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Research Article

Comparative Diagnostics of Different Histological Subtypes of Thyroid Carcinoma

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Abstract

The article examines differentiated approaches to the diagnostic of various histological types of thyroid cancer. Based on a comparative analysis, it was established that selecting an optimal diagnostic strategy requires considering both the morphological and molecular-genetic characteristic of the tumor. The study demonstrates that the integrated use of ultrasonography, fine-needle aspiration biopsy, and molecular-genetic testing ensures high diagnostic accuracy and allows for the optimization of treatment tactics.

Keywords: Thyroid cancer, Papillary carcinoma, Follicular carcinoma, Medullary carcinoma, Anaplastic carcinoma, Oncocytic carcinoma, Diagnostics, Molecular markers.

Introduction

Thyroid cancer (TC) is the most common malignancy of the endocrine system, arising from the transformation of follicular or parafollicular epithelium [1]. According to global data, more than 300,000 new cases are recorded annually (approximately 1.5% of all oncological pathologies). In the Republic of Belarus, this figure is about 1,200 new cases per year. The patient population is predominantly female over the age of 40, who suffer from TC four times more often than men. The prognosis is closely linked to the stage of the disease: the 5-year survival rate reaches 99.9% for stage I, whereas for stage IV it decreases to 62.9%, highlighting the critical importance of early detection [2].

According to the 2022 WHO Classification (5th edition), thyroid tumors are categorized based on their morphological, immunophenotypic, and molecular-genetic characteristics [3,4]. Among follicular cell-derived malignancies, the classification distinguishes: papillary thyroid carcinoma (BRAF-like) with its morphological variants, follicular thyroid carcinoma (RAS-like), oncocytic carcinoma (formerly Hürthle cell carcinoma), and encapsulated invasive follicular carcinoma (previously considered a variant of papillary carcinoma). Furthermore, the high-grade follicular cell-derived carcinomas now include differentiated high-grade thyroid carcinoma and poorly differentiated thyroid carcinoma. The C-cell tumor group is represented by medullary thyroid carcinoma, for which a two-tier histological grading system has been introduced. A separate category comprises low-risk neoplasms, such as NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features), as well as rare tumors including cribriform-morular thyroid carcinoma and thyroblastoma. Anaplastic thyroid carcinoma remains a distinct entity, while squamous cell carcinoma has lost its status as a separate category and is now interpreted as one of the morphological patterns of anaplastic carcinoma.

The primary etiological factors include radiation exposure (including the consequences of the Chernobyl disaster), endemic iodine deficiency, genetic predisposition (particularly characteristic of the medullary type), as well as proliferative processes in the thyroid tissue and endocrine imbalance.

In the early stages, thyroid cancer is often asymptomatic and

manifests as a firm nodular mass. As the disease progresses, enlargement of regional lymph nodes (lymphadenopathy) is observed. Typical findings include symptoms of compression of adjacent organs (dysphonia, dysphagia, and stridor), and less frequently, manifestations of paraneoplastic syndrome or symptoms caused by distant metastasis.

Diagnosis and prognosis of thyroid cancer (TC) are based on a comprehensive approach combining non-invasive and invasive methods. At the initial stage, palpation of the thyroid gland and regional lymph nodes is mandatory. This method allows for the identification and preliminary assessment of clinically significant nodules (larger than 1 cm). Ultrasound (US) is the key imaging modality, with results interpreted according to the international TI-RADS system. This method can detect small lesions (from 0.3 cm) and signs of malignancy, such as hypoechogenicity, irregular margins, and microcalcifications.

Ultrasound-guided fine-needle aspiration biopsy (FNAB) is the gold standard for diagnostic verification, determining the indications for surgical intervention. In cases of indeterminate cytological results (Bethesda categories IV-V, including follicular neoplasia), a diagnostic hemithyroidectomy followed by histopathological analysis is indicated.

Additional imaging techniques are used to assess tumor extent and rule out metastasis. Chest X-ray and abdominal ultrasound are primarily performed to detect secondary foci in the lungs and liver. Multislice computed tomography (MSCT) of the neck and mediastinum is indicated when tumor invasion into surrounding structures or a substernal component is suspected. In cases of suspected medullary thyroid cancer, serum calcitonin measurement is of primary importance, as it possesses higher diagnostic value compared to FNAB results.

Nevertheless, a definitive diagnosis can only be established through histopathological examination of surgical specimens.

Objective

The study aims to compare diagnostic strategies for various histological types of thyroid cancer based on a current literature review and to evaluate the prognostic significance of molecular genetic markers in diagnostic verification.

Materials and Methods

We conducted an analysis of scientific publications in the PubMed and ScienceDirect databases, as well as clinical guidelines (ATA, NCCN, WHO) for the period 2015–2025, focusing on the diagnosis and molecular pathology of thyroid cancer.

Results

Papillary thyroid carcinoma (BRAF-like) is the most prevalent malignancy of the thyroid gland, accounting for 80–85% of all cases [5]. Ionizing radiation is the primary etiological factor, as evidenced by the increased incidence among individuals exposed during childhood and adolescence. On ultrasonography, papillary carcinoma typically presents as a solid hypoechoic nodule with infiltrative (ill-defined) margins, microcalcifications, and a chaotic vascularization pattern. The diagnostic sensitivity of ultrasound in detecting malignant features reaches 86%. Ultrasound-guided fine-needle aspiration biopsy (FNAB) remains the "gold standard" for preoperative verification. The cytological profile of classic papillary carcinoma is characterized by specific nuclear alterations, including intranuclear cytoplasmic pseudoinclusions, nuclear grooves, and "ground-glass" (Orphan Annie eye) chromatin. Supplementing cytological examination with molecular profiling of FNAB samples demonstrates a high prevalence of the BRAF V600E mutation (84.45%). This mutation is associated with more aggressive tumor behavior and a high rate of lymph node metastasis (58.77%).

Follicular thyroid carcinoma (FTC) belongs to the group of RAS-like tumors and accounts for approximately 9% of cases. Preoperative diagnosis remains a significant challenge, as neither ultrasonography (US) nor fine-needle aspiration biopsy (FNAB) can reliably differentiate between follicular adenoma and carcinoma. The definitive criterion for malignancy is the presence of capsular or vascular invasion, which can only be evaluated through histopathological examination of the surgical specimen. Ultrasound features of FTC are often non-specific: it typically presents as an iso- or hypoechoic lesion with smooth, well-defined margins, mimicking a benign process (adenoma). The cytological diagnosis following FNAB is usually reported as "follicular neoplasia," which necessitates diagnostic hemithyroidectomy. Molecular testing of FNAB samples using targeted sequencing can improve preoperative diagnostic accuracy. The detection of RAS family gene mutations (NRAS, HRAS, KRAS) or PAX8/PPARγ chromosomal rearrangements indicates the neoplastic nature of the lesion. Of particular prognostic significance is the identification of TERT promoter mutations in FNAB material, as they are associated with a high risk of aggressive clinical behavior and a poor prognosis.

Oncocytic thyroid carcinoma (formerly Hürthle cell carcinoma) was reclassified as a distinct category in the 2022 WHO Classification of Thyroid Tumors. This tumor is characterized by a predominance (more than 75%) of oncocytic cells with abundant, eosinophilic, granular cytoplasm. The diagnosis of this cancer subtype presents the same challenges as follicular neoplasia: neither ultrasonography (US) nor fine-needle aspiration biopsy (FNAB) can reliably differentiate a benign oncocytic adenoma from a carcinoma. The definitive criterion for malignancy remains the presence of capsular or vascular invasion, which can only be identified via postoperative histological examination. The molecular profile of oncocytic carcinomas is unique: they are typically characterized by mitochondrial DNA mutations, alterations in GRIM-19 genes,

and a high frequency of chromosome 2 loss, which distinguishes them from follicular carcinoma.

Medullary thyroid carcinoma (MTC) arises from parafollicular C-cells and accounts for approximately 1.5% of all thyroid malignancies [6]. Its diagnostic approach fundamentally differs from that of follicular-cell-derived tumors. Serum calcitonin measurement is a mandatory component in the evaluation of nodular goiter and exhibits higher specificity than fine-needle aspiration biopsy (FNAB). The 2022 WHO Classification introduces a grading system for MTC based on mitotic activity, the presence of necrosis, and the Ki-67 proliferation index, allowing for more accurate risk stratification of patients. Molecular genetic testing is crucial for differentiating between sporadic and hereditary forms. Somatic mutations in the RET proto-oncogene (most commonly in codon 918) are identified in 66% of sporadic cases and are associated with a more aggressive clinical course. When a hereditary pattern is suspected (MEN2A, MEN2B), germline RET mutation testing is mandatory, as it determines the strategy for prophylactic thyroidectomy in the patient's relatives.

High-grade thyroid carcinomas represent a new category in the 2022 WHO Classification. This group encompasses tumors with an intermediate prognosis, positioned between differentiated and anaplastic thyroid cancers. The category includes differentiated high-grade thyroid carcinoma (DHGTC) and poorly differentiated thyroid carcinoma (PDTC). A diagnosis of DHGTC is established when a papillary, follicular, or oncocytic carcinoma retains its original differentiation features but acquires aggressive characteristics: ≥5 mitoses per 2 mm² and/or the presence of necrosis. PDTC is diagnosed according to the Turin criteria, which include a solid, trabecular, or insular growth pattern, the absence of conventional nuclear features of papillary carcinoma, and at least one of the following three features: a mitotic index of ≥3 per 10 high-power fields, foci of necrosis, or marked nuclear atypia. The diagnosis of these tumors requires meticulous histological examination with mandatory mitotic counting and assessment of necrosis, both of which significantly impact the prognosis and the choice of treatment strategy.

Anaplastic thyroid carcinoma (ATC) is a rare (less than 2%) and highly lethal malignancy, accounting for up to 50% of all thyroid cancer-related deaths [7]. The diagnosis is frequently established at the locally advanced or metastatic stage. Ultrasonography typically reveals an extensive invasive mass extending beyond the thyroid capsule and involving adjacent structures. Due to the aggressive clinical course and the need for rapid therapeutic decision-making, molecular profiling has become critically important. BRAF V600E mutations are identified in 35–52% of cases. Their detection enables the initiation of targeted therapy with BRAF (dabrafenib) and MEK (trametinib) inhibitors, which significantly improves overall survival. Furthermore, ATC is characterized by high PD-L1 expression, offering potential opportunities for immunotherapy. Current clinical guidelines emphasize the necessity of using NGS panels to identify all potentially actionable mutations in patients with this form of cancer.

Conclusions

The conducted analysis confirms that the diagnostic algorithm for thyroid nodules should be based on a comprehensive assessment of morphological features, immunophenotype, molecular-genetic profile, and biological tumor behavior. Papillary carcinoma is diagnosed based on its characteristic cytomorphological pattern and the BRAF V600E mutation; however, the encapsulated follicular variant and cribriform-morular carcinoma require distinct evaluation. A key diagnostic challenge for follicular and oncocytic carcinomas remains the necessity of histological confirmation of invasion, highlighting the need for improved preoperative molecular panels. The diagnosis of medullary carcinoma relies on serum calcitonin levels and RET mutation status, with mandatory grading. The classification of high-grade carcinomas (DHGTC and PDTC) requires pathologists to assess mitotic activity and necrosis for accurate staging. In cases of anaplastic carcinoma, including the squamous pattern, urgent molecular profiling is a prerequisite for selecting effective targeted therapy. In conclusion, the integration of ultrasound, cytology, and molecular-genetic methods enables a personalized approach to the diagnosis and treatment of patients with various forms of thyroid cancer.

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