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Review

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Contribution to Diagnostic Accuracy and Prognostic Significance of MicroRNAs in Thyroid Cancer

Kalliopi E. Stavrati[a], Efstathios T. Pavlidis[b], Alexandra G. Marneri[c], Christina Mouratidou[c], Athanasios Kofinas[d], Theodoros E. Pavlidis[b, e]

Abstract

The incidence of thyroid cancer, the most common endocrine malignancy, has increased significantly, underscoring the need for improved diagnostic and prognostic methods. MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression and play vital roles in cancer development. In thyroid cancer, they have gained attention as potential diagnostic and prognostic biomarkers. Current diagnostic methods, such as fine-needle aspiration cytology (FNAC), have limitations, particularly for indeterminate nodules (Bethesda III/IV), whereas conventional follow-up markers such as thyroglobulin (Tg) can be unreliable in certain patients. In this context, miRNAs offer a promising complementary approach. Several miRNAs, including miR-146b, miR-221, and miR-222, are consistently overexpressed in thyroid cancer and are associated with tumor presence and aggressive disease features. Circulating and exosomal miRNAs have shown good diagnostic accuracy in distinguishing malignant from benign thyroid nodules. Importantly, using multiple miRNA panels instead of single markers improves diagnostic performance and can reduce unnecessary surgeries in patients with indeterminate cytology. In addition to their diagnostic utility, miRNAs provide critical prognostic information. For instance, increased expression of miR-146b, miR-221, and miR-222 is associated with higher risk of recurrence, lymph node metastasis, and advanced tumor stages. In contrast, reduced expression of miRNAs such as miR-139-5p has been linked to persistent or progressive disease and unfavorable molecular features, including telomerase reverse transcriptase (TERT) promoter mutations. Furthermore, longitudinal changes in circulating miRNA levels may allow for early detection of disease progression, even when traditional biomarkers are inconclusive. At the molecular level, miRNAs operate within complex regulatory networks, including interactions with long non-coding RNAs and key signaling pathways to influence tumor growth and invasion. Their expression is also associated with common oncogenic mutations, such as those in the *BRAF* gene and *RAS* gene, suggesting a role in tumor heterogeneity and behavior. Recent studies highlight the potential of integrating miRNA profiles with other molecular data through multi-omics approaches, to improve risk stratification and support personalized treatment strategies. However, several challenges remain, including variability between studies, lack of standardized protocols, and limited large-scale prospective validation. In conclusion, miRNAs represent a promising and evolving class of biomarkers in thyroid cancer with direct applications in diagnosis, prognosis, and disease monitoring.

Keywords: Papillary thyroid cancer; Thyroid neoplasms; MicroRNAs; Thyroid cancer genomics; Targeted therapy

Introduction

As thyroid cancer is the most prevalent endocrine malignancy, its incidence has increased markedly—a trend potentially attributable to factors such as exposure to ionizing radiation, environmental factors, nutritional influences, and lifestyle-related stressors. It is true that this increase has been noted in many countries such as the United States, Europe, China, Australia, and South Korea; however, the mortality remained stable in most countries worldwide. A better diagnosis of micropapillary thyroid cancer (MPTC, < 1 cm) by improved new imaging methods, mainly ultrasound (US) and fine-needle aspiration cytology (FNAC), has contributed to the increasing incidence. Most experts agree that overdiagnosis can be avoided for this reason. Consequently, there is a critical need for enhanced diagnostic and prognostic methodologies [1–5]. MicroRNAs (miRNAs), which are small non-coding RNA molecules involved in regulating gene expression, are well-recognized for their pivotal role in oncogenesis. In the context of thyroid cancer, miRNAs have garnered considerable inter-

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[a]Surgical Department, Eugenideio Hospital, Athens 11528, Greece
[b]School of Medicine, Aristotle University of Thessaloniki, 2nd Department of Propedeutic Surgery, Hippokration General Hospital, Thessaloniki 54642, Greece
[c]Intensive Care Unit, Hippokration General Hospital, Thessaloniki 54642, Greece
[d]School of Medicine, Aristotle University of Thessaloniki, Department of Transplantation Surgery, Hippokration General Hospital, Thessaloniki 54642, Greece
[e]Corresponding Author: Theodoros E. Pavlidis, School of Medicine, Aristotle University of Thessaloniki, 2nd Department of Propedeutic Surgery, Hippokration General Hospital, Thessaloniki 54642, Greece.
Email: pavlidth@auth.gr

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Table 1. Types of Thyroid Cancer, Frequency, and Implicated Genes

n	Type	Frequency (%)	Implicated genes
1	Well differentiated		
1a	Papillary	84–88	*BRAF V600E, RAS, NTRK*
2a	Follicular	4–7	*RAS, PTEN, PAX8*
3a	Oncocytic carcinoma (Hurthle cell)	2–5	*TP53, NRAS, TERT*
4a	Invasive encapsulated follicular variant of papillary	7 of all papillary	*NRAS, HPAS, PAX8*
2	Poorly differentiated	2–3	*RAS, BRAF V600E, TP53*
3	Anaplastic	1–2	*TP53, BRAF V600E, PIK3CA, TERT*
4	Medullary	3–5	*RET*

est as promising biomarkers for both diagnosis and prognosis [3, 4]. Notably, the diagnostic sensitivity of miR-146b and miR-222 is high, validating their utility in identifying papillary thyroid cancer (PTC) [3]. Furthermore, circulating miRNAs correlate with PTC-specific clinicopathological parameters, including tumor location, tumor size, extrathyroidal extension, lymph node metastasis, the presence of the *BRAF V600E* gene mutation, advanced tumor node metastasis (TNM) stage, and tumor recurrence [4].

The types of thyroid cancer according to the latest World Health Organization (WHO) classification [6] are shown in Table 1.

PTC represents the most frequently diagnosed subtype of thyroid cancer. Although the overall prognosis for most patients is favorable, the presence of lymph node metastasis is recognized as a significant high-risk factor for the development of distant metastases, which constitute the primary predictor of mortality [7]. This malignancy has the potential to evolve into more dedifferentiated and aggressive forms, including poorly differentiated papillary thyroid carcinoma (PDPTC) and anaplastic thyroid carcinoma (ATC), both of which are associated with a poor prognosis [8].

The role of miRNAs in carcinogenesis has been increasingly elucidated. These molecules have emerged as promising markers for the diagnosis and prognosis of thyroid cancer. Furthermore, integrating miRNA expression profiles with mutational status may enhance the accuracy of cytological diagnosis [9].

The genes implicated in thyroid carcinoma include the *BRAF V600E* gene [4, 9–12], *RET* gene [13–16], *RAS* gene [17], *PTEN* gene [18, 19], *TP53* gene [20], *PIK3CA* gene [20], *NTRK* gene [17], and *TERT* gene [21], as shown in Table 1.

The diagnostic strategy for thyroid nodules includes high-frequency US, FNAC, thyroid function tests, computed tomography, and radionuclide imaging [1].

The proposed therapeutic approach for differentiated thyroid carcinoma is based on surgery, determined by tumor diameter (≥ 4 cm), combined with postoperative management. In addition to thyroidectomy, the surgical procedure often includes ipsilateral neck lymph node dissection. This may be prophylactic—performed for tumors larger than 4 cm without evidence of lymph node infiltration targeting the central compartment, or therapeutic regardless of tumor size—encompassing both central and lateral compartments in cases of advanced papillary carcinoma with cervical lymph node involvement (LNI), as well as medullary carcinoma [17, 22]. Adjuvant radioactive iodine therapy (^{131}I) may be indicated for well-differentiated thyroid carcinoma based on histopathological findings. Additionally, thyroid-stimulating hormone (TSH) suppression therapy and thyroglobulin (Tg) measurement as a tumor marker are essential for long-term follow-up [1].

This narrative review highlights recent developments, emphasizing the emerging diagnostic and prognostic roles of miRNAs, as well as the genetic background of thyroid cancer.

Diagnosis

Current diagnostic methods for thyroid nodules, including US and FNAC, have major limitations, particularly for indeterminate cytology (Bethesda III/IV). Approximately 20–30% of thyroid nodules fall into this category, and most of these lesions are found to be benign after surgery, leading to unnecessary procedures. In addition, conventional follow-up biomarkers such as Tg can be unreliable in certain clinical settings. Calcitonin, while a well-established marker for medullary thyroid carcinoma, is not applicable to the more common differentiated thyroid cancers [1–5]. The Bethesda classification system is used to categorize thyroid cytology findings and guide clinical management decisions (Table 2).

Notably, the greatest diagnostic uncertainty occurs in Bethesda categories III and IV, where additional molecular tools are most needed. In this context, miRNAs have emerged as promising complementary biomarkers that can improve diagnostic accuracy and reduce unnecessary surgeries [3, 4].

Circulating miRNAs have demonstrated high diagnostic performance in distinguishing malignant from benign thyroid nodules. A systematic review and meta-analysis of 35 studies reported a pooled sensitivity and specificity of 81%, with an area under the curve (AUC) of 0.88. Importantly, multi-miRNA panels significantly outperformed individual miRNAs, achieving a sensitivity of 88%, a specificity of 89%, and an AUC of 0.94 [23]. These findings suggest that combined miRNA signatures provide a more robust diagnostic approach than single biomarkers.

Among the individual miRNAs, miR-146b-5p is considered one of the most reliable diagnostic markers. Tissue-

Table 2. Bethesda Classification of Fine-Needle Aspiration Cytology

Bethesda category	Description	Risk of malignancy (%)	Recommended management
I	Non-diagnostic	5–10%	Repeat FNA
II	Benign	0–3%	Clinical follow-up
III	AUS/FLUS	10–30%	Repeat FNA/molecular testing
IV	FN/SFN	25–40%	Molecular testing/lobectomy
V	Suspicious for malignancy	50–75%	Surgical intervention
VI	Malignant	97–99%	Surgical intervention

FNA: fine-needle aspiration; AUS/FLUS: atypia undetermined significance/follicular lesion undetermined significance; FN/SFN: follicular neoplasm/suspicious follicular neoplasm.

based studies have shown high diagnostic accuracy (AUC 0.94, sensitivity 89%, and specificity 87%), while circulating miR-146a-5p has also demonstrated strong performance in differentiating PTC patients from healthy controls [24, 25]. Similarly, serum miR-221-3p shows a high diagnostic value (AUC of approximately 0.87), and the diagnostic accuracy of US and FNAC can be improved when miR-222 and miR-146b are significantly elevated in malignant nodules and are used as adjunct markers [26]. Additional miRNAs, including miR-21 and miR-187-3p, are upregulated in tumor tissue, and combined panels incorporating these markers have demonstrated satisfactory diagnostic performance [27].

Furthermore, miR-146b demonstrates strong diagnostic utility for both follicular thyroid adenoma (FTA) and follicular thyroid carcinoma (FTC) [28], while the use of miRNAs miR-183-5p and miR-375-5p shows promise for the diagnosis of medullary thyroid cancer (MTC) [29].

Exosomal miRNAs represent a particularly promising subset due to their stability in circulation. A meta-analysis of 12 studies comprising 1,164 patients reported a pooled sensitivity of 82% and a specificity of 76%. Notably, specific exosomal miRNA panels have achieved excellent performance, with AUC values approaching 0.98 and sensitivity and specificity above 90% [30]. These findings highlight the potential of exosomal miRNAs as non-invasive and highly accurate diagnostic biomarkers.

One of the most clinically relevant applications of miRNAs is their use in evaluating indeterminate thyroid nodules (Bethesda III/IV). Several miRNA-based diagnostic platforms have demonstrated strong performance in this setting. A 19-miRNA next-generation sequencing panel achieved a sensitivity of 91%, a specificity of 100%, and an overall accuracy of 94% [31]. Similarly, the mir-THYpe classifier, which analyzes 11 miRNAs from fine-needle aspiration (FNA) smear slides, showed a sensitivity of 94.6%, a specificity of 81%, and a high negative predictive value (NPV) of 95.9%, comparable to established commercial platforms such as Afirma GSC and ThyroSeq v3 [32].

Other approaches, such as the ThyGeNEXT/ThyraMIR platform, combine mutation analysis with miRNA profiling and have shown improved diagnostic performance compared with mutation testing alone [33]. In addition, newer methods based on pairwise miRNA expression ratios have further improved diagnostic accuracy and reduced the number of indeterminate results, highlighting the continuous evolution in this field [34].

Compared with widely used molecular diagnostic platforms, miRNA-based panels show comparable performance. A meta-analysis of 40 studies revealed that the sensitivity and specificity of miRNA panels were similar to those of Afirma GSC and ThyroSeq v3, with the added advantages of lower costs and potentially wider accessibility [34]. These findings suggest that miRNAs can play an important role either as standalone tools or within integrated diagnostic algorithms.

At the molecular level, miRNA expression is closely linked to key oncogenic mutations. The overexpression of miR-146b, miR-221, and miR-222 is associated with *BRAF V600E* gene and *RAS* gene mutations, suggesting that combining miRNA profiles with genetic data can further improve diagnostic accuracy and better reflect tumor biology [24].

From a clinical perspective, the primary applications of miRNAs include improving the diagnosis of indeterminate nodules, enhancing the accuracy of US and cytology, and reducing unnecessary surgeries [34]. Current clinical guidelines, such as the National Comprehensive Cancer Network (NCCN) Thyroid Carcinoma Guidelines, already recommend molecular testing in selected cases of indeterminate cytology, supporting a more personalized approach to patient management [35].

Overall, miRNAs represent a promising and rapidly evolving class of diagnostic biomarkers in thyroid cancer. Their use, particularly in combination panels and in challenging clinical scenarios such as indeterminate nodules, has the potential to significantly improve diagnostic accuracy and patient management. Despite these promising results, several challenges remain, including differences in laboratory methods, and a lack of standardized cut-off values. Addressing these issues will be essential before miRNA-based diagnostics can be fully integrated into the established protocol.

Prognosis

Accumulating evidence suggests that dysregulated miRNA expression is closely associated with tumor aggressiveness, recurrence, metastasis, and survival outcomes. Among the most consistently studied miRNAs, miR-146b, miR-221, and miR-222 are upregulated in PTC and are strongly associated with adverse clinical features and poor prognosis [4, 7].

A systematic review and meta-analysis demonstrated that increased miRNA expression is significantly associated with worse overall survival (hazard ratio (HR) = 5.94, 95% confidence interval (CI): 2.73–12.90) and disease- or recurrence-free survival (HR = 1.58, 95% CI: 1.08–2.32) [33]. Similarly, in another meta-analysis, miR-146b, miR-222, and miR-221 were identified as the strongest individual predictors of recurrence, with odds ratios (ORs) of 9.11, 6.56, and 3.88, respectively [36]. These findings support the role of specific miRNAs as reliable markers for risk stratification in patients with thyroid cancer.

In addition to survival outcomes, several miRNAs can predict key clinicopathological features. For example, miR-146b-5p and miR-221-3p have demonstrated a strong predictive value for lymph node metastasis and disease recurrence. A CRISPR-based blood assay revealed that these miRNAs performed well in predicting LNI (AUCs of 0.816 and 0.740, respectively) and recurrence (AUCs of 0.921 and 0.756), outperforming traditional systems such as TNM staging and American Thyroid Association (ATA) risk classification [37]. Similarly, miR-222-3p has been identified as an independent predictor of extrathyroidal extension and advanced tumor stage, further supporting its value in identifying high-risk disease [38].

In addition to their diagnostic role, miRNAs provide important prognostic information in thyroid cancer. Increased expression of miR-146b, miR-221, and miR-222 has been consistently associated with increased risks of recurrence, lymph node metastasis, and more advanced tumor stage [36]. In contrast, reduced expression of specific miRNAs, such as miR-139-5p, has been linked to persistent or progressive disease, as well as unfavorable molecular features, including telomerase reverse transcriptase (TERT) promoter mutations [21].

Furthermore, dynamic changes in circulating miRNA levels may allow for early detection of disease progression, even when conventional biomarkers such as Tg are inconclusive [25]. This highlights the potential role of miRNAs not only as prognostic markers, but also as tools for dynamic disease surveillance.

Additional miRNAs have also been associated with disease progression. High expression of miR-136, miR-21, and miR-127 has been linked to distant metastasis and recurrent or persistent disease, suggesting their involvement in tumor dissemination [36]. The expression of miR-155 is also upregulated in thyroid malignancies, with a weak association with LNI, although further validation is required [39].

At the molecular level, miRNAs are involved in complex regulatory networks, including interactions with long non-coding RNAs and key signaling pathways that influence tumor growth and invasion. Their expression is also associated with common oncogenic mutations, such as those in the *BRAF* gene and *RAS* gene, suggesting that they play a role in tumor heterogeneity and tumor behavior [24]. These findings indicate that miRNAs can act together with genetic alterations to drive tumor progression and could improve prognostic accuracy when used in combination.

Recent studies have also highlighted the potential of integrating miRNA profiles with other molecular data through multi-omics approaches, to improve risk stratification and support more personalized treatment strategies. This integrated approach can better capture the biological complexity of thyroid cancer and allow for a more accurate prediction of disease outcomes [40].

Epigenetic markers—including promoter hypermethylation of tumor suppressor genes, global DNA hypomethylation, and specific miRNAs such as miR-146b, miR-221, and miR-375—have emerged as promising indicators of aggressive disease progression in well-differentiated thyroid cancer [41].

LNI is a critical prognostic factor associated with unfavorable survival outcomes in MTC patients. The presence of desmoplastic stroma and elevated expression levels of miR-21 have been identified as robust predictors of LNI, potentially guiding surgical decision-making regarding the extent of cervical lymph node dissection in patients with large, sporadic MTCs lacking preoperative evidence of LNI [42].

Additionally, the expression of miR-224 is upregulated in RAS-mutated MTCs and is associated with an improved patient prognosis, suggesting its potential role as an independent prognostic biomarker in this disease [13].

Furthermore, miR-21 modulates the expression of programmed cell death 4 (PDCD4), with the miR-21/PDCD4 signaling axis demonstrating significant correlations with clinicopathological features and patient prognosis [14].

Importantly, the prognostic value of miRNAs can have implications for targeted therapy. Specific miRNA expression profiles are associated with key oncogenic pathways and molecular subtypes, which can influence treatment response. For example, the interaction of miRNAs with signaling pathways related to *BRAF* gene and *RAS* gene mutations suggests that they could help identify patients who will benefit from targeted therapies. However, the role of miRNAs in guiding therapeutic decisions is still under investigation and requires further clinical validation [40, 41, 43].

MicroRNA might be another tool to select patients more appropriately. This method is promising, but more documentation is needed. The studies show quite contradictory results especially concerning the cut-off values and the standardization of the protocols, as mentioned above [44, 45].

Overall, miRNAs represent a promising class of prognostic biomarkers in thyroid cancer. They provide important information regarding tumor behavior, risk of recurrence, and likelihood of disease progression, often complementing or even exceeding traditional clinical systems. Despite these encouraging findings, several limitations remain, including inter-study variability, a lack of standardized methodologies, and limited large-scale prospective validation. Further research is needed to establish standardized protocols and confirm the clinical utility of miRNAs in routine clinical practice.

Conclusions

miRNAs represent a rapidly evolving, promising class of biomarkers in thyroid cancer, with potential applications in diagnosis, prognosis, and disease monitoring. The combined analysis of miRNA expression profiles and mutational status may enhance the accuracy of cytological diagnosis. These

molecules have emerged as valuable predictors of tumor progression and aggressiveness. Furthermore, miRNAs provide a more precise assessment of the risk of adverse clinical outcomes and may inform the selection of targeted therapeutic strategies. Incorporating miRNAs into clinical protocols has the potential to improve patient management, particularly in complex diagnostic and follow-up contexts. However, several challenges remain, including variability across studies, a lack of standardized analytical methods, and a limited number of large-scale prospective studies assessing clinical outcomes.

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Conflict of Interest

The authors declared no potential conflict of interest.

Author Contributions

KES, ETP, and AM designed the research and analyzed the data. AK and CM performed the research, contributed new analytic tools, evaluated the data, and reviewed the paper. TEP analyzed the data review and approved the paper. All authors have read and approved the final manuscript.

Data Availability

All data generated or analyzed during this study are included in this published article, and further inquiries should be directed to the corresponding author.

AI Use Declaration

The manuscript was not AI-generated. The content was written and developed by the authors. AI tools were used solely for language editing and polishing to improve clarity and readability of the manuscript. The manuscript underwent standard academic revisions by the authors.

Abbreviations

ATA: American Thyroid Association; ATC: anaplastic thyroid carcinoma; AUC: area under the curve; AUS/FLUS: atypia undetermined significance/follicular lesion undetermined significance; Bethesda III/IV: indeterminate thyroid nodules; CI: confidence interval; FNA: fine-needle aspiration; FNAC: fine-needle aspiration cytology; FTA: follicular thyroid adenoma; FTC: follicular thyroid carcinoma; FN/SFN: follicular neoplasm/suspicious follicular neoplasm; HR: hazard ratio; ^{131}I: adjuvant radioactive iodine therapy; LNI: lymph node involvement; miRNAs: microRNAs; MTC: medullary thyroid cancer; MPTC: micropapillary thyroid cancer; NCCN: National Comprehensive Cancer Network; NPV: negative predictive value; OR: odds ratio; PTC: papillary thyroid cancer; PDCD4: programmed cell death 4; PDPTC: papillary thyroid carcinoma; Tg: thyroglobulin; TERT: telomerase reverse transcriptase; TNM: tumor node metastasis; TSH: thyroid-stimulating hormone; US: ultrasound; WHO: World Health Organization

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