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Clinical Research Article

A Data-Driven Approach to Refine Predictions of Differentiated Thyroid Cancer Outcomes: A Prospective Multicenter Study

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Abstract

Context: The risk stratification of patients with differentiated thyroid cancer (DTC) is crucial in clinical decision making. The most widely accepted method to assess risk of recurrent/persistent disease is described in the 2015 American Thyroid Association (ATA) guidelines. However, recent research has focused on the inclusion of novel features or questioned the relevance of currently included features.

Objective: To develop a comprehensive data-driven model to predict persistent/recurrent disease that can capture all available features and determine the weight of predictors.

Methods: In a prospective cohort study, using the Italian Thyroid Cancer Observatory (ITCO) database (NCT04031339), we selected consecutive cases with DTC and at least early follow-up data (n = 4773; median follow-up 26 months; interquartile range, 12-46 months) at 40 Italian clinical centers. A decision tree was built to assign a risk index to each patient. The model allowed us to investigate the impact of different variables in risk prediction.

Results: By ATA risk estimation, 2492 patients (52.2%) were classified as low, 1873 (39.2%) as intermediate, and 408 as high risk. The decision tree model outperformed the ATA risk stratification system: the sensitivity of high-risk classification for structural disease increased from 37% to 49%, and the negative predictive value for low-risk patients increased by 3%. Feature importance was estimated. Several variables not included in the ATA system significantly impacted the prediction of disease persistence/recurrence: age, body mass index, tumor size, sex, family history of thyroid cancer, surgical approach, presurgical cytology, and circumstances of the diagnosis.

Conclusion: Current risk stratification systems may be complemented by the inclusion of other variables in order to improve the prediction of treatment response. A complete dataset allows for more precise patient clustering.

Key Words: differentiated thyroid cancer, evidence-based guidelines, clinical practice, risk stratification

Abbreviations: ATA, American Thyroid Association; BMI, body mass index; DTC, differentiated thyroid cancer; ITCO, Italian Thyroid Cancer Observatory; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; RAI, radioactive iodine; Tg, thyroglobulin; TgAb, anti-thyroglobulin antibodies.

Appropriate risk stratification of patients with differentiated thyroid cancer (DTC) is crucial. Most cases have an indolent clinical behavior associated with very low mortality rates. This has led to a more conservative management approach, including less extensive surgery, selective use of radioiodine, and less intensive follow-up protocols (1). The ultimate clinical goal is to avoid unnecessary diagnostic procedures in low-risk patients and clinical inertia in cases likely to require more aggressive management (2). Several tools for the prognostic stratification of patients with DTC are available. One of the most widely used is included in the American Thyroid Association (ATA) guidelines, which aims to predict persistent or recurrent structural disease, and has been validated in several retrospective single-center studies (3–6) and also in our prospective cohort (7).

However, the system was developed based on literature data derived from a literature review including studies in different populations, settings, and timeframes. Much research has focused on the inclusion of other features (such as age (8, 9), gender (10), molecular profile of tumors (11)), or questioned the clinical relevance of currently included features (eg, minimal extrathyroidal extension (12–14), microscopic involvement of central compartment lymph nodes (15)).

In our prospective cohort study, we therefore analyzed data of more than 4000 DTC cases managed in 40 diverse healthcare settings in Italy. Our aims were to develop a comprehensive data-driven prediction model able to capture features available at the time of initial treatment, compare performance with the current ATA risk score, and determine the relative weight of the various potential predictors of persistent or recurrent disease.

Methods

The Italian Thyroid Cancer Observatory (ITCO) web-based database was created in 2013 at the Thyroid Cancer Center of Sapienza University of Rome (the network's coordinating center). Since then, it has expanded to include 49 other thyroid cancer centers in the country (16). The database now includes prospectively collected data on more than 10 000 patients with histologically confirmed diagnoses of differentiated, medullary, poorly differentiated, and anaplastic thyroid cancer. Cases are inserted into the database at the time of the initial treatment in the reporting ITCO center, or when the patient begins follow-up in the reporting center within 12 months after undergoing initial treatment in a non-ITCO center. Each case record contains information on patient demographics and biometrics, circumstances of the diagnosis, tumor pathology, surgical and radioactive iodine (RAI) treatments, and the results of periodic follow-up examinations. Since the database is designed to provide a picture of real-world practice, the network provides no guidance or restrictions in terms of patient management to the participating centers. Sensitive data are encrypted, and the database is anonymously managed for statistical analysis. The prospective study was approved by the Coordinating Center Ethics Committee (Sapienza University of Rome, ref. 3366). All patients signed the informed consent form.

For the purposes of the present study, we reviewed all records present in the database on data cutoff and selected consecutive cases with a histological diagnosis of DTC. For each case, the following data were available: demographic data; initial treatment for DTC (surgical approach—including total

thyroidectomy, near total thyroidectomy, and lobectomy; lymph node dissection—including central, and lateral neck dissection; use of radioiodine); histology; family history of thyroid or other cancers; personal history of other cancers; risk of persistent or recurrent DTC, calculated in accordance with the 2009 ATA guidelines and relevant modifications in the 2015 updated release (1). The circumstances of clinical detection (clinical diagnosis; incidental finding during imaging studies performed for other indications; screening for family history, or for other reasons), and diagnosis of cancer (presurgical—based on cytology suspicion—or postsurgical, ie, incidental diagnosis after surgery performed for other indications) were also recorded. The response to initial treatment was classified as *excellent*, *biochemical incomplete*, *structural incomplete*, or *indeterminate* on the basis of data collected during the clinical evaluation at the 1-year follow-up visit. The collected data included imaging findings (mainly cervical ultrasound and RAI scintigraphy, if performed), basal or stimulated serum thyroglobulin (Tg) levels, and anti-Tg antibody (TgAb) levels. Additional imaging studies were performed at the clinician's discretion. The results were classified as specified in the ATA guidelines (1) for patients who had undergone thyroidectomy followed by radioactive iodine remnant ablation (RRA), and as advocated by the European Society for Medical Oncology (17) for the increasing number of patients whose initial treatment consisted of surgery alone (thyroidectomy or lobectomy). Cervical lymph nodes with highly suspicious features on ultrasonography, as defined by European Thyroid Association guidelines (18), were considered imaging evidence of persistent disease; those displaying low-suspicion features were classified as nonspecific imaging findings (19, 20). Any structural findings identified by other imaging studies (ie, functional or cross-sectional) were classified by the treating physicians as nonspecific or suspicious of structural disease according to their clinical judgment. Further examinations (eg, fine-needle aspiration cytology, surgical biopsy, radioactive iodine scans) were performed at the discretion of the treating clinicians, according to relevant practice guidelines. The structure of the dataset with the collected variables is reported in Supplementary Table S1 (21).

Decision Tree

We built a decision tree, a relatively simple prediction model, to determine a risk index for each patient. The simplicity of the model allows to visualize the impact that different variables have in the prediction of risk level to be investigated in more detail and allows these results to be applied directly to clinical practice (22). We used the scikit-learn Python library (23): this package uses an optimized version of the CART (Classification and Regression Trees) algorithm, first presented in 1984 (24). The prediction models were trained using a 5-fold Cross-Validation.

Endpoints

The response to treatment was calculated at each visit, according to the available data. The 1-year evaluation was carried out at 12 ± 6 months; the median follow-up of this cohort was 26 months (interquartile range, 12-46 months; range, 6-84 months). Due to the changing nature of treatment response, when the time interval considered included multiple visits we used the following heuristics: if at least one structural incomplete response was present the response was considered as having a structural incomplete response, whereas if only excellent responses were present the response was considered excellent. If a mixture of indeterminate and biochemical incomplete responses was present, then the response was a weighted average of these 2 responses, where the weight was determined by the presumed timeframe in which the patient was in that class. The weighted average, considering indeterminate as 1 and biochemical incomplete response as 2, was then rounded to the nearest class. For the training of the model, all 4 categories were considered, being an excellent response the optimal response and the other 3 were graded according to their severity (from indeterminate, to biochemical incomplete response, to structural incomplete response). For each cluster, we then reported the probability of a structural incomplete response (ie, persistent/recurrent structural disease) at any time during the follow-up. No mortality data were considered.

Results

For inclusion in the model, 4773 patients were selected; their clinical features are described in Table 1. Of these, 2492 (52.2%) were classified as low, 1873 (39.2%) as intermediate, and 408 as high risk of persistent or recurrent disease, according to ATA risk estimation. Their initial treatment involved total thyroidectomy plus RAI treatment in 2484 cases (52.1%), total thyroidectomy alone in 2140 cases (44.8%), and lobectomy in 149 cases (3.1%). Their response to treatment during the entire follow-up (evaluated as specified above) was excellent in 2188 (45.8%), indeterminate in 1957 (41%), biochemical incomplete in 250 (5.2%), and structural incomplete in 378 (7.9%). The median follow-up is 26 months (interquartile range, 12-46 months; range, 6-84 months).

Decision Tree

A decision tree was used to assign a risk index to each patient, to be applied directly to clinical practice. The model can cluster patients according to their likelihood of incomplete responses by considering the combination of several features.

Two different models were adopted: the first included all available variables. Since radioiodine treatments were prescribed by clinicians based on the patient's baseline data, early response to treatment, and overall prediction of persistence/recurrence, it was not possible to assume independence between the treatment variable and cancer recurrence. For this reason, the second model excluded variables derived from radioiodine treatment (Fig. 1).

This second model was able to exceed the ATA risk stratification system, which was used as a benchmark. The sensitivity of high-risk classification for structural incomplete response increased from 37% to 49%. The negative predictive value for absence of persistence or recurrence of low-risk patients also increased, although only by approximately 3%.

If radioiodine-derived data (eg, decision of clinicians to administer RAI therapy, stimulated serum Tg and anti-Tg antibody levels before treatment) were retained as input to the model to predict the risk of recurrence, the sensitivity of high-risk classification for structural disease increased to 54.8%.

Feature Importance

The importance of the various features based on the division decisions made by the decision tree algorithm is reported in

Table 1. Clinical and demographic features of the study cohort

Feature	N	%
Age, median (IQR)	49.5 (39.3-60.3)	
Sex		
Female	3515	73.6%
Male	1258	26.4%
Histology subtype		
PTC, unknown variant	255	5.3%
PTC, classic variant	2275	47.7%
PTC, follicular variant	1301	27.3%
PTC, tall-cell variant	140	2.9%
PTC, other aggressive variants	116	2.4%
PTC, other variants	253	5.3%
FTC, not specified	15	0.3%
FTC, minimally invasive	160	3.4%
FTC, widely invasive	56	1.2%
Oxyphilic cell carcinoma	90	1.9%
Unknown malignant potential	22	0.5%
NIFTP	54	1.1%
Others	36	0.8%
Lymph node status[a]		
Nx	1313	27.5%
N0	2367	49.6%
N1a	618	12.9%
N1b	475	10.0%
Tumoral foci		
Unknown	64	1.3%
Unifocal	2937	61.5%
Multifocal	1772	37.1%
Extrathyroidal extension[a]		
No	3391	71.0%
Yes, minimal	1201	25.2%
Yes, extensive	146	3.1%
Yes, gross	16	0.3%
Unknown	19	0.4%
Surgical margins		
Rx	1319	27.6%
R0	2920	61.2%
R1	496	10.4%
R2	38	0.8%

Abbreviations: FTC, follicular thyroid cancer; IQR, interquartile range; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid cancer.
[a]According to the definitions of AJCC TNM staging system, 8th edition.

Table 2. Feature importance in the decision tree was measured as the reduction in impurity of a node weighted according to the probability of reaching that node, that is, the number of samples that reached that node divided by the total number of samples. The higher the value, the more important the feature. The table shows the most important features (percentages) for the 2 best trees using all columns and not using radioiodine-derived data. Only columns with importance greater than or equal to 1% are shown.

The tree with radioiodine-treatment-derived data gives a lot of weight to these variables (more than 40% of the total) and uses less data than the other. It is very interesting to note the relevant change in importance of some features from one model to the other. It is important to consider that many of the data that lost importance (eg, tumor size, extrathyroidal extension, presence of distant metastases) are likely to be highly correlated with the decision to administer radioiodine treatment.

Of note, some variables are not currently included as part of the ATA risk calculation (highlighted with a gray background), such as gender, body mass index (BMI), or age of cancer onset.

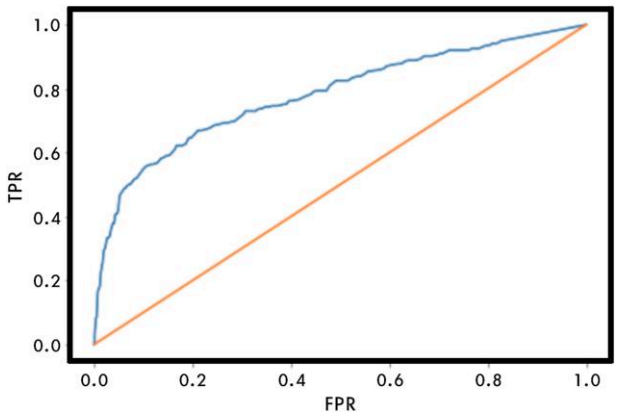

Figure 1. ROC curve showing the true positive rate (TPR) against the false positive rate (FPR) for the decision tree algorithm.

Clusters of Patients With Different Rates of Structural Disease

The decision tree allowed us to derive some clusters of patients with specific rates of persistent or recurrent structural disease. These data were used to revise the ATA-proposed concept of *continuum of risk*. In our preliminary model, the presence of distant and lymph node metastases generated the first discriminations, and more specific groups were then derived from the number of lymph node metastases, tumor size, completeness of surgical resection, oxyphilic cell histotype, BMI, and age. A simplified version is reported in Fig. 2.

Discussion

Prognosis in DTC patients is generally excellent, but a significant degree of overtreatment still exists because of the limited potential to identify cohorts who will experience a more aggressive form of the disease. Identifying these patients at an early stage would allow them to receive more aggressive treatment while avoiding unnecessary and invasive treatment in the vast majority of patients at low risk. A reliable estimate of the posttreatment risk of persistent or recurrent disease allows clinicians to apply a tailored personalized treatment and follow-up strategy (3, 25). The ATA risk stratification system was validated in different cohorts around the world (4–6, 26–32). However, the actual role of some features included (eg, minimal extrathyroidal extension) and not included (such as age, sex, and BMI) in the ATA risk stratification system is still a matter of debate. Many nomograms were proposed as an alternative to, or in addition to, ATA risk, usually derived from a retrospective single-center dataset. The current study was based on a large contemporary database that prospectively

Table 2. Feature importance according to the decision tree algorithm.

	No radioiodine-derived data	All data
Histological extrathyroidal extension	17.1	5.6
Histological tumor size	12.4	6.7
M status	10.4	1.2
Age at diagnosis	9.7	7.4
Number of metastatic lymph nodes	8	6.1
Body mass index	7.7	3.8
Surgical margins	3.5	2.5
Circumstances of thyroid nodule diagnosis	2.7	1.2
Histology subtype	2.6	1.2
Presurgical cytology	2.5	2.8
Family history of thyroid nodules	2.4	1.8
Surgical approach	2.3	1.9
Sex	2.1	<1
N status	2.1	1.3
Tumoral foci at surgical histology	2	<1
Family history of thyroid cancers	1.7	3.1
Number of removed lymph nodes	1.6	<1
Presence of (any) somatic mutation	1.3	<1
Histology vascular invasion	1.1	2.3
Circumstances of thyroid cancer diagnosis (pre- vs postsurgical)	1.1	0.9
Neck dissection	0.9	2.5
Patient preparation for RAI treatment	/	1.5
Anti-Tg antibodies before RAI treatment	/	2.3
Decision to perform RAI treatment	/	5.6
Stimulated Tg (ng/mL) before RAI treatment	/	33.4

Only columns with importance greater than or equal to 1% are shown.
Highlighted with a gray background rows include features not considered in the current ATA risk stratification system.
Abbreviations: ATA, American Thyroid Association; RAI, radioactive iodine; Tg, thyroglobulin.

collected data from many thyroid centers across Italy, including academic and nonacademic institutions.

The main findings of the present study are that, together with some well-recognized factors, BMI, age, gender, and circumstances of diagnosis (including presurgical cytology, family history, and incidental or nonincidental diagnosis) may also be weighted in the prediction of short- and long-term response to initial treatment. They may potentially be included in future versions of the ATA risk stratification system.

Age is already considered to be a predictor of disease-specific mortality (DSM) in thyroid cancer. For this reason, it is included in the TNM staging manual for thyroid cancer. Its role in DSM prediction was confirmed by several recent studies (33–35).

The role of overweight and obesity is also debated, with mixed results: some series reported an association between BMI and aggressive DTC features (36–39), while others excluded this association (40–44). Our data show that, regardless of the baseline association between BMI and aggressive features, body composition plays a role in the prediction of initial treatment response, a fact that could be explained by several hypotheses (such as more difficult ultrasound examination, surgery (45)). Of note, BMI acts as a risk modifier, refining clusters of patients only after the application of other discriminant factors (Fig. 2). It should be observed that in the whole analysis, both age and BMI assumed opposite meanings in different clusters of patients in this cohort, serving as either protective or risk features. This observation suggests that their interaction with other variables is complex, and they may act as a surrogate marker of other characteristics.

Finally, our data suggest that extrathyroidal extension is a significant predictor of incomplete treatment response. This is consistent with recent data reported from the same cohort (14) and by other authors, findings which question the removal of this feature from the TNM staging system (46). Multifocality seems to have a predictive role too, as suggested by others (47), even if much less important than other features (48). The circumstances in which thyroid cancer is suspected or diagnosed may impact treatment response, probably acting as a proxy of clinical significance and extension. Clinical features should be given attention in future analyses and be related to histology data.

It is noteworthy that the combination of specific features (as may occur in individual patients in real-life practice) significantly changes the risk estimates. A reliable and usable risk stratification system would require the adoption of tools such as nomograms and algorithms, which may be included in websites or mobile applications. These approaches are widely adopted in different fields of medicine (eg, cardiovascular disease (49), type 2 diabetes (50), emergency medicine and critical care (51)).

Our study has some limitations. We had to consider a number of indeterminate and biochemical incomplete responses using some assumptions for their classification; the models estimate a risk of non-excellent response, not only structural persistence or recurrence. This is due to the changing nature of treatment response and to the overall small number of recurrences in real-world DTC patients. The nonpapillary tumors represented in our cohort (follicular thyroid carcinomas and oxyphilic cell carcinomas) made up only 6.7% of the whole cohort. There is indeed growing evidence that these tumors behave differently from each other and from papillary thyroid carcinomas (52). Therefore, our current findings cannot shed light on the performance of specific features in patients with these less common thyroid cancer histotypes. Furthermore, we had no data to derive specific models for lesions of uncertain malignant potential or noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). The multicenter nature of this cohort is both a strength and a limitation. Interinstitutional variability has been reported in case load, surgical volume (53, 54), diagnosis of histological subtypes (52), detection and quantification of extrathyroidal extension (55), neck ultrasonographic examination, and RAI administration (56). However, we previously demonstrated that these differences did not impair outcome prediction (7). Finally, we could not explore the specific role of somatic mutations due to the limited number of tested samples, even though the presence of (any) somatic mutations was found to be a significant predictor. However, this effect may be due to the selection of tested cases (ie, patients may be proposed for mutational testing in case of persistent disease or unusual histology findings). For the same reason, we were unable to explore the interactions between mutational status, age,

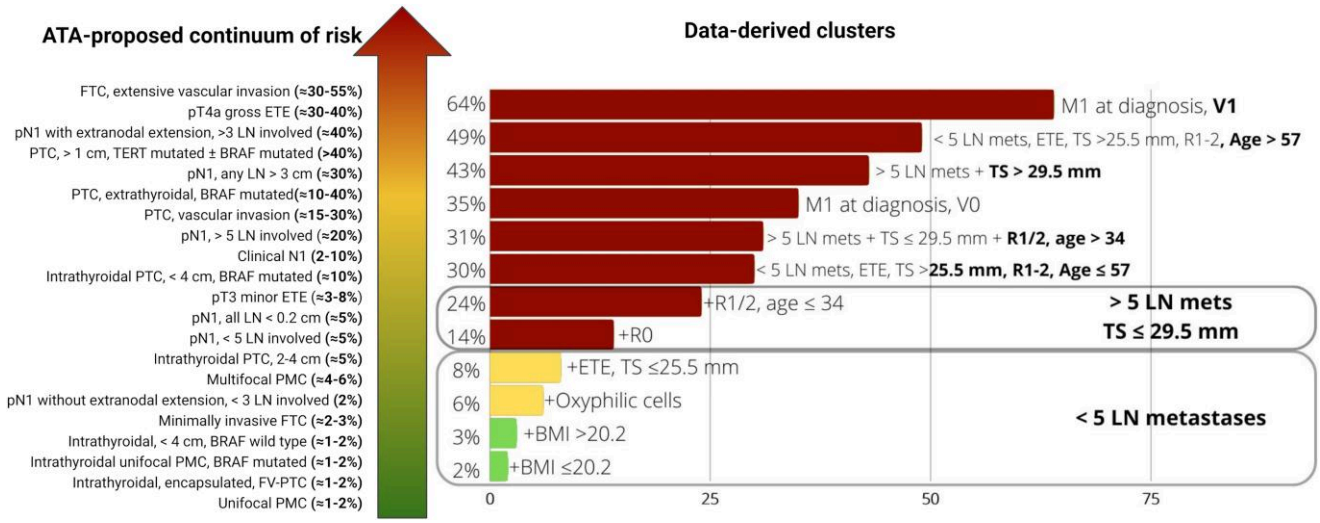

Figure 2. Comparison of continuum-of-risk concept proposed by the American Thyroid Association Guidelines and data-derived clusters (the reported rates indicate the prevalence of structural disease).
Abbreviations: BMI, body mass index; ETE, extrathyroidal extension; FTC, follicular thyroid cancer; FV-PTC, follicular variant PTC; LN, lymph nodes; M1, distant metastases at diagnosis; PMC, papillary microcarcinoma; PTC, papillary thyroid cancer; TS, tumor size; V1, vascular invasion at surgical histology.

and gender in this cohort. An external validation using an independent dataset has yet to be performed. The development of web-based applications is needed to make this strategy applicable in real-world practice.

In conclusion, current risk stratification systems may be complemented by the inclusion of some demographic, clinical, and anthropometric data to improve the prediction of treatment response in patients with DTC. The use of a complete set of variables allows for a more precise clustering of patients to predict their likelihood of excellent, incomplete, or indeterminate responses to treatment.

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Disclosures

The authors have nothing to disclose.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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