Journal of Biosciences and Medicines, 2026, 14(4), 395-407
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Research Progress on Efficacy Prediction of Radioiodine Therapy in Differentiated Thyroid Cancer

Zhiyue Tang, Hua Pang*

Department of Nuclear Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
Email: *phua1973@163.com

How to cite this paper: Tang, Z.Y. and Pang, H. (2026) Research Progress on Efficacy Prediction of Radioiodine Therapy in Differentiated Thyroid Cancer. *Journal of Biosciences and Medicines*, **14**, 395-407.
https://doi.org/10.4236/jbm.2026.144029

Received: March 26, 2026
Accepted: April 27, 2026
Published: April 30, 2026

Abstract

Differentiated thyroid cancer represents the most common pathological type of thyroid malignancy, for which postoperative radioiodine therapy serves as a crucial adjuvant treatment modality. However, significant inter-individual heterogeneity exists in the response to radioiodine therapy among differentiated thyroid cancer patients, which current staging systems, such as the tumor-node-metastasis staging and the American Thyroid Association risk stratification system, are insufficient to accurately predict. Currently, research into predicting the response to radioiodine therapy has progressively evolved from the identification of independent predictive factors and the construction of composite parameters, through the development of traditional statistical models, to the application of machine learning algorithms. This article aims to review the aforementioned research progress, critically evaluate the advantages and limitations of existing methods, and thereby provide a reference for the development of precise predictive models and the optimization of individualized treatment strategies.

Keywords

Differentiated Thyroid Cancer, Radioiodine Therapy, Response Prediction, Machine Learning

1. Introduction

Thyroid cancer is the most common malignancy of the endocrine system. Its incidence has steadily increased in recent years, largely due to the widespread application of imaging modalities such as neck ultrasound, attracting considerable attention from clinicians and researchers [1] [2]. Based on histopathological classi-

fication, thyroid cancer can be categorized into papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), medullary thyroid carcinoma, and anaplastic thyroid carcinoma. Among these, PTC accounts for approximately 90% of all cases, and FTC for about 4.4%, with these two subtypes collectively comprising differentiated thyroid carcinoma (DTC) [3].

DTC cells usually retain the differentiated functions of follicular epithelial cells, such as expressing the sodium-iodide symporter, which enables iodine uptake. This provides the molecular basis for targeted therapy with radioactive iodine (RAI). RAI therapy is a core part of standard adjuvant treatment for postoperatively assessed intermediate-to-high recurrence risk DTC patients, as well as low-risk patients who choose this therapy. It aims to reduce the risks of recurrence and distant metastasis by ablating residual thyroid tissue and occult micrometastases. Although DTC generally carries a favorable prognosis, with the majority of patients achieving a clinical disease-free state following standardized comprehensive treatment, a subset of patients still faces the risk of treatment resistance or long-term recurrence. The underlying reason lies in the significant inter-individual heterogeneity in the response to RAI therapy among DTC patients [4] [5]. Thus, accurately predicting RAI therapy efficacy in DTC patients has become an urgent problem to be solved in clinical practice and research.

Current research on predicting the efficacy of postoperative RAI therapy in DTC either employs DTC as the overall study population, wherein PTC constitutes the overwhelming majority of cases, or directly focuses on PTC for analysis. In contrast, evidence from studies specifically addressing FTC remains limited. Given this distribution of available evidence, the present review summarizes the research progress on the prediction of postoperative RAI therapy efficacy within the framework of DTC.

2. Clinical Needs and Challenges

According to the dynamic risk stratification system established in the 2015 American Thyroid Association (ATA) guidelines, the response to RAI therapy in patients with DTC can be categorized into four outcomes: excellent response (ER), indeterminate response (IDR), biochemical incomplete response (BIR), and structural incomplete response (SIR) [6]. This clinical continuum from ER to SIR highlights the complexity and significant individual differences in RAI therapy response.

Current clinical prediction of RAI therapy efficacy mainly relies on the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system or the 2015 ATA risk stratification system. However, both are essentially static, population-based risk classification tools, not specific predictive models for RAI response. Specifically, TNM staging depends largely on anatomical tumor characteristics, such as tumor size, extrathyroidal extension (ETE), and lymph node or distant metastasis. Similarly, the core of the ATA risk stratification system remains a postoperative risk classification based on immedi-

ate pathological data.

Growing clinical evidence shows that even DTC patients with the same TNM stage or ATA risk stratification may have significantly different actual responses to RAI therapy. These variations may be closely associated with heterogeneity among individual patients, distinct tumor biological behaviors, and differential capacities for radioiodine uptake [7] [8]. For example, in intermediate-risk PTC patients, some rapidly achieve ER, while others may progress to BIR or SIR [9]. This phenomenon highlights a fundamental limitation of traditional stratification tools: their inability to fully integrate multi-dimensional influencing factors, thereby failing to meet the clinical demand for personalized efficacy prediction.

Early and accurate prediction of RAI treatment efficacy has important clinical value and practical significance for DTC management. Clinically, early identification of patients prone to poor response allows timely adjustment of subsequent thyroid-stimulating hormone (TSH) suppression strategies or addition of alternative interventions, such as targeted therapy or external beam radiotherapy, ultimately improving patient prognosis. Furthermore, individualized follow-up protocols based on predictive results can facilitate the more rational allocation of healthcare resources, alleviate patient anxiety, and improve treatment adherence by tailoring the frequency and intensity of surveillance to the patient's actual risk profile.

Therefore, developing a predictive tool that goes beyond traditional static stratification, fully integrates multi-dimensional data, and enables early, individualized, and accurate prediction of all RAI therapeutic outcomes in DTC patients has emerged as a critical bottleneck requiring urgent resolution in both current clinical practice and research. This effort is not only a core part of risk-adaptive DTC management but also a key step in advancing thyroid cancer research into true precision medicine.

3. Predictive Factors and Traditional Prediction Models

Before reviewing specific predictive factors and models, it should be noted that some of the evidence discussed below is derived from PTC-specific cohorts. Accordingly, extrapolation of such findings to FTC or all DTC requires further validation.

3.1. Independent Predictive Factors

To overcome the limitations of AJCC/TNM staging and ATA risk stratification in predicting individual treatment outcomes, numerous studies have focused on identifying independent risk factors associated with the response to RAI therapy in patients with DTC. Among these, pre-ablation stimulated thyroglobulin (sTg) levels are currently recognized as one of the most powerful predictive factors. Multiple studies have confirmed that lower sTg levels are strongly associated with a higher rate of ER, whereas elevated sTg levels are strongly indicative of persistent disease or increased recurrence risk [10]-[12]. Notably, thyroglobulin antibody

(TgAb) has evolved from a pre-analytical variable that interferes with sTg measurement to an independent prognostic marker, with elevated titers significantly associated with poor therapeutic responses [13].

In addition to sTg and TgAb, multidimensional clinicopathological, molecular, and imaging factors have all been demonstrated to be closely associated with the efficacy of RAI therapy in DTC patients. Among clinical characteristics, age, TNM stage, and ATA risk stratification serve as fundamental predictive indicators [14] [15]. Regarding histopathological features, larger tumor size, ETE, and multifocality are all negative predictors of treatment response [16] [17]. In terms of lymph node metastasis, studies indicate that the optimal cut-off values for predicting the initial response to RAI are 5 for the number of metastatic lymph nodes and 0.30 for the lymph node ratio [18]. At the molecular level, BRAF V600E, RAS, and TERT promoter mutations are often associated with increased tumor aggressiveness and reduced RAI avidity. When BRAF or RAS mutations coexist with TERT promoter mutations, the adverse prognostic effect of the latter is further potentiated [19] [20]. Concerning imaging characteristics, post-therapy whole-body scanning (Rx-WBS) provides intuitive visualization of RAI uptake in lesions, and quantitative parameters of the thyroid bed (maximum standardized uptake value, mean standardized uptake value, and percentage of injected dose) can effectively predict the outcome of RAI therapy [21] [22]. Elevated metabolic activity of lesions on FDG PET/CT indicates tumor dedifferentiation and increased risk of RAI resistance [23].

Unlike the aforementioned well-validated factors, the impact of the interval between thyroidectomy and RAI therapy on treatment efficacy remains controversial. Conventional wisdom favors early postoperative RAI therapy to eliminate potential micrometastases. Relevant studies have confirmed that delayed RAI therapy (exceeding three months) in intermediate- and high-risk patients is associated with IDR [24]. Retrospective studies including low- and intermediate-risk patients also suggest that the time interval is an independent predictor of IDR [25]. However, other studies suggest that the timing of RAI therapy has no significant impact on patient prognosis or overall survival [26] [27]. These discrepancies indicate that the value of treatment timing as an independent predictor warrants further in-depth exploration and validation.

3.2. Composite Predictive Indicators

Since thyroglobulin (Tg) measurements are prone to interference from various factors, researchers have recently proposed several corrected derivative indicators to enhance predictive accuracy.

TSH directly regulates Tg synthesis and release, and higher serum TSH levels usually stimulate more Tg production. The sTg/TSH ratio is designed to mitigate the confounding effect of inter-patient TSH level differences on Tg release, thereby more accurately reflecting the actual Tg secretory capacity of the tumor or residual thyroid tissue per unit of TSH stimulation, essentially representing a

correction for tumor burden. For intermediate- to high-risk DTC patients, an sTg/TSH ratio > 0.095 before the initial ^{131}I ablation indicates poor treatment efficacy and shorter progression-free survival. Although sTg alone possesses predictive value, the sTg/TSH ratio demonstrates superior specificity, indicating enhanced capability for identifying patients with poor prognosis [28].

TgAb not only specifically binds to Tg to form complexes that accelerate Tg clearance and thereby reduce its serum levels, but also acts as a dynamically changing tumor marker. The sTg × TgAb product integrates these two interrelated indicators, providing a comprehensive quantitative measure of tumor burden. In DTC patients who have undergone total thyroidectomy, the pre-ablation sTg × TgAb product has been identified as an independent risk factor for ablation failure. This composite indicator demonstrates predictive value in both TgAb-negative and TgAb-positive subgroups, suggesting its potential applicability as a universal metric for all patients. Notably, in TgAb-positive patients, it addresses the blind spot inherent in relying solely on Tg monitoring [29].

Rx-WBS provides functional imaging information, visualizing lesional iodine-avid capacity. Recent studies [30] have combined biochemical and imaging modalities, proposing a stepwise integrated strategy: first, assessing lesion functional status based on the Rx-WBS iodine uptake pattern; then conducting a comprehensive evaluation by integrating pre- and post-therapy Tg dynamics. This Rx-WBS-calibrated Tg assessment approach enhances the predictive capability for RAI therapeutic efficacy.

It is worth emphasizing that, compared with absolute values obtained from single measurements, the rate of change in Tg concentration reflects disease activity earlier and more sensitively. Studies have demonstrated that thyroglobulin doubling time holds significant value in predicting therapeutic response, disease recurrence, and overall survival [31]. For patients with undetectable Tg, a greater than 50% decline in TgAb within the first postoperative year suggests an excellent prognosis [32]. Although these composite indicators partially correct biases and improve predictive accuracy, no consensus has been reached on their calculation methods or optimal cut-off values.

3.3. Traditional Statistical Models

Based on the identification of the aforementioned independent and composite predictive factors, research has advanced to constructing comprehensive predictive models using traditional statistical methods. Multivariate logistic regression and Cox proportional hazards models represent the core methodologies of this phase, enabling quantification of each factor's independent contribution to therapeutic response or survival-related outcomes and calculating individual risk scores to provide quantitative references for clinical decision-making.

In clinical practice, TSH suppression therapy is initiated shortly after RAI, and all early efficacy assessments therefore represent the combined effect of RAI and subsequent TSH suppression. Several studies have developed models for pre-

treatment prediction of non-excellent response (Non-ER) within the ATA dynamic response assessment system, a composite outcome comprising IDR, BIR, and SIR. In a dual-center study of intermediate- to high-risk DTC patients, Wen *et al.* [33] identified the number of metastatic lymph nodes, sTg, TgAb, and sTg/TSH ratio as independent predictors of Non-ER at 6 - 12 months after RAI therapy. The resulting nomogram demonstrated favorable discrimination and calibration in both training and validation cohorts. Wu *et al.* [34] focused specifically on the papillary thyroid microcarcinoma subtype. Multivariate logistic regression analysis revealed that positive ETE and sTg > 1.37 ng/mL were risk factors for Non-ER at approximately 6 months after initial RAI therapy, while TSH > 67.97 mU/L was associated with better therapeutic outcomes. The authors subsequently developed a visualized nomogram tool.

Turning to recurrence/prognosis prediction, Piccardo *et al.* [35] employed Cox proportional hazards models to demonstrate that an advanced model integrating pre-ablation Tg levels with Rx-WBS findings significantly outperformed a basic model based solely on TNM staging in predicting structural disease-free survival. Moreover, incorporating sex and age further improved the accuracy of mortality risk prediction.

However, traditional statistical models are constrained by inherent technical limitations in capturing nonlinear variable relationships, handling complex variable interactions, and adapting to high-dimensional or incomplete data, which has prompted the shift to more advanced machine learning algorithms for precise RAI therapy efficacy prediction.

4. Machine Learning Models

4.1. Overview and Clinical Application of Machine Learning

Machine learning (ML), a pivotal branch of artificial intelligence, excels at mining complex data features and recognizing patterns, offering novel approaches to improve upon traditional clinical predictive models. Unlike conventional statistical models dependent on predefined assumptions, ML algorithms can automatically detect nonlinear relationships and high-order interactions in data, rendering them well-suited for processing multidimensional and heterogeneous clinical information [36]. In medical research, researchers commonly employ diverse ML algorithms to build predictive models, and select optimal models via comparison and validation for use in disease diagnosis, treatment efficacy prediction, and prognostic evaluation [37] [38].

Toro-Tobon *et al.* [39] retrospectively analyzed AI applications in thyroid diseases, revealing that 64% of original studies focused on differentiating benign from malignant thyroid nodules, primarily aiming to optimize healthcare resource utilization, enhance diagnostic precision, and enable individualized management. Compared with the thyroid nodule field, research on ML-based prediction of RAI therapy response in DTC patients remains relatively limited but has demonstrated rapid development in recent years.

4.2. Machine Learning in Predicting RAI Efficacy in DTC

To date, several research teams have developed RAI efficacy prediction models with diverse patient cohorts and algorithmic approaches, demonstrating favorable discrimination, calibration, and clinical utility, thereby providing novel tools for individualized treatment decision-making. The machine learning models discussed herein should be applied cautiously, considering their original study populations.

Bülbül *et al.* [40] based their study on comprehensive pre- and post-RAI treatment data from 151 distant metastasis-free DTC patients to predict ER to RAI plus TSH-suppression therapy at 6 - 24 months, enabling early post-ablation response stratification. After balancing the dataset using the SMOTE oversampling technique, the authors applied nine algorithms to construct predictive models: k-nearest neighbors (KNN), random forest (RF), gradient boosting (GB), extreme gradient boosting (XGBoost), naive Bayes (NB), decision tree (DT), logistic regression (LR), neural network (NN), and adaptive boosting (AdaBoost). Results demonstrated that the XGBoost model achieved the highest area under the curve (AUC: 0.871), while the GB model attained the highest accuracy (81%). Notably, conventional statistical analysis only identified a significant difference in pre-treatment TgAb positivity rates between ER and Non-ER groups. In contrast, the machine learning models achieved precise efficacy prediction by uncovering complex associations among variables, highlighting the unique advantage of ML in processing seemingly unrelated predictors.

With different algorithmic strategies, Sa *et al.* [41] performed pre-treatment prediction of the response to RAI plus TSH-suppression therapy. They retrospectively analyzed 854 DTC patients without structural disease progression before or within six months of RAI treatment and defined effective response as undetectable suppressed thyroglobulin measured 4 - 6 months after treatment. The training and testing cohorts had comparable distributions of treatment response categories. During variable selection, LASSO regression identified eight core predictors from candidate variables: sex, TNM-N stage, ATA risk stratification, RAI uptake rate, suppressed Tg, stimulated Tg, stimulated TSH, and number of prior RAI treatments. Subsequently, six machine learning models were constructed: LR, support vector machine (SVM), RF, NN, AdaBoost, and GB. Among these, the RF model demonstrated superior predictive performance (AUC: 0.896, accuracy: 81.3%). SHAP analysis was used for model interpretation, further clarifying the contribution and predictive direction of each variable.

By contrast, Wang *et al.* [42], after excluding TgAb-positive and initial distant metastasis patients, utilized a 2244 PTC cohort to focus on structural recurrence in the context of recurrence/prognosis prediction. The study incorporated 29 variables across four dimensions: demographic characteristics and comorbidities, tumor-related variables, lymph node-related variables, and metabolic and inflammatory markers. To address data imbalance caused by the low recurrence rate (8.0%) in the cohort, one-sided selection under-sampling was further applied to

establish a balanced training set for subsequent model development. Following LASSO regression-based variable selection, predictive models were constructed using various algorithms. The RF model was identified as the optimal model for its generally consistent calibration, alongside favorable discrimination and interpretability. It significantly outperformed the ATA risk stratification system (AUC: 0.766 vs. 0.620, accuracy: 0.775 vs. 0.742, F1 score: 0.331 vs. 0.216), thus providing a novel tool for the early intervention of high-risk patients.

4.3. Limitations of Current Machine Learning Models

Despite the methodological advancement from traditional statistical models to ML algorithms in this field, current research still faces several critical limitations that impede its clinical translation and widespread application.

Collective critical appraisal of these three key machine learning studies reveals substantial methodological heterogeneity. Sample sizes were 151, 854, and 2244 patients, respectively. While Sa *et al.* [41] exhibited naturally balanced classes, the other two studies used distinct strategies (SMOTE oversampling and one-sided selection under-sampling) to address class imbalance. For TgAb-positive patients, only Wang *et al.* [42] imposed exclusion. The types of reported performance metrics varied across studies; nonetheless, AUC values ranged from 0.766 to 0.896 and accuracy from 77.5% to 81.3%. Notably, all studies relied exclusively on internal validation, with no prospective or external validation performed.

The binary classification design adopted in these studies fails to distinguish the four hierarchical RAI therapy response categories, which inevitably leads to the loss of critical clinical decision-making information and cannot meet the individualized management needs of patients across different risk strata. Additionally, few existing studies have explored the integration of such models into clinical workflows, engagement with clinical end-users, or long-term performance monitoring following clinical implementation.

5. Conclusion and Outlook

The prediction of response to postoperative RAI therapy in DTC has undergone a clear evolutionary trajectory, from macroscopic to microscopic perspectives, from static to dynamic assessments, and from single indicators to multidimensional integration, resulting in progressively improved predictive accuracy. This progress, however, is accompanied by two interrelated challenges. First, direct comparisons of predictors and model performance across studies are hampered by marked heterogeneity in endpoint definitions, such as ER/Non-ER based on the ATA response, suppressed Tg, structural recurrence, and disease-specific mortality. Second, the granularity of current predictive tools remains misaligned with the level of decision-making required in clinical management, hindering their ability to fully meet the demands of individualized treatment for DTC patients. Furthermore, the current evidence base for RAI efficacy prediction is overwhelmingly derived from the PTC population, which constitutes the major subtype of DTC,

while studies specifically addressing FTC remain extremely scarce, representing an urgent research gap to be filled.

Building upon the aforementioned research progress and existing limitations of the field, future predictive models for RAI efficacy in DTC patients should be developed toward greater precision, comprehensiveness, and clinical utility. For outcome design, future studies should move beyond the binary classification framework and adopt a multicategory strategy to finely distinguish the four response categories (ER, IDR, BIR, SIR), enabling true risk-adaptive management. For data construction, research efforts should include TgAb-positive populations, conduct multicenter studies to reduce selection bias, and pay attention to accumulating evidence for the FTC subtype. For model development, integrating multimodal data with explainability analysis methods will enhance clinical trust in predictive models. For validation and translation, it is imperative to strengthen prospective, multicenter external validation and develop user-friendly clinical tools to facilitate the translation of these models from research to routine clinical practice.

With the continuous advancement of methods and the in-depth development of multi-omics research, these multidimensional collaborative research efforts are expected to develop truly precise predictive tools that can effectively guide clinical practice for DTC. Ultimately, such advances will optimize individualized treatment decision-making for DTC patients and drive the field of thyroid cancer research further forward into the era of precision medicine.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

References

[1] Han, B., Zheng, R., Zeng, H., Wang, S., Sun, K., Chen, R., *et al.* (2024) Cancer Incidence and Mortality in China, 2022. *Journal of the National Cancer Center*, **4**, 47-53. https://doi.org/10.1016/j.jncc.2024.01.006

[2] Chen, D.W., Lang, B.H.H., McLeod, D.S.A., Newbold, K. and Haymart, M.R. (2023) Thyroid Cancer. *The Lancet*, **401**, 1531-1544. https://doi.org/10.1016/s0140-6736(23)00020-x

[3] Rossi, E.D., Pantanowitz, L. and Hornick, J.L. (2021) A Worldwide Journey of Thyroid Cancer Incidence Centred on Tumour Histology. *The Lancet Diabetes & Endocrinology*, **9**, 193-194. https://doi.org/10.1016/s2213-8587(21)00049-8

[4] do Prado Padovani, R., Duarte, F.B. and Nascimento, C. (2024) Current Practice in Intermediate Risk Differentiated Thyroid Cancer—A Review. *Reviews in Endocrine and Metabolic Disorders*, **25**, 95-108. https://doi.org/10.1007/s11154-023-09852-y

[5] Durante, C., Haddy, N., Baudin, E., Leboulleux, S., Hartl, D., Travagli, J.P., *et al.* (2006) Long-Term Outcome of 444 Patients with Distant Metastases from Papillary and Follicular Thyroid Carcinoma: Benefits and Limits of Radioiodine Therapy. *The Journal of Clinical Endocrinology & Metabolism*, **91**, 2892-2899. https://doi.org/10.1210/jc.2005-2838

[6] Haugen, B.R., Alexander, E.K., Bible, K.C., Doherty, G.M., Mandel, S.J., Nikiforov,

Y.E., *et al.* (2016) 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*, **26**, 1-133. https://doi.org/10.1089/thy.2015.0020

[7] Lu, L., Li, Q., Ge, Z., Lu, Y., Lin, C., Lv, J., *et al.* (2024) Development of a Predictive Nomogram for Intermediate-Risk Differentiated Thyroid Cancer Patients after Fixed 3.7GBq (100mCi) Radioiodine Remnant Ablation. *Frontiers in Endocrinology*, **15**, Article 1361683. https://doi.org/10.3389/fendo.2024.1361683

[8] Liu, J., Liu, R., Shen, X., Zhu, G., Li, B. and Xing, M. (2020) The Genetic Duet of *BRAF* V600E and *TERT* Promoter Mutations Robustly Predicts Loss of Radioiodine Avidity in Recurrent Papillary Thyroid Cancer. *Journal of Nuclear Medicine*, **61**, 177-182. https://doi.org/10.2967/jnumed.119.227652

[9] Li, Y., Rao, M., Zheng, C., Huang, J., Fang, D., Xiong, Y., *et al.* (2022) Analysis of Factors Influencing the Clinical Outcome after Surgery and 131I Therapy in Patients with Moderate-Risk Thyroid Papillary Carcinoma. *Frontiers in Endocrinology*, **13**, Article 1015798. https://doi.org/10.3389/fendo.2022.1015798

[10] Jayasekara, J., Jonker, P., Lin, J.F., Engelsman, A.F., Wong, M., Kruijff, S., *et al.* (2020) Early Postoperative Stimulated Serum Thyroglobulin Quantifies Risk of Recurrence in Papillary Thyroid Cancer. *Surgery*, **167**, 40-45. https://doi.org/10.1016/j.surg.2019.06.048

[11] Giovanella, L., Ceriani, L., Ghelfo, A. and Keller, F. (2005) Thyroglobulin Assay 4 Weeks after Thyroidectomy Predicts Outcome in Low-Risk Papillary Thyroid Carcinoma. *Clinical Chemistry and Laboratory Medicine* (*CCLM*), **43**, 843-847. https://doi.org/10.1515/cclm.2005.142

[12] Piccardo, A., Arecco, F., Puntoni, M., Foppiani, L., Cabria, M., Corvisieri, S., *et al.* (2013) Focus on High-Risk DTC Patients: High Postoperative Serum Thyroglobulin Level Is a Strong Predictor of Disease Persistence and Is Associated to Progression-Free Survival and Overall Survival. *Clinical Nuclear Medicine*, **38**, 18-24. https://doi.org/10.1097/rlu.0b013e318266d4d8

[13] Sun, D., Zheng, X., He, X., Huang, C., Jia, Q., Tan, J., *et al.* (2020) Prognostic Value and Dynamics of Antithyroglobulin Antibodies for Differentiated Thyroid Carcinoma. *Biomarkers in Medicine*, **14**, 1683-1692. https://doi.org/10.2217/bmm-2019-0432

[14] Kelly, A., Barres, B., Kwiatkowski, F., Batisse-Lignier, M., Aubert, B., Valla, C., *et al.* (2019) Age, Thyroglobulin Levels and ATA Risk Stratification Predict 10-Year Survival Rate of Differentiated Thyroid Cancer Patients. *PLOS ONE*, **14**, e0221298. https://doi.org/10.1371/journal.pone.0221298

[15] Wang, L., Yang, J., Zhu, Y. and Li, Z. (2025) The Value Analysis of Tumor Deposit in the Comprehensive Evaluation before Differentiated Thyroid Cancer RAI Therapy. *Frontiers in Oncology*, **15**, Article 1593603. https://doi.org/10.3389/fonc.2025.1593603

[16] Ribeiro, F.B.C., de Almeida, A.G.F.P., de Sá Caldas, A., Nascimento, G.C., Azulay, R.S.D.S., Parente, C.D.M.R.V., *et al.* (2025) Identifying Risk Factors Associated with Refractoriness to Radioiodine Therapy in Differentiated Thyroid Cancer. *Archives of Endocrinology and Metabolism*, **69**, 1-9. https://doi.org/10.20945/2359-4292-2025-0032

[17] Wijewardene, A., Gill, A.J., Gild, M., Learoyd, D.L., Glover, A.R., Sywak, M., *et al.* (2022) A Retrospective Cohort Study with Validation of Predictors of Differentiated Thyroid Cancer Outcomes. *Thyroid*, **32**, 1201-1210.

https://doi.org/10.1089/thy.2021.0563

[18] Yun, C., Xiao, J., Cao, J., Shao, C., Wang, L., Zhang, W., *et al.* (2021) Lymph Node Metastases > 5 and Metastatic Lymph Node Ratio > 0.30 of Differentiated Thyroid Cancer Predict Response to Radioactive Iodine. *Cancer Medicine*, **10**, 7610-7619. https://doi.org/10.1002/cam4.4288

[19] Ma, T., Xie, Y., Long, X. and Ye, F. (2025) High Risk Factors, Molecular Features and Clinical Management for Radioactive Iodine-Refractory Differentiated Thyroid Carcinoma. *Frontiers in Oncology*, **15**, Article 1644562. https://doi.org/10.3389/fonc.2025.1644562

[20] Song, Y.S., Lim, J.A., Choi, H., Won, J., Moon, J.H., Cho, S.W., *et al.* (2016) Prognostic Effects of *TERT* Promoter Mutations Are Enhanced by Coexistence with *BRAF* or *RAS* Mutations and Strengthen the Risk Prediction by the ATA or TNM Staging System in Differentiated Thyroid Cancer Patients. *Cancer*, **122**, 1370-1379. https://doi.org/10.1002/cncr.29934

[21] Wu, X., Gu, H., Gao, Y., Li, B. and Fan, R. (2018) Clinical Outcomes and Prognostic Factors of Radioiodine Ablation Therapy for Lymph Node Metastases from Papillary Thyroid Carcinoma. *Nuclear Medicine Communications*, **39**, 22-27. https://doi.org/10.1097/mnm.0000000000000777

[22] Mao, Y., Lin, R., Wang, Y. and Yu, J. (2024) Correlation Analysis between the Quantitative Parameters of Iodine-131 Single-Photon Emission Computed Tomography-Computed Tomography Thyroid Bed Uptake and the Efficacy of Radioactive Iodine Adjuvant Therapy for Papillary Thyroid Cancer. *Quantitative Imaging in Medicine and Surgery*, **14**, 3665-3675. https://doi.org/10.21037/qims-23-1723

[23] Lee, C., Lee, S., Son, S.H., Hong, C.M., Jeong, J.H., Jeong, S.Y., *et al.* (2019) Prognostic Value of Lymph Node Uptake on Pretreatment F-18 FDG PET/CT in Patients with N1B Papillary Thyroid Carcinoma. *Endocrine Practice*, **25**, 787-793. https://doi.org/10.4158/ep-2018-0607

[24] Yu, F., Li, X., Ji, Y., Tan, J., Zhang, G., Wang, P., *et al.* (2021) Delayed Initial Radioiodine Adjuvant Therapy Does Affect Biochemical Response in Intermediate- to High-Risk Differentiated Thyroid Cancer. *Frontiers in Endocrinology*, **12**, Article 743310. https://doi.org/10.3389/fendo.2021.743310

[25] Li, H., Zhang, Y., Wang, C., Zhang, X., Li, X. and Lin, Y. (2018) Delayed Initial Radioiodine Therapy Related to Incomplete Response in Low- to Intermediate-Risk Differentiated Thyroid Cancer. *Clinical Endocrinology*, **88**, 601-606. https://doi.org/10.1111/cen.13551

[26] Suman, P., Wang, C., Abadin, S.S., Block, R., Raghavan, V., Moo-Young, T.A., *et al.* (2016) Timing of Radioactive Iodine Therapy Does Not Impact Overall Survival in High-Risk Papillary Thyroid Carcinoma. *Endocrine Practice*, **22**, 822-831. https://doi.org/10.4158/ep151088.or

[27] Suman, P., Wang, C., Moo-Young, T.A., Prinz, R.A. and Winchester, D.J. (2016) Timing of Adjuvant Radioactive Iodine Therapy Does Not Affect Overall Survival in Low- and Intermediate-Risk Papillary Thyroid Carcinoma. *The American Surgeon*, **82**, 807-814. https://doi.org/10.1177/000313481608200942

[28] Yin, X., Lu, C., Sun, D., Ji, Y., Wang, Y., Zheng, H., *et al.* (2024) Stimulating Thyroglobulin to TSH Ratio Predict Long-Term Efficacy of 131I Therapy in Patients with Differentiated Thyroid Cancer after Total Thyroidectomy: A Retrospective Study. *Endocrine*, **84**, 1064-1071. https://doi.org/10.1007/s12020-023-03663-6

[29] Pan, M., Li, Z., Jia, M. and Lu, X. (2022) Combination of Stimulated Thyroglobulin and Antithyroglobulin Antibody Predicts the Efficacy and Prognosis of 131I Therapy

in Patients with Differentiated Thyroid Cancer Following Total Thyroidectomy: A Retrospective Study. *Frontiers in Endocrinology*, **13**, Article 857057. https://doi.org/10.3389/fendo.2022.857057

[30] Yoo, S.W., Chowdhury, M.S.A., Jeon, S., Kang, S., Cho, S., Kim, J., *et al.* (2020) Optimization of Predictive Performance for the Therapeutic Response Using Iodine Scan-Corrected Serum Thyroglobulin in Patients with Differentiated Thyroid Carcinoma. *Cancers*, **12**, Article 262. https://doi.org/10.3390/cancers12020262

[31] Giovanella, L., Garo, M.L., Albano, D., Görges, R. and Ceriani, L. (2022) The Role of Thyroglobulin Doubling Time in Differentiated Thyroid Cancer: A Meta-Analysis. *Endocrine Connections*, **11**, e210648. https://doi.org/10.1530/ec-21-0648

[32] Kim, W.G., Yoon, J.H., Kim, W.B., Kim, T.Y., Kim, E.Y., Kim, J.M., *et al.* (2008) Change of Serum Antithyroglobulin Antibody Levels Is Useful for Prediction of Clinical Recurrence in Thyroglobulin-Negative Patients with Differentiated Thyroid Carcinoma. *The Journal of Clinical Endocrinology & Metabolism*, **93**, 4683-4689. https://doi.org/10.1210/jc.2008-0962

[33] Wen, R., Zhao, M., Chen, C., Yang, Y. and Zhang, B. (2023) A Novel Nomogram Integrated with Preablation Stimulated Thyroglobulin and Thyroglobulin/Thyroid-Stimulating Hormone Ratio to Predict the Therapeutic Response of Intermediate- and High-Risk Differentiated Thyroid Cancer Patients: A Bi-Center Retrospective Study. *Endocrine*, **84**, 989-998. https://doi.org/10.1007/s12020-023-03625-y

[34] Wu, R., Liu, W., Li, N., Wang, X., Sun, D., Ji, Y., *et al.* (2022) Analysis of Correlation Factors Influencing the Outcome of Initial 131I Remnant Ablative Therapy in Intermediate- to High-Risk Patients with Papillary Thyroid Microcarcinoma. *Nuclear Medicine Communications*, **43**, 669-674. https://doi.org/10.1097/mnm.0000000000001554

[35] Piccardo, A., Siri, G., Raffa, S., Castellana, M., Foppiani, L., Bottoni, G., *et al.* (2021) How to Better Stratify the Risk of Differentiated Thyroid Carcinomas: The Key Role of Radioactive Iodine Therapy, Age, and Gender. *European Journal of Nuclear Medicine and Molecular Imaging*, **48**, 822-830. https://doi.org/10.1007/s00259-020-05020-5

[36] Goldstein, B.A., Navar, A.M. and Carter, R.E. (2017) Moving Beyond Regression Techniques in Cardiovascular Risk Prediction: Applying Machine Learning to Address Analytic Challenges. *European Heart Journal*, **38**, 1805-1814. https://doi.org/10.1093/eurheartj/ehw302

[37] Geng, Z., Yang, C., Zhao, Z., Yan, Y., Guo, T., Liu, C., *et al.* (2024) Development and Validation of a Machine Learning-Based Predictive Model for Assessing the 90-Day Prognostic Outcome of Patients with Spontaneous Intracerebral Hemorrhage. *Journal of Translational Medicine*, **22**, Article No. 236. https://doi.org/10.1186/s12967-024-04896-3

[38] Hou, F., Zhu, Y., Zhao, H., Cai, H., Wang, Y., Peng, X., *et al.* (2024) Development and Validation of an Interpretable Machine Learning Model for Predicting the Risk of Distant Metastasis in Papillary Thyroid Cancer: A Multicenter Study. *eClinicalMedicine*, **77**, Article ID: 102913. https://doi.org/10.1016/j.eclinm.2024.102913

[39] Toro-Tobon, D., Loor-Torres, R., Duran, M., Fan, J.W., Singh Ospina, N., Wu, Y., *et al.* (2023) Artificial Intelligence in Thyroidology: A Narrative Review of the Current Applications, Associated Challenges, and Future Directions. *Thyroid*, **33**, 903-917. https://doi.org/10.1089/thy.2023.0132

[40] Bülbül, O. and Nak, D. (2024) Predicting Excellent Response to Radioiodine in Differentiated Thyroid Cancer Using Machine Learning. *Acta Otorhinolaryngologica*

Italica, **44**, 261-268. https://doi.org/10.14639/0392-100x-n3029

[41] Sa, R., Yang, T., Zhang, Z. and Guan, F. (2024) Random Forest for Predicting Treatment Response to Radioiodine and Thyrotropin Suppression Therapy in Patients with Differentiated Thyroid Cancer but without Structural Disease. *The Oncologist*, **29**, e68-e80. https://doi.org/10.1093/oncolo/oyad252

[42] Wang, H., Zhang, C., Li, Q., Tian, T., Huang, R., Qiu, J., *et al.* (2024) Development and Validation of Prediction Models for Papillary Thyroid Cancer Structural Recurrence Using Machine Learning Approaches. *BMC Cancer*, **24**, Article No. 427. https://doi.org/10.1186/s12885-024-12146-4