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Cytological features of the diagnosis of recurrent nodular hyperplasia of thyroid gland

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Abstract. The study aimed to improve diagnostic approaches to the assessment of recurrent nodal tumours in the remaining thyroid tissue after surgical treatment, incorporating morphological, ultrasound and clinical and anamnestic features. The methodology included the examination of 69 patients with recurrent lesions classified as *Bethesda* categories *III* and *IV*, who underwent fine-needle aspiration core biopsy under ultrasound imaging, Doppler ultrasound with blood flow assessment, histological verification, and immunocytochemical staining. The results showed that in the *Bethesda III* group, the presence of malignant tumours was confirmed in 37% of cases, while in *Bethesda IV* only 24%, which casts doubt on the traditional notions of the risk of neoplasia in these categories. The *Bethesda III* was dominated by signs associated with malignancy: hypoechogenicity (57%), vertical orientation of the nodule (43%), intranodular blood flow (57%), and indistinct or irregular contours (25%). In group *IV*, follicular adenomas with benign echostructural features were more common (38%). Three morphotypes were identified: proliferative (69.6%), pseudo-recurrent inflammatory fibrous (14.5%) and true neoplastic (13%), with severe cellular atypia recorded in 2.9% of cases. A low correspondence between cytological and histological results (12-16%) was found, which justifies the need for a comprehensive diagnosis. The study determined that the presence of three or more independent risk factors significantly increases the probability of neoplastic transformation. The practical significance of the study is the formation of a multifactorial stratification system that can increase the accuracy of preoperative diagnosis, justify the choice of surgical tactics and reduce the frequency of misdiagnosis in clinical practice

Keywords: cellular atypia; hypoechoic structure; fibrous transformation; risk stratification; neoplastic transformation

Introduction

Recurrent nodular hyperplasia of the thyroid gland is an urgent problem of modern endocrinology and clinical pathology. Their significance is determined by the prevalence of thyroid diseases and the difficulty of diagnosing recurrent nodules in the tissue left after surgery. The differentiation between benign and malignant processes is complicated by the similarity of clinical and ultrasound signs. The discrepancy between cytology and histology results increases the risk of incorrect diagnostic decisions, which can lead to unnecessary surgery or delayed cancer detection. In this context, it is important to improve diagnostic algorithms, including the development of a multifactorial risk stratification system based on morphological, ultrasound, and clinical and anamnestic data. In the study, the term "neoplasia" is used to refer to the process of uncontrolled cell growth regardless of their nature, and "neoplastic transformation" to the transition of tissue to autonomous reproduction with the risk of malignant evolution.

One of the key diagnostic problems is the ambiguity of cytological findings in *Bethesda III-IV* cases. The presence of atypical follicular cells or follicular neoplasia makes it difficult to exclude malignancy. Yu.V. Buldygina *et al.* [1] noted that in these categories, there are often contradictions between cytological and histological findings, which

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limits the effectiveness of fine needle aspiration biopsy. Even with a typical cellular structure, the risk of malignant transformation remains significant, which emphasises the need to expand the diagnostic criteria.

Hypoechogenicity of nodes as a sign of malignancy is interpreted ambiguously. Some authors regard it secondary, but A. Pasko & V. Skrypko [2] found that the combination of hypoechogenicity, intraductal blood flow and vertical orientation significantly increases the risk of neoplasia. The detection of three or more of these signs justifies the need for surgical treatment even in the presence of questionable cytological findings. Intranodular blood flow is considered an important diagnostic marker. V. Hoperia *et al.* [3] proved that high vascularisation is characteristic of malignant neoplasms, but its prognostic value increases only in combination with other echographic features.

The problem of pseudo-recurrence also creates significant diagnostic difficulties. D. Sgró *et al.* [4] noted that inflammatory fibrotic changes can mimic proliferative lesions and lead to false suspicions of malignancy. In this case, a comprehensive approach to nodal evaluation is required. Immunocytochemical markers are proposed as a method to increase the specificity of diagnosis. H.S. Ahn *et al.* [5] demonstrated that the use of markers such as galectin-3 and HBME-1 increases the specificity of cytological analysis, although positive staining is not absolute proof of malignancy without histological confirmation.

The frequency of follicular adenomas among recurrent nodules calls into question the feasibility of repeated operations. J. Chen *et al.* [6] found that most adenomas have a typical echostructure without aggressive features. He proposed a model of dynamic surveillance with repeated biopsy only when the characteristics of the node change, which reduces the number of unnecessary operations. The role of clinical and anamnestic factors (age, gender, family history, duration of the disease) was previously underestimated. G. Grani *et al.* [7] proved that their combination has a greater prognostic value than individual echographic or cytological features. Morphotyping of recurrent tumours is becoming increasingly important in risk stratification. N.P. Ohori & N. Nishino [8] proposed a classification of nodes according to the degree of proliferation and the nature of the atypia, distinguishing nodes with minimal changes, active benign proliferation, and suspected neoplasia. This approach reflects the variety of histological variants, although it has limitations for differentiating between reactive and neoplastic processes after surgery.

Thus, the diagnosis of recurrent thyroid nodules is a complex multifactorial process that requires the integration of morphological, echographic, clinical and anamnestic data. The study aimed to improve the cytological diagnosis of recurrent nodal hyperplasia by incorporating ultrasound, morphological and clinical characteristics.

Materials and Methods

The study was conducted in the period from 1998 to 2023 at the Medbud Medical Centre (MC) and the Department of Endocrine Surgery of the Kyiv City Clinical Hospital No. 3, a municipal non-profit enterprise (MNE) in Kyiv, Ukraine. Kyiv, Ukraine, with the involvement of the Laboratory of Pathological Anatomy and the Department of Ultrasound Diagnostics. The study included patients with nodular formations in the thyroid residue, detected by routine clinical and instrumental monitoring after subtotal resection or hemiresection.

The inclusion criteria were thyroid surgery, presence of neoplasms in the thyroid residue according to ultrasound, technical feasibility of fine needle aspiration biopsy (FNAB), availability of complete clinical documentation, and informative cytological specimen. Exclusions were made in cases of unsatisfactory smear quality, inability to perform control histology, or lack of a complete ultrasound examination. All participants provided written informed consent to participate in the study following the principles of the WMA Declaration of Helsinki [9] and the rules of good clinical laboratory practice (GCLP) [10].

Ultrasound imaging was performed using a *MyLab™ ClassC* device (Esaote, Italy) with a linear transducer with a frequency of 7.5-10 MHz. The standard procedure included a preliminary assessment of the anatomy of the thyroid residue, detection of nodular masses, measurement of their size in three planes, assessment of echogenicity, internal structure, presence of hypo- or hyperechoic inclusions, contours, capsule, shape, and orientation of the mass relative to the transverse axis. Calcifications (micro- or macrocalcifications), cystic components, areas of fibrosis, and the presence of echolocation shadows were analysed. Doppler examination included assessment of intra- and perinodular blood flow in colour and energy Doppler modes with determination of spectral characteristics of vessels.

FNAB was performed under ultrasound guidance using 22G needles and a 10 ml syringe. In total, 122 FNAB procedures were performed, which resulted in the preparation of 366 cytological smears (three smears from each punctured node). One of the smears was fixed in 96% ethanol for further Papanicolaou staining, the second in the air for Romanowsky-Gimza staining, and the third was reserved for possible immunocytochemical analysis. The specimens were analysed by light microscopy with multiple magnifications up to ×1,000 with the involvement of at least two independent cytologists. Interpretation was performed according to The *Bethesda* System for Reporting Thyroid Cytopathology (TBSRTC) classification, which provides a standardised approach to risk stratification [11].

Surgical interventions were performed in 69 patients: resection of the remaining thyroid tissue was performed in 52 cases, and dissection of regional lymphatic collectors was performed in 15 cases with subsequent histological verification of the removed lymph nodes. Histological examination of recurrent nodal masses was performed in all 69 cases. The average age of the examined patients was 45.3 ± 12.6 years (range 19 to 72 years). The gender distribution included 47 women (68%) and 22 men (32%). The study of anamnestic data included a

mandatory analysis of the type of primary surgical intervention and morphological characteristics of the primary pathological process: Subtotal resection was performed in 45 patients and hemi-resection in 24 patients. Primary histological findings included nodular goitre (29 cases), follicular adenoma (25 cases), and papillary thyroid cancer (15 cases).

Laboratory preparation of biological material for histology included fixation in 10% neutral formalin, embedding in paraffin, making 4-5 μm thick sections on a microtome *HM 325* (Thermo Fisher Scientific, USA), followed by staining with haematoxylin and eosin. The standards of diagnostic morphological description followed the recommendations of the WHO Classification of Tumours [12]. The analysis of lymphatic collectors was performed by ultrasound evaluation of regional lymph node groups (central, lateral and supraclavicular zones) with subsequent morphological verification in cases of surgical removal. The number of affected groups and morphological features of the lymphoid tissue were covered to objectify the degree of prevalence of the pathological process and predict the risk of neoplastic transformation.

Results

The analysis of anamnestic data formulated a generalised characteristic of patients with recurrent thyroid nodular formations. Primary surgical interventions included subtotal resection in 45 patients and hemi-resection in 24 patients. According to the results of a morphological examination of the initially removed thyroid tissue, nodular goitre (n = 29), follicular adenoma (n = 25) and papillary thyroid cancer (n = 15) were most often verified. Table 1 shows the distribution of primary operations and corresponding morphological diagnoses.

Table 1. Primary surgical interventions and morphological diagnoses in patients with recurrent thyroid tumours

Type of primary transaction	Primary cytological diagnosis	Nature of subsequent recurrence (benign/malignant)
Subtotal resection	Nodular goitre (n = 18)	Benign
Subtotal resection	Follicular adenoma (n = 14)	Benign
Subtotal resection	Papillary cancer (n = 13)	Malignant
Hemiresection	Nodular goitre (n = 11)	Benign
Hemiresection	Follicular adenoma (n = 11)	Benign
Hemiresection	Papillary cancer (n = 2)	Malignant

Notes: cases of malignant recurrence were evaluated separately according to postoperative histology
Source: compiled by the author

As can be seen from Table 1, most primary interventions were performed for benign processes (nodular goitre or follicular adenoma). Malignant tumours were detected in 15 patients at the stage of primary treatment, which led to increased oncological alertness during follow-up. Accordingly, among the recurrences, malignant neoplasms were found only in patients with primary carcinoma. The analysis of cytological specimens obtained by FNAB in patients with recurrent thyroid masses identified three main morphological phenotypes: benign proliferative changes, pseudo-recurrent inflammatory fibrous transformations, and true recurrence of the neoplastic process. These changes required differentiation from highly differentiated forms of carcinoma (Table 2).

Table 2. Cytological characteristics of lesions in the remaining thyroid tissue

Cytomorphological type of formation	Number of cases	Share	Main cytological features
Benign proliferative changes	48	69.6%	Colloid, thyroid cells without atypia, dense clusters
Pseudo relapse (lymphoid aggression)	10	14.5%	Lymphocytes, plasma cells, fibroblasts, isolated thyroid cells
True recurrence (neoplasia)	9	13%	Epithelial proliferation, fibrosis, blood supply
Severe atypia	2	2.9%	Anisocytosis, mitosis, chromatin structure disorders

Notes: a true recurrence of the neoplastic process was the re-formation of tumour tissue after surgical treatment. A pronounced atypia was not considered cancer without morphological confirmation
Source: compiled by the author

The cytological examination of the remaining thyroid tissue in the postoperative period determined a clear morphological and functional stratification of the detected focal lesions. The study of the points obtained by FNAB under the control of ultrasound Doppler revealed the presence of four main cellular patterns: benign proliferative, lymphoid-inflammatory, fibrous-remodelling and malignant atypical. Each of them has unique microscopic features that determine the diagnostic and prognostic value. The most common variant (in 69.6% of cases) was a benign proliferative pattern characterised by the presence of thyroid follicular cells tightly grouped in compact microarchitectural structures. These cells had small, rounded nuclei with uniform chromatin, without nucleolar structures.

The cytoplasm was moderately basophilic, cell boundaries were clear, and there were no mitotic figures. Colloids in the form of amorphous or droplet-like masses were present in the background. Such a picture was indicative of a stable, reactive proliferative state, which is often found in the remaining thyroid tissue after hemiresection or limited resection. Clinically, these lesions demonstrate slow or no growth, low TSH levels, no lymphadenopathy, and do not require urgent surgical correction.

The second most frequent (14.5%) was the lymphoid-inflammatory pattern, which was accompanied by the presence of many mature and immature lymphoid elements. Of diagnostic difficulty were preparations with a predominance of young lymphocyte nuclei morphologically similar to blasts, as well as the detection of plasma cells, macrophages with phagocytosed colloid, and neutrophils. These components formed dense foci with a pronounced background, whereas the thyroid epithelium was presented in the form of individual cells or small groups with slight variability of nuclei. In 30% of these cases, the detection of fibroblasts and fibrocytes was diagnostically important, confirming the presence of an active immune or granulomatous process. In clinical practice, this is associated with pseudo-recurrences in the setting of chronic Hashimoto's thyroiditis or postoperative fibrosis with intense remodelling.

The third morphotype was the fibrotic-reactive variant, detected in 13% of patients. It combined proliferative thyroid cells with a dense stromal component. It was characterised by the presence of mature fibroblasts, collagen fibres, and increased microvascular density. The vessels had an elongated shape, sometimes with pronounced endothelial swelling, which is an indirect sign of neoangiogenesis. However, in most cases, the nuclear architecture of thyroid cells remained monotonous, without signs of carcinomatous atypia. This was indicative of a reactive dystrophic process, often associated with previous surgery, local ischaemic syndrome, or postbiopsy changes. This pattern is an example of pseudotumour transformation, which can potentially be interpreted as a suspected neoplasia.

The smallest but most clinically significant cytomorphological type of malignant cellular atypia was 2.9% of cases. These samples were dominated by cells with pronounced anisocytosis, hyperchromia, mitotic activity, and frequent pseudoinclusions in the nuclei. In a few cases, nuclear furrows characteristic of *papillary thyroid carcinoma* were observed. The usual architectural distribution was disturbed, the nuclei were arranged chaotically, and the cytoplasm was vacuolated, with foci of granulation. Preparations of this type were accompanied by active vascularisation and clinical signs of palpable lymph nodes and subfibrillation. Thus, the cytological differentiation of foci in the thyroid residue should be not only quantitative but also qualitative. A thorough analysis of the cellular composition identified not only the morphology but also the pathogenetic nature of the lesion, which significantly increases the accuracy of preoperative diagnosis and reduces the risk of erroneous clinical decisions.

In the study, which included patients with recurrent thyroid nodules after surgery, assessment of the diagnostic accuracy of the *Bethesda* cytological report was emphasised. A total of 69 patients with cytological findings of categories *III* and *IV* were analysed. In the *Bethesda III* group (n = 19), thyroid cancer (7 cases) and nodular goitre (5 cases) were most often detected, which indicates the difficulty of differential diagnosis with uncertain morphological criteria. In the *Bethesda IV* group (n = 50), the main diagnosis based on histological verification was follicular adenoma (19 cases), indicating a significant number of benign lesions among cases suspected of neoplasia (Table 3).

Table 3. Types of focal lesions in patients after surgery with uncertain cytological findings *Bethesda III* and *IV*

Type of focal formation	*Bethesda III* (n = 19)	Coincidence with cytology	*Bethesda IV* (n = 50)	Coincidence with cytology	Initial cytological diagnosis	Nature of the malignant process (recurrence/new)	Node sizes (for *Bethesda IV* only)
Thyroid cancer	7	2	12	0	Papillary cancer (history/new diagnosis)	*Bethesda III*: 4 relapses, 3 new cases; *Bethesda IV*: 2 relapses, 10 new cases	11 knots ≤10 mm / 20 knots >10 mm
Follicular adenoma	4	0	19	6	Follicular adenoma	N/A	N/A
Nodular goitre	5	3	10	1	Nodular non-toxic goiter	N/A	N/A
Autoimmune thyroiditis	3	2	9	2	Lymphoid thyroiditis (Hashimoto's)	N/A	N/A

Notes: number of verified cases of cancer after re-examination in patients with *Bethesda III* (n = 19) and *Bethesda IV* (n = 50), including both recurrences and new diagnoses of malignancies, are demonstrated. Therefore, the total number of cases of PCa in this table (n = 19) exceeds the number of newly diagnosed malignancies (n = 15) reported in Table 1. The columns "Coincidence with cytology" show the frequency of complete correspondence between cytological and histological diagnoses. The cytological diagnosis detected cancer in only 2 of 19 patients (10.5%), which indicates the limited sensitivity of the *Bethesda* system in the postoperative setting. The low percentage of matches is explained by the morphological overlap of reactive, hyperplastic and neoplastic changes, as well as background inflammatory and fibrous transformations that complicate cytological differentiation. The nature of the malignant process (recurrence or neoplasm) is indicated separately
Source: compiled by the author

An in-depth analysis of the results of histological verification of recurrent nodal masses in patients after thyroid surgery shows the ambiguity of the diagnostic value of the *Bethesda* cytological classification, in particular its *III* and *IV* categories. Despite the generally accepted notion of a higher risk of malignancy in *Bethesda IV* cases, the study results demonstrate a different trend: malignant tumours in the *Bethesda III* group were detected in 37% of patients, which is significantly higher than in the *Bethesda IV* group (24%). This result indicates the complexity of cytomorphological differentiation of focal processes in the remaining thyroid tissue, especially in the context of postoperative changes and reactive transformations.

This paradox is partly explained by the presence of a morphological overlap between reactive, hyperplastic, inflammatory and neoplastic changes. Patients with *Bethesda III* often show proliferative thyroid epithelial complexes, background colloid, destructive components, infiltrates of polymorphic lymphocytes, and single atypical cells with vague signs of malignancy. These cytograms can be interpreted as benign or questionable, although they hide the early stages of the neoplastic process. Furthermore, in this group, in 15.8% of cases, background autoimmune thyroiditis was recorded, which can mask the initial signs of malignancy and create a false impression of lymphoid aggression or pseudo-recurrence.

In contrast, the *Bethesda IV* category is characterised by a significant proportion of benign neoplasms, in particular follicular adenomas (38% in this group). Such adenomas, especially those with microfollicular architecture and the presence of Ashkinase-Gurthle cells, are often cytologically interpreted as follicular neoplasia or suspected follicular carcinoma. This leads to a tendency to surgical treatment without a real oncological threat. However, despite the lower overall incidence of malignancy, cases of papillary cancer have also been reported in *Bethesda IV* patients, especially in younger patients and with nodules up to 1 cm in size, which underscores the importance of a comprehensive approach to risk stratification.

The diagnostic consistency of cytological and histological findings remained low: only 12-16% of cases had a complete agreement. This level of consistency is insufficient to make categorical decisions about treatment tactics. False negatives in the *Bethesda III* category are particularly dangerous, as they can lead to a delay in adequate oncological intervention. These data confirm the need not only to improve the standards of cytological interpretation but also to introduce immunocytochemical markers (Galectin-3, HBME-1, CK19) that differentiate between reactive and neoplastic cell complexes.

Ultrasound and Doppler evaluation of nodules in the remaining thyroid tissue revealed several characteristic echostructural features that correlated with the cytological findings of *the Bethesda III* and *IV* categories. In patients of the *Bethesda III* group (n = 19), the features traditionally associated with an increased risk of malignancy prevailed: hypoechogenicity, fuzzy contours, irregular shape and vertical location of the lesion. These characteristics were more frequently found in the subgroup with suspected neoplasia than in cases of benign cytological findings (Table 4).

Table 4. Ultrasound and Doppler signs of focal lesions in the thyroid residue

Characteristic	*Bethesda III* benign (n = 12)	*Bethesda III* neoplasia (n = 7)	*Bethesda IV* benign (n = 38)	*Bethesda IV* neoplasia (n = 12)
Hypoechoic zone	4 (33%)	4 (57%)	20 (53%)	6 (50%)
Hyperchogenic zone	2 (17%)	2 (29%)	3 (8%)	3 (25%)
Fine calcification	2 (17%)	1 (14%)	2 (5%)	3 (25%)
Continuous calcification	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Fuzzy contours	1 (8%)	2 (29%)	1 (3%)	2 (17%)
Incorrect form	0 (0%)	1 (14%)	0 (0%)	2 (17%)
Vertical positioning	0 (0%)	3 (43%)	0 (0%)	0 (0%)
Cystic degeneration	6 (50%)	1 (14%)	10 (26%)	2 (17%)
Areas of fibrosis	3 (25%)	2 (29%)	7 (18%)	2 (17%)
Intranodular blood flow enhancement	2 (17%)	4 (57%)	7 (18%)	4 (33%)

Notes: shows the absolute number of cases of each sign within the respective subgroup; in parentheses, the proportion (%) of the total number of patients in this subgroup
Source: compiled by the author

The analysis of ultrasound and Doppler characteristics of focal lesions in the thyroid residue demonstrated a clear differentiation of echostructural parameters depending on the category of the *Bethesda* cytological report. In patients with suspected neoplasia, both groups showed an increased frequency of ultrasound features considered to be factors of increased risk of malignancy: hypoechogenicity, fuzzy or irregular contours, the vertical location of the lesion in the transverse scan, the presence of microcalcifications and intranodular blood flow.

In the *Bethesda III* category, which is traditionally regarded as a group of uncertain risk, the most informative echo signals of malignancy were hypoechoicity (recorded in 57% of cases), the presence of fuzzy contours (25%) and vertical orientation of the lesion in cross-section (43%). At the same time, intranodular enhancement of blood flow was observed in 57% of lesions with suspected neoplasia, which is significantly higher than in the subgroup of benign processes of the same category. Cystic degeneration, on the contrary, prevailed in the benign

subgroup (50%), indicating its relatively high specificity in excluding malignancy.

The *Bethesda IV* group was characterised by less clear distinctions between benign and suspicious lesions. Despite a slightly higher frequency of fine calcification (25%) and fibrous changes (50%) in cases of suspected neoplasia, these signs were also found in 5-18% of cases in the benign subgroup. Hyperechogenic areas, traditionally associated with benign processes, were detected in both the benign and suspicious subgroups (8% and 25%, respectively), which reduces diagnostic significance in the context of this category. Solid calcification was recorded in only one case and can be considered a rare but highly specific marker.

Notably, indistinct contours and irregular shape of the lesion were more common in suspicious neoplasia cases in both categories, but these features showed higher sensitivity in *Bethesda III* (43% vs. 17% in *Bethesda IV*). Thus, despite the formal interpretation of *Bethesda IV* as riskier, the ultrasound picture revealed a higher concentration of malignancy-associated features in patients with *Bethesda III*. This confirms the previous morphological findings of a high degree of neoplastic transformation within a category with a less clearly defined atypia.

The analysis of patients with recurrent thyroid nodules who underwent cytological diagnosis identified the main markers that influence the clinical decision to repeat surgery. These markers are conditionally divided into three blocks: morphological (cytological) features, sonographic (Doppler ultrasound) characteristics and clinical and anamnestic parameters. The most predictive morphological signs of malignancy include severe cellular atypia, anisocytosis, mitosis and polymorphism, especially in combination with a lymphoid and fibrous background. Significant ultrasound features were found to be hypoechogenicity, blurred contours, the vertical location of the nodule in the transverse section, intranodular enhancement of blood flow, and the presence of microcalcifications. From the clinical point of view, the growth of the left stump, the appearance of cervical lymphadenopathy, young age (under 30 years), and nodes up to 1 cm in size showing growth or vascularisation were of decisive importance. The complex combination of three or more of these factors in one clinical case indicates a high risk of neoplastic transformation and is an absolute indication for surgical intervention, incorporating the feasibility of lymph node dissection. Instead, single markers without clinical progression require dynamic follow-up with control cytological or immunocytochemical analysis (Table 5).

Table 5. Comprehensive assessment of risk factors for recurrent thyroid tumours

Category of factors	Specific features	Diagnostic significance
Cytological	Cellular atypia, mitosis, anisocytosis, polymorphism	High
	Fibrotic-lymphoid background with epithelial proliferation	Average
Doppler ultrasound	Hypoechoic, fuzzy contours, vertical orientation	High
	Microcalcifications, intranodular blood supply	High
	Cystic changes, hyperechogenicity	Low (indicates benignity)
Clinical	Age <30 years, stump growth, lymphadenopathy, nodule ≤1 cm	High
	No dynamics, no vascular signal	Low

Source: compiled by the author

The systematisation of clinical, ultrasound and cytomorphological data in patients with recurrent masses in the thyroid residue has revealed close correlations between the total number of risk factors and the final treatment strategy. Cases with an uncertain cytological conclusion of *Bethesda III* and *IV* categories, which are characterised by a "grey area" of diagnosis, are notable. For these categories, a multifactorial approach to risk assessment is most justified. The results of the study indicate that the presence of three or more high-risk factors (morphological, sonographic, or clinical) in a single case is a reliable predictor of malignant transformation. In particular, the combination of hypoechogenicity, blurred contours, intranodular blood flow with pronounced cellular atypia, a background of lymphoid aggression and clinical signs (e.g., enlargement of the node in patients under 30 years of age) significantly increases the probability of detecting thyroid carcinoma during follow-up histological examination. Such patients are subject to active surgical intervention with an extended scope (including prophylactic dissection of cervical lymph nodes).

In contrast, in the presence of single or isolated features (e.g., fibrosis alone or single microcalcification without clinical dynamics), a conservative approach with dynamic follow-up is acceptable. In these cases, it is advisable to repeat FNAB after 6 months, as well as the use of immunocytochemistry to differentiate between pseudoatypia and early manifestations of neoplasia. In *Bethesda III*, the results showed a more aggressive profile of ultrasound changes, as well as a higher percentage of verified malignancy compared to category *IV*, suggesting a potential underestimation of this group in existing protocols. This requires increased oncological alertness even in cases of shapeless morphology accompanied by severe sonographic pathology. In this context, the *Bethesda IV* category often demonstrated a high rate of benign lesions (especially follicular adenomas), albeit with clear echostructural risk markers (indistinct contours, calcifications, irregular shape). Thus, the derived risk assessment model based on comprehensive stratification avoids overdiagnosis, which leads to unnecessary reoperation, and underdiagnosis, which can lead to delayed detection of the cancer process. This approach facilitates

individualised clinical decision-making for each patient, covering the morphological, echographic and clinical profile within the framework of an integrated diagnostic model.

Discussion

The study conducted a comprehensive analysis of the diagnostic efficacy of the *Bethesda* classification in the context of recurrent thyroid nodules after surgery. One of the key findings was the detection of a higher level of malignancy among cases of the *Bethesda III* category compared to *Bethesda IV*, which contradicts the established ideas about the grading of oncological risk. This trend is consistent with the data of M. Kujdowicz *et al.* [13], which indicate that morphological uncertainty in the *Bethesda III* category often hides early forms of neoplastic transformations. At the same time, D. Suster *et al.* [14] argued that the *Bethesda IV* category has the highest prognostic unfavourability, but the results of this study indicate the need to revise such ideas incorporating the ultrasound and cytomorphological characteristics of the nodes.

The predominance of malignant processes in the *Bethesda III* group is partly explained by the cytomorphological overlap of reactive and neoplastic changes, especially in the setting of autoimmune thyroiditis. M. Melo *et al.* [15] addressed the difficulty of interpreting thyroid cells in chronic inflammation, which increases the risk of misdiagnosis. At the same time, according to M.T. Macvanin *et al.* [16], the impact of the autoimmune process is secondary, and the level of malignancy in the *Bethesda III* category is overestimated. However, the analysis revealed a significant frequency of hypoechogenicity, vertical nodule orientation, and concomitant cytological atypia, which indicates a real oncological risk in this category. Histological verification of the material showed a high percentage of benign follicular adenomas among the *Bethesda IV* nodes. This correlates with the findings of L. Giovanella *et al.* [17] and W. Chatchomchuan *et al.* [18], which indicate the redundancy of surgical interventions in such cases and the need to improve the criteria for cytological suspicion.

Of particular importance in the diagnosis are clear echographic markers of malignancy, among which hypoechogenicity, fuzzy contours, vertical orientation and intranodular enhancement of blood flow dominated. These characteristics, according to M. Ali *et al.* [19] and Z. Xu *et al.* [20], have high sensitivity in detecting malignancy and may in some cases exceed morphological criteria in diagnostic information content. At the same time, in the *Bethesda IV* category, echographic features had lower specificity, which is consistent with the results of E. Haaga *et al.* [21], noting that hyperechoic areas, calcifications, and fibrosis are not reliable markers of malignancy. Contradictory data were presented by P. Bhagwat & S. Pomplun [22], who emphasised the possible significance of calcifications, but in this study, they were more common in benign nodes, which reduced their predictive value.

The cytological analysis identified four main morphotypes of nodes. The most abundant was the benign proliferative type, which fully corresponds to the characteristics proposed by I. Kholová *et al.* [23]. The detection of a lymphoid-inflammatory pattern in 14.5% of cases confirms the hypothesis of V.J. Bernet & A.-M. Chindris [24] regarding the role of chronic thyroiditis in the formation of pseudo-recurrence, although L. Chouhan *et al.* [25] noted the risk of missed malignancy. The fibrotic remodelling type, found in 13% of patients, was interpreted mainly as reactive, according to Y. Ito *et al.* [26], who associated it with tissue restructuring after surgery. However, Y. Alwelaie *et al.* [27] suggested that this morphotype may be associated with the early stages of neoplastic processes. In this study, morphological signs of malignancy were not detected: structural orderliness of collagen fibres, absence of cellular atypia, mitotic activity and neoangiogenesis were observed, which can be used to interpret these lesions as pseudotumour fibro-dystrophic transformations that do not require aggressive surgical tactics.

The smallest, but most significant group was made up of cases with severe cytological atypia (2.9% of samples). The detected nuclear furrows, anisocytosis, and mitoses met the criteria described by A. Harahap & C. Jung [28] for papillary cancer. Verification by histological data confirmed the diagnosis of oncopathology, which coincides with the approach proposed by H. Rahmati-Holasoo *et al.* [29]. Comprehensive risk assessment revealed three main groups of predictors: morphological, sonographic and clinical factors. The presence of three or more factors significantly increased the risk of malignancy, which is consistent with the multivariate analysis model described by E.A. Hall *et al.* [30]. At the same time, the critique of Z. Tang *et al.* [31] regarding the complexity of such models does not address the specifics of the postoperative transformation of thyroid tissue.

The age group of patients under 30 years, where an increased incidence of papillary cancer was observed even with small nodule sizes, was emphasised. This pattern is consistent with the data of M. Kumar *et al.* [32], highlighting the increased oncogenetic vulnerability of young people due to the activation of the *MAPK* and *PI3K/AKT* signalling pathways. The observations of J. Townsend & M. Perez-Machado [33] regarding the significance of nodule size were partially confirmed, as it was found that a combination of small diameter and high vascularisation as a sign of neoangiogenesis is more important. Improving diagnostic accuracy can be achieved by using immunocytochemical markers. In particular, the use of *Galectin-3*, *HBME-1*, and *CK19* verified the initial stages of neoplastic transformations, as described by M.-H. Wu *et al.* [34]. This is especially relevant for the *Bethesda III* category, where background inflammatory changes can mask true neoplasia. Thus, the results of the study justify the need to revise the risk stratification in the *Bethesda III* and *Bethesda IV* categories. Increased oncological alertness should primarily concern the Bethesda *III* category, while *Bethesda IV* requires a cautious assessment given the predominantly benign nature of the changes. The proposed multifactorial model can be used to optimise treatment tactics,

minimising the risks of over- and underdiagnosis in patients with recurrent thyroid nodules.

Conclusions

The *Bethesda III* and *IV* cytological classification has limited prognostic value in the diagnosis of recurrent thyroid nodules. A higher incidence of malignancy in the *Bethesda III* category (37%) compared to *Bethesda IV* (24%) indicates an underestimation of cancer risk in cases of uncertain cytomorphology. The morphological overlap of reactive, hyperplastic, inflammatory and neoplastic changes makes it difficult to reliably differentiate nodular lesions. Autoimmune thyroiditis masks early signs of malignancy, which affects the accuracy of cytological analysis. Echostructural features (hypoechogenicity, fuzzy contours, vertical location) were found to be important predictors of malignancy in the *Bethesda III* category. The presence of intranodular blood flow enhancement on Doppler increases the reliability of sonographic risk assessment. Four main cytological patterns were identified, which clarify the nature of recurrent nodal lesions. The benign proliferative type is the most common cytological variant among recurrent nodules. Cases of malignant atypia were detected in 2.9% of samples, which confirms the critical need for careful morphological analysis. A multifactorial approach (ultrasound + cytology + clinical dynamics) is optimal for risk stratification and selection of treatment tactics. Limitations of the study include a small sample (69 patients) and the lack of multicentre confirmation of the results, as well as limited study of metastasis to surrounding organs and tissues. The integration of genetic, immunohistochemical and molecular markers to improve the diagnosis of recurrent nodal tumours is a promising area.

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Conflict of Interest

None.

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Цитологічні особливості діагностики рецидивних вузлових гіперплазій щитоподібної залози

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Анотація. Метою дослідження було вдосконалення діагностичних підходів до оцінки рецидивних вузлових утворень у залишеній тканині щитоподібної залози після хірургічного лікування, з урахуванням морфологічних, ультразвукових та клініко-анамнестичних ознак. Методологія включала обстеження 69 пацієнтів із рецидивними утвореннями, класифікованими за категоріями *III* та *IV* системи *Bethesda*, яким виконували тонкоголкову аспіраційну пункційну біопсію під контролем ультразвукової візуалізації, допплерографічне дослідження з оцінкою кровотоку, гістологічну верифікацію та імуноцитохімічне фарбування. Результати показали, що у групі *Bethesda III* наявність злоякісних пухлин підтверджено у 37 % випадків, тоді як у *Bethesda IV* – лише у 24 %, що ставить під сумнів традиційні уявлення про ризик неоплазії у цих категоріях. У *Bethesda III* домінували ознаки, асоційовані з малігнізацією: гіпоехогенність (57 %), вертикальна орієнтація вузла (43 %), інтранодулярний кровотік (57 %), нечіткі або нерівні контури (25 %). У групі IV частіше спостерігались фолікулярні аденоми (38 %) з доброякісними ехоструктурними ознаками. Виділено три морфотипи: проліферативний (69,6 %), псевдорецидивний запально-фіброзний (14,5 %) і справжній неопластичний (13 %), причому виражена клітинна атипія зафіксована у 2,9 % випадків. Встановлено низьку відповідність між цитологічними та гістологічними результатами (12-16 %), що обґрунтовує потребу в комплексній діагностиці. Виявлено, що наявність трьох або більше незалежних факторів ризику суттєво підвищує ймовірність неопластичної трансформації. Практичне значення дослідження полягає у формуванні багатофакторної системи стратифікації, яка дозволяє підвищити точність передопераційної діагностики, обґрунтувати вибір хірургічної тактики та знизити частоту хибнодіагностичних рішень у клінічній практиці

Ключові слова: клітинна атипія; гіпоехогенна структур; фіброзна трансформація; стратифікація ризику; неопластична трансформація