Molecular genetic markers of highly differentiated thyroid cancer (literature review and personal observations)

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Thyroid cancer (TC) is the most common malignant disease among endocrine tumours, and it ranks 5th among neoplasms in women [1]. Highly differentiated thyroid cancer is the most common in the population. Papillary carcinomas account for 80% of all malignant thyroid tumours, follicular carcinomas – 10%. The incidence of Grtše’s carcinoma as a type of follicular carcinoma ranges from 2 to 3% [2]. In about half of patients, thyroid cancer is diagnosed incidentally by imaging methods, in particular, neck ultrasound, and in most of these patients it is predominantly small papillary thyroid cancer [3].

Fine-needle aspiration biopsy (FNAB) is the diagnostic test of choice for distinguishing between benign and malignant thyroid nodules. The Bethesda system, which is actively used in practice by clinicians, is a highly effective and reliable classification scheme. It includes six categories: I – uninformative examination; II – benign neoplasm; III – atypia/follicular lesion of uncertain significance; IV – follicular neoplasm/suspected follicular neoplasm; V – suspected malignancy; VI – malignant neoplasm [4].

In 70% of observations, this system helps to distinguish between benign and malignant thyroid neoplasms. However, 30% of thyroid nodules remain in the so-called grey cytological zone, when cytomorphological diagnosis of malignancy is difficult [5]. Indeterminate cytology includes two different categories: Bethesda III and Bethesda IV. According to follow-up data, cancer risk rates in these categories range from 6 to 48% for Bethesda III and from 14 to 34% for Bethesda IV [6]. Such a wide range of cancer risk rates implies that diagnostic hemithyroidectomy is still performed to distinguish between benign and malignant nodules.

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The issues of the “grey cytological zone”, the choice of the scope of surgery for small thyroid carcinomas, early diagnosis of radioiodine resistance and the choice of treatment for common metastatic forms of highly differentiated thyroid cancer remain unresolved. It is expected that the study and implementation of molecular genetic carcinogenesis mechanisms into clinical practice will help to solve many issues of diagnosis and treatment of thyroid cancer.
The BRAF gene encodes a protein of the RAF family of serine–threonine protein kinases, which are central mediators of MAPK [10]. The RAS family genes (HRAS, KRAS and NRAS) encode highly homologous G–proteins located on the inner surface of the cell membrane and are involved in signal transduction from growth factor receptors, activating both MAPK and PI3K/AKT/mTOR signalling pathways [11].

Thus, changes in the activity of the BRAF, RAS, and RET genes can lead to constitutive transduction of signals that activate cell proliferation and inhibit cell death. Mutations in these genes are the most common tumour–initiating event, occurring in more than 70% of patients with papillary thyroid carcinomas and are associated with specific clinical, histopathological and biological characteristics of tumours [12].

More rarely, thyroid carcinogenesis is associated with deregulation of the PI3K/AKT signalling pathway as a result of activated mutations of the PIK3CA and AKT1 genes or mutation of the negative regulator of the PI3K/AKT signalling pathway PTEN, which leads to loss of its function. Activation of PI3K/AKT is critical for the initiation of follicular thyroid cancer and can be triggered by activation of mutations in RAS,
PIK3CA and AKT1, as well as inactivation of PTEN, which negatively regulates this pathway [13].

The pathogenesis of thyroid cancer may also be associated with other signalling pathways. Mutations in the CTNNB1 gene, which encodes β–catenin and is involved in cell adhesion and regulation of the Wnt signalling pathway, have been described [14].

Mutations that cause loss of activity of the tumour suppressor gene TP53, which plays a key role in cell cycle regulation, or, conversely, increased activity of the telomerase gene TERT, are particularly important in the process of malignant transformation [15].

The molecular genetic structure of the causes of thyroid cancer includes the following components: mutations (point mutations, chromosomal rearrangements and changes in the number of gene repeats), patterns of aberrant DNA methylation and aberrant microRNA expression [16].

The progression and dedifferentiation of thyroid cancer to low–grade carcinoma and anaplastic thyroid cancer involves a number of additional mutations affecting other cell signalling pathways, such as p53 and Wnt/β–catenin. More recently, TERT promoter mutations have been described in all histological types of thyroid carcinomas, with a much higher prevalence in aggressive and undifferentiated tumours, indicating their role in cancer progression [17].

Morphological forms of benign and malignant thyroid tumours are extremely diverse and have many subtypes. Recent studies have shown the nature of genetic changes in different phenotypes of thyroid tumours (Table 1) [18–20].

The study of somatic genetic mutations in the clinic has become one of the most important areas in the study of thyroid carcinogenesis. Molecular testing to study somatic changes is an important addition to the diagnosis and treatment of many types of cancer, and is generally used in thyroid disease as a preoperative method to clarify the cancer risk of cytologically indeterminate thyroid nodules, in risk stratification and selection of a therapeutic programme [21, 22].

**BRAF**

According to a number of studies, the BRAF V600E mutation is the most commonly found in papillary thyroid cancer. It has been proven that for papillary thyroid carcinomas, the initial BRAF mutation status of tumours is the most important molecular marker reflecting the aggressiveness of biological behaviour and treatment prognosis [23].

The BRAF V600E mutation leads to destabilisation of the RAF kinase gene, which ultimately leads to activation of the MAP kinase pathway and increased mitotic and proliferative activity of the cell. In a study of histological material from patients operated on for thyroid cancer, the frequency of BRAF V600E mutation was 38 – 69% [24].

The presence of the BRAF V600E mutation correlates with aggressive tumour behaviour, high incidence of lymph node metastasis, extrathyroidal spread and loss of radioiodine avidity [24, 25].

It is known that the BRAF mutation is detected only in papillary and anaplastic carcinomas with a prevalence of up to 45% and that it is absent in tumour tissue in follicular, medullary carcinomas and benign thyroid lesions [25]. The frequency of BRAF gene mutation in papillary thyroid carcinomas varies widely, from 29 to 83% [23–25]. The results of several studies have shown the relationship of BRAF with histological variant, age, extrathyroidal tumour spread, disease stage and regional lymph node metastasis. It has been confirmed that the presence of BRAF is associated with the likelihood of thyroid cancer recurrence even in patients with the initial stage of the disease [26–28].

A meta–analysis of 1168 observations proved that BRAF mutation is associated with invasion of neighbouring organs

<table>
<thead>
<tr>
<th>Phenotypes of thyroid tumours and associated genetic changes</th>
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<tbody>
<tr>
<td><strong>Phenotype</strong></td>
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<tr>
<td>Toxic adenoma</td>
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<tr>
<td>Benign thyroid nodules</td>
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<tr>
<td>Non-invasive follicular tumour with papillary features</td>
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<tr>
<td>Infiltrative follicular variant of papillary thyroid carcinoma</td>
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<td>Papillary thyroid carcinoma</td>
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<tr>
<td>Columnar cell, high-grade variants of papillary thyroid carcinoma</td>
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<td>Diffuse sclerotic variant of papillary thyroid carcinoma</td>
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<td>Follicular carcinoma of the thyroid gland</td>
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<td>Gurtile cell carcinoma</td>
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<tr>
<td>Low-grade thyroid carcinoma</td>
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<tr>
<td>Anaplastic thyroid cancer</td>
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<tr>
<td>Medullary thyroid cancer</td>
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</table>
The BRAF V600E mutation is the only independent prognostic factor for metastasis to the central neck tissue in papillary thyroid cancer [30].

Also, BRAF mutation is an independent predictor of occult papillary carcinomas in the other lobe of the thyroid [31] and a marker of increased likelihood of tumour recurrence even in stages I and II of the disease [30, 31].

The results of a study showing that BRAF mutation plays a role as an unfavourable prognostic factor can be considered as arguments in favour of the fact that BRAF mutation is often detected in metastatic lymph nodes. Of particular interest is the detection of a BRAF mutation in lymph nodes when it is not present in the primary tumour. This may serve as a sign of tumour dedifferentiation due to this genetic defect and be a marker of poor prognosis [32].

It is most important for the surgeon to properly stratify the strategy before starting treatment, especially for small thyroid carcinomas. In recent years, the BRAF V600E mutation has become a promising prognostic factor in assessing the risk of papillary thyroid cancer [23]. It is probably the only molecular marker available before surgery that plays a role as a risk factor [29]. The detection of BRAF mutation with the assessment of preoperative staging allows to divide small papillary carcinomas into "low" and "high" risk tumours before treatment. Many authors have noted that the absence of BRAF mutation in small papillary carcinomas simplifies further follow-up of patients: for example, prophylactic neck dissection, unnecessary postoperative radioiodine therapy, or even unilateral hemithyroidectomy can be avoided [23, 25, 29].

Personalisation of surgical strategies should be based on a combined assessment of clinical and molecular markers such as multifocality, capsular invasion, lymph node involvement and BRAF status [28].

Tumour multifocality is a factor justifying thyroidectomy. Recently, it has been shown that there is no clear evidence that the BRAF V600E mutation is associated with a higher tumour multifocality score, and it is impossible to predict intrathyroidal dissemination in the presence of a positive BRAF status [33].

The involvement of the neck lymph nodes is a sign that significantly affects the recurrence rate. It has been more clearly established that BRAF mutation tends to be associated with a higher incidence of lymph node metastasis, which is often resistant to radioactive iodine [34].

A positive BRAF status justifies the need for routine lymphadenectomy of the central neck even in the presence of small carcinomas without signs of enlarged nodes at the preoperative imaging stage.

Capsular invasion is the most significant parameter affecting recurrence and mortality rates. This parameter showed the highest correlation with the BRAF mutation, which was positive both in small carcinomas of the pT1 category with capsular invasion and in larger tumours of the pT3 category [35].

However, there is an opposite opinion, namely that there is no association of BRAF mutation with aggressive course and unfavourable prognosis. The recurrence rate in patients with BRAF–positive tumours did not exceed the corresponding rate in patients with BRAF–negative tumours [36].

In the Taiwanese population, a high frequency of BRAF mutation was noted, but it was not associated with unfavourable clinical and pathological types, which denies the possibility of using BRAF mutations as a potential prognostic factor [37].

RET/PTC

The RET/PTC rearrangement indicates the presence of papillary thyroid carcinoma, which is important in the case of an indeterminate cytology [38]. The correlation between RET/PTC rearrangement and prognosis in papillary thyroid carcinoma requires further clarification. It has been suggested that RET/PTC1 is associated with favourable biological behaviour of papillary carcinoma [39].

In contrast to BRAF and RAS mutations, RET/PTC1 rearrangements are associated with a very low probability of dedifferentiation of papillary carcinomas. RET/PTC3 rearrangement, however, may indicate a greater propensity for dedifferentiation and more aggressive biological behaviour [40].

The proto–oncogene RET/PTC encodes a tyrosine kinase receptor that is not normally expressed in thyroid follicular cells (it is expressed in parafollicular C cells), but can be activated by chromosomal rearrangement–translocation of RET/PTC [41].

RET/PTC translocation has been associated with a younger age at diagnosis and a higher propensity for lymph node metastases [42]. RET/PTC1 is detected in 60–70% of cases and is associated with less aggressive tumours than RET/PTC3, which is associated with radiation–induced tumours [43]. However, patients with RET/PTC translocations are highly responsive to radioactive iodine [43].

TERTp

More recently, mutations in the human telomerase reverse transcriptase promoter gene (TERTp) have been found to be associated with advanced and aggressive thyroid cancer [44]. TERTp mutations, namely C228T and C250T, are detected in 5–25% of patients with papillary and 35% of patients with follicular thyroid cancer [45]. They may cause increased telomerase activity, which leads to aggressive papillary thyroid cancer [46].

Sequencing of the next generation of highly differentiated advanced thyroid carcinomas showed that the TERTp mutation is second only to the BRAF mutation in frequency, being detected in 61% of patients with papillary thyroid carcinomas and 71% of patients with advanced follicular thyroid carcinomas [47]. TERTp mutations are associated with poor prognosis, tumour invasion, and reduced survival [44, 47]. The simultaneous presence of TERTp and BRAF V600E mutations in a tumour dramatically increases the number of recurrences and mortality of patients [48].
RAS

RAS–like mutations include HRAS, NRAS, KRAS, PAX8/PPARγ genes. RAS mutations are a marker for tumours that are difficult to diagnose by cytology alone, namely follicular variant papillary carcinoma and follicular carcinoma. Moreover, RAS–positive follicular adenomas are likely to be precursors of RAS–positive follicular carcinomas and possibly follicular variants of papillary carcinomas [8]. The RAS mutation may be a predictor of dedifferentiation and aggressive behaviour of well–differentiated cancer. Thus, surgical removal of RAS–positive follicular adenomas may be justified [49].

According to the results of a number of studies, RAS mutations were mainly associated with cancer (74%) and follicular adenoma (26%), while BRAF or RET/PTC mutations were always associated with cancer [8, 50]. RAS mutations are most common in follicular thyroid cancer (66% in case of disease progression) [51].

The most common mutations in thyroid cancer are found in NRAS in both patients with papillary (6 – 20%) and follicular (40 – 50%) carcinoma [52]. NRAS mutations are targets of the PI3K/AKT signalling pathway. However, they are considered only as precursors; further mutations are required for carcinogenesis, especially in follicular carcinoma and follicular variant papillary thyroid cancer [53]. There is also evidence of a positive correlation between RAS mutations and distant metastatic disease and a reduced survival rate in highly differentiated carcinoma [49].

PAX8/PPARγ

Genetic mutations of PAX8/PPARγ are more common in young patients with small tumours with vascular invasion [54, 55]. A PAX8/PPARγ mutation is not a diagnostic sign of malignancy, but should prompt a thorough search for vascular or capsular invasion. It may be necessary to examine the entire capsule at several levels [56].

Molecular genetic markers in the practice of diagnosis and treatment of thyroid nodules and thyroid malignancies

At present, the molecular genetic structure of thyroid cancer is well understood and the main driver mutations have been identified [19]. However, their large number, diversity of types, and the absence of mutations that dominate in frequency have long prevented the diagnosis of thyroid cancer using molecular genetic methods. The introduction of high–throughput sequencing methods into clinical practice has made it possible to develop diagnostic systems that take into account most of the known mutations in thyroid cancer, which has significantly improved the accuracy of diagnosis and treatment efficacy [57].

In recent years, the molecular portrait of thyroid tumours has been widely used in clinical practice [58].

Firstly, it is a mutational screening of thyroid nodules with uncertain cytology to select treatment tactics, which reduces the number of diagnostic lobectomies.

Secondly, the scope of surgical treatment of patients with small papillary thyroid carcinomas is still under discussion. The use of a personalised individual approach in the treatment of small carcinomas became possible on the basis of preoperative study of the genetic heterogeneity of the tumour.

Thirdly, the molecular landscape of thyroid cancer is the basis for the implementation of targeted therapy. Targeted therapy drugs directly target one or more specific molecular pathways in cancer cells.

Genetic testing of cytologically indeterminate Bethesda III and Bethesda IV thyroid nodules

Molecular markers are a useful diagnostic tool, especially when dealing with cytologically indeterminate thyroid nodules. Over the past few years, significant progress has been made in the development of molecular markers for clinical use in TAPB samples, including gene mutation and classifier gene expression panels [59]. With the advent of next–generation sequencing technology, gene mutation panels can be expanded to simultaneously examine multiple genes and provide even more accurate diagnostic information [20].

The use of molecular genetic testing is justified in the case of uncertain cytological findings (diagnostic categories III, IV according to the Bethesda classification) and when it is expected that its results will affect the clinical management of the patient [4].

A negative prognostic value of genetic testing may influence clinical decision–making about treatment. Consideration may be given to not performing surgery on a cytologically indeterminate thyroid nodule with negative genetic testing results if an informed patient wishes to do so and it is clinically appropriate. Negative molecular testing results can reduce the risk of cancer by up to 5%, which is roughly equivalent to the corresponding rate for benign findings from FNAB [60].

It is important to understand that molecular testing complements, but does not replace, cytological assessment. Analysis of the results of ultrasound, cytological and genetic tests can help classify risk and determine the need for surgery. Molecular testing is not recommended for thyroid nodules with established benign or malignant cytological characteristics [61]. In addition, molecular testing is not appropriate if thyroidectomy is already planned for other indications, in case of large goiters, compression syndrome, and thyrotoxicosis.

Predictive genetic marker–based risk stratification and choice of treatment for thyroid cancer

Surgery is the main method of treatment for thyroid cancer. The choice of surgical volume for minimally invasive papillary carcinomas remains a controversial issue [62]. Surgical intervention can be performed as a lobectomy (hemithyroidectomy), when one lobe of the thyroid gland is removed, or as a thyroidectomy, when the entire thyroid gland is removed. After thyroidectomy, the next stage of treatment for highly differentiated thyroid cancer is radioactive iodine therapy.
BRAF status assessment in the treatment of papillary thyroid carcinomas has been most widely used in clinical practice. The conducted studies allowed clinicians in Italy (Professor Paolo Miccoli, Director of the University Centre for Endocrine Surgery, Pisa) to formulate a surgical strategy for assessing BRAF status in the treatment of papillary thyroid carcinomas (Figs. 2, 3) [63].

There are two options for the study of BRAF mutations: preoperative, when cytological samples of tumour specimens are examined, which may affect the choice of primary treatment, and postoperative, when histological specimens are examined, which is clinically relevant for determining indications for definitive thyroidectomy if resectional surgery is performed [63].

If the presence of BRAF mutations is known before surgery, more aggressive behaviour of the carcinoma should be assumed, which justifies more extensive treatment, including total thyroidectomy, prophylactic lymphadenectomy of the central neck compartment, followed by ablation with radioactive iodine. In the absence of BRAF mutations in the specimens of minimally invasive T1 carcinoma, hemithyroidectomy can be discussed [63].

The study of BRAF mutations in postoperative histological specimens will allow to objectify the further treatment programme. In the case of primary hemithyroidectomy and the presence of BRAF mutations, definitive thyroidectomy with radioactive iodine ablation is justified. In the absence of BRAF mutations in minimally invasive pT1 carcinomas, hemithyroidectomy can be considered sufficient and radioactive iodine therapy can be avoided without risk to the patient [63].

These data are confirmed by the studies of N. Paul Ohori [64] from the University of Pittsburgh, according to which patients with BRAF V600E mutation and most patients with...
If thyroidectomy is indicated, it is important to consider the role of molecular genetic testing. Molecular genetic testing complements cytological assessment, not replaces it; according to the Bethesda classification (strong recommendation, moderate–quality evidence).

**Indications for molecular genetic testing:** uncertain TAPP results (diagnostic categories III, IV according to the Bethesda classification); molecular genetic testing complements cytological assessment, not replaces it.

**Targeted therapy for aggressive or radioactive iodine–resistant forms of thyroid cancer**

The last few years have seen rapid progress in understanding the molecular mechanisms underlying thyroid carcinogenesis. The identification of key genes that contribute to the development and progression of the disease has enabled the introduction of new biological therapies [66]. Molecular genetic testing has made it possible to use a selective approach and new therapeutic strategies in the treatment of patients with different types of thyroid cancer, in particular, personalised targeted treatment of disseminated and radioiodine–resistant forms of thyroid carcinoma.

Thyroid cancer is characterised by molecular changes in genes responsible for cell proliferation, differentiation and apoptosis. Therefore, in recent years, the discovery of thyroid cancer–specific molecular targets has led to the development of a number of targeted drugs for the treatment of aggressive forms of thyroid cancer [67].

The drugs lenvatinib and sorafenib are tyrosine kinase inhibitors and have been successfully used to treat radioiodine–refractory metastatic differentiated thyroid cancer [68, 69].

There is evidence that pretreatment with mitogen–activated protein kinase inhibitors, such as trametinib and selumetinib, restores radioiodine avidity in previously radioiodine–refractory differentiated forms of thyroid cancer [70].

The drugs vandetanib and cabozantinib as tyrosine kinase inhibitors are approved by the FDA for the treatment of thyroid cancer [71].

The use of a combination of BRAF/MEK inhibitors dabrafenib and trametinib has revolutionised the treatment of anaplastic thyroid cancer with a positive BRAF V600E mutation. The combination of these drugs can also be used to treat patients who cannot have their tumours surgically removed completely [72].

**Clinical guidelines of the American Association of Endocrine Surgeons on the use of molecular genetic testing**

The latest 2020 American Association of Endocrine Surgeons guidelines for the treatment of thyroid disease have defined the role of molecular genetic testing of thyroid nodules in clinical practice [73].

**Molecular test systems in modern clinical practice**

Currently, three molecular test systems are available in clinical practice. The earliest form of molecular testing was the 7–gene panel (7GP), which is designed to assess point mutations in BRAF (V600E and K601E), H–, K–, and N–RAS, as well as RET/PTC 1/3 and PAX8/PPARg [74]. The 7–gene test demonstrates sensitivity and specificity ranging from 18 to 100%. The wide variation in these parameters may be due to different approaches to cytopathological diagnosis and differences in cancer prevalence in the population [75]. The 7–gene test is now included in two commercially available tests: ThyGenX + ThyraMIR (which combines 7GP with a panel of 10 microRNAs) and ThyroSeq, which is an advanced multi–gene panel. The ThyroSeq panel is a next–generation sequencing–based assay. ThyroSeq v2 replaced the 7–gene panel, which allows the examination of 56 genes for point mutations, fusions, and abnormal expression, and had a positive predictive value in 83% of observations [76]. A multicentre prospective study of ThyroSeq v3, which included 247 Bethesda III and Bethesda IV nodules for which neither the pathologist nor clinicians were aware of the molecular testing data, showed a sensitivity of 94%, specificity of 82%, cancer prevalence of 28%, and detection rate of 61% for benign disease [77].

Using a different molecular testing strategy, the Afirma Gene Expression Classifier (GEC) provided an RNA–based panel specifically selected for association with benign nodules. The Afirma GEC from Veracyte Inc. is a microarray–based test with a proprietary algorithm that analyses the mRNA expression of a panel of 167 genes. Afirma GEC has been previously reported to have a fairly high sensitivity but low specificity, suggesting it is a good “rule–out” test [78].

A multi–platform approach combines a mutation panel (ThyGenX) and a microRNA classifier test (ThyraMIR), which
has been shown to provide high negative predictive and positive predictive values [79]. In fact, a negative test result is an ideal reason to refuse surgery. The new interpretation of the genomic sequencing classifier was supplemented with additional expression markers for medullary cancer, G\textsuperscript{pt}s, and RET/PTC fusion [80].

An alternative approach for early diagnosis and rapid detection of disease persistence or recurrence is liquid biopsy, i.e., sampling and non-invasive analysis of circulating material obtained from the tumour [81]. Although the development of circulating biomarkers for thyroid cancer is still in its early stages, it has several advantages, such as the rapid, inexpensive, non-invasive nature of sample collection and the capture of intra–tumour and inter–metastatic genetic heterogeneity.

Experience in the clinical application of molecular genetic testing based on the materials of the Shalimov National Research Centre of Surgery and Transplantation

During the period from November 2022 to November 2023, 71 patients were operated on for thyroid pathology in the Department of Retroperitoneal Pathology. We analysed 9 observations of preoperative molecular genetic testing of thyroid nodules and compared them with the morphological examination of the surgical material (Table 2). In 4 observations, positive BRAF V600E mutations were noted and in one observation – positive mutations of the KRAS gene (codons 12, 13, 61). In 3 observations of BRAF–positive nodules, papillary thyroid carcinomas were morphologically noted. One BRAF–positive nodule was a non–invasive follicular neoplasia with papillary-like nuclear features. Positive mutations of the KRAS gene (codons 12, 13, 61) were also morphologically noted in one case of non–invasive follicular neoplasia of the thyroid with papillary–like nuclear features. In 3 observations of papillary thyroid carcinomas, a 7–gene test at the preoperative stage did not reveal genetic mutations.

Conclusions

Understanding of the molecular genetic mechanisms of thyroid cancer development opens up wide opportunities for the use of molecular testing in differential diagnosis, surgery, prognosis of the disease and treatment of aggressive forms of thyroid carcinomas.

The introduction of sequencing methods into clinical practice has made it possible to develop diagnostic systems

Table 2. Preoperative mutational screening of thyroid nodes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cytological examination</th>
<th>7-gene test</th>
<th>Transaction volume</th>
<th>Morphological study</th>
</tr>
</thead>
<tbody>
<tr>
<td>P., 38 p.</td>
<td>Left lobe nodule with a size of 8 mm - papillary carcinoma BSRTC:VI</td>
<td>Mutations not detected</td>
<td>Total thyroidectomy</td>
<td>Papillary thyroid carcinoma pT1aN0M0</td>
</tr>
<tr>
<td>K., 39.</td>
<td>Isthmus nodule - nodular goiter BSRTC:II</td>
<td>BRAF V600E</td>
<td>Total thyroidectomy</td>
<td>Non-invasive follicular neoplasia with papillary-like nuclear features</td>
</tr>
<tr>
<td>N., 47 p.</td>
<td>Left lobe nodule with a size of 11 mm - BSRTC papillary carcinoma: VI</td>
<td>BRAF V600E</td>
<td>Total thyroidectomy, central lymphadissectio n</td>
<td>Papillary carcinoma with multicentric growth. In the central group of lymph nodes - metastasis of papillary carcinoma pT1a(m) pN1a(1/2) M0</td>
</tr>
<tr>
<td>Ch. 68.</td>
<td>Right lobe nodule size 42 mm - BSRTC papillary thyroid carcinoma: VI</td>
<td>Mutations not detected</td>
<td>Total thyroidectomy, central lymphadissectio n</td>
<td>Encapsulated papillary thyroid carcinoma without signs of angioinvansion pT2N0M0</td>
</tr>
<tr>
<td>Ch. 38.</td>
<td>Left lobe nodule with a size of 7 mm - BSRTC papillary carcinoma: VI</td>
<td>BRAF V600E</td>
<td>Total thyroidectomy, central lymphadissectio n</td>
<td>Papillary thyroid carcinoma without signs of angioinvasion and extrathyroidal spread pT1aN0M0</td>
</tr>
<tr>
<td>D., 37 p.</td>
<td>Nodule 26 mm - nodular goiter with BSRTC cystic degeneration: II</td>
<td>Mutations not detected</td>
<td>Right-sided hemithyroidectomy</td>
<td>Papillary microcarcinoma, follicular variant (1 mm in size). Follicular adenoma pT1aN0M0</td>
</tr>
<tr>
<td>D., 37 p.</td>
<td>Left lobe nodule with a size of 47 mm - BSRTC adenomatous nodule: II</td>
<td>No mutation detected</td>
<td>Total thyroidectomy</td>
<td>Multinodular small-normal-macrofollicular goiter</td>
</tr>
<tr>
<td>P., 58 p.</td>
<td>Macrol follicular nodule with signs of proliferation and atypia, suspected BSRTC carcinoma: V</td>
<td>KRAS (codons 12,13,61)</td>
<td>Right-sided hemithyroidectomy</td>
<td>Non-invasive follicular thyroid neoplasia with papillary-like nuclear features</td>
</tr>
<tr>
<td>K., 55 years old.</td>
<td>Right lobular nodule with a size of 16 mm - suspected BSRTS papillary carcinoma: V</td>
<td>BRAF V600E</td>
<td>Total thyroidectomy</td>
<td>Encapsulated papillary thyroid carcinoma without signs of angioinvasion pT1bN0M0</td>
</tr>
</tbody>
</table>
that take into account most of the known mutations in highly differentiated thyroid cancer, which significantly improves the accuracy of cytological diagnosis.

The optimal set of molecular tests for thyroid tumours includes the determination of mutations in the genes BRAF, RET/PTC, RAS (KRAS, HRA, NRAS), PAX8/IPAR to more accurately assess the nature of pathological changes in the thyroid and choose the optimal personalised treatment strategy.

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22. PMID: 30733375; PMCID: PMC6711777.
20. PMID: 34668462.
19. PMID: 34072194; PMCID: PMC8198461.
18. PMID: 34276852.
17. PMID: 30181547.
16. PMID: 32768523.
15. PMID: 30733375; PMCID: PMC6711777.
14. PMID: 31561592; PMCID: PMC6826397.
13. PMID: 3081547.
12. PMID: 31097454; PMCID: PMC6675855.
11. PMID: 32347351; PMCID: PMC8350963.
10. PMID: 31097454; PMCID: PMC6675855.
9. PMID: 30467698.
8. PMID: 31285550; PMCID: PMC6756069.
7. PMID: 30181547.
6. PMID: 31097454; PMCID: PMC6675855.
5. PMID: 30978703.
4. PMID: 3081547.
3. PMID: 35716104; PMCID: PMC9545367.
2. PMID: 30467698.
1. PMID: 3081547.


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