Time to Separate Persistent From Recurrent Differentiated Thyroid Cancer: Different Conditions With Different Outcomes

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Context: Differentiated thyroid cancer (DTC) has an excellent prognosis, but up to 20% of patients with DTC have disease events after initial treatment, indistinctly defined as persistent/recurrent disease.

Objective: To evaluate the prevalence and outcome of "recurrent" disease (relapse after being 12 months disease-free) compared with "persistent" disease (present *ab initio* since diagnosis).

Design: Retrospective analysis of persistent/recurrent disease in patients with DTC (1990 to 2016) with 6.5 years of mean follow-up.

Setting: Tertiary referral center for thyroid cancer.

Patients: In total, 4292 patients all underwent surgery ± ^{131}I treatment of DTC.

Main Outcome Measures: DTC cure of disease persistence or recurrence.

Results: A total of 639 of 4292 (14.9%) patients had disease events after initial treatment, most (498/639, 78%) with persistent disease and 141 (22%) with recurrent disease. Relative to patients with recurrent disease, patients with persistent disease were significantly older (mean age 46.9 *vs* 45.7 years) and with a lower female to male ratio (1.9/1 *vs* 4.8/1). Moreover, in this group, structured disease was more frequent (65.7% *vs* 41.1%), and more important, distant metastases were significantly more frequent (38.4% *vs* 17.0%). At multivariate analysis, male sex (OR = 1.7), age (OR = 1.02), follicular histotype (OR = 1.5), T status (T3; OR = 3), and N status (N1b; OR = 7.7) were independently associated with persistent disease. Only the N status was associated with recurrent disease (N1b; OR = 2.5).

Conclusions: In patients with DTC not cured after initial treatment, persistent disease is more common and has a worse outcome than recurrent disease. Postoperative status evaluated during first-year follow-up may have important clinical implications for planning tailored treatment strategies and long-term follow-up procedures. **(*J Clin Endocrinol Metab* 104: 258–265, 2019)**

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy (1), and its incidence, relatively stable until the early 1990s, has been rapidly increasing worldwide over the past two decades (2). In addition, the death rate has slightly increased over the past 10 data years (3), despite earlier diagnosis and better treatment.

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Abbreviations: AAT, antithyroglobulin antibody; ATA, American Thyroid Association; DTC, differentiated thyroid cancer; IQR, interquartile range; RAI, radioiodine; Tg, thyroglobulin.

DTC is generally associated with an excellent prognosis: the 5-year survival rate is near 100% for localized disease, 98% for regional disease, and 56% for metastatic disease (4).

Total thyroidectomy is the first-line treatment of DTC, although lobectomy or even active surveillance can be considered in selected low-risk patients (5). After surgery, radioiodine (RAI) remnant ablation has been largely used in DTC because it allows more accurate postoperative staging and facilitates postsurgical follow-up. Today, the American Thyroid Association (ATA) guidelines do not routinely recommend RAI therapy for low-risk patients with DTC but rather only for selected intermediate-risk and all high-risk patients (5).

Up to 20% of patients with DTC have disease events after initial surgery (5), but whether these events truly represent a relapse after a period of disease-free status or persistent disease after incomplete therapy is often unclear. The ATA guidelines 2015 (5) define disease-free status as the absence of clinical and imaging evidence of disease after surgery and thyroglobulin (Tg) serum levels (unstimulated and/or stimulated) lower than cutoff values in the absence of interfering antithyroglobulin antibodies (AATs). When this disease-free condition persists for at least 1 year after initial surgery, occurring disease events indicate a true recurrence. In contrast, the presence of positive Tg, persisting/increasing Tg antibody levels, or occurrence of structural disease within 1 year after surgery is defined as persistent disease.

In most studies, persistence or recurrence of DTC after initial surgery is not evaluated independently.

Few studies investigated the difference between persistent and recurrent disease in terms of reoperation requirement (69 patients studied) (6), predictors of outcome (190 cases) (7), and predictors of recurrent/persistent disease (evaluated together) and cancer-specific survival rates for the two groups of patients with early or late recurrence (8). Differences between the two conditions in terms of predictors of outcome are not yet well investigated.

Therefore, in the current study, we retrospectively evaluated, in a continuous series of 4292 patients with DTC, the outcome related to persistent *vs* recurrent disease, subdividing patients into four risk classes according to their clinical and pathological characteristics (Table 1).

The results obtained may help to establish a personalized treatment approach based on patient and tumor features.

Patients and Methods

We retrospectively analyzed a consecutive series of 4292 patients with DTC, all having undergone total thyroidectomy with or without lymph node dissection for DTC from 1990 to 2016 and all followed at our thyroid clinic [median follow-up, 59.4 months; interquartile range (IQR), 22.4 to 111.4 months].

Table 1. Clinical and Histopathological Characteristics of the 4292 Patients With DTC Studied

Characteristic	Value
No. of patients	4292
Follow-up duration, median (IQR), y	59.4 (22.4–111.4)
Age, median (IQR), y	45.8 (36.4–56.1)
Sex, female/male ratio	3.9/1.0
Histotypes, n (%)	
Papillary	3828 (89.2)
Follicular	464 (10.8)
TNM (seventh ed.), n (%)	
T status (T)	
T1a	1909 (44.5)
T1b	826 (19.2)
T2	466 (10.9)
T3	1063 (24.8)
T4	28 (0.6)
N status (N)	
N0	826 (19.2)
N1	1217 (28.4)
Nx	2249 (52.4)
Multifocality, n (%)	851 (19.8)
Risk categories at first evaluation after surgery,[a] n (%)	
Very low	1098 (25.6)
Low	1329 (31.0)
Intermediate	1837 (42.8)
High	28 (0.7)

[a]Risk categories: very low (T1a N0/Nx), low (T1a/T1b/T2 to N0/Nx), intermediate (T3 or N1), and high (T4).

Clinical and histopathological characteristics are shown in Table 1. Most patients were females (79.8%) with a female to male ratio of 3.9/1.0. Median age at diagnosis was 45.8 years (IQR, 36.4 to 56.1 years). Histotype was papillary in 3828 (89.2%) cases and follicular in 464 (10.8%).

Tumors were staged according to the seventh edition of the TNM (9): T (the extent of the primary tumor) and N (regional lymph node metastases) were assessed on the basis of the pathological examination, whereas M (distant metastases) was defined according to the first postsurgical ^{131}I whole-body scan.

Patients with known distant metastases at surgery were excluded from the study because they presented with advanced disease and, therefore, were of minor relevance for investigating the difference between persistent and recurrent disease.

Overall, 74.6% of cases fell in the T1 or T2 TNM categories, whereas 24.8% were T3 and 0.7% were T4. Regarding the N status, 19.2% patients were classified as N0, 28.4% as N1, and 52.4% as Nx. Multifocality was present in 19.8% cases.

According to TNM categories, patients were subdivided into the following risk groups: 56.6% were either very low risk (T1a N0/Nx) or low risk (multifocal T1a/T1b/T2-N0/Nx), 42.8% were intermediate (T3 or N1) risk, and only 0.7% cases were high risk (T4) (Table 1).

All patients underwent postoperative evaluation of the disease status with neck ultrasound and Tg and AAT measurements.

Postsurgery RAI therapy (^{131}I 30 to 100 mCi or 1110 to 3700 MBq), ablative or adjuvant, was given to 2672 (62.3%) patients having one or more of the following characteristics: tumor size >1.0 cm, tumor extension to adjacent soft tissues (pT3), multifocality, nodal metastases (N1), or also having

postsurgery large thyroid remnant and/or elevated Tg serum levels (postoperative Tg value >5 to 10 ng/mL) (5). Also, patients with personal risk factors (*i.e.*, familial thyroid cancer and/or previous external radiotherapy involving the neck area) were treated with ^{131}I.

The response to initial therapy (surgery ± ^{131}I treatment) was assessed within 12 months of diagnosis with neck ultrasound and both AAT and serum Tg measurements, either basal or TSH stimulated (with levothyroxine withdrawal, or recombinant human TSH administration), in RAI-treated patients. Considering the response to initial therapy obtained within 12 months after initial treatment, patients were subdivided into three groups: (1) 3653 "disease-free" with a median follow-up of 57.8 months (IQR, 21.7 to 110.0 months), (2) 498 patients with "persistent disease" (disease events occurring within 12 months) with a median follow-up of 53.9 months (IQR, 21.1 to 98.8 months), (3) 141 cases with "recurrent disease" (events diagnosed after 1 year or a longer disease-free status following initial treatment). In these patients, total follow-up duration was 116.3 months (IQR, 74.2 to 185.4 months), and recurrence occurred after 40.8 months (median value).

The presence of disease was defined according one or more of the following criteria: (1) serum Tg (either under suppressive levothyroxine therapy or after TSH stimulation) at detectable levels, as defined by the assay sensitivity limits at the time of measurement; (2) steady or increasing titer of anti-Tg antibodies at 6 to 12 months after initial treatment (overall, only 15/4292 or 0.35% of patients were classified according to this criterion); (3) presence of metastatic lymph nodes, identified at neck ultrasound examination and confirmed by fine-needle aspiration biopsy with Tg measurement in the washout sample; and (4) positive ^{131}I whole-body scan. In patients with persistent/recurrent disease, additional morphological examinations such as computed tomography, magnetic resonance imaging, bone scan, and positron emission tomography were performed when required. When patients were not cured, further treatments (RAI therapy, repeated surgery, or other therapies) were carried out.

Statistical analysis

Categorical variables were expressed as frequencies and percentages (%) and analyzed using the χ^2 test with Yates correction or the Fisher test. Normally distributed quantitative variables were expressed as mean ± SD, whereas nonnormally distributed variables were expressed as median and IQR. Variables' normality was tested with the Kolmogorov-Smirnov test. Quantitative variables were analyzed by the Student *t* test or the Mann-Whitney *U* test. Multiple logistic regression analysis was performed for all variables having significant results at univariate test to identify risk factors associated with either persistent or recurrent disease.

A P value <0.05 was considered statistically significant for all analyses. Data analysis was performed using the SPSS statistical software version 13.0 for Windows.

Results

Outcome and risk factors for persistent *vs* recurrent disease

Most patients with DTC (3653 or 85.1%) presented an excellent response and had no cancer event after initial treatment (disease-free): 1465 (40.1%) after surgery and 2188 (59.9%) after surgery and ^{131}I treatment. In contrast, 639 of 4292 patients (14.9%) presented with a disease event after initial treatment: most (78%, 498/639) had persistent disease, whereas 141 of 639 (22%) had recurrent disease.

Significant differences regarding both host and tumor features characterized the three groups (Table 2). In particular, in patients with persistent disease, average age at diagnosis was significantly higher (46.9 years) than in the other groups, and the female/male ratio was significantly lower (female/male = 1.9/1 *vs* 4.4/1 disease-free patients and 4.8/1 in patients with recurrent disease). Moreover, the follicular histotype was more frequent in patients with posttherapy tumor events (both persistent and recurrent disease) relative to cured patients.

As expected, cancer characteristics such as T and N status were more favorable in patients cured after initial treatment (disease-free during follow-up) compared with patients having persistent or recurrent disease (Table 2). Major differences, however, were observed between patients with DTC having either persistent or recurrent disease: the latter group had more favorable features, often similar to those of the DTC-cured group (Table 2). More specifically, the T1 status was more frequent in patients with recurrent disease, whereas the T3 and T4 statuses were more frequent in patients with persistent disease. In these patients, the N1 status (both N1a and N1b) was also significantly more frequent (Table 2).

As expected, disease events increased through risk categories, being more frequent in intermediate- and high-risk patients (Table 2). This increase was very clear in patients with persistent disease: both disease events during follow-up (3.0%, 6.8%, 19.4%, and 64.3%) and disease presence at last visit (2.5%, 5.4%, 17.0%, and 57.2%) progressively increased in very low-, low-, intermediate-, and high-risk categories, respectively (Tables 2, 3, and 4). In contrast, in patients with DTC with recurrences, both disease events during follow-up and disease presence at last visit were very low and fairly similar across the different risk categories (Tables 3 and 4).

These data indicate that persistent disease, much more than recurrence, is a marker of the severity of the risk of unfavorable outcome in patients with DTC (Table 3, Table 4, and Fig. 1).

Biochemical or structural disease

The less favorable condition of patients with DTC who had persistent disease was also indicated by the more frequent occurrence, in this group, of structural rather than biochemical disease, whereas the opposite occurred in patients with recurrent disease (Table 5). Of

Table 2. Host and Cancer Clinical Characteristics at Presentation in Patients With DTC, Who After Initial Therapy Were Disease-Free During Follow-Up or Had Persistent or Recurrent Disease

Characteristic	Disease Free	Persistent	Recurrent
No. of patients	3653	498	141
Follow-up duration, median (IQR), y	57.8 (21.7–110)	53.9 (21.1–98.8)	116.3 (74.2–185.4)
Age, median (IQR), y	45.7 (36.7–55.4)	46.9 (34.7–64.4)[a]	43.8 (35.4–56.5)
Sex, female/male ratio	4.4/1	1.9/1[a,b]	4.8/1[a]
Histotypes, % (n)			
Papillary	89.9 (3285)	85.1 (424)[a,b]	84.4 (119)
Follicular	10.1 (368)	14.9 (74)	15.6 (22)
TNM (seventh ed.), % (n)			
T status (T)			
T1a	47.7 (1743)	23.3 (116)[a,b]	42.6 (60)
T1b	19.8 (725)	14.9 (74)[a]	19.1 (27)
T2	10.3 (379)	13.1 (65)	15.6 (22)
T3	22.1 (807)	45.2 (225)[a,b]	22.0 (31)
T4	0.2 (9)	3.6 (18)	0.7 (1)
N status (N)			
N0	21.1 (769)	8.4 (42)[a]	10.6 (15)[a]
Nx	54.1 (1976)	36.9 (184)[a,b]	63.9 (90)[a]
N1	24.8 (908)	54.7 (272)[a,b]	25.5 (36)
N1a	15.7 (573)	22.9 (114)[a,b]	14.2 (20)
N1b	9.1 (335)	31.8 (158)[a,b]	11.3 (16)
Multifocality, % (n)	20.9 (762)	13.9 (69)[a]	14.2 (20)
Risk categories, % (n)			
Very low	28.1 (1026)	6.6 (33)[a,b]	27.7 (39)
Low	32.6 (1191)	18.1 (90)[a,b]	34.0 (48)
Intermediate	39.1 (1427)	71.7 (357)[a,b]	37.6 (53)
High	0.2 (9)	3.6 (18)	0.7 (1)
RAI use, % (n)			
Postsurgical ^{131}I (ablation)	59.8 (2185)	90.8 (452)[a,b]	24.8 (35)[a]
Therapeutic ^{131}I because of events during follow-up	–	77.5 (386)[b]	65.2 (92)
Not cured at last control	0	427 (85.7)[b]	61 (43.3)

[a] $P < 0.01$, persistent and recurrent *vs* disease-free.

[b] $P < 0.01$ persistent *vs* recurrent.

special relevance is the much higher occurrence of lymph node metastases (217/498, 43.6%) and distant metastases (191/498, 38.4%) in the group of patients with persistent disease relative to patients with recurrent disease (lymph node metastases in 41/141 cases or 29.1% and distant metastases in 24/141 patients or 17.0%) (Table 5).

Additional treatments after initial surgery

Initial postsurgical RAI (ablation of residual thyroid tissue) was administered to 452 of 498 patients with persistent disease (90.8%) and only to 35 of 141 (24.8%) patients with recurrent disease ($P < 0.001$) (Table 2).

Thereafter, RAI was administrated to 386 of 498 (77.5%) patients with persistent disease and to 92 of 141 (65.2%) patients with recurrent disease because of persisting/recurring disease events during follow-up ($P < 0.01$) (Table 2).

Moreover, 117 of 498 (23.5%) and 28 of 141(19.9%) patients with persistent and recurrent disease, respectively, have undergone surgery during follow-up (P = not significant). Finally, multimodal therapy (^{131}I, surgery, external beam radiation, tyrosine kinase inhibitors) was administered to 157 of 498 (31.5%) and to 32 of 141 (22.7%) patients with persistent and recurrent disease, respectively ($P = 0.04$).

Final outcome

Finally, 427 of 498 (85.7%) patients with persistent disease were not cured at last control visit compared with only 61 (43.3%) patients with recurrent disease, despite the more aggressive and more frequently repeated treatment in the former group and the longer follow-up in the latter group. Overall, 151 of 639 (23.6%) patients with DTC with disease events after initial treatment were cured with a recovery rate higher in patients with recurrent *vs* persistent disease (Table 2).

Predictors of persistent *vs* recurrent disease at univariate and multivariate analyses

Applying univariate and multivariate analyses separately for persistent or recurrent disease, several risk factors were identified as predictors of persistent disease (Table 6).

At multivariate analysis, both male sex and more advanced age were patient features independently predicting

Table 3. Disease Events During Follow-up in 4292 Patients With DTC According to the Four Risk Categories and the Presence of Either Persistent or Recurrent Disease

Characteristic	Total (n = 639/4292, 14.9%)	Very Low (n = 72/1098, 6.6%)		Low (n = 138/1329, 10.4%)		Intermediate (n = 410/1837, 22.3%)		High (n =19/28, 67.9%)	
		Persistent	Recurrent	Persistent	Recurrent	Persistent	Recurrent	Persistent	Recurrent
Disease, n (%)		33 (3.0)	39 (3.6)	90 (6.8)	48 (3.6)	357 (19.4)	53 (2.9)	18 (64.3)	1 (3.6)
Biochemical	254/639 (39.7)	23 (2.1)	29 (2.6)	33 (2.5)	33 (2.5)	113 (6.2)	21 (1.1)	2 (7.1)	0
Structural	385/639 (60.3)	10 (0.9)	10 (1.0)	57 (4.3)	15 (1.1)	244 (13.2)	32 (1.8)	16 (57.2)	1 (3.6)
Only LN metastasis (N+), n	170	6	9	23	10	104	15	3	0
Only distant metastasis (M+), n	127	3	1	23	5	78	10	6	1
Both (N+) and (M+), n	88	1	0	11	0	62	7	7	0

Abbreviation: LN, lymph node.

persistent disease (OR = 1.7 and 1.02, respectively, $P < 0.001$ for both) (Table 6).

For the tumor characteristics, the follicular histotype (OR = 1.5, $P < 0.007$) was a significant risk factor for persistent but not recurrent disease, as well as the T status (T2, T3, and T4; OR = 2.5, 3.0, and 13.6, respectively, $P < 0.001$ for all) (Table 6).

The presence of nodal metastases in the central (N1a) and/or laterocervical compartments (N1b) was also a significant and independent risk factor for the patient not cured by first-line therapy. The risk was significantly higher for N1b relative to N1a in patients with persistent or recurrent disease and was significantly higher in patients with persistent disease (OR = 3.7 for N1a and 7.7 for N1b patients) relative to patients with recurrent disease (OR = 1.8 and 2.5 for N1a and N1b patients, respectively) (Table 6).

Discussion

Relapse of DTC after initial treatment is a relatively frequent occurrence (15% to 40%) (10–16) that heavily influences the subsequent management of the primary tumor. This observation has determined a risk-adapted approach to thyroid cancer management that will change over time based on the patient response to treatment after surgery and defined as "ongoing" risk stratification. Among factors determining this risk level, little attention has been given to the time of disease events occurring after surgery: persistent or recurrent diseases have been usually evaluated together as a single clinical condition.

The recent definition from the ATA guidelines (5) of "recurrent" disease when disease events occur after at least 1 year of disease-free status, whereas "persistent" disease is the ascertained presence of disease within the first year after initial therapy, has called attention to the specific clinical consequences of the two conditions.

Our study addresses this issue by studying a large and consecutive series of patients with DTC (n = 4292), all having undergone surgery ± RAI ablation (>70% by the same surgical team at the Surgical Oncology of the Garibaldi Medical Center) and all followed at the thyroid clinic of the same hospital, a tertiary referral center for thyroid cancer. During a median follow-up of 5.0 years, most cases (>85%) were cured (disease-free) at the last control visit. However, despite the low rate of disease events (only 14.9% of studied cases), the investigated cohort was large enough to include 639 cases with disease after initial therapy, a sample sufficiently large for separately estimating outcome and predictors for DTC persistence and recurrence.

The large series studied and the homogeneous protocol, therefore, are the major strengths of our investigation. On the other hand, limitations are the retrospective design and the not well-defined effectiveness of RAI treatment on patient outcome. Initial

Table 4. Disease Status at Last Visit in 4292 Patients With DTC According to the Four Risk Categories and the Presence of Either Persistent or Recurrent Disease

Characteristic	Total (n = 488/4292, 11.4%)	Very Low (n = 40/1098, 3.6%)		Low (n = 92/1329, 6.9%)		Intermediate (n = 339/1837, 18.5%)		High (n = 17/28, 60.7%)	
		Persistent	Recurrent	Persistent	Recurrent	Persistent	Recurrent	Persistent	Recurrent
Disease, n (%)		27 (2.5)	13 (1.1)	72 (5.4)	20 (1.5)	312 (17.0)	27 (1.5)	16 (57.2)	1 (3.6)
Biochemical	171/488 (35.0)	20 (1.8)	9 (0.8)	27 (2.0)	13 (1.0)	95 (5.2)	6 (0.3)	1 (3.6)	0
Structural	317/488 (65.0)	7 (0.7)	4 (0.3)	45 (2.4)	7 (0.5)	217 (11.8)	21 (1.2)	15 (53.6)	1 (3.6)
Only LN metastasis (N+), n	107	3	3	12	2	80	4	3	0
Only distant metastasis (M+), n	123	3	1	22	5	76	10	5	1
Both (N+) and (M+)	87	1	0	11	0	61	7	7	0

Abbreviation: LN, lymph node.

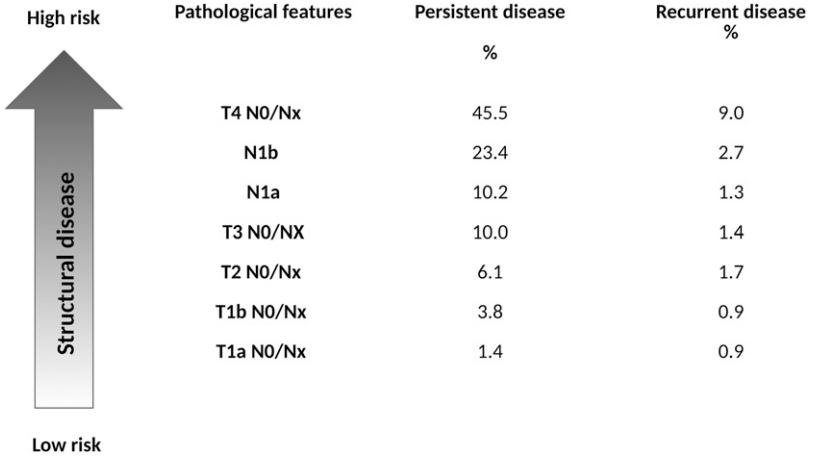

Figure 1. Risk of structural disease in patients with DTC with no identifiable evidence of structural disease after initial therapy. Numbers indicate the percentage of structural disease occurrence according to various clinicopathological features.

postsurgical RAI was decided on the basis of initial cancer staging, using similar criteria in all patients. Despite the criteria for RAI ablation and treatment changing over time with a reduced utilization in the past decade, we found no significant time-dependent change in the rate of recurrent *vs* persistent disease related to the different use of RAI in more recent years. Persistent DTC has a more aggressive behavior after diagnosis, and consequently, 481 of 498 (97%) patients with persistent disease *vs* only 35 of 141 (24.8%) patients with recurrent disease underwent postsurgical RAI therapy.

Our study was not designed to address the controversy on the role of postsurgical RAI in each risk category, and at present, two prospective trials (HiLo and Estimabl) have been started with the aim of identifying patients with DTC who will really benefit from RAI treatment.

In our series, DTC persistence and recurrence were, in fact, different conditions in terms of outcome. Patients with persistent disease, both biochemical and structural, had clearly worse outcomes relative to patients with recurrent disease: 85.8% were not cured at last visit *vs* only 43.3% patients with recurrent disease ($P < 0.001$). Moreover, structural disease and distant metastases were more prevalent among patients with persistent disease (Table 5). The worse outcome of persistent disease is most likely the consequence of the more severe cancer features at presentation, as indicated by both the T and N status and the higher prevalence of persistence in patients with DTC classified in the higher risk categories (Tables 3 and 4).

Analyzing clinical and histopathological predictors in the two groups of persisting or relapsing DTC, we observed that at univariate analysis, persistent disease was associated with male sex, older age, follicular histotype, T status, lymph node metastases, and multifocality. These risk factors were significant also at multivariate analysis except for multifocality, confirming data previously reported in several studies and indicating that these factors are associated with a higher risk of unfavorable outcome in terms of being cured after initial surgery (5, 16–18).

In contrast, at univariate analysis, recurrent disease was associated only with male sex and lymph node metastases, which, at multivariate analysis, was the only independent variable predicting recurrence (Table 6). The N1b status, in fact, was the most important predictor for both persistent and recurrence disease except for patients with very advanced tumors (T4 status) (Table 6).

In previous studies, we reported that involvement of laterocervical lymph nodes (N1b status) is the most effective marker of negative prognosis in patients with DTC in terms of both distant metastases and cancer-related death (17, 18). We now confirm that the N1b status is also the major predictor of DTC relapse (both persistent and recurrent disease).

The difference between persistent and recurrent disease in patients with DTC already has been observed in smaller and less homogeneous series, with persistence

Table 5. Outcome of Patients With Either Persistent or Recurrent DTC: Presence of Biochemical or Structural Disease

Characteristic	Persistent Disease, n (%)	Recurrent Disease, n (%)
Disease events during follow-up, n	498	141
Biochemical	171/498 (34.3)	83/141 (58.9)
Structural	327/498 (65.7)	58/141 (41.1)
Only LN metastasis (N+)	136/498 (27.3)	34/141 (24.1)
Only distant metastasis (M+)	110/498 (22.1)	17/141 (12.1)
Both (N+) and (M+)	81/498 (16.3)	7/141 (4.9)
Disease-free at last visit	71/498 (14.3)	80/141 (56.7)

Abbreviation: LN, lymph node.

Table 6. Multivariate Analysis of Risk Factors for Predicting Persistent or Recurrent Disease

	Persistent Disease		Recurrent Disease	
Risk Factor	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Male sex	1.7 (1.4–2.2)	<0.001	1.1 (0.7–1.8)	0.56
Age	1.02 (1.01–1.03)	<0.001	Not significant at univariate	
Histotypes				
Papillary	1.0			
Follicular	1.5 (1.1–2.0)	0.007	Not significant at univariate	
T status				
T1a	1.0			
T1b	1.3 (0.9–1.8)	0.06		
T2	2.5 (1.8–3.5)	<0.001	Not significant at univariate	
T3	3.0 (2.3–3.9)	<0.001		
T4	13.6 (5.7–32.6)	<0.001		
N status				
N0	1.0		1.0	
Nx	1.6 (1.1–2.2)	0.01	2.3 (1.3–4.1)	0.03
N1a	3.7 (2.5–5.4)	<0.001	1.8 (0.9–3.6)	0.08
N1b	7.7 (5.3–11.3)	<0.001	2.5 (1.2–5.1)	0.01
Multifocality	0.9 (0.7–1.3)	0.6	Not significant at univariate	

being more frequent (9), resulting in a worse outcome (10), and having an association with a more frequent requirement of reoperation (11).

The differences between the two conditions have plausible causes in the variety of DTC biology and multiple preoperative, intraoperative, and postoperative factors. First, time of recurrence is, of course, shorter in more advanced, more aggressive, and faster growing tumors, as documented by the higher frequency of DTC persistence in cases with high-risk cancers relative to intermediate- or low-risk cancers (Tables 3 and 4). Second, persistent disease is favored by deficiencies in the preoperative staging (mainly overlooking lymph node metastases) and inadequate intraoperative procedures (incomplete surgery, not effective in fully eradicating the tumor) (19). Third, the presence of subclinical, micrometastatic DTC might be not evident even at accurate postsurgery evaluation, including serum Tg measurements. In these patients, rapid growing cancers (because of their own genetic characteristics and/or lack of immune system leverage or other factors) (20–26) will become clinically evident in a short time and result as "persistent" disease. In contrast, indolent tumors may remain subclinical for a long period and become clinically evident only after many years ("recurrent" disease).

From a biological point of view, therefore, the presence of DTC events after initial therapy indicates persistent disease in all cases. Complete initial cure, with no residual malignant cell, in fact, cannot allow recurrence. The difference between persistent and recurrent, therefore, is only clinical, between cases clinically identifiable from the beginning (persistent disease) and cases that take longer time to become clinically apparent (recurrent disease). Clinical persistence is the consequence of more aggressive and more advanced tumors and also of incomplete initial treatment, all conditions that predispose to a worse outcome.

These are the most plausible explanations why persistence, in most DTC cases, is a predictor of a less favorable outcome than recurrent disease.

These considerations should suggest a combined effort to reduce the frequency of persistent disease in patients with DTC by a better characterization of the cancer genotype, by improving preoperative assessment and the adequacy of initial surgery and defining a better personalized management in terms of postsurgical diagnosis and treatment.

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