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RESULTS OF APPLYING COMPLEX THERAPEUTIC METHODS IN DIFFERENTIATED THYROID CANCER

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Keywords: differentiated thyroid cancer, complex therapy, surgical treatment, targeted therapy, molecular-genetic analysis, prognosis, personalized treatment.

Abstract. This research focuses on analyzing the effectiveness of combined treatment for differentiated thyroid cancer (DTC), taking into account both morphological features and the molecular-genetic profile of the tumor. Between 2014 and 2024, 300 patients with confirmed DTC were examined at the branch of Tashkent city of the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology. A comparative study was conducted between an improved diagnostic-therapeutic algorithm—including ultrasound, fine-needle aspiration biopsy, molecular testing, and individualized surgical and targeted therapy—and the conventional approach. Findings demonstrated that the improved algorithm provided higher two-year disease-free survival (78.1% versus 66.5%; p=0.033). Adverse prognostic indicators were associated with TERT, RAS, PAX8-PPAR-γ, and BRAF-V600E mutations, particularly their combinations (e.g., RAS+PAX8-PPAR-γ, HR=4.271; p=0.005). Extended thyroidectomy with lymph node dissection improved locoregional control and reduced recurrence risk. In conclusion, the integration of molecular profiling and personalized surgical strategy into standard DTC management enhances survival, reduces recurrence rates, and proves economically beneficial, reducing treatment costs by an average of 3.8 million UZS per patient.

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Introduction. According to data from the World Health Organization, more than eight hundred thousand new cases of thyroid cancer have been identified worldwide, with the number of deaths exceeding forty-seven thousand. The incidence rate among women is significantly higher — 13.6 per 100,000, while among men it is 4.6. It is projected that by 2050, the number of new cases will reach 1.1 million, and mortality will increase to 91 thousand [1]. Historically, the leading method of treatment for differentiated thyroid carcinoma (DTC) has been thyroidectomy. In cases of small neoplasms (<4 cm), limited resections were performed, whereas large tumors and metastatic disease required total thyroidectomy with lymph node dissection [4].

In recent years, new treatment modalities have been actively introduced, including targeted therapy, immunotherapy [3], and external radiation therapy, which have contributed to improved disease control and increased survival [1]. Currently, the treatment strategy for DTC is based on a combination of surgical intervention with molecular genetic analysis and targeted therapy [2]. This integrated approach ensures the personalization of therapy and a significant improvement in its effectiveness.

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The objective of the study was to optimize the outcomes of combined therapy for differentiated thyroid carcinoma (DTC) through the use of extended surgical interventions, taking into account the morphological characteristics of the excised regional lymph nodes.

Materials and methods of the study. The work was designed as a pro-retrospective cohort randomized study and was conducted at the Tashkent City Branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of Uzbekistan during the period from 2014 to 2024. The study included 548 patients presenting with clinical signs of thyroid gland neoplasms. Of these, 300 patients with a confirmed diagnosis of differentiated thyroid carcinoma (DTC) were selected using block randomization.

Among these 300 patients, there were 85 men (28.3%) and 215 women (71.7%). The median age was 43 years [IQR: 38–49], with a minimum of 26 years and a maximum of 69 years. The age indicators for men (Me=44 [39–50]) and women (Me=42 [38–49]) did not show statistically significant differences (p=0.489) (Fig. 1).

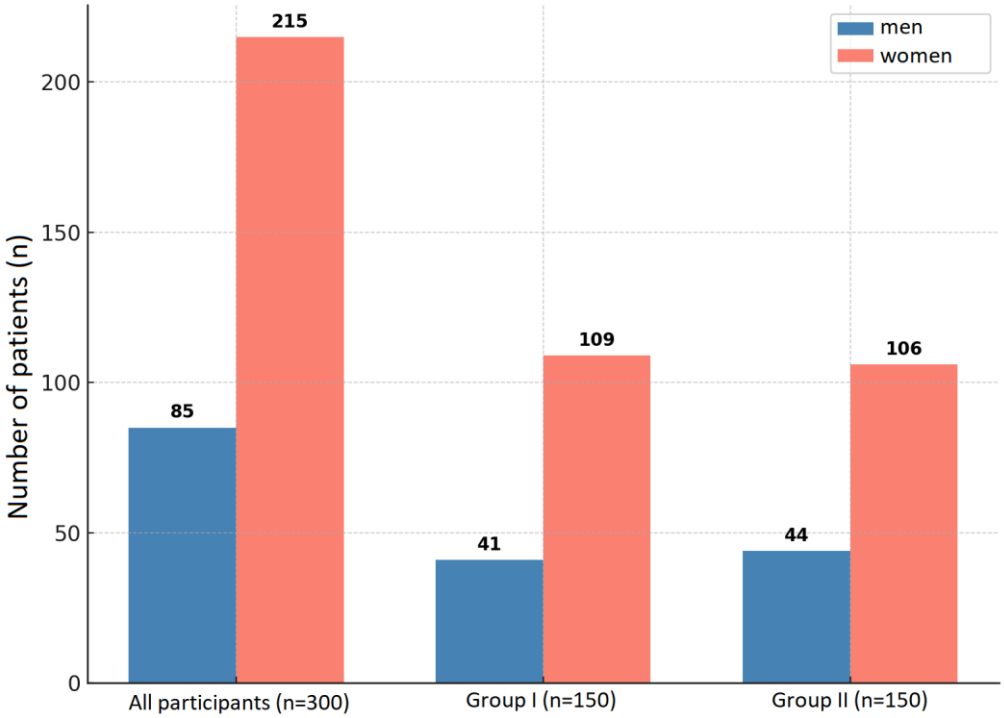

Figure 1. Distribution of patients by sex and study groups.

As a result of randomization, two equal cohorts were formed:

Group I (n=150): 41 men (27.3%) and 109 women (72.7%), median age — 42 years [37–49].

Patients in this group were treated according to an improved diagnostic and therapeutic protocol, which included ultrasound, ultrasound-guided fine-needle aspiration biopsy (FNAB-US), CT, and molecular-genetic tumor profiling followed by individualized adjuvant therapy selection.

Surgical intervention consisted of endovideo-assisted total thyroidectomy or hemithyroidectomy depending on the extent of the disease.

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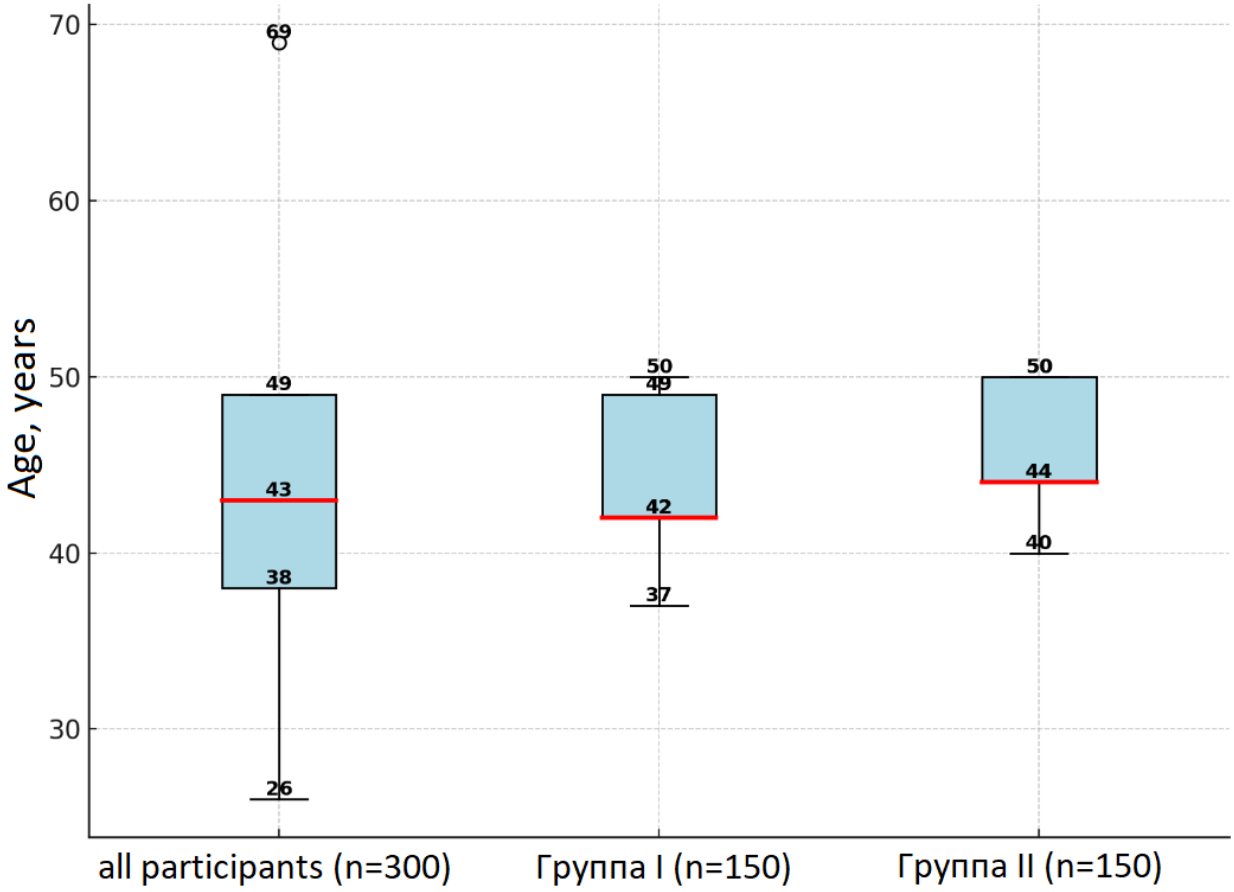

Fig. 2. Distribution of patients by age and study groups.

Group II (n=150): 44 men (29.3%) and 106 women (70.7%), median age — 44 years [40–50]. Patients underwent standard diagnostic procedures (ultrasound, fine-needle aspiration biopsy under ultrasound guidance, and CT). Surgical management consisted of open total thyroidectomy with lymphadenectomy aimed at reducing the likelihood of micro- and locoregional metastasis.

Characteristics of diagnostic methods. Fine-needle aspiration biopsy (FNAB) was performed in patients with thyroid nodules ≥10 mm in diameter, as well as in nodules <10 mm when ultrasound features were suggestive of malignancy. In cases of multinodular involvement, aspiration was performed from each nodule under ultrasound guidance. Disposable needles of 21G and 20G caliber were used. The obtained material was fixed and stained according to standard protocols. Cytological interpretation was carried out in accordance with the Bethesda classification (2010), which includes six diagnostic categories — from non-diagnostic (I) to malignant (VI) [27].

Genetic analysis. The molecular analysis covered five key genes: BRAF V600E, RET/PTC, TERT, RAS, and PAX8-PPAR-γ. To identify point mutations, polymerase chain reaction (PCR) and sequencing techniques were used, while translocations were detected using reverse transcription PCR (RT-PCR) and fluorescence in situ hybridization (FISH); when required, quantitative PCR was applied. The most characteristic findings included: BRAF

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V600E mutation for papillary thyroid carcinoma (PTC); RET/PTC translocations for PTC; TERT mutations as markers of aggressive progression in both PTC and follicular thyroid carcinoma (FTC); RAS mutations typical of FTC; and PAX8-PPAR-γ translocations specific to FTC.

Characteristics of antitumor treatment methods. The therapeutic strategy differed depending on the study group.

Neoadjuvant and adjuvant therapy. In the main group (Group I), a three-stage approach was applied, including the preoperative phase, surgical intervention, and subsequent adjuvant therapy. Neoadjuvant treatment was prescribed for patients with tumors larger than 40 mm, metastatic forms of differentiated thyroid carcinoma (DTC), and iodine-refractory disease. Various targeted agents were used: a combination of dabrafenib and trametinib in cases with BRAF/MEK mutations; sorafenib for alterations in RAS/TERT genes; selpercatinib for RET/PTC translocations. In cases with PAX8-PPAR-γ mutations, specific agents were unavailable, and lenvatinib was administered as a universal therapeutic option.

In the control group (Group II), targeted therapy was limited to the administration of lenvatinib prior to surgical treatment.

Surgical treatment. The choice of surgical intervention volume was determined by both the clinical and molecular-genetic characteristics of the tumor.

In the presence of the BRAF-V600E mutation, an endovideo-assisted total thyroidectomy with central and lateral lymphadenectomy was performed in cases of advanced disease.

For patients with the RET/PTC translocation, hemithyroidectomy was indicated for tumors smaller than 40 mm, while total thyroidectomy was performed for larger lesions; if lymph node involvement was detected, the surgery was supplemented with lymphadenectomy.

When TERT mutations were identified, total thyroidectomy with extended lymphadenectomy was performed.

In cases of RAS and PAX8-PPAR-γ mutations, hemithyroidectomy or total thyroidectomy (for tumors >40 mm) was performed, along with lymphadenectomy if regional lymph nodes were involved.

In the control group (Group II), the standard approach remained open total thyroidectomy with lymphadenectomy when indicated.

Thus, the surgical strategy varied from endovideo-assisted hemithyroidectomy to extended thyroidectomy with central and lateral lymph node dissection, and its selection was determined by molecular-genetic markers and the clinical course of the disease.

Data processing. Statistical analysis was performed using IBM SPSS Statistics v.22 (Windows 11, Microsoft, USA). Quantitative and categorical variables were described using absolute values, proportions (%), and 95% confidence intervals (95% CI) calculated by the Clopper–Pearson method. The odds ratio (OR) with a 95% CI was used as a measure of effect when comparing relative values. For proportion analysis, the Pearson χ^2 test was applied when expected frequencies were >10, and Fisher's exact test was used when expected frequencies were <10. For multi-field contingency tables, the Pearson χ^2 test was employed.

Research Results. Recurrence-Free Survival. Using Cox proportional hazards regression, a model of proportional risks was constructed, demonstrating that the greatest impact on recurrence probability was exerted by TERT mutations (HR = 4.207; $p < 0.001$),

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PAX8-PPAR-γ mutations (HR = 3.850; p = 0.006), the combined BRAF-V600E + TERT mutation (HR = 4.749; p < 0.001), and the RAS + PAX8-PPAR-γ combination (HR = 10.964; p < 0.001) (see Table 1).

When comparing groups, the use of the improved diagnostic-treatment algorithm in the main cohort provided significantly higher two-year recurrence-free survival rates — 78.1% (95% CI: 68.8–85.0%) versus 66.5% (95% CI: 56.1–74.9%) in the standard-approach group (p = 0.033).

Dependence on TNM Stage. The poorest outcomes were observed in T3N0M0 (15.3%; HR = 8.47; p < 0.001) and T3N1M0 (37.7%; HR = 6.23; p < 0.001) stages, regardless of therapy type.

Role of Molecular-Genetic Mutations. The presence of a BRAF-V600E mutation increased the recurrence risk 1.545-fold (p = 0.032); the two-year survival rate was 75.9% versus 85.2% in patients without this mutation. The TERT mutation increased recurrence risk 7.117-fold (p < 0.001), and the RAS mutation — 3.056-fold (p = 0.034); in these cases, two-year survival was only 65.0% (95% CI: 35.1–83.7%).

Histological Variant. The most unfavorable course was observed in papillary-medullary carcinoma: recurrence-free survival reached only 25.0% (95% CI: 0.9–66.5%), and the recurrence risk increased 12.907-fold (p < 0.001).

Summary. The application of an enhanced algorithm based on molecular-genetic profiling and personalized selection of surgical and adjuvant therapy led to a statistically significant improvement in recurrence-free survival among patients with differentiated thyroid cancer (DTC).

Overall Survival. According to the Cox proportional hazards model, the key factor that significantly increased the risk of death was the combined RAS + PAX8-PPAR-γ mutation (HR = 4.271; 95% CI: 1.554–11.739; p = 0.005). Other mutation variants, including BRAF-V600E, RET/PTC, TERT, and their combinations, showed no statistically significant impact on overall survival (see Fig. 3).

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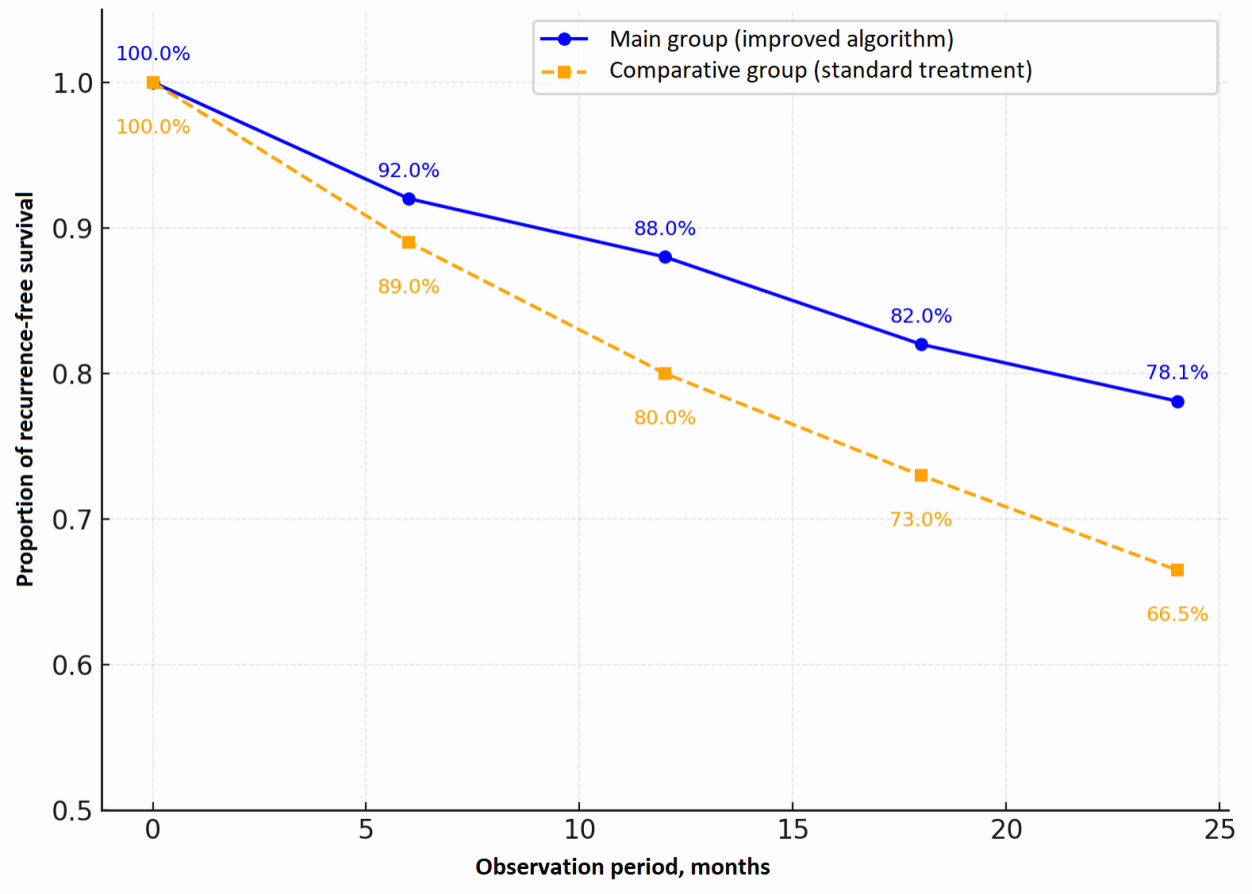

Figure 3. Evaluation of 2-year recurrence-free survival in patients with DTC.

Sex and age. The median survival in both study groups was 24 months (95% CI: 24.0 – ∞). No statistically significant differences were found between males and females (p=0.498), although the risk of death was slightly higher among men (HR=1.131; p=0.494). With increasing age, a trend toward a higher risk was observed (HR=1.019; p=0.059), but it did not reach statistical significance.

TNM and morphological characteristics. For most TNM stages, the median survival was 24 months, except for stage T3N1M0, where the 75th percentile was 19 months (p=0.830). No significant differences were found by histological type (p=0.656); however, patients with papillary-medullary carcinoma had a 3.824-fold higher risk of death (p=0.025).

TI-RADS and Bethesda. Patients classified as TI-RADS TR-5 tended to have a poorer prognosis (HR=1.387; p=0.053), while those with Bethesda category VI demonstrated an increased risk (HR=1.493; p=0.068), although both associations did not reach statistical significance.

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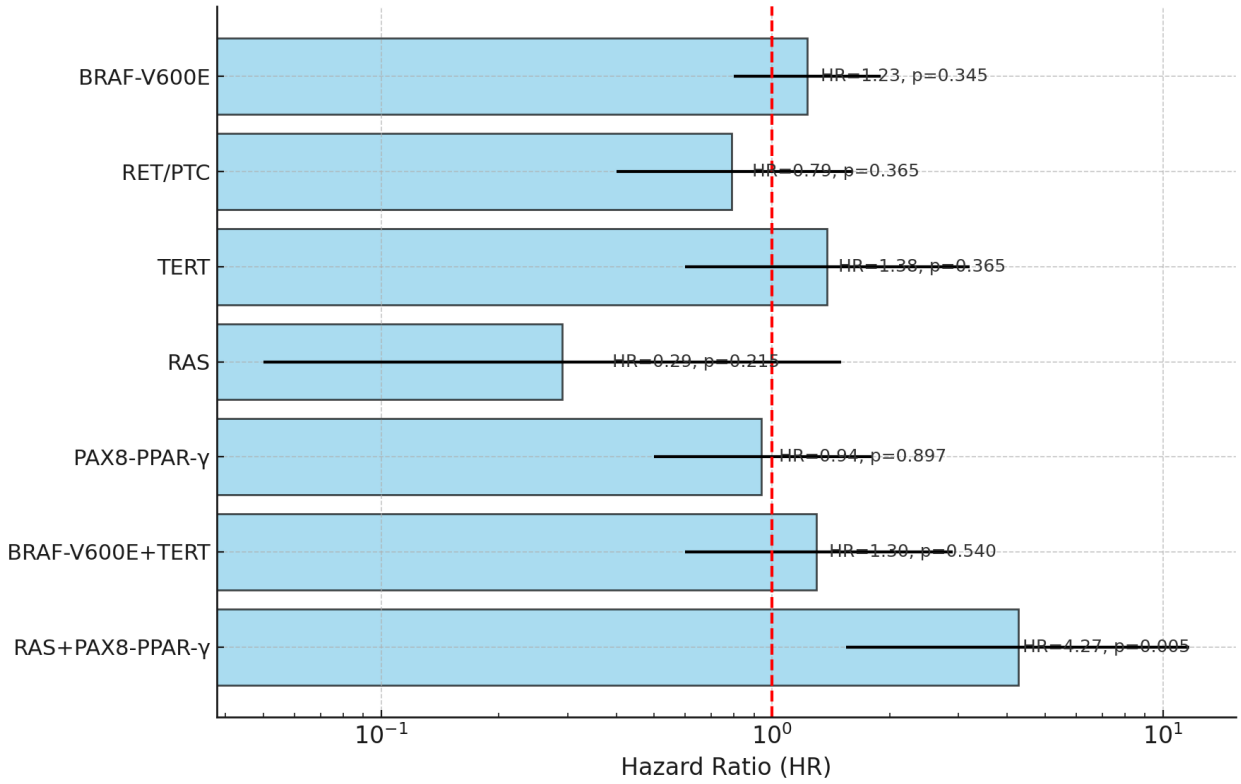

Figure 4. Genetic and clinical factors influencing the risk of mortality in DTC.

Summary. The two-year overall survival analysis demonstrated that the most adverse factors were combined mutations—particularly RAS+PAX8-PPAR-γ—and mixed histological tumor variants. These findings emphasize the necessity of incorporating molecular-genetic markers into prognostic models and treatment individualization for patients with differentiated thyroid carcinoma (DTC).

Conclusion. The analysis of two-year recurrence-free and overall survival in patients with differentiated thyroid carcinoma (DTC) revealed that the key unfavorable prognostic factors include mutations in BRAF-V600E, TERT, RAS, and PAX8-PPAR-γ, with the TERT mutation exerting the most significant negative impact by substantially increasing the risk of recurrence. Furthermore, the RAS+PAX8-PPAR-γ combination was significantly associated with a higher risk of death (HR=4.271; p=0.005), reflecting its aggressive biological potential.

Implementation of the improved diagnostic and treatment algorithm—which integrated molecular-genetic testing, prognostic marker evaluation, and personalized selection of antitumor therapy—resulted in higher two-year recurrence-free survival rates: 78.1% compared to 66.5% in the control group (p=0.033). The most pronounced benefit was observed in patients who underwent extended thyroidectomy with regional lymph node dissection, ensuring better locoregional control and reduced recurrence risk.

Thus, the treatment strategy for DTC should be based on a comprehensive, personalized approach incorporating molecular-genetic profiling to guide clinical decision-making. For BRAF-V600E mutation carriers, the optimal strategy combines BRAF/MEK inhibitors with surgical intervention (p=0.005). In aggressive disease variants, including TERT-associated forms, extended surgery with lymph node dissection is justified.

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Integration of molecular-genetic analysis and extended surgical management into standard DTC treatment not only improves medical outcomes but also holds substantial social significance by reducing recurrence rates and enhancing patients' quality of life. Economic evaluation confirmed that the introduction of this strategy decreases average treatment costs by 3.8 million UZS per patient, demonstrating its cost-effectiveness.

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