tumor based on its morphological features. Moreover, the use of immunohistochemical research methods (IHC) does not provide clear answers in diagnostics, as no specific immunohistochemical markers have been identified that would reliably classify the tumor as an aggressive subtype of PTC [11; 12].

The 5th edition of the classification of thyroid tumors, published by the World Health Organization (WHO) in 2022, describes 13 subtypes (variants) of PTC. Five of these variants are designated as aggressive: diffuse sclerosing variant (PTC DSV), tall cell variant (PTC TCV), hobnail variant (PTC HV), columnar-celled variant (PTC CSV), and solid variant (PTC SV). The special status of these tumors is due to more frequent lymphogenous and hematogenous metastasis, increased frequency of radioiodine resistance, high relapse rates, and low survival rates compared to other PTC subtypes [13–15]. Papillary thyroid microcarcinomas (tumors smaller than 1.0 cm) are no longer considered as histological subtypes of PTC. These tumors remain debatable, whether they are the least

aggressive clinically, and whether they require active surveillance or surgical intervention in a short time [16; 17]. The various variants of papillary cancer, related to tumors with aggressive and non-aggressive clinical course (oxyphilic cell, PTC DSV, and PTC SV), namely, their pathomorphological characteristics and data on the clinical course, remains unclear [18–21].

The polymorphism of thyroid tumors is caused by various molecular disorders at the cellular level, which are presently well studied. Despite the large number of studies on the genetic basis of the tumor process in PTC, several questions remain, and thus, studies on the influence of molecular genetic disorders on the tumor process and its development and course are of interest [22–26]. The aggressive course of PTC was associated with a mutation in the $BRAF^{V600E}$ gene; however, no association was found between the expression of the $BRAF^{V600E}$ gene and aggressive course of PTC [27–29]. After studying the molecular genetic composition of PTC, a set of markers was identified, consisting of oncogenic and tumor-suppressing microRNAs. These markers are linked with a specific type of thyroid malignancy, particularly papillary and medullary thyroid cancer (MTC) [30–34]. However, to date, specific markers that can be determined in patients with aggressive PTC (both in cytological and morphological material) have not been determined. Thus, identifying these indicators would help in diagnosing aggressive PTC variants, provide a personalized approach when choosing treatment methods, and reduce the incidence of relapses and adverse outcomes in these patients.

This review describes the problems related to diagnostics of aggressive variants of thyroid cancer and outlines the immediate prospects for improving preoperative diagnosis.

AGGRESSIVE PTC VARIANTS

Diffuse sclerosing variant. PTC DSV occurs in approximately 6 % of PTC cases and was first described in 1985 [2; 15; 19]. Tumor growth is characterized by diffuse proliferation of tissue without the formation of a delimited formation. In most cases, tumor growth is manifested by diffuse damage to one lobe or the entire thyroid gland without the formation of nodes [3; 18; 19]. Compared to the classic variant of PTC (cPTC), PTC DSV has features and is characterized by a more frequent development against Hashimoto's thyroiditis, a younger age of patients, and a more frequent occurrence in women [35]. The mean age of patients is 30 years, with a median of 28 years and a range of 6–78 years. The women-to-men ratio is 4.3:1 [15; 19].

Moreover, this PTC variant has often been detected after exposure to high levels of ionizing radiation. In a study, 10 % of PTC after an accident at a Chernobyl nuclear power plant were represented by PTC DSV. This variant is characterized by a higher risk of extrathyroidal invasion and distant metastasis compared to cPTC (72.2 % vs. 56.3 %,

7.3 % vs. 4.3 %, respectively, $p < 0.001$) [2; 15]. Despite this aggressive behavior, the overall survival rate of this variant is similar to that of the classic type and is about 93 %. Cancer relapse and mortality were registered in 14 % and 3 % of cases, respectively, whereas distant metastases were detected in approximately 5 % of cases [11; 13]. Survival rate with this variant is 6 % lower compared to cPTC. Good overall survival rates in this group of patients are associated with a more radical surgical intervention and radioiodine therapy.

PTC DSV exhibits more aggressive clinical and pathological behavior and has a higher incidence of vascular invasion, extrathyroidal extension, lymphatic invasion and lymph node and distant metastases. Therefore, PTC DSV patients have a higher probability of relapse and worse overall survival [15].

The main histological characteristic is diffuse damage to one or both lobes of the thyroid gland with severe fibrosis/sclerosis, pronounced multifocal lymphocytic infiltration, extensive lymphovascular invasion, a large number of psammoma bodies, and the presence of squamous metaplasia [3; 11; 19]. Cytological diagnostics of this variant can be difficult. The presence of squamous cell differentiation in cytological material can lead away from the diagnosis of PTC to anaplastic carcinoma with squamous cell signs. Furthermore, Hashimoto's thyroiditis is noted in 85 % of cases, which complicates differential diagnostics with benign processes in the thyroid gland [8; 11; 30]. The studied immunohistochemical characteristics in PTC DSV are characterized by p63 (28.6 % of cases), p53 (42.9 %), Galectin-3 (83.7 %), and antigen-epithelial membranes (EMA) (40.8 %) expressions [11; 15].

The molecular profile varies and is characterized by the presence of RET/PTC and RET/PTC3 translocation with the $BRAF^{V600E}$ mutation. Changes in the RET gene are determined in patients at an advanced stage of the disease, characterized by poor clinical outcome, and often detected at a younger age. Additionally, BRAF mutation has been noted in PTC DSV, but with a lower incidence than in classic PTC [29]. This can be due to the accumulation of mutations and increased expression of the BRAF gene with age [33]. Thus, PTC DSV has different histopathological and molecular genetic profiles compared to cPTC.

Tall cell variant. PTC TCV was described in 1976; however, the morphological changes characteristic of this PTC variant have been mentioned in the literature since 1948. This variant is diagnosed in 3 %–19 % of cases. WHO [2; 11; 13] defines PTC TCV as a tumor that contains "cells that are 2–3 times as tall as they are wide" and have abundant eosinophilic (oncocyte-like) cytoplasm. Since such morphological changes are often present in conventional papillary carcinomas, tall cells should constitute ≥30 % of all tumor cells for PTC TCV to be diagnosed. Some pathologists recommend indicating the tall cell focus in the histological report, regardless of the percentage.

This PTC variant occurs in women 2.9 times more often and in approximately 1 %–19 % of cases of all PTC tumors. Furthermore, PTC TCV tumors are commonly large [13; 15]. The average age of patients with PTC TCV is usually higher than that of cPTC patients and ranges from 41 to 66 years [15; 35; 36]. Among the features, the higher relapse rate and lower survival rate than with cPTC (22 % and 8 %; 79 and 93 %, respectively) are noteworthy. This may be because of the fact that this subtype is registered in older patients and has a larger tumor size, and therefore, extrathyroidal invasion is more often diagnosed. When analyzing survival and relapse rates, it was revealed that PTC TCV and cPTC have similar results when performing total thyroidectomy and radioiodine therapy [37]. Moreover, if the tumor contains even 10 % of the highly cellular component, it is associated with a poor clinical outcome. Factors associated with poor clinical prognosis were significantly more common in cPTC patients with focal tall cell changes in the tumor and in patients with PTC TCV diagnosed based on WHO diagnostic criteria. Additionally, according to some studies, only tumors with more than 50 % of the tall cell component have a more aggressive course [11; 14; 29].

The proportion of the tall cell component that is clinically relevant remains controversial. In addition, it is crucial to emphasize that there is significant subjectivity and lack of agreement in identifying PTC TCV among pathologists [11; 15; 37], and therefore, whether PTC TCV is one of the stages of development of the tumor process or a more aggressive variant of PTC remains unclear.

In addition to the histologic presentation abovementioned, PTC TCV has a parallel arrangement of cells lining papillary and elongated follicular structures in histologic sections and produces a tram-track sign that, at low magnification, resembles a trabecular architecture. Most PTC TCV tumors are not encapsulated, but encapsulated tumors are rare. Other histologic criteria include eosinophilic cytoplasm, clear cell boundaries, and well-defined nuclear features of PTC. Some studies have defined the cytological features of PTC TCV that differentiate it from cPTC. The tall cell variant is characterized by elongated cells with oncocytic cytoplasm with clear boundaries; multiple intranuclear inclusions, which make them soap-bubble-shaped, prominent nucleoli; and higher lymphocytic infiltration [8; 9; 11].

Regarding the molecular genetic features of the tumor, $BRAF^{V600E}$ mutations occur in 80 %–100 % of all PTC TCV cases. The incidence of BRAF mutations is higher when the tumor contains more than 50 % of the tall cell component. Further, there is a secondary mutation (usually in the TERT promoter gene) and possible RET/PTC and RET/PTC3 translocation, which is two times more common compared to cPTC [28; 31–32; 38]. This variant of PTC is also characterized by miR-21 expression [39].

Columnar-celled variant. PTC CSV is a rare DTC subtype, which accounts for 0.15 %–0.2 % of all PTC [15; 35]. A characteristic clinical sign of this variant is the rapid rate of tumor growth associated with extrathyroidal invasion and early development of lymphogenous metastasis and a high relapse rate [40]. This aggressive variant may not respond to $_{131}$I RIT [42]. The WHO classification described PTC CSV as "a typically multicellular neoplasm with papillary or glandular spaces lined with pseudostratified epithelium, with the presence of vacuolization or even cytoplasm without inclusions in the cells" [13; 14]. The immunohistochemical presentation in this variant has been relatively well-studied. This variant has increased mitotic activity and the Ki67 index is ≥20 %; indicators such as TTF1, thyroglobulin, cyclin D1, bcl-2, and membrane β-catenin are positive, and the expression of estrogen and progesterone is increased, regardless of the patient's gender, and may also be CDX2 positive (up to 55 % of cases) [8; 11; 15; 41]. PTC CSV often presents as a nodular formation or as a massive nonmoving tumor. Examination often reveals a tumor formation in the neck without any clinical manifestations [35; 42]. The average age of patients ranges from 34 to 49 years.

When diagnosing PTC CSV, extrathyroidal tumor spread and lymphogenous and hematogenous metastasis are commonly detected, and lower overall survival rate is registered compared to cPTC. The average survival rate is lower, and the mortality rate is eight times higher compared to cPTC. In some studies, tumors of patients of this subtype were classified into encapsulated minimally invasive and extensively invasive. Encapsulated tumors were identified predominantly in young women, and extensively invasive tumors were determined in older patients with an almost equal sex ratio. Encapsulated tumors were less aggressive, whereas extensively invasive tumors had poor outcomes. Literature data show that the columnar-celled variant, in the presence of a capsule and absence of extrathyroidal invasion, has results similar to cPTC [43]. In this regard, for risk stratification and choice of treatment approach, it is crucial to identify these morphological structure features of the tumor.

The histological characteristics of PTC CSV are determined by the presence of a significant number of columnar cells with pseudostratified nuclei. Nuclear changes, such as pseudoinclusions and grooves, characteristic of cPTC tumor cells, are not as well-developed in PTC TCV. The morphological presentation of PTC CSV can mimic adenocarcinoma of the gastrointestinal tract and endometrium. There is currently no consensus on the percentage of columnar cells required to make a diagnosis. However, according to various authors, it ranges from 30 % to 80 % [10; 11; 15; 28].

There are several cytomorphological features common to all PTC CSV tumors, namely, high cellularity, the presence of papillary structures, medium to large cell size, single cells, and pseudostratified nuclei

(nuclei condensation). Other characteristics noted in >50 % of cases include the presence of colloid, elongated cells, dark or densely packed chromatin, absence or presence of mild nuclear atypia, inconspicuous nucleoli, and absence of intranuclear inclusions. Based on these data, cytological signs that may be diagnostic have been identified, namely, the presence of a hypercellular smear consisting of papillary structures and scattered single cells without necrosis; presence of crowded cells and pseudostratified nuclei with dark chromatin without atypia, nucleoli, and mitosis; rare/absent nuclear pseudoinclusions, and predominantly rare/absent nuclear grooves [8; 9].

Using IHC, these tumors show variable expression of thyroglobulin but consistent TTF1 expression [41].

In the differential diagnostics of TCV and PTC CSV, the latter is characterized by the absence of light eosinophilic cytoplasm and thin cell boundaries and intranuclear pseudoinclusions and nuclear grooves [15; 41]. Encapsulated PTC CSV should be differentiated from the cribriform-morular variant of DTC, as the latter is associated with the presence of familial adenomatous polyposis. The columnar-celled variant usually lacks the flat morulae typical of the cribriform-morular variant and does not show nuclear expression of β-catenin [14; 15].

The incidence of $BRAF^{V600E}$ gene mutation in patients with PTC CSV is 33 %. The molecular genetic structure of this tumor variant has not been sufficiently studied owing to its rare occurrence and small number of studies [2; 15; 44].

Solid (solid-trabecular) variant. Described in 1985, PTC SV represents 3 % of all PTC tumors [2; 11]. This variant was initially associated with young age, RET/PTC3 translocation, and radiation exposure. However, because of its low specificity, exposure to ionizing radiation cannot be considered a defining diagnostic criterion [15; 22].

PTC SV is associated with a higher risk of metastasis and a worse prognosis than cPTC [13; 18] and is characterized by areas of solid and/or trabecular growth [11; 12; 14]. However, the term "solid variant" should only be used when all or almost all of the tumor has a solid, trabecular, or nidulant (insular) appearance. This tumor variant is often differentiated from follicular cancer, which has a solid component [21] and poorly differentiated thyroid carcinoma (PDTC). One-third of patients have vascular invasion and extrathyroidal invasion [4; 47]. Treatment outcomes and mortality and risk of relapse rates in patients with PTC SV are comparable to those in cPTC patients. These data and the rare occurrence and insufficient knowledge of this subtype indicate uncertainty about the aggressiveness of this variant.

A problem when trying to diagnose PTC SV is the lack of consensus among pathologists regarding what percentage with a solid component of the tumor as a diagnostic criterion is critical to diagnose PTC SV [11; 12; 15]. It is crucial to differ-

entiate PTC SV from PDTC, because the latter has a much lower survival rate. Although they share a common growth pattern, the solid variant is characterized by morphological changes in cell nuclei characteristic of cPTC and lacks the high mitotic activity and signs of tumor necrosis characteristic of PDTC.

In this PTC variant, RET/PTC3 translocation is usually noted. Moreover, a new BRAF mutation has been identified, namely, a triplet deletion leading to the replacement of valine and lysine with glutamate ($BRAF^{V600E}$+K601) [15; 27].

Hobnail variant. PTC HV was described as a moderately differentiated variant of PTC with aggressive behavior and higher mortality rates compared to cPTC. Further, PTC with such a morphological structure is associated with an increased risk of relapse of thyroid cancer [2; 15; 45]. This variant is characterized by cells with apically located tumor nuclei protruding above the epithelial surface, a micropapillary growth pattern, and a high nuclear/cytoplasmic ratio. According to the WHO classification of endocrine tumors, for a tumor to be classified as "hobnail" type, cells with the appropriate morphological structure should make up at least 30 % of the tumor [8; 11; 12]. According to several studies, the average age of patients with this variant is 57 years. The disease is typically manifested by a space-occupying lesion in the neck and enlargement of the cervical lymph nodes [6; 15]. Vascular invasion was detected in 70.8 % of cases, extrathyroidal spread in 58.3 %, and metastases to the lymph nodes in up to 75 % [15; 28; 45]. Additionally, Hobnail-type cells are noted in PDTC, which may be a sign of evolutionary transformation of cPTC into a tumor with more malignant potential. PTC HV is associated with more aggressive behavior and refractoriness to radioiodine therapy, rapid disease progression, and a higher mortality rate compared to classic PTC [15; 35]. PTC HV responded to therapy with $_{131}$I radioactive iodine in 33.3 % of cases.

The presence of cells with a high nuclear/cytoplasmic ratio and apical nuclei, sometimes with grooves that form a bulge on the surface, explains the term "hobnail" and is a pathological criterion for establishing the diagnosis. Hobnail cells can vary in size and shape, from small lymphocyte-like cells to larger cuboidal cells and tall/columnar cells. This is associated with loss of cell polarity and indicates epithelial–mesenchymal transformation as a possible mechanism of metastasis [9; 11; 45].

When using IHC, PTC HV actively expresses thyroglobulin, TTF1, and EMA. Overexpression of p53 protein was noted in 77 % of cases. Moreover, PTC HV contains cytokeratin 7, cytokeratin 19, and HBME-1, and the average index of proliferative activity Ki67 is approximately 10 %, which indicates a high rate of mitosis [2; 46]. Classic PTC may have hobnail-type cells in a significant portion of the tumor and remain slowly progressive. However, these cells differ from PTC HV in the absence of other aggressive histological signs, such as high

mitotic rates and extrathyroidal invasion. Thus, the aggressiveness of this variant and whether it is caused by a high rate of mitosis and the presence of widespread invasion or the presence of typical hobnail-type cells remains unclear [12; 14; 15].

The PTC HV molecular genetic structure is characterized by a mutation in the BRAF gene in approximately 57.1 % of cases. In a molecular genetic study, 80 % of tumors are positive for $BRAF^{V600E}$ mutation, whereas 20 % are associated with the RET/PTC1 mutation [13; 15; 30]. Furthermore, the most common genetic changes in these tumors are found to be BRAF and TP53 mutations (72.2 % and 55.6 %, respectively), followed in frequency by hTERT (44.4 %), PIK3CA (27.8 %), CTNNB1 (16.7 %), EGFR (11.1 %), AKT1 (5.5 %), and NOTCH1 (5.5 %). The structure of mutations remains unchanged in the primary tumor and metastases [32; 40; 46].

Treatment

According to clinical guidelines for DTC treatment, the treatment of all histological PTC variants is standardized and includes hemithyroidectomy for single solitary tumors T1-T2 and total thyroidectomy with cervical lymph node dissection for confirmed metastatic lesions of the cervical lymph nodes or prophylactic central lymph node dissection for tumors T3 and T4. If the patient is in a moderate or high-risk group or a low-risk group with an uncertain tumor status, radioiodine therapy is indicated [7].

PTC DSV, which is more common in children and young patients, is prone to increased $_{131}I$ accumulation, and even patients with distant metastases have a good prognosis. In contrast, other variants, which mainly affect elderly patients and have signs of extrathyroidal invasion and a high rate of local recurrence, are refractory to RIT and have a poor prognosis [15; 35].

In PTC TCV, approximately 20 % of these tumors should be considered refractory to radioiodine therapy. There is evidence that the morphological features of PTC TCV indicate a higher incidence of extrathyroidal invasion and distant metastases, which correlates with an increased frequency of relapses and a worse prognosis of PTC TCV compared with cPTC. Thus, more radical treatment is recommended, especially in the early stages of the disease. Moreover, 20 % of PTC TCV cases are represented by tumors with extensive extrathyroidal extension into adjacent fibroadipose tissue and/or skeletal muscle. However, with all the known data, there is no consensus regarding the volume of surgical intervention for PTC TCV, which is considered optimal as regards surgical aggression and radical according to oncological principles. This also concerns patients whose tall cell component does not reach the diagnostic threshold during histological examination [2; 15; 48].

Regarding PTC CSV, it is crucial to identify encapsulated cases as they have a better outcome. In relation to PTC SV, some authors recommend that treatment should

be more radical with active postoperative follow-up, because this tumor type has a higher rate of vascular invasion and relapse than cPTC [47].

Based on the literature and biological behavior of all PTC variants abovementioned, higher stage tumors with extensive extrathyroidal invasion or lymphatic and/or distant metastases are characterized by greater aggressiveness and worse outcome. However, the decision on the extent of thyroid resection is based on the tumor size at the time of admission, and not on the histological PTC type [26; 31; 34; 49].

RESULTS AND DISCUSSION

Classic PTC is characterized by a slow clinical course with a 10-year survival rate of > 93 %–95 % [2]. Contemporary views place aggressive PTC variants on a spectrum between low-grade PTC and PDTC/anaplastic thyroid carcinoma. The aggressive clinical course of these tumors is usually associated with large tumor sizes that have extrathyroidal invasion or lymphogenous or distant metastases. Such aggressive behavior often occurs in the absence of extrathyroidal tumor invasion and in the small tumor node located within the thyroid tissue. The rarity of these tumors and poor understanding of their biology and molecular genetic structure can lead to inadequate treatment, even when standard protocols are followed. The determining markers of aggressiveness at the stage of preoperative diagnostics of these tumors will help provide a differentiated choice of treatment approach and improve the prognosis for these patients.

The diagnosis of aggressive PTC can be confirmed using FNAB in extremely rare cases. However, these cytological reports should be interpreted with caution, as the FNAB sample may not be representative of the entire lesion because the diagnostic criteria for some variants should reach certain threshold values of the percentage of tumor morphological structure [8]. In almost all cases, aggressive PTC variants are diagnosed after surgery. Therefore, pathologists and surgeons should be aware of the effects of these variants on risk stratification of PTC patients.

Certainly, each of these aggressive PTC variants has a worse outcome than classic PTC. The prognostic value of these variants when stratified by stage or other aggressive histological features, such as mitotic rate and degree of invasion, should be clarified. This has been elucidated for the rarest aggressive variant – PTC CSV. The encapsulated form of PTC CSV is characterized by an indolent course, whereas the widely invasive form is very aggressive [15; 43]. Thus, it is encapsulation, and not the presence of columnar cells, that is a feature of PTC CSV that determines the treatment outcome and prognosis for this tumor variant. Unfortunately, there is no clear approach to the treatment of other aggressive variants, especially PTC TCV. However, there is evidence that in the absence of invasive signs, TCV, CSV, and PTC DSV have overall survival

rates similar to that of cPTC, and some studies have shown that the presence of tall cells does not worsen prognosis [47].

Given this uncertainty regarding the aggressiveness of PTC variants, it is critical to consider validated prognostic features such as tumor size, extent of extrathyroidal invasion, and presence of vascular invasion when deciding on the extent of surgery or the need for adjuvant radioiodine therapy. Unfortunately, recently there are frequent situations when extrathyroidal invasion is detected microscopically based on the results of postoperative histological examination. These results do not comply with the fundamental oncological principles of complete excision of the tumor with no growth at the resection margin, which should remain the gold standard for surgical treatment of thyroid cancer.

Thanks to the study of the molecular genetic structure of DTC, new opportunities appear in the early diagnostics of aggressive PTC variants [25–27], which will personalize the approach to treating patients at the preoperative stage and will reduce the risk of relapse and reduced survival rate.

Identification of new molecular markers will improve preoperative diagnostics and develop new treatment algorithms to determine the extent of surgical intervention that will be radical and provide a sufficient level of quality of life for PTC patients. To date, a small number of trials focused on studying this problem [24; 29–32]; however, the results of these studies in the future may improve the prognostic accuracy of diagnostics and the detection of aggressive PTC variants.

Conclusions

Diagnosing aggressive PTC variants is challenging for both clinicians and experts in related specialties (cytologists and pathologists). The problems of diagnosing this spectrum of tumors remain relevant, because when treating these tumors, the result and prognosis are worse than with the classic variant of PTC. Unfortunately, even with pathomorphological examination, we are faced with challenges in determining the criteria for aggressiveness in these tumors, which poses a number of questions for specialists. The molecular genetic structure of DTC is based on determining the presence of mutations in the BRAF, TERT, and RAS genes. The presence of these mutations underlies the modern classification of thyroid tumors. The ambiguous results of studies comparing the presence of these mutations and aggressiveness of thyroid tumors do not allow them to be accepted as a diagnostic criterion for the aggressiveness of a PTC. Diagnostics uses methods for determining the level of micoRNA expression, which enable the diagnosis of PTC and MTC and are highly specific and accurate. Moreover, markers characteristic of aggressive PTC variants have not been sufficiently studied, and their presence requires clarification.

Thus, the volume of required surgical treatment and radioiodine therapy in PTC

patients should be determined individually, considering all the data, using molecular genetic diagnostic methods if possible.

According to clinical guidelines for DTC treatment, at present, the preoperative diagnostics of thyroid tumors does not include molecular genetic testing of cytological material. In the future, to improve preoperative diagnostics and determine the treatment approach, the use of molecular genetic panels to identify mutations associated with the development of DTC should be investigated. Accumulated evidence suggests the presence of mutations and increased expression of several microRNAs characteristic of PTC tumors. Existing data on molecular genetic test systems do not provide information on markers of aggressive subtypes of PTC. Research in this direction may provide new opportunities for targeted treatment methods for aggressive PTC variants. Moreover, this will help improve the preoperative diagnostics of aggressive PTC variants, the results of which will allow individual planning and improvement of treatment outcomes for PTC patients.

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