Clinical Research Article

Course and Predictive Factors of Incomplete Response to Therapy in Low- and Intermediate-Risk Thyroid Cancer

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Abstract

Context: Controversy surrounds the extent and intensity of the management of American Thyroid Association (ATA) intermediate- and low-risk patients with differentiated thyroid cancer (DTC). Understanding the natural history and factors that predict outcome is important for properly tailoring the management of these patients.

Objective: This work aims to study the natural course and predictive factors of incomplete response to therapy in low- and intermediate-risk DTC.

Patients and Methods: We studied a cohort of 506 consecutive patients [418 women (82.6%) and 88 men (17.4%)] with low and intermediate risk with a median age of 35 years (interquartile range [IQR], 27-46 years). We analyzed the natural course and the predictive factors of biochemically or structurally incomplete response.

Results: Of 506 patients studied, 297 (58.7%) patients were in the low-risk group and 209 (41.3%) were in the intermediate-risk group. Over a median follow-up of 102 months (IQR, 66-130 months), 458 (90.5%) patients achieved an excellent response, 17 (3.4%) had a biochemically incomplete status, and 31 (6.1%) had a structurally incomplete status. In univariable and multivariable analyses, age ($\geq$ 33 years) (*P* < .0001, odds ratio 1.06 [1.04-1.08]) and lateral lymph node metastasis (LNM; *P* < .0001, odds ratio 3.2 [1.7-5.9]) were strong predictive factors for biochemically and structurally incomplete response to therapy. Sex, tumor size, multifocality, extrathyroidal extension, and lymphovascular invasion did not predict incomplete response to therapy.

Conclusions: Patients with low- and intermediate-risk DTC have favorable outcomes. Age and lateral LNM are strong predictors of an incomplete response to therapy. This suggests that older patients and those with LNM should be managed and followed up more actively than younger patients and those without LNM.

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy [1-3], and its incidence has been increasing over the last 40 years [1-4]. The widespread use of neck ultrasonography and other imaging studies has contributed significantly to the detection of a significant number of these cases that would otherwise have remained undiscovered [3, 5]. The majority of cases are small papillary thyroid cancer (PTC) with low risk for recurrence and mortality [3, 5-7]. Studies over the last decade have shown that less than 30% of cases of DTC are high risk, whereas the majority are low and intermediate risk [8-11]. Realizing these facts, there has been a paradigm shift in the management of DTC with emphasis on a risk-based approach that tailors the intensity of the initial management and follow-up to the risk of recurrence and mortality [12-15]. The American Thyroid Association (ATA) guidelines in 2009 and 2015 emphasized these concepts [14, 16]. In 2009, the ATA guidelines proposed a new risk-stratification system for predicting DTC recurrence [16]. This was initially based on expert opinion but subsequent studies have validated it [8, 9, 17, 18]. The 2015 ATA guidelines slightly modified the definitions of the low-, intermediate-, and high-risk groups and suggested that the risk is a continuum but maintained the 3 risk categories [14]. The ATA guidelines recommend a risk-based approach in which the intensity of therapy and surveillance is based on the staging system [14]. Whereas there is essentially no controversy on the need for near-total or total thyroidectomy ± lymph node dissection followed by radioactive iodine (RAI; iodine-131 [I-131]) ablation in patients with ATA high-risk stage, much of the controversy lies in the management of the low- and intermediate-risk categories [14, 19]. For example, opinions differ on the extent of surgery, use of I-131 ablation, the level of thyrotropin (TSH) suppression post initial management, and the frequency and tools used to follow those patients [14]. Patients in low and intermediate ATA stages are generally at low risk of recurrence and mortality [8, 9, 18]. However, about 3% to 9% of patients in the low-risk and 13% to 45% in the intermediate-risk stages develop recurrence [20], and up to 10% die of their disease over the next 10 years [21]. It is not fully clear which patients in these risk categories are more destined to develop recurrence and suffer mortality. Predicting those patients would entail a more active approach to their management, including performing complete surgery and administering I-131 for initial management and careful follow-up with more frequent use of serum thyroglobulin (Tg), neck ultrasonography, and other imaging studies. In this report we attempted to study the natural history of patients in low- and intermediate-risk groups and to identify factors that are predictive of an incomplete response to therapy in these patients. Knowing these data is expected to help in the decision making as to the intensity of the initial management and follow-up of the majority of DTC patients since most DTC patients are usually in low- or intermediate-risk groups.

1. Materials and Methods

This study was undertaken at the King Faisal Specialist Hospital & Research Centre (KFSHRC), Riyadh, Saudi Arabia. Institutional review board approval was obtained from the KFSHRC Office of Research Affairs. KFSHRC is the premier tertiary care institution and the main cancer care center in Saudi Arabia. About 200 to 300 patients with newly diagnosed thyroid cancer are referred to KFSHRC every year for management and long-term follow-up. More than 6000 DTC patients have been treated at this center and the majority are still on follow-up. The management of thyroid cancer has followed international standards and guidelines since 1998. Except for very low-risk patients (T1N0M0), our practice had been in the form of near-total or total thyroidectomy and therapeutic lymph node dissection if pathological lymph nodes are found on preoperative evaluation or intraoperative examination. I-131 ablation has been administered to most cases except very low-risk patients (T1aN0M0). Thyroid hormone suppression was prescribed aiming at a serum TSH level of 0.1 to 0.5 mU/L for low- to intermediate-risk and less than 0.1 mU/L for high-risk patients. Patients were usually evaluated 6 to 18 months after I-131 ablation with measurement of serum TSH, free thyroxine (FT4), Tg, anti-Tg antibodies (Abs), and neck ultrasonography. Iodine-123 diagnostic whole-body scan and stimulated Tg level measurements were usually performed once after I-131 ablation/therapy for patients with high- and intermediate-risk features without evidence of distant metastasis and more frequently as a preparation for more I-131 therapies for those with distant metastasis. Patients with an excellent or indeterminate response were usually seen on a yearly basis for follow-up, mostly with suppressed Tg, anti-Tg Abs, TSH, FT4, and neck ultrasonography. Other imaging studies (including computed tomography of the lungs and neck and F-18 fluorodeoxyglucose positron emission

tomography and others) and more frequent follow-ups were practiced in patients with evidence of local disease or distant metastasis.

A. Patients

We studied all patients seen at KFSHRC during January 2004 to December 2006. We chose this interval to achieve a long-term follow-up period that enables us to assess the outcome of DTC over time. During this period, a total of 814 consecutive patients were managed. We excluded patients with medullary (19 patients), anaplastic (18 patients), poorly differentiated (18 patients), ATA high-risk DTC (83 patients), and patients without enough data for accurate staging (62 patients). Because one of the main objectives of this study was to assess factors that predict outcome at the last follow-up visits, we also excluded patients who had an indeterminate response to therapy status (83 patients) since this group of patients cannot be confidently classified as free of the disease or otherwise. Finally, we excluded patients who were lost to follow-up without clear status (25 patients). The remaining 506 patients with ATA low- or intermediate-risk DTC were included in the study. Definitions for low- and intermediate-risk tumors were based on the ATA guidelines [14]. ATA low-risk tumors are completely intrathyroidal without lymph node (LNM) or distant metastasis or with only 5 or fewer lymph node micrometastases (size ≤ 0.2 cm). The tumor should be completely removed and have no features of locoregional invasion, vascular invasion, or aggressive histology. When RAI whole-body scanning was performed in low-risk tumors, no uptake should have been seen outside the thyroid bed area [14]. Intermediate-risk tumors are those with microscopic soft-tissue invasion, aggressive histology, LNM in more than 5 lymph nodes or fewer than 5 lymph nodes but with a metastasis size of greater than 0.2 cm and less than 3 cm, and when there is a clinical N1 or uptake outside the thyroid bed on RAI scans [14]. High-risk tumors are those with gross soft-tissue invasion, distant metastasis, LNM greater than 3 cm, or incomplete tumor resection [14]. We used the response to therapy status (dynamic risk stratification) to assess the outcome as described in the ATA guidelines [14]. An excellent response indicates no clinical, biochemical, or radiological evidence of disease with a suppressed serum Tg level less than 0.1 ng/dL or stimulated Tg level of less than 1 ng/dL in the absence of anti-Tg Abs and negative imaging studies. Biochemically incomplete status refers to a significant elevation of serum Tg (suppressed ≥ 1 ng/dL or stimulated ≥ 10 ng/dL) in the absence of radiological or cytological evidence of disease. Structurally incomplete status refers to the presence of disease on

radiological, cytological, and/or histopathological investigations, usually accompanied by a significant elevation of serum Tg or anti-Tg Abs. An indeterminate response refers to a situation when residual or recurrent disease cannot be confidently excluded with mild elevation of Tg (suppressed Tg 0.2-1 ng/dL or stimulated Tg 1-10 ng/dL), positive anti-Tg Abs, and/or nonspecific findings on imaging studies. For patients who had lobectomy only (18 patients) or did not receive I-131 remnant ablation (48 patients), modified criteria for these different statuses were used [22, 23].

All the patients included in this study were uniformly managed and followed up at a single institution (KFSHRC) from time of presentation until their last follow-up. Their management and follow-up followed a specific thyroid cancer management protocol that was consistent with the international standards of care at that time. Of 506 patients, 192 patients (38%) had one neck surgery at our facility. The remainder had surgeries in outside hospitals (314 patients). Patients presenting to our hospital were assessed with an ultrasound of the neck ± computed tomography scan of the neck and chest and, iodine-123 diagnostic whole-body scan for residual or metastatic disease. Those with incomplete surgery (residual thyroid tissue > 1-1.5 cm) or fine-needle aspiration–proven LNM underwent completion thyroidectomy ± lymph node dissection. Of the 314 patients who had surgery in outside hospitals, only 93 were assessed to have had adequate surgery and did not need completion thyroid surgery and/or neck dissection, whereas the other 221 patients (43.7%) underwent a second thyroid surgery (completion thyroidectomy ± lymph node dissection) at our institution. All of this resulted in a uniform situation of total or near total thyroidectomy ± lymph node dissection in 488 (96.4%) patients and lobectomy for very low-risk DTC in 18 patients (3.6%). Of the 506 patients, 413 (81.6%) had initial thyroid surgery at our institution (192 primary exploration and 221 completion surgery).

B. Biochemical Measurements

Serum Tg level, anti-Tg Abs [24], TSH, and FT4 measurements were all performed by electrochemiluminescence assays on a Cobas e 801 immunoassay analyzer (Roche Diagnostics GmbH). The Tg assay has a lower limit of detection of 0.02 ng/dL.

C. Statistical Analysis

SPSS version 20 (IBM Co) was used to analyze data. Numerical values are expressed as median and

interquartile range (IQR) and categorical values as percentages and ratios. Kaplan-Meier analysis and log-rank test were used to analyze the relationship between ATA staging and long-term outcome. Univariable and multivariable logistic regression and Cox proportional hazard models were used to study the relationship between potential prognostic factors and outcome (response to therapy) over time. A *P* value of less than .05 was considered significant.

2. Results

A. Patient Characteristics

Included in this study are a total of 506 patients with low- and intermediate-risk DTC [418 women (82.6%) and 88 men (17.4%)] with a median age of 35 years (IQR, 27-46 years). Their demographic, clinical, and pathological features are summarized in Table 1. Near-total or total thyroidectomy was performed in 488 patients (96.4%) and lymph node dissection in 337 patients (66.7%). The median tumor size was 2.0 cm (IQR, 0.9-3.2 cm). Classic PTC was the most common type, occurring in 378 patients (74.7%), followed by follicular variant PTC, occurring in 80 patients (15.8%). Other subtypes were much less common (see Table 1). The cohort includes 297 (58.7%) patients in ATA low-risk and 209 (41.3%) in intermediate-risk groups. The vast majority of patients were in American Joint Committee on Cancer Tumor Node Metastasis (AJCC TNM) stage I (92.1%) or II (7.5%). I-131 was given to 458 (90.5%) patients with a median administered activity of 126 MCi (IQR, 100-149 MCi).

B. Natural History and Long-term Outcome of Patients With Low and Intermediate American Thyroid Association Stages

After the initial management (thyroid surgery ± I-131 ablation), 89 (17.6%) patients needed one or more additional interventions during their follow-up for persistent or recurrent disease (Table 2). More patients in the intermediate-risk (52/209 patients, 24.9%) than in the low-risk group (37/297 patients, 12.5%) needed additional interventions (*P* < .001). Of the 89 patients who had additional interventions, 69 (77.5%) achieved an excellent status, 6 (6.7%) a biochemically incomplete status, and 14 (15.7%) a structurally incomplete status at the last follow-up. Patients who did not need additional interventions were more likely to achieve an excellent status (389/417 patients, 93.3%) at the last follow-up than those who needed additional interventions (69/89 patients, 77.5%) with a *P* value of less than .001.

Table 1. Demographic and pathological characteristics of 506 patients with low- and intermediate-risk differentiated thyroid cancer

Characteristic	No. (%)
Median age (IQR), y	35 (27.7-46)
Sex (male:female)	88:418
Median tumor size, cm (IQR)	2.0 (1.0-3.0)
Tumor type	
CPTC	379 (74.9%)
FV-PTC	80 (15.8%)
TC-PTC	9 (1.8%)
DSV-PTC	3 (0.6%)
FTC	10 (2.0%)
HCC	9 (1.7%)
Other rare types	16 (3.2%)
Tumor multifocality	205 (40.5%)
Extrathyroidal invasion	208 (41.1%)
Lymphovascular invasion	79 (15.6%)
Lymph node metastasis	199 (39.3%)
Distant metastasis	0 (0%)
ATA risk staging	
Low	297 (58.7%)
Intermediate	209 (41.3%)
High	0
AJCC TNM 8	
Stage I	466 (92.1%)
Stage II	38 (7.5%)
Stage III	1 (0.2%)
Stage IVb	1 (0.2%)
Median I-131–administered activity, MCi	126 (100-149)
Additional interventions	89 (17.6%)

Abbreviations: AJCC TNM 8, American Joint Committee on Cancer Tumor Node Metastasis, eighth edition; ATA, American Thyroid Association; CPTC, classic papillary thyroid cancer; DSV-PTC, diffuse sclerosing variant papillary thyroid cancer; FTC, follicular thyroid cancer; FV-PTC, follicular variant papillary thyroid cancer, HCC, Hürthle cell cancer; I-131, iodine-131; IQR, interquartile range; TC-PTC, tall cell variant papillary thyroid cancer;

Table 2. Additional therapeutic interventions in 89 low- and intermediate-risk patients who had incomplete response to therapy and received one or more additional interventions

Additional therapeutic intervention	No. of patients (%)
Surgery	39 (43.8)
I-131	33 (37.1)
Surgery + I-131	11 (12.4)
XRT	1 (1.1)
Surgery + XRT	1 (1.1)
Ethanol injection	1 (1.1)
Surgery + I-131 + XRT	1 (1.1)
I-131 + ethanol injection	2 (2.2)

Abbreviations: I-131, iodine-131; XRT, external beam radiotherapy.

The other 417 (82.4%) patients did not need any further interventions and were followed up for several years. Overall, at a median follow-up of 102 months (IQR, 66-130 months), 458 (90.5%) patients achieved an excellent response, 17 (3.4%) patients had a biochemically incomplete status, and 31 (6.1%) had a structurally incomplete status. None of the patients in this cohort died of DTC. Patients with ATA low-risk status had a significantly lower risk (13 patients, 4.4%) of an incomplete response compared with intermediate-risk patients (35 patients, 16.7%), with a *P* value of less than .0001. This is also demonstrated in a Kaplan-Meier analysis (Fig. 1), showing a significant difference in disease-free survival between the ATA low- and intermediate-risk groups (*P* .001).

C. Factors Predicting Incomplete Response to Therapy

Factors predictive of biochemically or structurally incomplete response to therapy at the last follow-up are summarized in Table 3. In univariable analysis, age and LNM were significantly associated with incomplete response to therapy (see Table 3). In a multivariable analysis, these factors remained significantly associated with incomplete response to therapy (see Table 3). In a Cox proportional hazard model in which age at diagnosis and LNM were included as covariates, all remained significantly associated with outcome with age [(*P* < .0001, odds ratio 1.06 (1.04-1.08)] and LNM [(*P* < .0001, odds ratio 3.2 (1.7-5.9)]
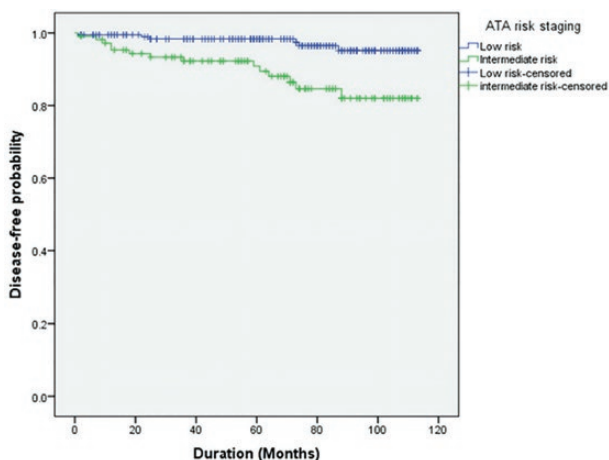
Log-rank test; X^2 =11.5, P 0.001

Figure 1. Kaplan-Meier analysis comparing disease-free survival between differentiated thyroid cancer (DTC) patients in the American Thyroid Association (ATA) low-risk and intermediate-risk categories. The intermediate-risk group shows a significantly higher risk of recurrence compared with the low-risk group.

over a median follow-up duration of 102 months (IQR, 66-130 months).

D. Age and Lymph Node Metastasis as Prognostic Factors in Low- and Intermediate-Risk Differentiated Thyroid Cancer

We further analyzed age as a strong predictor of outcome. Table 4 shows that age starts to be a significant predictive factor for incomplete response at 33 years, and the significance increases as age increases (see Table 4). LNM analysis showed that central LNMs alone were not significantly associated with outcome but lateral or lateral with central lymph nodes were significantly associated with higher risk of incomplete response (Table 5)

3. Discussion

The management of DTC has undergone substantial changes in the last decade, shifting from the old practice of "one size fits all" to a more personalized approach by which the extent of the management is based on the predicted risk of recurrence and mortality [12, 14, 15, 20]. Mortality is rare in DTC but recurrence is common [1, 2, 4, 8, 25, 26]. Although mortality usually occurs in patients with recurrent/persistent disease, the ATA risk stratification was designed and validated to assess the risk of recurrence and the AJCC TNM staging to predict mortality [12, 14, 27, 28]. It has been shown that these systems perform well, and they are now routinely used in the clinical care of patients with DTC [12, 20, 23]. The majority of patients with DTC are in the low- and intermediate-risk groups [8, 26, 29]. Only about 15% to 30% are in the high-risk group [8, 18, 20, 23]. It is recommended and widely accepted that patients in the high-risk category be treated more actively with total or near-total thyroidectomy with or without lymph node dissection followed by I-131 ablation and long-term thyroid hormone suppression [14]. These are followed by close follow-up and additional interventions when necessary [14, 18]. More controversial issues and different practices surround the management of patients with low- and intermediate-risk disease [19]. Generally, the management of patients in these risk groups follows a more conservative approach, with limited surgery when appropriate, selective use of I-131, and less degree of thyroid hormone suppression [14]. Their follow-up is also less frequent and involves a limited diagnostic workup [14]. However, a significant percentage of patients in the low- and especially intermediate-risk categories may continue to have evidence of disease, develop metastasis, and die of their disease [21, 30-32]. Identifying factors that predict this subgroup of patients

Table 3. Univariable and multivariable analyses of predictive factors for incomplete response to therapy in 506 patients with low- or intermediate-risk differentiated thyroid cancer

Factor	Excellent response, n = 458	Incomplete response[a], n = 48	Unadjusted P[b]	Adjusted[c] P	OR (95%CI)
Age, y	36.4 ± 12.7	45.4 ± 15.15	< .0001	<0.0001	1.06 (1.04-1.08)
Tumor size, cm	2.1 ± 0.91	2.34 ± .94	.15		
Sex (male)	76 (16.6)	12 (25.0)	.16		
Tumor multifocality	180 (39.3)	25 (52.1)	.09		
Extrathyroidal extension	22 (4.8)	5 (10.4)	.16		
Lymphovascular invasion	67 (14.6)	12 (25.0)	.09		
Lymph node metastasis	169 (36.9)	30 (62.5)	.001	< .0001	3.2 (1.7-5.9)
I-131 treatment	418 (92.3)	40 (85.1)	.1		
Other interventions	69 (15.1)	20 (41.7)	.000		

Abbreviations: I-131, iodine-131; OR, odds ratio.
[a]Biochemically and structurally incomplete response.
[b]Using bivariate analysis.
[c]Using multivariable logistic regression analysis.

Table 4. Incomplete response to therapy with respect to different age cutoff limits showing significant difference in outcome starting at age 33 years and increasing with increasing age

Age limit, y	Incomplete response in ≤ Age limit	> Age limit	P
25	6/105 (5.7)	42/401 (10.5)	.19
28	10/134 (7.5)	38/372 (10.2)	.39
29	10/148 (6.8)	38/358 (10.6)	.24
30	11/165 (6.7)	37/341 (10.5)	.15
31	11/186 (5.9)	37/320 (11.6)	.053
32	13/209 (6.2)	35/297 (11.8)	.052
33	13/218 (6.0)	35/288 (12.2)	.028
34	13/234 (5.6)	35/272 (12.9)	.008
35	14/254 (5.5)	34/252 (13.5)	.004
40	16/316 (5.1)	32/190 (16.8)	< .0001
45	23/374 (6.1)	25/132 (18.9)	< .0001
50	28/425 (6.6)	20/81 (24.7)	< .0001
55	33/356 (7.2)	15/50 (30.0)	< .0001

with a less-favorable course is of great clinical importance to treat them more appropriately at the initial management and follow them more closely during subsequent months to years. In this study, we analyzed the natural course of the disease over a relatively long period of follow-up and attempted to identify predictive factors of incomplete biochemical or structural response in these groups of patients with low and intermediate risk. Our findings showed that 1) the overall outcome of patients in these risk groups is favorable, with more than 90% of them achieving an excellent response (see Table 1); 2) the ATA risk stratification performs well with less numbers of incomplete response to therapy in the low-risk compared to intermediate-risk groups (see Fig. 1); 3) age at diagnosis and lateral LNM are strong predictors of incomplete response to therapy (persistent disease) in these ATA categories (see Tables 3-5). This last finding suggests that patients in the ATA low- and intermediate-risk categories with one or more of these features (old age and lateral LNM) should be managed more aggressively and followed up closely. That could mean a more complete thyroid surgery and lower threshold for performing neck dissection, I-131 ablative/adjunctive therapies, and a higher degree of thyroid hormone suppression for patients with these features. It also entails a more careful follow-up after initial management.

Age has been a well-known strong predictive factor for recurrence and mortality and is included in almost all old and current staging systems [33-38]. It is also a major determinant of the AJCC TNM staging system: Age 45 years in AJCC TNM7 and 55 years in the more recently introduced AJCC TNM8 have a major impact on the TNM stage of DTC [28, 29, 32, 39, 40]. In a study of more than 30 000 patients with PTC from the Surveillance, Epidemiology, and End Results registry (SEER), age was a consistent predictive factor [41]. In another study using the same database with more than 19 000 patients with PTC, age older than 45 years, large tumor size, LNM, and distant metastasis predicted poor outcome [42]. More recently, it has been shown that age affects prognosis in a continuous rather than categorical way so that the older the patient, the more likely he or she is to have a recurrence and die of DTC [43-46]. This is also observed in our study, where age started to be an important predictive factor at 33 years and its significance increased with increasing age (see Table 4). Although the

Table 5. Impact of site of lymph node metastasis on outcome

Type of lymph node metastasis	Excellent response	Incomplete response	P
Central	73/362 (20.2)	5/23 (21.7)	.79
Lateral	96/385(24.9)	25/43 (58.1)	< .0001
Central and lateral	169/458 (36.9)	30/48 (62.5)	.001

patients in this study are generally young (median age 35 years), age was a strong predictor of incomplete response in univariable and multivariable analyses, supporting the previous studies that age is a continuous prognostic factor rather than a dichotomous one [46-48]. Adam et al analyzed age as a prognostic factor in more than 31 000 patients with PTC from the SEER data. They found a linear relationship between patient age and risk of mortality without any specific cutoff age limit [47]. Similarly, Orosco and colleagues analyzed a much larger cohort from the same SEER data including 85 750 patients and showed a strong association between age and risk of death without any specific age limit [43]. Shah and Boucai showed that age is a strong predictor of recurrence, response to therapy, and survival in 320 high-risk DTC patients from one institution. Age 55 years and older was associated with higher rates of biochemically and structurally incomplete response to therapy than age younger than 55 years. They suggested that incorporation of age in the ATA risk stratification would increase its power to predict response to therapy and mortality [49]. On the other hand, a few studies have not shown an important role for age in the estimation of risk of recurrence [50]. Pitoia et al retrospectively reviewed 268 patients with DTC (88.4% of them were ATA low- and intermediate-risk stages) with a median age at diagnosis of 45.9 years (range, 18-87 years) and found no impact of age on the probability of a structurally incomplete response at the initial evaluation and at last follow-up [50]. They also could not find an age cutoff limit after which the risk of structural disease increases [50]. However, this study is small in size and the overall evidence is overwhelming in favor of the strong role that age plays in the risk of recurrence and mortality.

LNM is a characteristic feature of PTC [14, 51]. Its prevalence depends on the method of detection, with ultrasonography detecting up to 30% of cases [52-56] and histopathologic examination reporting up to 50% to 90% of DTC patients having LNM [57, 58]. The prognostic implication of LNM has been controversial [14, 19, 59-61]. Some studies have shown no significant difference in the outcome between DTC patients with and without LNM [61]. Others showed a strong predictive value for LNM even in patients with small PTC [7]. Some other studies

showed an age-dependent prognostic value for LNM in patients older than 45 years but not in those younger than this age [41]. While other studies have evaluated LNMs in the whole spectrum of patients ranging from low- to high-risk disease, our study looked specifically at the predictive value of LNM in patients with low- and intermediate-risk DTC. This is important because decision making for the extent of management is complicated in these subgroups and the presence of lateral LNM may call for more active management interventions as suggested by the strong predictive power of LNM shown in this study.

Our study has a number of limitations that are important to highlight. It is retrospective in nature and some patients had incomplete data. It also reflects the surgical and medical practices of 15 years ago, which have significantly changed over the last decade. However, total thyroidectomy ± lymph node dissection and I-131 thyroid remnant ablation are still the most commonly practiced initial management for the majority of patients with DTC. The exact number and size of LNM was not always available. However, this did not affect the staging because patients who could not be staged were excluded (see "Materials and Methods"). On the other hand, the sample size is large and the management was uniform, making this sample a homogeneous group of patients who were approached according to the standard of care at the time of evaluation. The low- and intermediate-risk groups were both of large size and their courses were clearly different as shown by the Kaplan-Meier analysis (see Fig. 1). The follow-up time is long, allowing for analysis of the course over time.

In summary, this study of a large cohort of patients with low- and intermediate-risk DTC showed an excellent outcome in the majority of cases. Patients with low risk had a better outcome with a significantly less rate of biochemically and structurally incomplete disease than patients with intermediate risk. Age at diagnosis and lateral LNM are strong predictive factors of incomplete response to therapy and persistent disease. This study suggests that in the large majority of patients with low- to intermediate-risk DTC, the presence of one or more of these factors should be considered in the decision making for partial vs complete thyroid surgery, administering I-131 ablation, the degree of thyroid hormone suppression, and closer monitoring and follow-up.

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Additional Information

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