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CLINICAL SIGNIFICANCE OF THE IDENTIFIED MICRO-RNAs AS PREDICTORS OF THYROID CANCER AND DISEASE COURSE

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Abstract. Differentiated thyroid cancer represents the most common malignancy of the endocrine system and is generally associated with a favorable long-term prognosis; however, a considerable subset of patients develops aggressive forms of the disease characterized by early local recurrence, regional lymph node involvement, distant metastases and partial or complete resistance to conventional therapeutic approaches, including surgery and radioactive iodine therapy. Despite advances in diagnostic imaging and treatment strategies, accurate prediction of disease behavior remains challenging. Currently used clinicopathological risk stratification models, based on tumor size, histological subtype and stage, do not fully reflect the underlying molecular and biological heterogeneity of thyroid tumors, which limits their prognostic accuracy and highlights the need for reliable molecular biomarkers capable of predicting disease progression, recurrence risk and treatment outcomes.

MicroRNAs have emerged as key post-transcriptional regulators of gene expression involved in critical cellular processes such as proliferation, differentiation, apoptosis, angiogenesis and metastatic potential. Their dysregulation has been increasingly linked to carcinogenesis and tumor progression in various malignancies, including thyroid cancer. Altered microRNA expression profiles may influence tumor aggressiveness, invasion capacity and response to therapy, making them promising candidates for prognostic and biomarkers.

The aim of this study was to identify selected microRNAs with potential prognostic significance in thyroid cancer and to assess their association with clinicopathological characteristics and patient survival. A comprehensive bioinformatic analysis was conducted using the UALCAN platform based on data derived from The Cancer Genome Atlas, evaluating the expression profiles of six microRNAs in thyroid cancer tissues compared with normal thyroid samples. Associations between microRNA expression levels and patient age, tumor stage, lymph node status, histological subtype and overall survival were statistically analyzed.

In addition, a retrospective clinical analysis of 749 patients with thyroid pathology treated between 2019 and 2024 was performed in order to correlate molecular findings with real-world clinical outcomes and disease course. The results revealed significant overexpression of hsa-miR-15a-5p, hsa-miR-146b-5p, hsa-miR-221-5p and hsa-miR-222-3p in malignant thyroid tissues, whereas hsa-miR-199b-5p and hsa-miR-484 were markedly downregulated. Distinct expression patterns were closely associated with patient age, tumor stage, lymph node metastases and histological variants, suggesting their involvement in tumor progression and invasive behavior.

Survival analysis demonstrated that increased expression of hsa-miR-199b-5p was associated with an approximately thirty-five percent reduction in five-year overall survival, indicating its substantial prognostic relevance. These findings support the critical role of microRNA dysregulation in thyroid carcinogenesis and disease progression and suggest that the identified microRNAs, particularly hsa-miR-199b-5p, may serve as valuable biomarkers for improved preoperative risk stratification, optimization of clinical decision-making and advancement of personalized therapeutic strategies in patients with differentiated thyroid cancer.

Keywords: thyroid cancer, microRNA, gene expression, prognostic biomarkers, survival.

Introduction. Among malignant neoplasms of the endocrine system, thyroid cancer (TC) accounts for approximately 3,4 % of all oncological diseases worldwide [1].

A persistent upward trend in the incidence of thyroid cancer over the past decade has largely been attributed to advances in diagnostic imaging techniques and the wider implementation of screening programs, which facilitate more frequent detection of thyroid nodules. At the same time, mortality rates associated with this pathology demonstrate an opposite trend and have been gradually declining [2], which is likely a consequence of earlier diagnosis and timely application of effective therapeutic approaches.

Despite the generally favorable prognosis, the clinical course of thyroid cancer is not always indolent. In a subset of patients, the disease is characterized by aggressive biological behavior, development of recurrences, and disease progression. The vast majority of malignant thyroid tumors are differentiated forms, primarily papillary and follicular carcinomas, which together account for more than 90 % of TC cases. In contrast, poorly differentiated and anaplastic carcinomas occur much less frequently (approximately 5 % and 1 % of cases, respectively), but are associated with extremely aggressive behavior, resistance to standard therapies, and a very poor prognosis, with average survival limited to several years or even months [1].

At the same time, even in differentiated thyroid cancer, the risk of an unfavorable course remains clinically significant: more than 10 % of patients die due to disease progression, and the recurrence rate exceeds 15 % [3, 4]. These data highlight the limitations of existing clinicopathological prognostic criteria and underscore the need to identify new molecular markers capable of reflecting

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tumor biology and enabling timely identification of high-risk patient groups.

A promising direction in modern oncoendocrinology is the study of microRNAs (miRNAs)—short non-coding RNA molecules approximately 22 nucleotides in length that regulate gene expression post-transcriptionally through interaction with complementary regions of target mRNAs. MicroRNAs play a crucial role in controlling fundamental cellular processes, including proliferation, apoptosis, differentiation, cell cycle regulation, and immune response. Dysregulation of miRNA expression is closely associated with the initiation and progression of malignant neoplasms, including thyroid cancer [5, 6]. Depending on the functional context, miRNAs may exert either oncogenic or tumor-suppressive effects, forming complex regulatory networks that determine tumor cell invasiveness and sensitivity to treatment [6, 8, 11].

Despite the growing volume of experimental and clinical data, miRNA expression profiles in different clinicopathological variants of thyroid cancer remain insufficiently studied. Of particular relevance is the identification of associations between the expression levels of individual miRNAs and clinical features such as tumor aggressiveness, metastatic potential, and risk of recurrence [10, 12]. Identification of such molecular markers may form the basis for a personalized approach to patient management, improved prognostic assessment, and development of new therapeutic strategies. In this context, further investigation of the role of miRNAs in thyroid cancer represents an important step toward the implementation of precise, reliable, and potentially non-invasive molecular tools in clinical practice.

Accordingly, the aim of this study was to identify microRNAs that may be used as prognostic biomarkers of thyroid cancer.

Object and methods of research. The analysis of expression levels of the investigated microRNAs in tumor tissue of patients with thyroid cancer compared with normal thyroid tissue was performed using the web-based platform UALCAN (University of Alabama at Birmingham Cancer Data Analysis Portal), available at: http://ualcan.path.uab.edu.

UALCAN is an interactive online resource that provides access to data from The Cancer Genome Atlas (TCGA) project and other publicly available databases. The platform enables quantitative and statistical analysis of gene, microRNA, and long non-coding RNA expression, as well as assessment of DNA methylation levels in promoter regions across 33 types of malignant tumors, including thyroid cancer.

The study included a comparative analysis of the expression of selected microRNAs between tumor and normal thyroid tissues. Additionally, stratified analyses were performed according to major clinicopathological parameters, including patient age, disease stage, regional lymph node status, and histological tumor type, in order to identify potential associations between microRNA expression levels and clinical characteristics of thyroid cancer.

Furthermore, overall survival analysis was conducted using UALCAN tools to evaluate patient survival depending on the expression levels of tumor-associated microRNAs, thereby assessing their potential prognostic significance.

In the clinical part of the study, the results of examinations and treatment of 749 patients with thyroid pathology treated at the Precarpathian Clinical Oncology Center between 2019 and 2024 were analyzed. The mean age of patients was 51.3 years, with an age range from 45.6 to 59.1 years. Age distribution was as follows: 30.5 % of patients were aged 45–50 years, 43.2 % were 51–55 years, and 26.3 % were 56–60 years.

The distribution by nosological forms was as follows: nodular colloid goiter was detected in 75.6 % of cases (566 of 749; 95 % CI 723–78,6), nodular adenomatous goiter with follicular neoplasia in 72 patients (9.6 %; 95 % CI 7.7–11.6), papillary carcinoma in 54 patients (7.2 %; 95 % CI 5.7–8.7), suspected papillary carcinoma in 17 patients (2.3 %; 95 % CI 1.5–3.3), medullary carcinoma in 12 patients (1.6 %; 95% CI 0.8–2.4), and anaplastic carcinoma in 6 patients (0.8 %; 95 % CI 0.3–1.3).

At the next stage, 82 patients (57 %; 95 % CI 49–65) diagnosed with follicular neoplasia were selected for further analysis. Surgical interventions included hemithyroidectomy in 57 patients with follicular adenoma (69.5 %; 95 % CI 58.1–80.9) and total thyroidectomy in 25 patients with follicular carcinoma (30.5 %; 95 % CI 20.1–40.8). Following hemithyroidectomy, histological examination revealed malignancy in 5 patients (8.7 %; 95 % CI 1.44–16.1), necessitating repeat radical surgical interventions.

Research results and their discussion. Based on a preliminary analysis of contemporary scientific literature, a panel of six microRNAs with potential diagnostic and prognostic value in thyroid cancer was selected. Subsequent analysis using the UALCAN bioinformatics resource enabled in silico comparison of expression levels of the selected microRNAs in thyroid carcinoma tissue and normal thyroid tissue, as well as evaluation of their association with clinical characteristics of disease progression.

The results demonstrated that thyroid carcinoma tissue is characterized by a significant increase in the expression of certain microRNAs. Specifically, expression levels of miR-15a-5p, miR-146b-5p, miR-221-5p, and miR-222-3p were higher in tumor tissue compared with normal tissue by 1.40-fold ($p<0.0001$), 63.39-fold ($p<0.0001$), 9.27-fold ($p<0.0001$), and 7.67-fold ($p<0.0001$), respectively.

In contrast, bioinformatic analysis revealed a significant decrease in miR-199b-5p expression in tumor tissue - by 3.29-fold ($p<0.0001$) compared with normal thyroid tissue. A similar trend was observed for miR-484, whose expression was also significantly reduced by 3.29-fold in thyroid carcinoma samples (Fig. 1).

Further analysis focused on the association between microRNA expression levels and major clinical characteristics. In patients aged 81 –1 00 years, expression of miR-15a-5p was significantly lower compared with patients aged 21 – 40, 41 – 60, and 61 – 80 years by 1 16-fold ($p<0.05$), 1 24-fold ($p<0.005$), and 1 24-fold ($p<0.001$), respectively.

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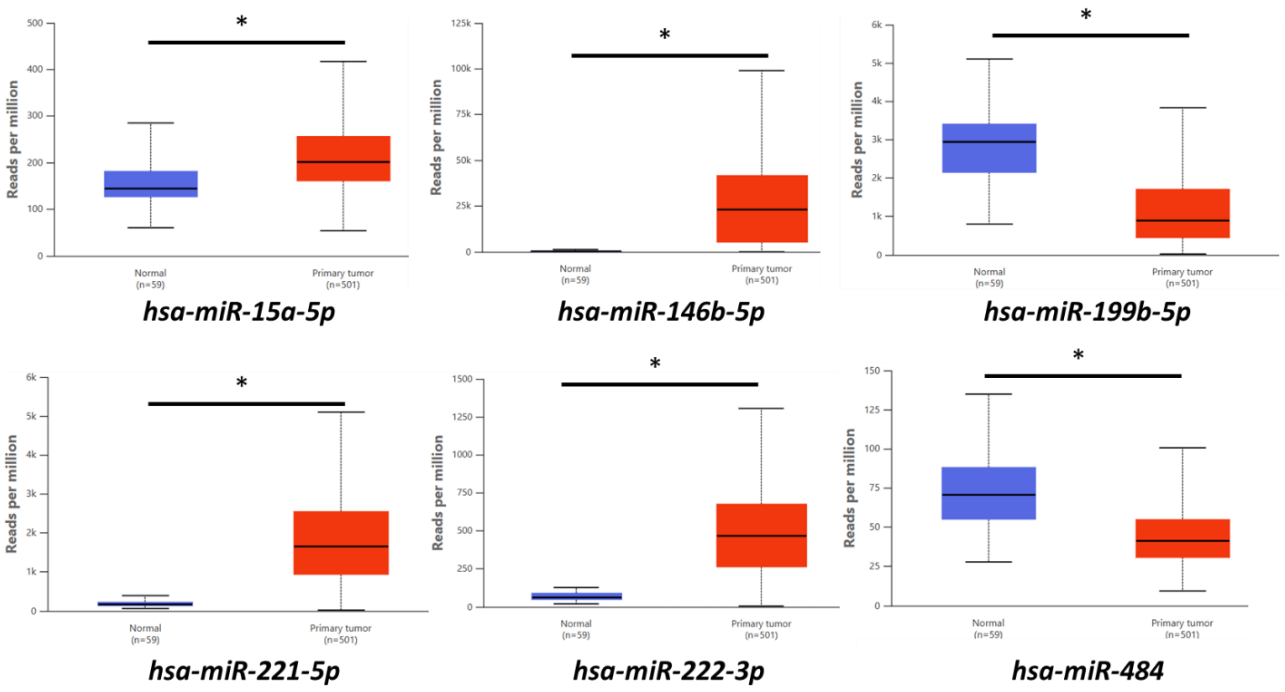

Fig. 1. Expression levels of microRNAs in normal and malignant thyroid tissue

A similar age-related pattern was observed for miR-146b-5p, with significantly lower expression in the oldest age group compared with patients aged 21 – 40, 41 – 60, and 61 – 80 years by 1 43-fold ($p<0.05$), 1 73-fold ($p<0.05$), and 1 46-fold ($p<0.05$), respectively. For miR-221-5p, a 1,57-fold decrease in expression ($p<0.05$) was noted in patients aged 61 – 80 years compared with those aged 21 – 40 years. No age-related associations were identified for miR-199b-5p, miR-222-3p, or miR-484.

Stage-dependent analysis showed that stage II thyroid carcinoma was associated with significantly lower miR-15a-5p expression compared with stage III tumors. In contrast, stage IV disease demonstrated a marked increase in miR-146b-5p expression - by 6 94-fold ($p<0.05$) compared with stage II and by 1 37-fold ($p<0.005$) compared with stage III.

Expression of miR-199b-5p in stage II tumors was significantly lower than in stages I, III, and IV by 1.38-fold, 2.27-fold, and 2.16-fold, respectively (all $p<0.0001$). A similar pattern was observed for miR-221-5p. Increased expression of miR-222-3p was noted in stage IV tumors compared with stages I and II. No significant stage-related differences were found for miR-484.

Analysis based on regional lymph node status demonstrated that metastatic involvement (N1) was associated with a 2.29-fold increase in miR-146b-5p expression compared with N0 tumors. Expression levels of miR-199b-5p, miR-221-5p, and miR-222-3p were also higher in N1 tumors, whereas miR-484 expression was higher in non-metastatic tumors.

Histological analysis revealed that follicular thyroid carcinoma was characterized by a marked reduction in miR-146b-5p expression compared with papillary and well-differentiated carcinomas. Similar trends were observed for miR-199b-5p, miR-221-5p, and miR-222-3p. No significant dependence on histological type was found for miR-15a-5p or miR-484.

Survival analysis demonstrated no significant impact of miR-15a-5p, miR-221-5p, miR-222-3p, or miR-484 expression on overall survival. However, high miR-199b-5p expression was associated with a 35 % reduction in 5-year overall survival ($p<0.0001$). A trend toward association between miR-146b-5p expression and overall survival was also observed ($p=0.096$) (Fig. 2).

It was found that after hemithyroidectomy, histological examination revealed a malignant process in 5 of 57 patients (8.7 %, 95 % CI 1.44–16,1); consequently, repeat radical surgical interventions were performed. Repeat surgical procedures are technically challenging and are often associated with intraoperative complications. Postoperative follow-up lasting up to 24 months after surgery showed that in 3 patients, signs of regional metastasis were detected after repeat thyroidectomy, which required additional radioiodine therapy.

Conclusions. The development and progression of thyroid neoplasms are associated with increased expression of miR-15a-5p, miR-146b-5p, miR-221-5p, and miR-222-3p against the background of a significant decrease in miR-199b-5p and miR-484 expression in tumor tissue.

Significant associations were identified between microRNA expression levels and patient age, tumor stage, regional lymph node metastasis, and histological tumor type. High expression of tumor-associated hsa-miR-199b-5p was shown to be associated with a 35 % reduction in 5-year overall survival in patients with thyroid cancer.

Identification of highly informative predictors of thyroid cancer, including analysis of the investigated microRNAs, may improve the quality of preoperative assessment and contribute to more accurate selection of optimal therapeutic strategies.

Conflict of interest: absent.

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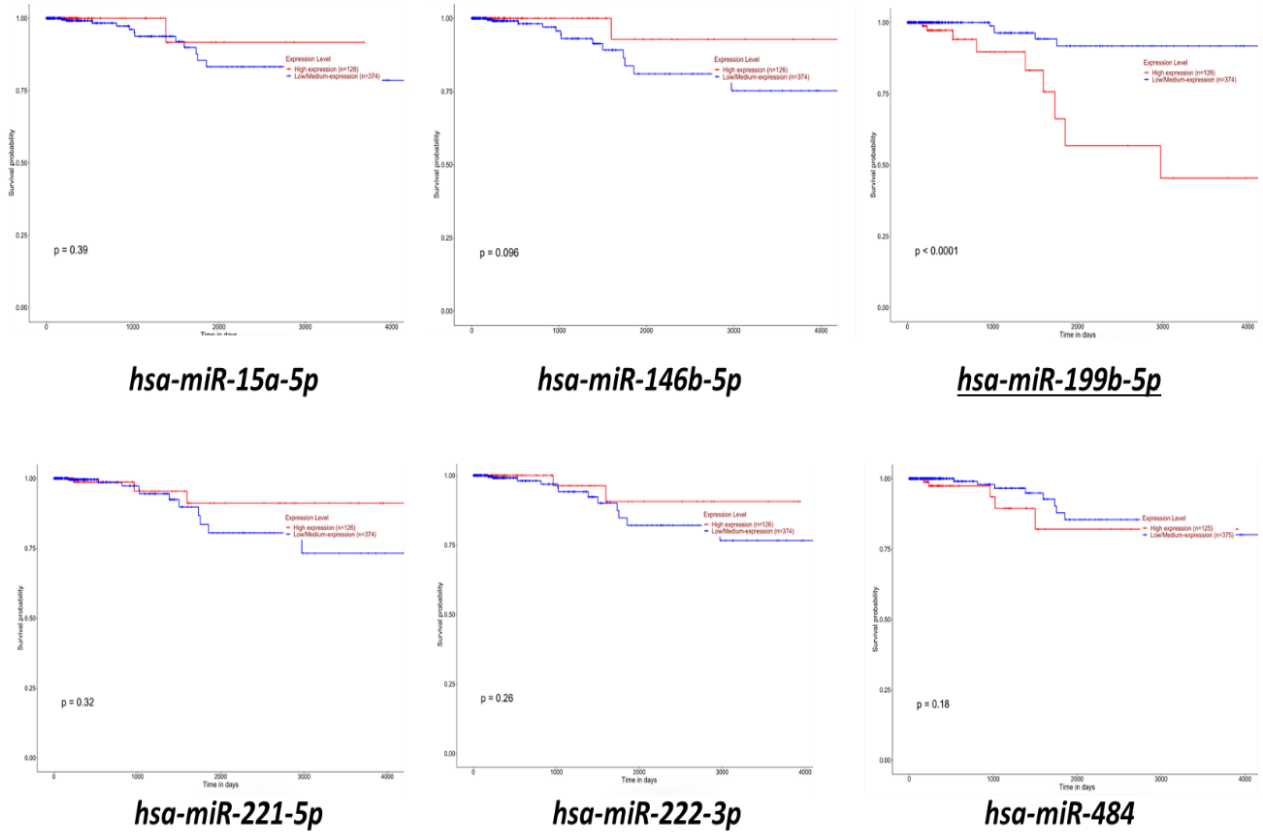

Fig. 2. Survival of patients with thyroid carcinoma depending on the expression levels of the identified microRNAs

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КЛІНІЧНЕ ЗНАЧЕННЯ ВИЗНАЧЕНИХ МІКРОРНК ЯК ПРЕДИКТОРІВ РАКУ ЩИТОПОДІБНОЇ ЗАЛОЗИ І ПЕРЕБІГУ ЗАХВОРЮВАННЯ

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Резюме. Попри загалом сприятливий прогноз диференційованих форм раку щитоподібної залози (РЩЗ), у частини пацієнтів спостерігається агресивний перебіг захворювання, що супроводжується рецидивами та метастазуванням. Обмежена прогностична цінність традиційних клініко-морфологічних критеріїв зумовлює пошук нових молекулярних біомаркерів, зокрема мікроРНК.

Мета роботи – визначення мікроРНК як прогностичного біомаркера раку щитоподібної залози.

Проведено біоінформатичний аналіз експресії панелі із шести мікроРНК у пухлинній і нормальній тканині щитоподібної залози з використанням платформи UALCAN (дані TCGA). Проаналізовано асоціації рівнів експресії мікроРНК із віком пацієнтів, стадією захворювання, статусом регіонарних лімфатичних вузлів, гістологічним типом пухлини та загальною виживаністю. Клінічну частину дослідження виконано на основі аналізу результатів лікування 749 пацієнтів із патологією щитоподібної залози за 2019–2024 роки.

У пухлинній тканині РЩЗ виявлено підвищення експресії hsa-miR-15a-5p, hsa-miR-146b-5p, hsa-miR-221-5p та hsa-miR-222-3p на тлі зниження рівнів hsa-miR-199b-5p та hsa-miR-484. Встановлено статистично значущі асоціації експресії мікроРНК із віком пацієнтів, стадією пухлинного процесу, метастатичним ураженням регіонарних лімфатичних вузлів і гістологічним варіантом РЩЗ. Показано, що високий рівень експресії hsa-miR-199b-5p асоціюється зі зниженням п’ятирічної загальної виживаності на 35 % ($p < 0,0001$).

Отже, дисрегуляція експресії мікроРНК є важливим чинником розвитку та прогресування раку щитоподібної залози. Ідентифіковані мікроРНК, зокрема hsa-miR-199b-5p, можуть розглядатися як потенційні прогностичні біомаркери РЩЗ і бути корисними для персоналізованого вибору лікувальної тактики.

Ключові слова: рак щитоподібної залози, мікроРНК, експресія, прогностичні біомаркери, виживаність.

Конфлікт інтересів: відсутній.

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