RESEARCH ARTICLE

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Prognostic Stratification of Highly Differentiated Thyroid Cancer Based on Molecular Genetic Studies

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Abstract

Background: The aim of this literature review was to identify the critical role of molecular-genetic and epigenetic factors in predicting the course of differentiated thyroid carcinoma (DTC), to improve diagnostic and therapeutic strategies for this disease. **Methods:** Analytical and comparative review methods of publications available in the databases of Scopus, Web of Science, and PubMed were employed. **Results:** The results demonstrated that the presence of specific mutations and epigenetic modifications significantly influenced the likelihood of recurrence, metastatic potential, and tumour sensitivity to conservative treatment, including radioactive iodine therapy. Mutations in the B-Raf kinase family protein, telomerase reverse transcriptase, rat sarcoma genes, and rearranged during transfection/papillary thyroid carcinoma rearrangements were shown to be associated with an increased risk of recurrence, metastatic activity, and reduced efficacy of radioiodine treatment. Epigenetic markers such as promoter methylation of tumour suppressor genes, global hypomethylation, and microRNAs (miR-146b, miR-221, miR-375) emerged as promising predictors of aggressive disease progression. The review outcomes indicate that a personalized approach based on identifying the molecular profile of the tumour allows for more accurate risk assessment of adverse outcomes and determination of prospects for targeted therapy. **Conclusion:** The practical significance of this work lies in the possibility of considering the identified genomic and epigenomic features when choosing surgical intervention and adjuvant therapy, thereby increasing the chances for long-term remission. Additionally, it emphasizes the standardization of analytical methods and the development of a unified system for evaluating the combined genetic alterations, which could enhance the quality of prognostic stratification and more effectively tailor treatment strategies.

Keywords: Remission - Epigenetic factors - Tumour aggressiveness - Recurrence risk - Personalized approach

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Introduction

Differentiated thyroid carcinoma (DTC) is one of the most common malignant tumours of the endocrine system [1]. Despite the generally favourable prognosis, a subset of patients exhibits a tendency toward recurrence and progression, necessitating more precise prognostic stratification methods. Clinical and morphological features (tumour size and location, extent of invasion into surrounding tissues, histological structure) traditionally form the basis for treatment strategy decisions. However, this approach does not always effectively predict the individual course of the disease, especially in cases of atypical tumour behaviour.

In the present study, prognostic markers refer to genetic and epigenetic modifications that reveal the probable trajectory of DTC irrespective of treatment, including the risks of recurrence, metastasis, and disease advancement. These encompass mutations like *BRAF* V600E, *RAS*, and *TERT*, which are associated with more aggressive disease variants and inferior outcomes, regardless of treatment approaches. Predictive indicators especially suggest a tumour's expected response or resistance to certain treatments, notably concerning medicines such as radioiodine. *BRAF* mutations indicate resistance to radioiodine therapy, but *TERT* mutations are associated with diminished efficacy of radioiodine in DTC patients. *NTRK* and *PLEKHS1* mutations similarly forecast resistance to radioiodine, informing the use of alternate therapeutic approaches. By differentiating these signs, doctors can more precisely customise treatment plans, utilising prognostic markers to evaluate risk and predictive markers to enhance therapeutic response.

From 2010 to 2024, molecular-genetic diagnostic research has attracted considerable attention due to advances in next-generation sequencing technologies and the accumulation of oncogenesis knowledge. At the genetic level, mechanisms influencing tumour aggressiveness, therapy sensitivity, and metastatic potential often reside. A major current challenge remains the lack of a unified system to confidently interpret genetic test results and form comprehensible prognostic algorithms suitable for

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routine clinical practice.

In recent years, many researchers have attempted to incorporate molecular-genetic findings into prognostic models for DTC. The study by Yip et al. [1] investigated the role of molecular profiling in differentiated thyroid carcinoma, identifying B-Raf kinase family protein (*BRAF*) and telomerase reverse transcriptase (*TERT*) mutations as associated with an increased risk of distant metastases and poorer prognosis. These data underscore the need to integrate genetic information for more accurate patient stratification. The review by Sloneva et al. [2] emphasizes expanding the panel of genetic markers for risk stratification in patients with well-differentiated thyroid carcinoma, enabling more effective detection of aggressive disease forms and adjustment of therapeutic strategies. The prognostic utility of glycolysis-associated genes in recurrence prediction was demonstrated by Wu et al. [3]. Their model based on expression of adrenomedullin (ADM), MKI67 (proliferation marker *Ki-67*), glycoprotein CD44), and thymidylate synthase (TYMS) showed high predictive accuracy (AUC 0.767), outperforming standard clinical approaches. These findings support the inclusion of molecular data in treatment decision-making.

Risk stratification systems analysis by van Velsen et al. [4] demonstrated improved survival prediction when molecular markers are integrated with clinical data. In particular, the TNM system supplemented with molecular indicators outperforms existing stratification models. The study by Gulec et al. [5] showed that a theranostic approach, including molecular profiling, significantly increases the accuracy of treatment outcome predictions, allowing more rational determination of surgical extent and radioiodine therapy necessity. Mu et al. [6] confirmed the significance of *BRAF* and *TERT* mutations as key predictors of radioiodine resistance. These mutations were detected in 63.2% of patients with distant metastases, highlighting their role in risk stratification and therapeutic decision-making. Further research is needed to refine the prognostic value of molecular markers such as *BRAF* and *TERT* and integrate them into clinical practice. Prospects for studying these mutations are linked to the development of personalized treatment approaches for well-differentiated thyroid carcinoma.

Current study on DTC underscores the intricacy of forecasting its clinical trajectory, with numerous studies concentrating on genetic abnormalities such as *BRAF* and *TERT* and their influence on disease advancement. Nonetheless, a disparity persists in the incorporation of molecular-genetic and epigenetic indicators into a cohesive, standard clinical prognostic framework. Despite advancements in next-generation sequencing and molecular profiling that have greatly improved the comprehension of DTC, the absence of standardised protocols for integrating these discoveries into clinical practice continues to pose a substantial problem. The novelty of the present research resides in its goal to fill these gaps by delivering an exhaustive examination of the amalgamation of molecular-genetic markers with clinical data for enhanced prognostic classification and individualised treatment strategies.

The objective of this article is to analyse current achievements in molecular-genetic research aimed at improving prognosis in patients with DTC. This includes examining key genetic and epigenetic markers, assessing possibilities for integrating clinical and morphological parameters with molecular-genetic criteria, and defining prospects for developing a unified prognostic stratification algorithm suitable for routine clinical use.

Materials and Methods

A literature search was conducted among sources published between 2020 and 2024 in major abstract and full-text databases, including but not limited to PubMed, Web of Science, and Scopus. Article selection was performed without strict limitations on publication type, encompassing peer-reviewed and non-peer-reviewed sources, covering the period from 2010 to 2024. Publications in both Russian and English languages were included, allowing for a comprehensive review of results from various scientific schools. Key search terms included "differentiated thyroid carcinoma," "molecular-genetic markers," "*BRAF*," rearranged during transfection/papillary thyroid carcinoma ("RET/PTC"), "risk stratification," "tumour aggressiveness," and related terms. This approach yielded 452 articles ranging from clinical and experimental studies to review papers reflecting the current state of the issue across different regions and research groups. Following the elimination of duplicates and irrelevant studies, 198 articles were chosen for comprehensive assessment according to the inclusion criteria. The criteria concentrated on studies investigating the prognostic significance of molecular-genetic and epigenetic markers in DTC. Studies were removed for not meeting the inclusion criteria, including insufficient methodological details, small sample numbers, inconsistent data, or the absence of novel information. A total of 45 articles were included in the analysis.

During the review process, special attention was paid to the adequacy of methodological descriptions, reliability of presented data, and their potential value for understanding the prognostic role of molecular-genetic alterations in DTC. Based on the overall collection of identified publications, a selection of the most substantive and relevant sources was made for discussion and analysis in the final part of the review.

Inclusion criteria were: research focus on well-differentiated thyroid carcinoma and factors affecting prognosis (including genetic or epigenetic analysis); clear correlation between study results and clinical outcomes, tumour aggressiveness, or recurrence likelihood; use of modern molecular-genetic testing methods ensuring data reliability and reproducibility; and comprehensive presentation of results, including identified markers, discussion of possible mechanisms, and influence on disease course.

Exclusion criteria included the absence of methodological details, which impeded assessment of study quality and analytical methods; small sample sizes that did not ensure statistically valid conclusions; duplication of previously published data without new information or clarification; and substantial

inconsistencies in the presentation of results, which hindered interpretation and comparison with other studies.

Following the preliminary selection of publications, a detailed evaluation was conducted to verify the completeness of the presented data and the applicability of results to the issues of prognostic stratification in DTC. The literature review method incorporated elements of data synthesis, allowing for a structured approach to selecting and analysing peer-reviewed articles. A descriptive approach was employed, whereby each study was examined according to key parameters: identified molecular markers, clinical characteristics of the study cohort, and the potential influence of specific genetic alterations on tumour progression. To systematise the findings, brief summaries were compiled for each study, highlighting the most significant aspects of the results, such as the association of *BRAF* mutations with tumour aggressiveness or the potential role of epigenetic changes in metastasis formation. The subsequent step involved comparing findings across different author groups to identify common patterns and contradictions. Where relevant, additional factors were taken into account, such as combinations of genetic alterations with traditional clinical criteria, patient age, and histological features of the tumour.

Results

Current understanding of the clinical significance of differentiated thyroid cancer

DTC, most commonly represented by papillary and follicular subtypes, is traditionally considered the most favourable form among thyroid malignancies. This type of cancer has become a subject of increasing interest for both clinicians and basic researchers, as advances in imaging techniques, fine-needle aspiration biopsy, and histological verification have significantly improved early tumour detection. However, despite its relatively "mild" clinical course, a proportion of patients exhibit aggressive forms, characterised by recurrence and metastasis. Understanding the factors that determine the shift from a "standard", relatively indolent course to a more severe trajectory remains one of the core challenges in contemporary endocrine oncology.

A distinguishing feature of DTC is its high sensitivity to radioiodine therapy, owing to tumour cells retaining certain characteristics of normal thyrocytes, in particular the ability to absorb iodine via specific transporter proteins. Nonetheless, iodine uptake capacity may vary substantially depending on the tumour's genetic and epigenetic profile. For some patients, radioiodine therapy proves highly effective in achieving long-term remission, while for others, molecular disruptions in iodine-handling mechanisms diminish treatment efficacy and negatively impact prognosis.

Research has shown considerable variability in the effectiveness of radioiodine therapy, largely attributable to molecular-genetic and epigenetic factors, which in turn influence patient prognosis and therapeutic response. Oh and Ahn [7] demonstrated that genetic alterations, such as mutations in *BRAF*, rat sarcoma (*RAS*), and RET/PTC rearrangements, significantly impair sodium-iodide symporter NIS expression, reducing the tumour's ability to concentrate iodine. This leads to radioiodine resistance and poorer treatment outcomes in a subset of patients. In contrast, Wächter et al. [8] reported that epigenetic interventions, particularly the use of histone deacetylase inhibitors, can restore NIS expression, enhance iodine uptake, and suppress oncogenic signalling. While Oh and Ahn highlight the detrimental effects of genetic mutations, Wächter et al. propose a potential solution via epigenetic modulation.

Spitzweg et al. [9], on the other hand, emphasised the role of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase signalling pathways, noting that disruptions in these pathways also impair iodine uptake. The authors suggest that targeted therapies aiming to restore these pathways may enhance the effectiveness of radioiodine therapy, complementing Wächter et al.'s [8] findings regarding molecular correction strategies. Meanwhile, Mu et al. [10] focused on the prognostic significance of *BRAF* and *TERT* mutations, identifying their association with radioiodine resistance and more severe disease courses in 63.2% of patients with distant metastases. This underscores the need for molecular diagnostics in risk stratification and contrasts with the therapeutic focus of Wächter et al. [8] and Spitzweg et al. [9]. Thus, while all studies converge on recognising the central role of genetic (*BRAF*, *TERT*, *RAS, RET/PTC*) and epigenetic factors in modulating the response to radioiodine therapy, their approaches differ: Oh and Ahn [7] describe resistance mechanisms, Mu et al. emphasise diagnostic stratification, whereas Wächter et al. [8] and Spitzweg et al. [9] propose therapeutic strategies to overcome these limitations. Collectively, these findings provide a comprehensive understanding of the issue and highlight the promise of integrating molecular and epigenetic approaches in DTC treatment.

Clinical interest also extends to cases involving microcarcinomas – minute tumour foci often discovered incidentally during ultrasound examinations or prophylactic thyroid tissue removal for unrelated reasons. Although many of these findings do not progress into clinically significant disease, some microcarcinomas may possess hidden aggressiveness that cannot be predicted solely based on tumour size or morphological features. Kayhan et al. [11] confirmed the influence of tumour size and lymph node metastases on prognosis, identifying tumours larger than 5 mm and lymph node involvement as indicators of greater aggressiveness. Important recurrence predictors such as age under 45 years, tumour size ≥6 mm, and angioinvasion were reported by Medas et al. [12]. These indicators support the need for active surveillance or more aggressive treatment in high-risk groups. As a result, the period from 2010 to 2024 has been marked by active searches for molecular markers that enable more objective differentiation between stable tumours and those likely to progress rapidly.

In addition, DTC has historically been associated with younger age groups compared to other malignancies. Many authors emphasise that patients aged under 45–50 years tend to have a better prognosis; however, the

presence of aggressive genetic alterations may lead to rapid tumour growth and metastatic progression even in young individuals. Therefore, identifying factors that determine "masked" aggressiveness remains equally relevant for both younger and older patient populations.

The role of molecular genetic disorders in the pathogenesis and progression of highly differentiated tumours

The development of highly differentiated thyroid cancer is associated with point mutations, gene rearrangements, and changes in the expression level of multiple cellular proteins involved in the regulation of growth, division, and apoptosis. It is known that *BRAF* V600E mutation capable of activating MAPK signalling cascade is the most frequent in papillary variant (Table 1).

There is a theory suggesting that this genetic alteration increases tumour cells' capacity for aggressive growth, although in some cases conflicting data exist regarding the actual clinical impact of *BRAF*. Scheffel et al. [13] established that the *BRAF* V600E mutation leads to hyperactivation of the MAPK signalling pathway, causing uncontrolled cell proliferation and reducing the effectiveness of radioiodine therapy by 30%. This is consistent with the findings of Śmiech et al. [14], who reported that *BRAF* V600E enhances cellular proliferation by an average of 70% and is associated with novel mutation types (classes II and III) that interact with other signalling pathways and increase tumour aggressiveness. Thus, both studies highlight the link between the mutation and enhanced proliferative activity, while Śmiech et al. [14] additionally emphasise its impact on tumour heterogeneity. Ge et al. [15] found that in 58.6% of patients with the *BRAF* V600E mutation, radioiodine therapy proved ineffective, which correlated with elevated thyroglobulin levels following treatment. This observation supplements the findings of Scheffel et al. [13] regarding the reduced therapeutic response, but draws particular attention to clinical markers such as thyroglobulin, positioning the mutation as an important prognostic indicator.

At the same time, Orozco et al. [16] demonstrated that *BRAF* V600E increases the expression of the CLDN1 protein, associated with tumour progression and invasion, in 67% of cases. This study broadens the understanding of the mutation's role by pointing to its contribution to invasiveness, not merely to treatment resistance. Gao et al. [17] add another dimension by showing that *BRAF* V600E prevents apoptosis through inhibition of mitochondrial membrane permeability, thereby enhancing tumour cell survival in 75% of patients with papillary thyroid carcinoma. This mechanism differs from the emphasis on proliferation and resistance, underscoring the mutation's anti-apoptotic effect as a key factor in tumour persistence. In comparing the results, it becomes apparent that the studies agree on the negative impact of *BRAF* V600E on DTC outcomes, though they differ in focus: Scheffel et al. [13] and Śmiech et al. [14] focus on proliferation and signalling pathways, Ge et al. [15] on clinical resistance, Orozco et al. [16] on invasiveness, and Gao et al. [17] on cell survival. Together, these data underline the multifaceted importance of the mutation as a biomarker requiring a comprehensive approach to diagnosis and treatment.

In parallel, the role of *RAS* mutations is discussed, which may differently influence tumour differentiation and proliferative potential depending on the specific subtype (*NRAS, KRAS, HRAS*). Bikas et al. [18] found that *RAS* mutations, when combined with additional oncogenic alterations, significantly worsen prognosis: the likelihood of advanced-stage disease (III-IV) increases to 67% compared to 3% for isolated mutations, while the risk of mortality increases more than tenfold (20% vs 1.8%). This indicates a synergistic effect of combined genetic alterations. Ahmadi and Landa [19] support these findings, noting that the combination of *RAS* and *TERT* mutations increases the risk of recurrence and metastasis by a factor of 2.3.

Liu et al. [20] identified a correlation between *RAS* mutation frequency and histology: 61.5% in follicular carcinomas, 15% in adenomas, and 4.8% in classic papillary carcinomas. Moreover, tumour diameter in patients with *RAS* mutations was 40% larger. These findings contrast with those of Guan et al. [21], who showed that 58.9% of *RAS*-positive nodules were benign, with only 28.6% being malignant, and that isolated *RAS* mutations were associated with a low risk of recurrence. Thus, while Liu et al. [20] emphasise the link between mutations and histological aggressiveness, Guan et al. [21] highlight their frequent benign nature and favourable prognosis when isolated. Lai et al. [22] examined *RAS* mutations in the context of anaplastic thyroid cancer, identifying their association with extremely poor survival: median overall survival was only six months four times shorter than in patients with *BRAF* V600E mutations. This stands in stark contrast to Guan et al. [21]'s data regarding low recurrence risk in isolated *RAS* mutations, highlighting the substantial impact of tumour type benign or highly aggressive on mutation effects. Comparing the

Table 1. Genetic Markers and Their Clinical Significance

Genetic Marker	Clinical Significance
BRAF V600E	Reduced radiosensitivity, increased aggressiveness
RAS	Advanced disease stage, risk of metastasis
RET/PTC	Active proliferation via the MAPK/ERK pathway
TERT	Risk of metastasis, decreased therapy effectiveness
NTRK	Increased risk of metastasis and aggressiveness
PLEKHS1	Risk of radioiodine resistance, metastases

Source: compiled by the authors based on [7-9]. Notes: *PLEKHS1*, pleckstrin homology domain-containing S member 1; *NTRK*, neurotrophic tyrosine receptor kinase.

findings, *RAS* mutations exhibit a dual nature: isolated mutations are often associated with favourable prognosis, while their combination with other genetic alterations or presence in anaplastic tumours significantly worsens outcomes. Liu et al. [20] add histological context, showing their predominance in follicular carcinomas. These differences underscore the necessity for a differentiated approach to evaluating *RAS* mutations, based on the patient's clinicopathological profile.

The evidence on the prognostic and predictive significance of *BRAF* V600E and *RAS* mutations in DTC is contentious, as research presents contradictory findings. Although numerous studies indicate that *BRAF* V600E correlates with diminished radiosensitivity and heightened aggressiveness, other research presents evidence showing minimal or no substantial effect on patient outcomes [23, 24]. *RAS* mutations, deemed crucial in certain studies for forecasting severe disease and metastasis, exhibit a more benign impact in other research, particularly when occurring in isolation [10, 18]. These inconsistencies underscore the heterogeneity of DTC, as the impact of specific mutations may differ depending on parameters such as tumour subtype, co-occurring genetic abnormalities, and the assessment methodology. Moreover, the absence of standard genetic testing techniques and discrepancies in study designs exacerbate these inconsistencies, highlighting the necessity for more comprehensive, large-scale investigations to address these variations and enhance prognostic models.

In follicular carcinoma, mutations in genes related to cellular ageing and translocations activating specific signalling pathways are often mentioned. Notably, these alterations may affect TSH receptors or mechanisms responsible for iodine transport. As a result, the tumour, which initially retains some "benign" characteristics, may lose the ability to uptake radioiodine or suppress the expression of proteins directly involved in iodine accumulation. This, in turn, leads to less successful treatment outcomes and increased risk of recurrence. Iodine transporters such as the sodium-iodide symporter (NIS) and *PENDRIN* play a key role in the uptake of iodine by thyroid cells and in ensuring the efficacy of radioiodine therapy. Studies confirm that these proteins are actively involved in the transmembrane transport of iodide ions in thyroid cells. Jankovic et al. [25] demonstrated that *NIS* and *PENDRIN* expression is significantly higher in follicular carcinoma cells, confirming their role in the disease's pathogenesis. Concurrently, Huang et al. [26] found that dysfunction of NIS and *PENDRIN* is associated with alterations in signalling pathways such as mTOR and MAPK. These pathways regulate cell proliferation, apoptosis, and invasion, making iodine transporters potential therapeutic targets. Moreover, the authors noted that dysfunction of iodine transporters may not only reduce radioiodine therapy efficacy but also contribute to tumour progression. Reduced NIS activity is also linked to its decreased expression on the cell membrane. Lee et al. [27] confirmed that diminished membrane localisation of NIS limits tumour cells' capacity to uptake iodine, thus reducing therapeutic effectiveness and potentially worsening patient prognosis. Innovative approaches proposed by Han et al. [28] include the use of mesenchymal stem cells to restore NIS expression in radioiodine-resistant tumours. This may become a promising strategy to increase tumour sensitivity to radioiodine therapy by delivering NIS genes directly to affected cells.

In addition to the aforementioned genes, researchers are actively investigating the role of RET/PTC rearrangements, which are particularly significant in populations exposed to radiation (e.g., nuclear accidents). It is believed that RET activation may initiate active proliferation via the MAPK/ERK pathway. Such mechanisms are often detected in papillary carcinoma, where the clinical course may range from relatively "mild" to highly aggressive, depending on the specific type of rearrangement.

Another important area of study is epigenetic regulation – specifically, promoter methylation of tumour suppressor genes and chromatin structure modification. It is hypothesised that the combination of epigenetic changes and point mutations leads to more stable activation of oncogenic pathways. This suggests that even if only one "key" mutation (e.g., *BRAF* V600E) is identified during diagnostics, the actual array of modifications may be much broader and more complex than standard analysis implies.

Epigenetic factors and micrornas: Expanding research horizons

In recent years, there has been a growing interest within the scientific community in microRNAs (miRNAs) and other non-coding RNAs, which have the capacity to regulate the expression of hundreds of proteins simultaneously, thereby exerting a significant influence on the clinical behaviour of tumours. Functionally, these short RNAs may act either as oncomiRs (promoting proliferation) or as suppressors (inhibiting growth). In the context of DTC, the analysis of various miRNA combinations often provides a more nuanced picture than the detection of one or two DNA-level mutations alone (Table 2). For instance, certain clusters of miRNAs have been identified that collectively indicate an increased capacity of tumour cells for angiogenesis and basement membrane penetration, suggesting a higher metastatic potential. Conversely, decreased levels of specific miRNAs may serve as markers of a more indolent tumour course and a more favourable response to standard treatments.

Table 2. Epigenetic Factors and Their Clinical Significance

Epigenetic Factor	Clinical Significance
Promoter Methylation	Silencing of tumour suppressor genes, reduced immune response
Global Hypomethylation	Increased tumour aggressiveness
microRNA miR-146b	Prediction of recurrence, risk of metastasis
microRNA miR-221	Associated with aggressive tumour forms
microRNA miR-375	Poorer prognosis, decreased survival

Source: compiled by the authors based on [31-33].

These observations are supported not only by theoretical models but also by clinical case studies in which miRNA dynamics have been associated with recurrence rates or the speed of metastatic progression. One of the most promising directions in this field is the development of miRNA panels – sets of key regulatory RNAs – that enable more precise tumour profiling, potentially allowing for more refined prognostic assessments. However, the broader implementation of such approaches remains challenging due to the lack of universal standards for sample isolation, storage, and analysis, as well as the limited availability of large-scale multicentre studies to confirm the reproducibility of these tests. Epigenetic mechanisms, including DNA methylation and histone modifications, play a crucial role in the regulation of miRNAs, which in turn affects tumour progression and prognosis across a range of cancer types, including thyroid cancer. Pajares et al. [29] emphasised that miRNA dysregulation through epigenetic alterations creates a new foundation for their potential use as diagnostic and prognostic biomarkers. Silaghi et al. [30] demonstrated the prognostic relevance of miR-146b, miR-221, and miR-222 in thyroid cancer recurrence. Patients with elevated expression levels of these miRNAs were found to be at significantly increased risk of recurrence, particularly in the papillary subtype (OR=9.11, 95% CI: 3.00-27.52, $p<0.001$).

Discussion

The study by Sawicka et al. [31] identified altered miRNA levels in children with autoimmune thyroid diseases. Specifically, the level of miR-15a-5p was significantly reduced (21.61 vs. 50.22 amol/μL, p=0.03), suggesting a heightened risk of malignant transformation. Manso et al. [32] investigated 27 miRNAs associated with medullary thyroid carcinoma, confirming their diagnostic and therapeutic significance. These miRNAs exhibited unique expression patterns distinct from normal tissue. Li et al. [33] identified 483 epigenetically regulated long non-coding RNAs (lncRNAs) that significantly influence the progression of thyroid cancer. Among them, lncRNA AC110011 was linked to lymph node metastasis and increased tumour size, making it a potentially important prognostic marker. In comparing these findings, Pajares et al. [29] propose a general framework for the epigenetic role of miRNAs, while Silaghi et al. [30] and Manso et al. [32] specify this within the contexts of papillary and medullary thyroid carcinoma, respectively. Sawicka et al. [31] extend the discussion to pre-malignant states in children, and Li et al. [33] shifts the focus to lncRNAs, highlighting their association with metastasis. Together, these studies underscore the diversity of epigenetic markers and their potential for personalised medicine, while differing in terms of application specificity and tumour types.

Apart from microRNAs, the epigenetic field increasingly highlights the phenomenon of global hypomethylation or localised promoter hypermethylation, leading to the "silencing" of tumour suppressor genes. Some researchers associate such epigenetic alterations with mechanisms of immune evasion, which may open up new horizons for immunotherapy in DTC, although this area is still in its early stages of development. In the future, the ability to modulate the epigenetic landscape using epigenomic drugs (such as DNA methylation or histone acetylation inhibitors) appears particularly promising, as such approaches could enhance the efficacy of conventional radioiodine therapy and reduce tumour progression.

The impact of molecular-genetic status on treatment strategy and prognosis

In addition to their fundamental scientific value, molecular-genetic and epigenetic studies also have direct clinical relevance. Over time, it is becoming increasingly evident that patients with aggressive genetic profiles may require more intensive surveillance and broader therapeutic interventions. For example, in the presence of a suspected *BRAF* V600E mutation – which is often associated with reduced sensitivity to radioiodine – patients may need additional pharmacological treatment or more frequent diagnostic evaluations aimed at early detection of recurrence.

Clinically, particular attention is given to the combination of morphological characteristics (such as solid growth, vascular invasion, or tumour size) and the identified molecular-genetic status. If both sets of features indicate high risk, the prognosis becomes more concerning, and clinicians may recommend radical surgical intervention, including total thyroidectomy with regional lymph node dissection. In cases of the follicular subtype with impaired iodine uptake, early implementation of targeted therapy may also be discussed, although such measures remain under consideration and are not yet standard practice. Another important issue is the optimal management strategy in the early postoperative period. If the molecular profile indicates a high risk of metastasis, aggressive adjuvant therapy may be required even after complete tumour resection, including radioiodine treatment and prolonged suppression of thyroid-stimulating hormone (TSH). This strategy is aimed at minimising the chance of tumour cells with aggressive genomic patterns entering a latent state that could later lead to recurrence. Pekova et al. [34] reported that *NTRK* rearrangements are found in 6.7% of patients with papillary carcinoma and 20% of those with poorly differentiated carcinoma, increasing the risk of metastasis by 2.5-fold and correlating with aggressive tumour behaviour. This underscores the need for *NTRK* inhibitors in such patients. Jung et al. [35] described the *PLEKHS1* mutation, which increases the risk of radioiodine resistance by 38% and is associated with distant metastases in 62% of cases, indicating the need for alternative therapeutic approaches.

Kwak et al. [36] found that *RAS* and *TERT* mutations increase the likelihood of metastasis by 1.8-fold and are linked to aggressive follicular cancer in 48% of patients, highlighting their prognostic relevance. Guo et al. [37] proposed a model based on pyroptosis-associated genes (IL6, TP63), which demonstrated predictive accuracy with an AUC of 0.74; high-risk patients by this model

experienced a 25% decrease in survival, indicating the potential utility of such markers in outcome assessment. Zeyghami et al. [39] noted that liquid biopsies (circulating tumour DNA and circulating tumour cells) enable 28% more accurate metastasis detection and allow for earlier identification of therapy failure by 35%, underscoring the value of non-invasive monitoring methods. Liu and Xing [39] found that *TERT* mutations are frequently associated with poor prognosis and tumour aggressiveness, improving risk stratification. Cao et al. [40] showed that *CDKN2A* gene expression is linked to tumour aggressiveness and a 34% decrease in survival in high-expression groups, serving as an indicator of unfavourable outcomes. Shen et al. [41] confirmed that TGF-beta and FN1, which interact with the extracellular matrix, increase recurrence risk by 29%, emphasising their role in tumour progression. Radi et al. [42] discovered that patients with high *Ki-67* indices have a 42% higher recurrence risk, and vascular invasion is observed in 51% of such patients, making *Ki-67* a classical proliferation marker.

Zhao et al. [43] established that the combination of *BRAF* V600E and *TERT* mutations significantly increases the risk of metastasis (OR=5.74), representing one of the most potent prognostic combinations for tumour aggressiveness. Niciporuka et al. [44] highlighted those genes involved in epithelial-mesenchymal transition (EMT) raise tumour aggressiveness by 31%, pointing to invasion mechanisms. Staubitz-Vernazza et al. [45] showed that AHNAK2 and FN1, correlated with *TERT* mutations, increase recurrence risk by 36%, reinforcing the prognostic value of *TERT*. Ruiz et al. [46] proposed an innovative 25-gene panel capable of predicting lymph node metastasis with 86% sensitivity and 62% specificity, and of forecasting recurrence-free survival (HR=2.64) in early-stage papillary carcinoma, demonstrating the potential of integrative diagnostics. Romeo et al. [45] found that high miR-375 expression is associated with poorer overall survival in DTC patients (HR=6.24), confirming the importance of this epigenetic marker as a prognostic tool. J. Capdevila et al. [46], through RNA-seq analysis, classified tumours into three groups – *BRAF*-like, *RAS*-like, and non-*BRAF*/non-*RAS*-like – and showed that patients with *BRAF*-like profiles had better recurrence-free survival outcomes (11.8 months vs. 6.2 and 5.5), respectively. Although this approach is novel for DTC, it already shows promise in tumour control and warrants further large-scale randomised trials to validate its clinical relevance.

Analysis of these sources demonstrates that the molecular-genetic status of DTC substantially influences treatment strategies and prognosis, enabling a personalised approach. Firstly, risk stratification based on such mutations allows identification of high-risk groups requiring aggressive treatment, while patients with low-risk profiles may avoid overtreatment [47-49]. Secondly, radioiodine resistance necessitates the use of targeted therapies, and liquid biopsies facilitate timely treatment adjustments. Thirdly, survival forecasts are refined by molecular markers, helping to identify patients with better or worse prognoses [50, 51]. Fourthly, molecular testing shows promise for cost-effectiveness, optimising resource use and improving patient quality of life, but further clinical validation is needed to confirm these benefits. Finally, innovations improve diagnostic and prognostic accuracy, supporting standardised clinical protocols. Thus, molecular-genetic markers not only refine prognosis but also inform decisions between surveillance, radioiodine therapy, and targeted treatments, ultimately improving DTC outcomes and reinforcing the need to integrate such data into routine clinical practice [52-55].

The *BRAF* V600E mutation correlates with more aggressive tumour behaviour, an increased probability of distant metastases, and diminished efficacy of radioiodine therapy. In individuals with *BRAF* mutations, complete thyroidectomy is typically advised over lobectomy due to the heightened risk of recurrence and the necessity for more comprehensive surgical procedures to exclude potential metastatic dissemination. The *TERT* mutation, frequently observed in more aggressive instances of DTC, indicates a poor prognosis and diminished effectiveness of radioiodine therapy, consequently affecting the choice of total thyroidectomy and increased post-surgical monitoring. When radioiodine resistance is suspected, especially with *BRAF* or *TERT* mutations, clinicians should commence targeted medications, such as *BRAF* inhibitors or other molecularly targeted drugs that inhibit the MAPK pathway. The coexistence of *BRAF* and *TERT* mutations may necessitate more aggressive management, including the consideration of adjunct medicines, such as targeted medications alongside conventional treatments, to enhance treatment efficacy and mitigate the risk of disease progression. Integrating these molecular markers into clinical algorithms enables the development of a personalised, risk-adapted approach, ensuring treatment decisions coincide with the tumour's genetic profile for optimal patient outcomes.

Innovative technologies, including liquid biopsies, artificial intelligence-driven integration of multi-omics data, and single-cell sequencing, present considerable potential for enhancing the diagnosis and treatment of DTC. Liquid biopsies, especially those examining circulating tumour DNA, provide a non-invasive approach to discover genetic alterations, assess disease progression, and identify minimum residual disease [38, 56, 57]. This method facilitates real-time observations of therapy efficacy and recurrence identification, thereby providing a more adaptive and individualised treatment strategy. Similarly, the integration of multi-omics data with artificial intelligence (AI), encompassing genetic, epigenetic, transcriptomic, and proteomic information, may yield more precise prognostic models by addressing the complexity and heterogeneity of DTC [58-60]. Single-cell sequencing facilitates an in-depth examination of tumour heterogeneity at the cellular level, yielding insights into the genetic determinants of cancer aggression and therapeutic resistance.

Nonetheless, despite their promise, these technologies encounter considerable obstacles in clinical validation and practical application. The clinical efficacy of liquid biopsies, although promising, remains impeded by the necessity for rigorous standardisation and validation among varied patient populations [38, 61]. The cost

constitutes a significant obstacle, since the higher expenses of these innovative diagnostic approaches restrict their extensive implementation, especially in resource-limited environments. The integration of AI with multi-omics data, while promising for uncovering intricate patterns in extensive datasets, encounters challenges regarding model correctness, generalisability, and interpretability, particularly in clinical contexts. Single-cell sequencing offers critical insights into cancer biology but is constrained by its technical complexity, high expense, and the necessity for sophisticated bioinformatics tools to analyse the extensive data produced. Future research must concentrate on tackling these issues via extensive clinical trials, cost-reduction initiatives, and the establishment of standardised protocols, which will facilitate the eventual integration of these technologies into ordinary clinical practice for DTC management.

Although this approach is still considered relatively novel for differentiated thyroid cancer, it is already demonstrating effectiveness in tumour control for a subset of patients. However, definitive conclusions regarding the clinical utility of such therapies await the accumulation of sufficient observational data and the completion of large-scale randomised trials.

Prospects for the implementation of molecular markers and future research

Despite the rapid advancement of molecular genetic technologies, their widespread integration into routine clinical practice still faces several barriers. Firstly, not every medical facility possesses the infrastructure necessary for high-precision genetic diagnostics. Secondly, there is currently no unified, guideline-based consensus regarding which specific gene panels or epigenetic tests should be universally conducted for all patients. There is a risk that excessive testing may lead to confusion in data interpretation and result in unnecessary expenses. On the other hand, insufficient analysis may hinder the timely identification of genuinely threatening patterns that deserve clinical attention.

A crucial area for future research in the field of DTC (differentiated thyroid cancer) is clarifying the role of marker combinations. Even at this stage, it is evident that examining a single marker – whether *BRAF* V600E or RET rearrangement – rarely provides a comprehensive picture. Multivariate models that incorporate not only several genes but also features of metabolic pathways, immune responses, and the tumour microenvironment appear far more promising. New approaches are emerging in which genetic data are integrated with artificial intelligence capable of predicting tumour behaviour through machine learning, based on hundreds or thousands of parameters that include both biological and clinical factors.

Moreover, the potential of epigenetic regulation in restoring tumour radiosensitivity is becoming increasingly apparent. Should future studies confirm that certain agents targeting methylation or acetylation can restore iodine uptake in tumours, this may represent a revolutionary step in treating radioiodine-refractory forms of DTC. In practice, this would mean that patients initially deemed "radioiodine-resistant" could regain sensitivity and achieve positive therapeutic outcomes, thus improving both survival and quality of life.

Another key direction is the development of targeted agents that inhibit signalling pathways activated by mutations in genes such as *BRAF*, *RAS*, *RET*, and others. For aggressive forms of well-differentiated tumours that do not adequately respond to standard therapies, such drugs may serve as alternatives or adjuncts to surgery and radioiodine therapy. Although there are already examples of "precision" therapy that can slow tumour progression, durable remission remains elusive, underscoring the need for further research in this area.

In summary, differentiated thyroid cancer, once considered a relatively homogeneous and easily manageable malignancy, is now recognised as exhibiting significant heterogeneity. Molecular genetics and epigenetic factors influence not only the fundamental tumour characteristics but also its potential to follow an aggressive course, evade radioiodine treatment, and recur years after initial therapy. The primary challenge is to determine which specific combinations of genetic and epigenetic alterations are the most reliable predictors of poor prognosis and how to translate this knowledge into clinical algorithms that allow physicians to define treatment strategies in advance.

Thus, this study highlights substantial progress in understanding the biological basis of well-differentiated thyroid cancer. Nevertheless, there remains a need for continued investigation and collaboration among specialists from diverse fields – geneticists, endocrinologists, bioinformaticians, pathologists, and clinical oncologists. Only through a comprehensive approach incorporating the study of mutations, epigenetics, immune surveillance factors, and tumour microenvironment can a full-fledged system of prognostic stratification be developed, thereby allowing optimal use of the therapeutic potential of current technologies.

Well-differentiated thyroid cancer continues to attract significant attention, as its generally favourable prognosis in most cases contrasts with the occurrence of rare but severe aggressive variants. This creates a clinical demand for achieving the optimal balance between overtreatment and undertreatment. Solving this problem largely depends on further elucidation of the role of molecular genetics and epigenetic markers, which must be adapted to real-world clinical settings and, in the long term, incorporated into patient management guidelines. Only then can a more personalised, biologically informed approach be achieved – one that maximises the chances for long-term remission and a high quality of life in patients with DTC.

In conclusions, this review demonstrates that well-differentiated thyroid cancer, despite its reputation as a relatively "mild" disease, can exhibit a wide range of clinical behaviours. In some patients, the tumour remains stable for an extended period and responds to standard treatment, while in others, it suddenly adopts aggressive traits, including metastatic spread and resistance to radioiodine therapy. Molecular genetic analysis, including the detection of specific mutations and epigenetic alterations, enables the identification of subgroups at higher risk of recurrence and metastasis

– even when the initial histological diagnosis appears "favourable". Consequently, early and targeted detection of such factors can significantly improve treatment and follow-up strategies.

This study confirms that a tumour's genetic profile – including point mutations in specific genes, rearrangements, and regulatory RNA expression levels – can aid in refining prognosis and selecting the most appropriate therapy regimen. Such a personalised approach not only minimises the risk of recurrence but also avoids overtreatment in cases where the tumour does not show aggressive behaviour.

However, this research is limited by the insufficient number of large-scale randomised clinical trials, which complicates definitive conclusions regarding the clinical efficacy of some molecular genetic approaches, such as RNA sequencing and targeted therapy. Additionally, variability in testing methods and the limited availability of long-term outcome data for patients with rare mutations (e.g., *NTRK*, *PLEKHS1*) reduce the generalisability of the findings. The practical significance of these findings lies in the potential for integrating molecular genetic data into clinical practice to enhance decision-making regarding the extent of surgery, the need for adjuvant radioiodine therapy, and subsequent monitoring. Future work should focus on refining genetic testing methodologies and expanding the evidence base through large-scale studies, which would help to standardise prognostic stratification criteria. Such standardisation would promote the development of a unified framework for clinical risk assessment in DTC and facilitate the design of targeted and epigenetic therapies directed at key pathogenic pathways. This strategy holds promise for significantly improving patient survival and quality of life by enabling timely intervention and more accurate prediction of possible complications.

Author Contribution Statement

Nina Sloneva contributed to the conceptualization, methodology, and original draft preparation. Dilyara Kaidarova was responsible for data collection, formal analysis, and reviewing and editing the manuscript. Murat Kaibarov contributed to supervision, validation, and final approval of the manuscript.

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Conflict of Interest

The authors declare no conflicts of interest.

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