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The Initial ATA Risk Classification, but Not the AJCC/TNM Stage, Predicts the Persistence or Relapse of Differentiated Thyroid Cancer in Long-Term Surveillance

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Abstract: Background: The American Joint Commission on Cancer on Tumor Node Metastasis (AJCC/TNM) staging system provides adequate information on the risk of differentiated thyroid cancer (DTC)-specific mortality in totally thyroidectomized patients, but its role in predicting persistence and relapse of disease is uncertain. The relatively new 2015 American Thyroid Association (ATA) guidelines recommend stratifying patients at the time of DTC diagnosis with its own risk classification system, in order to identify those at high risk of residual or recurrent morbidity who may benefit from post-operative radioiodine (RAI) administration and/or need additional work-up. Methods: To verify the prevalence proportion of persistence or relapse of disease, a consecutive cohort of 152 patients with a diagnosis of DTC, subjected to total thyroidectomy (+/– post-operative RAI administration as per guidelines indication) and to neck ultrasonography (US), as well as biochemical surveillance for a minimum of 2 years at the Endocrinology Unit of Mater-Domini Hospital (Catanzaro, Italy), was enrolled. The prognostic role of the AJCC/TNM stage and ATA risk classification system was analyzed by logistic regression. Results: At a mean of 9 years after surgical treatment, DTC was found to persist or relapse in 19 (12.5%) participants. The initial risk for these outcomes, based on the ATA classification, was mostly low (53.9%) or intermediate (39.5%). AJCC/TNM stages were predominantly stage I or stage II. Despite a small representation in this cohort, high-risk patients according to the ATA classification had 8-fold higher odds of persistence or relapse of disease than those of low-risk participants, while controlling for potential risk modifiers, including age at DTC diagnosis, male gender, and post-operative RAI administration ($p = 0.008$). In contrast, the AJCC/TNM stage was not associated with the disease status at the last follow-up visit ($p = 0.068$ for the 7th Edition; $p = 0.165$ for the 8th Edition). Furthermore, low-risk participants subjected to post-operative RAI administration had the same probability of persistence or relapse of DTC when compared to those who had undergone total thyroidectomy only. Conclusions: There is a need for the endocrine community to revise the current work-up of DTC. The initial ATA risk classification is a reliable tool for predicting the persistence or relapse of disease in long-term surveillance.

Keywords: differentiated thyroid cancer; prognostic factors; AJCC/TNM stage; ATA classification; radioiodine

1. Introduction

Differentiated thyroid cancer (DTC) represents about 90% of all thyroid cancer cases and is the first-leading endocrine malignancy [1]. In the last three decades, the widespread diffusion of high sensitivity diagnostic tools, including neck/thyroid ultrasonography

(US) and fine needle aspirations, has dramatically enhanced its diagnostic rates, especially in women [1]. However, a large majority of these tumors have an excellent prognosis, and mortality from DTC is generally regarded as a rare event (1.5% of all DTC cases in the United States) [2]. Hence, there is a need for the endocrine community to revise the diagnostic and therapeutic work-up of DTC in a more cost-effective manner, as many thyroid tumors are indolent [3], and only a subgroup of patients would experience a failure of conservative surgical treatment [4]. These individuals may more likely benefit from aggressive interventions, including cervical lymph node dissection, and post-operative radioiodine (RAI) administration, as well as intense and prolonged neck US and biochemical surveillance, in addition to total thyroidectomy [4,5].

The American Joint Commission on Cancer on Tumor Node Metastasis (AJCC/TNM) staging system provides adequate information on the patient risk of DTC-specific mortality [6], but its role in predicting persistence and relapse of disease, which are far more frequent occurrences in the long-term clinical management of patients with DTC [7], is uncertain. With respect to the 2010 version, the updated AJCC/TNM 8th Edition staging system has introduced several changes, often resulting in the reclassification of patients into lower risk categories (i.e., stage I or stage II) [8]. In particular, the age threshold to define patients at high risk of DTC-related death (i.e., from 45 to 55 years) has been increased, while the negative prognostic value of neck lymph node metastases and microscopic extrathyroidal extension (ETE) in identifying patients at substantial risk of dying from thyroid malignancies has been considerably reduced [6]. However, if it is important to assess the clinical and pathological factors associated with DTC-specific mortality, the same should be done with factors relevant to persistent or recurrent morbidity, as this outcome has now gained the highest priority in the work-up of differentiated thyroid tumors [9]. In this regard, the 2015 American Thyroid Association (ATA) guidelines recommend stratifying patients at the time of DTC diagnosis with its own risk classification system, in order to identify those at high risk of disease relapse and poor responders to conservative management [10].

Thus, this retrospective-longitudinal study was aimed at verifying the prevalence proportion of persistence or relapse of DTC in a consecutive cohort of patients subjected to total thyroidectomy (+/− post-operative RAI administration as per guidelines indication [10,11]) at our tertiary care Institution who had undergone neck US and biochemical surveillance for a minimum of 2 years. The role of both AJCC/TNM stage and ATA risk stratification system in predicting these events was investigated as a secondary aim.

2. Patients and Methods

2.1. Study Participants

For this retrospective-longitudinal study, all the consecutive surgical patients with DTC who have been managed at the tertiary care Mater-Domini Hospital of Catanzaro, Italy (Endocrinology Unit) from 2005–2020 were assessed for participation eligibility. Exclusion criteria were a final diagnosis of medullary thyroid carcinoma (MTC); partial thyroidectomy as the surgical strategy of choice for the management of DTC; a duration of follow-up shorter than 2 years and missing pre-operative clinical data. In order to limit selection bias when addressing study outcomes, patients with an incidental histological diagnosis of unifocal papillary thyroid carcinoma (PTC) of less than 10 mm diameter and considered to be at very low risk of recurrence [10], were prevented from participating in this study. Figure 1 illustrates the participant selection workflow which has been followed for our retrospective analysis. Medical records of eligible participants with DTC, including PTC subtypes, follicular thyroid carcinoma (FTC), and oncocytic carcinoma (OCA) histology as per the recent WHO classification [12], who underwent total thyroidectomy and at least 2 years of follow-up visits, were reviewed by trained endocrinologists. Retrospectively collected data included patient demographics, histological findings at the time of diagnosis (i.e., maximum tumor size, tumor focality, DTC histology, presence of angioinvasion, ETE (microscopic or gross), cervical lymph node status when dissection was performed), initial

tumor stage (according to AJCC/TNM 7th and 8th Edition) and ATA risk category (low, intermediate, or high) by malignant tumor features [10] and information on post-operative RAI administration (generally not exceeding 100 mCi dose). Furthermore, duration of follow-up and detailed information on response to therapy, based on periodical neck US and biochemical evaluations and/or additional imaging findings, were collected in order to assess the study outcomes.

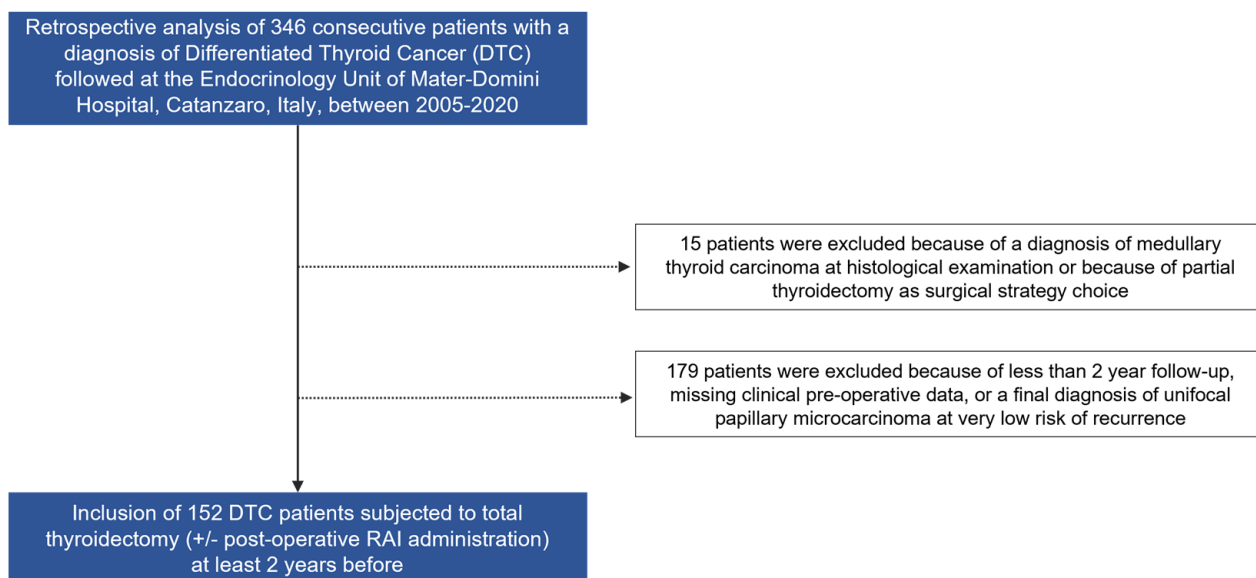


Figure 1. Participant selection workflow.

2.2. Outcome Assessment

Response to DTC therapy (subcategorized into excellent, indeterminate, biochemically incomplete, and structurally incomplete, according to ATA guidelines [10]) was retrospectively evaluated in a longitudinal manner (i.e., at the time of first evaluation after surgical treatment and at the last follow-up visit) on the basis of available data in medical records. As per ATA guidelines [10] and Italian national adaptations [11], standard of care of PTC, FTC, and OCA in totally thyroidectomized patients at our Institution comprises the biochemical evaluation of basal or stimulated serum thyroglobulin (Tg) on the fully automated LIAISON XP Analyzer (DiaSorin S.p.A., Saluggia, Italy), and dosage of anti-Tg antibodies with the ADVIA Centaur Immunoassay System (ADVIA Centaur, Siemens Healthcare Diagnostics Inc., Camberley, UK) at the near Clinical Pathology Unit (Mater-Domini Hospital of Catanzaro), associated with neck US, while additional imaging tests are reserved to specific cases. An excellent response indicates no clinical, biochemical, or neck US evidence of the disease with basal serum Tg level < 0.2 ng/mL or stimulated serum Tg level of < 1 ng/mL and negative anti-Tg antibodies. An indeterminate response indicates a situation when residual or recurrent disease cannot be definitely excluded because of a mild elevation of serum Tg (i.e., basal Tg 0.2 – 1 ng/mL or stimulated Tg 1 – 10 ng/mL), positive anti-Tg antibodies, and/or nonspecific imaging findings. A biochemically incomplete response refers to a significant elevation of serum Tg (i.e., basal Tg > 1 ng/mL or stimulated Tg > 10 ng/mL) in the absence of structural evidence of disease on neck US and/or other imaging tests. A structurally incomplete response indicates the presence of disease on neck US and/or other imaging tests, usually accompanied by a significant elevation of basal serum Tg or positive anti-Tg antibodies [10,13]. Post-operative neck US sessions were conducted with the use of a high-resolution System (10 MHz, Aplio XG, Model SSA 790A, Toshiba Corp., Tokyo, Japan) by two clinically experienced endocrinologists, trained in cervical ultrasonography, under routine medical practice conditions in all patients.

For the purpose of the study, patients with an excellent response to DTC therapy at the last follow-up visit (i.e., after a minimum of 2 years since total thyroidectomy) were classi-

fied as those with “no evidence of disease”. Patients with persistent biochemical/structural incomplete response or with indeterminate response to DTC therapy at both time points, and those switching from an excellent response at the time of the first evaluation to an indeterminate response or biochemical/structural incomplete response at the last follow-up visit, were classified as those with “persistence or relapse of disease”. No DTC-related deaths occurred in this selected study population.

2.3. Statistical Analysis

In descriptive statistics, categorical and continuous variables were respectively expressed as numbers and percentages or as means and standard deviations (SD) with interquartile ranges. In order to assess the relative risk of persistence or relapse of disease in patients diagnosed with DTC and followed up for a minimum of 2 years, a series of logistic regression models were calculated, using the initial ATA risk classification or the AJCC/TNM stage (7th and 8th Edition) as the explanatory factors by adjusting for potential confounders, identified by univariate analysis or knowledge of previous literature reports [14,15]. Risk estimates were expressed as adjusted odds ratios (OR) with 95% confidence intervals (CI). However, in view of the recent controversy about the role of post-operative RAI administration in determining a better outcome for low-risk DTC [16], and in the absence of clear and strict recommendations on its administration in current national and international guidelines [10,11], particular attention has been given to this factor. Probabilities of persistent or recurrent morbidity as per post-operative RAI administration in thyroid tumors categorizable as low-risk DTC (according to the initial ATA classification) were compared with Fisher’s exact test. Statistical analysis was performed with JASP Graphical Statistical Software Version 0.14.1 (University of Amsterdam, Amsterdam, The Netherlands) based on R Stats packages. A significance level of $p < 0.05$ was set for a type I error in all analyses.

3. Results

3.1. Characteristics of Participants and Prevalence Proportion of Persistence or Relapse of DTC

As shown in Figure 1, 152 patients subjected to total thyroidectomy due to DTC were eligible for participation in this study. All of them were followed up for a minimum of 2 years since surgical treatment. Their clinical characteristics are shown in Table 1.

The mean age of participants at the time of DTC diagnosis was 43 years and 123 (80.9%) were women. Histological examination revealed mostly PTC (92.1%), with a mean tumor size (i.e., maximum diameter) of 25 mm. Almost a quarter of participants had multifocal DTC (i.e., two or more tumor foci in the same thyroid lobe, or a bilateral DTC) and/or ETE. Furthermore, 28 participants subjected to cervical lymph node dissection had microscopic and/or macroscopic neck lymph node metastases. However, in consideration of their relatively young age and reduced risk of DTC-related death using either 45 or 55 years as the age thresholds for stage grouping, AJCC/TNM stages were mostly stage I (71.0% according to the AJCC/TNM 7th Edition, 89.5% according to the AJCC/TNM 8th Edition). The initial risk of participants for residual or recurrent morbidity, estimated at the time of DTC diagnosis based on the ATA classification [10], was low (53.9%) or intermediate (39.5%). Only 10 patients were classified as at high risk of persistence or relapse of DTC because of clinical and/or pathological features. Post-operative RAI was administered to 131 (86.1%) patients.

Table 1. Clinical and pathological data of 152 DTC patients submitted to total thyroidectomy with or without post-operative radioiodine (RAI) administration. All patients were followed up for a minimum of 2 years since surgical treatment.

Clinical and Pathological Characteristics	N (%) or Mean \pm SD (Range)
Female gender, N	123 (80.9)
Age at DTC diagnosis, yr	43 \pm 14 (33–52)
Follow-up duration, yr	9.0 \pm 6.2
Post-operative RAI administration, N	131 (86.1)
Multifocality, N	33 (21.7)
Lymph node metastases, N	28 (18.4)
Maximum tumor size, mm	25 \pm 12.7 (15–30)
PTC histology, N	139 (92.1)
Aggressive subtypes *	25 (17.9)
FTC histology, N	7 (4.6)
OCA histology, N	6 (3.9)
Angioinvasion, N	16 (10.5)
Extrathyroidal extension, N	34 (22.3)
Microscopic	30 (88.2)
Initial risk category, N	
<u>AJCC/TNM 7th Edition</u>	
Stage I	108 (71.0)
Stage II	19 (12.5)
Stage III	19 (12.5)
Stage Iva	5 (3.3)
Stage IVb	0 (0)
Stage IVc	1 (0.7)
<u>AJCC/TNM 8th Edition</u>	
Stage I	136 (89.5)
Stage II	14 (9.2)
Stage III	1 (0.7)
Stage IV	0 (0)
Stage IVb	1 (0.7)
<u>ATA risk classification</u>	
Low	82 (53.9)
Intermediate	60 (39.5)
High	10 (6.6)

AJCC/TNM: American Joint Cancer Committee on tumor-node-metastasis stage; ATA: American Thyroid Association; PTC: papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; OCA, oncocytic carcinoma; N: number of patients; yr: years. * Aggressive subtypes refer to PTC with tall cells, diffuse sclerosing, infiltrative follicular, and/or solid/trabecular features [12].

Then, we addressed the prevalence proportion of persistence and/or relapse of disease at the last follow-up visit, grossly coincident with a mean of 9.0 years after surgical treatment. DTC was found to persist or recur in 19 (12.5%) participants, which is similar to the distribution of response observed at 3 years of follow-up in a recent prospective study with low-risk patients [17] (Table 2).

Table 2. Disease status of study participants at last follow-up.

Disease Status	N (%)
No evidence of disease	133 (87.5)
Persistence or relapse of disease (neck US or biochemical testing)	19 (12.5)

3.2. Outcome Assessments by ATA Risk Classification System and Other Prognostic Factors

Next, we investigated the differences in clinical and pathological factors in patients stratified by disease status at the last follow-up visit. As shown in Supplementary Table S1, patients with persistent or relapse of DTC differed from those with no evidence of disease for a number of features. In particular, angioinvasion or ETE were far more frequent

histological findings in those patients that went through persistence or relapse of DTC during follow-up (8.2% vs. 26.3% for angioinvasion, $p = 0.017$; 18.7 vs. 47.3% for ETE, $p = 0.005$). Furthermore, stage grouping according to the AJCC/TNM (7th and 8th Edition), significantly differed between patients with no evidence of disease with respect to those experiencing the persistence or relapse of DTC at the last evaluation, predominantly related to changes in the distribution of stage I and stage II cases (both indicative of a non-disseminated cancer condition at the time of diagnosis). As expected, since the ATA classification has been modeled to reflect tumor biology and predict DTC recurrence as a continuum of risk that ranges from less to 1% in very low-risk patients to over 50% in high-risk patients [10], the proportions of patients grouped into this three-tier system significantly differed based on disease outcomes. In fact, while over half of participants with an excellent response to therapy could be classified as at low risk, more than 70% of those experiencing persistence or relapse of disease were at intermediate or at high risk at the time of first evaluation ($p = 0.004$).

As the initial staging is used to guide treatment decisions (i.e., the need for adjuvant RAI), we validated and quantified the prognostic role of the ATA classification with logistic regression models by controlling for potential risk modifiers, including age at DTC diagnosis, post-operative RAI administration, and male gender, which tended to be more prevalent in patients experiencing persistence or recurrence of disease at univariate analysis and in previous works (Supplementary Table S1) [14,15]. As shown in Table 3, the odds of persistence or relapse of disease in patients at high risk according to ATA classification were 8-fold higher than those of low-risk participants ($p = 0.008$), notwithstanding wide confidence bounds in view of the limited data.

Table 3. Relative risk of persistence or relapse of disease at last follow-up as per initial ATA risk classification.

ATA Risk Classification	Patients with Persistent or Recurrent Disease, N (%)	OR (95%CI)	p-Value
Low	5 (6.1)	Reference	-
Intermediate	10 (16.7)	2.722 (0.842–8.800)	0.094
High	4 (40.0)	9.223 (1.792–47.465)	0.008

Age at DTC diagnosis, male gender, and adjuvant RAI ablation have been included as covariates in the logistic regression model. Bold values denote statistical significance at p level < 0.05.

While all patients at high risk according to the ATA classification were subjected to post-operative RAI administration, a fraction of low-risk participants, and a minority of those at intermediate risk, were managed with surgery only. If there is a consensus in ATA guidelines to avoid post-operative RAI administration in patients with unifocal PTC of less than 10 mm diameter (excluded from the present study), the recommendations for adjuvant RAI ablation of the remaining normal thyroid tissue in low-risk DTC are more controversial due to a lack of strong evidence for benefits [10]. In agreement with a recent, and already mentioned, prospective study on this topic [17], low-risk participants subjected to post-operative RAI administration in our work had the same probabilities of persistence or relapse of DTC at follow-up when compared to those subjected to total thyroidectomy only (Table 4).

Table 4. Relative risk of persistence or relapse of disease at last follow-up as per post-operative RAI administration in DTC stratified by initial ATA risk classification.

ATA Risk Classification	Patients Subjected to RAI, N (%)	Risk of Persistence or Relapse of DTC with RAI, N (%)	Risk of Persistence or Relapse of DTC without RAI, N (%)	p-Value
Low	65 (79.2)	4/65 (6.2)	1/15 (6.7)	1.000
Intermediate	56 (93.4)	10/56 (17.8)	0/2 (0.0)	1.000
High	10 (100)	4/10 (40)	n.a.	n.a.

p -value calculations have been performed with Fisher's exact test.

Finally, we investigated the significance of the AJCC/TNM stage (historically introduced as a clinical and pathological tool for selecting patients at high risk of disease-specific death [6,8]) in predicting persistent or recurrent morbidity in patients with DTC (Table 5). Patients classified as stage III or IV according to the AJCC/TNM 7th Edition were estimated, with borderline significance, to have almost 2-fold higher odds of persistence or relapse of disease with respect to those grouped into lower risk categories ($p = 0.068$). Conversely, the updated AJCC/TNM 8th Edition was not associated with disease status at the last follow-up ($p = 0.165$), given that 18 out of 19 events occurred in participants classified as stage I or II, which comprise the almost totality of patients with DTC that are routinely managed at our Endocrinology Unit (Table 1) and other institutions [6,8,18].

Table 5. Relative risk of persistence of relapse of disease at last follow-up as per AJCC/TNM stage.

AJCC/TNM 7th Edition	Patients with Persistent or Recurrent Disease, N (%)	OR (95%CI)	p-Value	AJCC/TNM 8th Edition	Patients with Persistent or Recurrent Disease, N (%)	OR (95%CI)	p-Value
Stage I-II	13 (10.3)	Reference	-	Stage I-II	18 (12.0)	Reference	-
Stage III-IV	6 (24.0)	2.745 (0.930–8.103)	0.068	Stage III-IV	1 (50.0)	7.3 (0.439–122.443)	0.165

Due to the relative sample size, AJCC/TNM stages I, II and III, IV have been grouped to calculate risk estimates.

4. Discussion

In an effort to predict how patients with DTC will respond to the initial surgical treatment in terms of residual or recurrent morbidity, the 2015 ATA guidelines recommend their categorization into a three-tier classification system, by capturing the malignant biological features of a tumor at the time of diagnosis (i.e., maximum tumor size, presence of aggressive histological subtypes, presence of large cervical lymph node metastases, angioinvasion, ETE, and/or distant metastasis) [10]. Each ATA risk category is associated with an estimated rate of tumor relapse, whose chance ranges from very low to high [10].

Shortly after its introduction in the routine endocrinological practice, the prognostic role of the ATA risk classification has been validated by a number of retrospective, single-center studies [13,19], other than a recent prospective multicentric investigation in Italy [20]. However, none of these has specifically involved patients from Calabria, a Southern Mediterranean region characterized by a former iodine deficit and a relatively high incidence of DTC [1]. Furthermore, the relatively short duration of follow-up in some of the previous works might have been inadequate to secure all the events associated with recurrence of disease after an initial excellent response to DTC therapy (i.e., switch to a biochemically incomplete or an indeterminate response) [19,20]. Herein, by specifically selecting a patient population managed at our Endocrinology Unit for an extended period of time, and while controlling for potential confounders, we demonstrate that an initial high-risk category according to the ATA classification matches well with poor response to treatment in the long run.

In our retrospective-longitudinal study, the initial ATA risk of persistence or relapse of disease was classified as low in 53.9% of participants and intermediate in 39.5%, closely resembling the distribution of the initial ATA estimates of risks for DTC persistence/recurrence among patients attending other endocrinology clinics in Italy examined by Grani et al. [20]. In such an instance, the DTC cases, classified as indeterminate or high-risk because of clinical and pathological factors, have been reported to possess a significantly higher probability of a “less-than-excellent response” (i.e., indeterminate, or biochemically incomplete or structurally incomplete) at one year of prospective follow-up, with respect to low-risk ones [20], which agrees with our findings, as well as with the estimates of tumor relapse rates anticipated by the ATA classification itself [10].

Still, for the interpretation of our results, it might be relevant to also consider the efforts made by other groups to understand the natural course of the different statuses of response to DTC therapy after the initial management over time [13]. Indeed, the risk stratification concepts of the ATA guidelines are intended to guide the choice of additional work-up, as well as the intensity and frequency of surveillance, after the initial management, tailored on

the basis of available clinical image and biochemical data at the time of evaluation [10]. The use of this “dynamic” strategy for risk assessment is crucial to avoid overtreatment and intensive follow-up for the vast majority of patients who will have a very good prognosis, and, on the other hand, it allows to focus aggressive interventions (i.e., extensive surgery or post-operative RAI administration) and/or surveillance on those who will have a worse prognosis, in terms of recurrence, progression or mortality [19]. Nevertheless, notwithstanding a late tendency toward a more conservative surgical management in case of very low-risk papillary tumors [4], total thyroidectomy (with or without cervical lymph node dissection) followed by adjuvant RAI remains the most commonly practiced intervention for intermediate and high-risk patients with DTC and even for a good proportion of those considered to be at low-risk according to the initial ATA classification [21]. That said, in a recent retrospective, single-center study in the Middle East [13], the status of response to DTC therapy at the first evaluation after the initial management, consisting of total thyroidectomy and post-operative RAI administration, has been found predictive of the status of response at the last follow-up visit (without any additional therapy) after a median interval of 8 years. Coincidentally, the initial ATA classification was highly predictive of the long-term outcome in these patients, with reports of 16.6% and 4.9% of indeterminate- and low-risk DTC cases, respectively, going through persistence or relapse of disease, which coincides with our results at a mean of 9 years of follow-up [13].

In this work, we had also the opportunity to corroborate new evidence from the ESTIMABL2 trial [17], assessing the prognostic role of adjuvant RAI in low-risk DTC with a prospective randomized design. Patients with low-risk DTC subjected to total thyroidectomy showed no improvements in outcomes (i.e., persistence or relapse of disease during 3 years of observation) with post-operative RAI administration compared to those managed with surgery only [17]. Taken as a whole, both our real-world data and the ESTIMABL2 [17] suggest that low-risk patients should be spared this common additional treatment and that there is a need to revise the 2015 ATA guidelines, providing now strong recommendations against the use of post-operative RAI for low-risk DTC [16].

Previous retrospective studies have already questioned the usefulness of post-operative RAI administration in reducing DTC-related death or the occurrence of functional, structural, and biologic events according to patient’s risk stratification, yielding conflicting results when low-risk DTC was considered [22]. However, in most cases, patient’s risk of disease recurrence was based on the classic clinical and pathological AJCC/TNM staging system and not on the, relatively new, ATA classification [10]. Thus, our work has made it possible to enhance the knowledge of this issue. In this respect, the AJCC/TNM 7th Edition stage, but not the updated 8th Edition, has been found predictive of risk of persistence or relapse of DTC in several investigations [6,23,24]. These findings have been replicated, at least to some extent, also in our work. Prognostic differences between the 7th and 8th Editions of the AJCC/TNM staging system can be largely attributed to changes in the age thresholds that define patients at substantial risk of DTC-related mortality, and to a less extent to changes in specific tumor features [6,23,24]. In any case, by leading to the downstaging of a large group of patients with DTC (i.e., aged between 45 and 55 years and estimated to be at low risk of death from thyroid malignancies), the AJCC/TNM 8th Edition may induce endocrinologists to overlook those predisposed to structural or biochemical recurrence, potentially causing some uncertainties during the initial therapeutic decision-making [6,24,25]. As the high clinical burden associated with persistence or relapse of DTC, which were not negligible events in our relatively young population (i.e., 12.5%), could be avoided with proper patient management, it was important to clarify the prognostic relevance of both systems (i.e., the ATA risk category and the AJCC/TNM stage) in the initial classification of tumor aggressiveness.

We are aware that this study is not void of limitations, mostly related to its retrospective observational design and limited sample size, which may have reduced the power of statistical analyses. Furthermore, no data on molecular profiling of preoperative thyroid FNA samples could be available for risk stratification, as those additional analyses were not

covered by national reimbursement policies during the study period. However, in view of its single-center tertiary care setting, our study has the advantage of a long follow-up of a homogeneous population, both in genetical terms [26], strategies for assessing the response to DTC therapy (i.e., laboratory determinations of serum Tg and anti-Tg antibodies) [20], and initial therapeutic management [27], thereby preventing the rise of potential biases when interpreting the results.

In conclusion, our data add up to the evidence indicating the need for an optimal risk determination at the time of diagnosis to improve the current work-up of DTC, as it may help reduce the access to post-operative RAI in low-risk patients without the negative effects of poor disease control. The initial ATA classification, but not the updated AJCC/TNM 8th Edition stage, can predict the persistence or relapse of DTC in long-term surveillance, an endocrinological problem far more common than disease-related death.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/endocrines3030041/s1>, Supplementary Table S1: Clinical and pathological data of 152 DTC patients stratified by disease status at last follow-up.

Author Contributions: Conceptualization, S.G., M.M. and E.C.; methodology, S.G., V.T., A.D. and S.I.; formal analysis, M.M., E.C. and A.S.; writing—original draft preparation, M.M.; writing—review and editing, E.C., D.P.F., A.A. and A.B.; supervision, A.B.; project administration, A.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and complies with principles of Good Clinical Practice. Data collection was approved by the ethics committee of Regione Calabria Sezione Area Centro (protocol registry no. 343 of 21 November 2019) and performed by endocrine researchers directly accessing to medical records.

Informed Consent Statement: As the data were analyzed anonymously, and in consideration of the retrospective observational nature of the study, written informed consent from participants was waived.

Data Availability Statement: Data supporting the reported results are available from the corresponding Author upon request.

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Conflicts of Interest: The authors declare no conflict of interest.

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