Prognostic Factors for Persistent or Recurrent Disease of Papillary Thyroid Carcinoma with Neck Lymph Node Metastases and/or Tumor Extension beyond the Thyroid Capsule at Initial Diagnosis

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Context: Reliable prognostic factors are needed in papillary thyroid cancer patients to adapt initial therapy and follow-up schemes to the risks of persistent and recurrent disease.

Objective and Settings: To evaluate the respective prognostic impact of the extent of lymph node (LN) involvement and tumor extension beyond the thyroid capsule, we studied a group of 148 consecutive papillary thyroid cancer patients with LN metastases and/or extrathyroidal tumor extension. Initial treatment, performed at the Institut Gustave Roussy between 1987 and 1997, included in all patients a total thyroidectomy with central and ipsilateral en bloc neck dissection followed by radioactive iodine ablation.

Results: Uptake outside the thyroid bed, demonstrating persistent disease, was found on the postablation total body scan (TBS) in 22% of the patients. With a mean follow-up of 8 yr, eight patients (7%) with a normal postablation TBS experienced a recurrence. Ten-year disease-specific survival rate was 99% (confidence interval, 97–100%). Significant risk factors for persistent disease included the numbers of LN metastases (>10) and LN metastases with extracapsular extension (ECE-LN >3), tumor size (>4 cm), and LN metastases location (central). Significant risk factors for recurrent disease included the numbers of LN metastases (>10), ECE-LN (>3), and thyroglobulin level measured 6–12 months after initial treatment after T_4 withdrawal.

Conclusion: We highlight an excellent survival rate and suggest risk classifications of persistent and recurrent disease based on the numbers of LN metastases and ECE-LN, LN metastases location, tumor size, and thyroglobulin level. (*J Clin Endocrinol Metab* **90:** 5723–5729, 2005)

N ECK LYMPH NODE (LN) metastases are found in up to 70% of cases of papillary thyroid carcinoma (PTC), depending on the tumor characteristics, extent of surgery, and number of LN sections examined by the pathologist (1). Disease-specific survival rate exceeds 90% at 10 yr in PTC patients, but recurrences may occur in more than 30% of cases (2–10).

The presence of neck LN metastases and tumor extension beyond the thyroid capsule at diagnosis have been identified as independent risk factors of recurrence (3, 5, 6, 10–15). Other independent risk factors of recurrence include age at diagnosis, tumor size, pathological subtypes, and completion of surgical resection (3–6, 9, 10, 16–18). Initial LN metastases have also been identified as an independent risk factor for distant metastases (2, 3, 10, 19). Finally, in some studies, a deleterious impact of LN metastases on survival has been reported (3, 14, 20, 21).

The 2002 pathological tumor node metastasis (pTNM) classification separates proximal metastatic LN (pN1a) from distant metastatic LN (pN1b) and tumor with minimal extrathyroidal extension (pT3) from tumor limited to the thyroid (pT1–2) (22). However, the respective impact of the extent of LN involvement and the extrathyroidal extension remains to be elucidated. To our knowledge, no study has yet demonstrated to what extent the number of LN metastases or their location affect PTC recurrence and survival. The adverse influence on outcome of minimal extrathyroidal extension has also not been clearly established.

The aim of this study was to assess the impact of LN involvement and extrathyroidal extension on disease-free survival and disease-specific survival in a series of PTC patients operated in a single center by a single surgeon with a standardized initial therapeutic approach and follow-up protocol.

Patients and Methods

Patients

Patients were retrospectively included in the study if they met the following five criteria: 1) PTC with LN metastases or tumor extension beyond the thyroid capsule; 2) a total thyroidectomy; 3) a neck dissection performed by a single surgeon (J.-P.T.), during the thyroidectomy procedure or within 6 months after thyroidectomy in patients referred to the Institut Gustave Roussy for neck dissection; 4) postoperative ^{131}I treatment; and 5) absence of distant metastases at presentation.

Records of the 345 consecutive PTC patients who underwent a neck dissection between 1987 and 1997 were reviewed. LN metastases were present in 173 patients (50%) among which 140 fulfilled the inclusion criteria. Among the other 172 patients without LN metastases, eight patients with an extrathyroidal tumor extension were also included. Overall, 148 patients formed the basis of this report.

Surgery

The surgical procedure included a total thyroidectomy and a dissection of the central neck (level VI) and ipsilateral (levels III and IV) compartments in all patients (23). A contralateral neck dissection was performed in 55 patients (37%) for bilateral thyroid tumor. Neck dissection was performed together with total thyroidectomy in 128 patients and during a second surgical procedure in the remaining 20 patients. Surgery was macroscopically complete in all cases.

The central neck dissection consisted in the removal of all soft tissues containing LN from the hyoid bone superiorly to the innominate vessels inferiorly and jugular veins laterally. When frozen section revealed metastatic involvement of levels III or IV, the dissection was extended to levels II and V. This lateral neck dissection always preserved the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve.

The parathyroid glands were identified with the use of methylene blue staining. If a parathyroid gland was removed, it was sliced and autotransplanted after a frozen section analysis confirmed it was indeed parathyroid tissue.

Surgical complications

Laryngeal nerve palsy was considered definitive when persisting at endoscopic examination for more than 1 yr.

Serum calcium and PTH 1–84 levels were serially measured until normalization. When they remained low for more than 1 yr and calcium and vitamin D supplementation could not be withdrawn, hypoparathyroidism was considered definitive.

Pathological diagnosis

Diagnosis of PTC was confirmed in all patients by the same pathologist. Size, unimultifocality, and unibilaterality of the thyroid tumor and tumor extension beyond the thyroid capsule were assessed. Two-millimeter sections of each LN without apparent metastasis were routinely performed. In case of macroscopic metastasis, fewer sections were performed. In case of suspicion of micrometastasis, thyroglobulin (Tg) immunostaining was performed. Patients were classified according to the 2002 pTNM scoring system (22).

Radioiodine (^{131}I) ablation

Four to 6 wk after surgery during which thyroid hormone treatment was withheld, all patients had TSH level above 30 mU/liter and were treated with ^{131}I. The ^{131}I treatment dose was 3.7 MBq/kg body weight in four children and 3.7 GBq in the other patients. A total body scan (TBS) was performed 3 or 4 d after ^{131}I administration using a dual-head γ-camera (DHD-SMV, Sopha Medical, Buc, France) equipped with high-energy collimators and thick crystals. In addition, a neck scan was performed using a rectilinear scanner (MO4L, Mecaserto, St. Thibault des Vignes, France). L-T$_4$ treatment was then initiated with the aim of decreasing TSH to low levels without inducing clinical thyrotoxicosis. In case of foci of ^{131}I uptake outside the thyroid bed, classified as persistent disease, specific therapeutic procedures were performed.

Follow-up of patients with normal postablation ^{131}I TBS

In patients without detectable ^{131}I uptake outside the thyroid bed on the postablation TBS, thyroid hormone treatment was withdrawn 6–12 months later, and thyroglobulin (Tg/TSH) measurement was obtained (Dynotest Tg, functional sensitivity of 1 μg/liter; BRAHMS, Berlin, Germany). Tg level was considered as not accurately measured when the recovery test (performed in all serum samples) was less than 80%.

Patients with undetectable Tg/TSH (≤1 μg/liter) were subsequently followed up at a yearly interval at the outpatient clinic of the Institut

Gustave Roussy with a clinical examination and a serum Tg measurement on L-T$_4$ treatment. In patients with detectable Tg/TSH (>1 μg/liter), clinical, and morphological evaluations, including neck ultrasonography, chest x-ray, or computed tomography and bone scan were performed. Patients with elevated Tg/TSH level and no other evidence of disease were followed up on a yearly basis at the outpatient clinic. When a recurrence was documented, specific treatments were given.

Statistics

Data were analyzed with SAS software (SAS/STAT user's guide, version 8; SAS Institute, Cary, NC).

Univariate analyses were performed on the age, gender, tumor size, tumor bilaterality and multifocality, extrathyroidal tumor extension, number of metastatic LN, number of metastatic LN with extracapsular extension (ECE-LN), location of metastatic LN, and Tg/TSH level. Unconditional logistic regression analysis was used for the evaluation of risk factors of persistent disease on the postablation TBS and a Cox proportional hazard model used for the evaluation of the risk of recurrence. Both types of multivariate analysis included the variables that were significant in the univariate analysis (significance level: $P \leq 0.10$) and were performed with a backward variable selection technique. For all analyses, two-sided tests were employed, and the 0.05 level of significance was used. Because the number of metastatic LN and the number of ECE-LN were closely related (Pearson's correlation coefficient = 0.78, $P < 0.0001$), they were studied in separate models. Tests of interaction could not be performed due to limited sample sizes. Of note, in the logistic regression, the absence of persistent disease in patients without central LN metastases precluded odds ratio (OR) estimates and the adjustment on the central LN metastases in the multivariate analysis. Ninety-five percent confidence intervals (CIs) were calculated for the ORs in the unconditional logistic regression analysis and the relative risks (RRs) in the Cox proportional hazard regression analysis. Disease-free and disease-specific survival rates were estimated using the actuarial method.

Results

Clinical characteristics

The clinical characteristics of the 148 patients (110 females, 38 males, mean age 42 yr, range 9–74) are reported in Table 1. Palpable neck lymph nodes were found at presentation in 57 patients (39%).

Pathological characteristics

PTC tumors were pT1N1, pT2N1, pT3N1, pT4N1, pTxN1, or pT3N0 in 44, 26, 61, 8, 1, and 8 patients, respectively. According to pTNM staging, patients were classified as stage I, II, III, IV in 71, 14, 22, 41 cases, respectively. Thyroid involvement was multifocal (two or more foci) in 89 patients (60%), bilateral in 68 (48%), and unknown in two.

The mean number of resected LN per patient was 36 (range four to 157; median 32). The mean numbers of resected LN in the central, ipsilateral, and contralateral compartments were 10 (range one to 56; median nine), 20 (range zero to 76; median 18) and 13 (range two to 35; median 12), respectively.

In the 140 patients with LN metastases, 31 (22%) had central metastases only, 17 (12%) had ipsilateral metastases only, 73 (52%) had both central and ipsilateral metastases, 18 (13%) had central, ipsilateral and contralateral metastases, and finally one had ipsilateral and contralateral metastases. The mean number of metastatic LN was nine (range one to 66; median six).

ECE-LNs were present in 65 patients (44%). They were found in the central compartment only; the ipsilateral compartment only; both compartments; and the central, ipsilat-

TABLE 1. Characteristics of patients

Sex	
Male/females	38/110
Mean age (range) [median]	42 (9–74) [41]
Palpable LN	57 (39%)
Stage	
I	71 (48%)
II	14 (9%)
III	22 (14%)
IV	41 (28%)
Classification	
pT1N1	44 (30%)
pT2N1	26 (18%)
pT3N1	61 (41%)
pT4N1	8 (5%)
pT3N0	8 (5%)
pTxN1	1 (1%)
Bilateral tumor	68 (46%)
Multifocal tumor	89 (60%)
Tumor extension beyond the thyroid capsule	72 (49%)
Tumor size (mm)	
≤20	78 (53%)
20–40	51 (34%)
>40	18 (12%)
Unknown	1 (1%)
CND	
Central + ipsilateral	93 (63%)
Central + bilateral	55 (37%)
LN metastases	
Present	
Central only	31 (21%)
Central and lateral	91 (62%)
Lateral only	18 (12%)
Absent	8 (5%)
Mean no. of resected LN (range) [median]	
Overall	36 (4–157) [32]
Central compartment	10 (1–56) [9]
Ipsilateral compartment	20 (0–76) [18]
Contralateral compartment	13 (2–35) [12]
Mean no. of metastatic LN (range) [median]	
Overall	9 (1–66) [6]
Central compartment	5 (1–54) [5]
Ipsilateral compartment	5 (1–19) [4]
Contralateral compartment	3 (1–9) [2]
Mean no. of ECE-LN (range) [median]	
Overall	8 (1–57) [4]
Central compartment	6 (1–48) [3]
Ipsilateral compartment	4 (1–15) [4]
Contralateral compartment	2 (1–4) [2]

CND, Cervical neck dissection; LN, lymph node.

eral, and contralateral compartments in 17 (26%), 16 (25%), 26 (40%), and six (4%) patients, respectively. The mean number of ECE-LN was eight (range one to 57; median four).

Surgical complications

Postoperative laryngeal nerve palsy, observed in 37 patients, remained definitive in 19 (13%). Among these 19 patients, the laryngeal nerve palsy was present preoperatively in two, and the recurrent nerve was deliberately killed during surgery because of tumor extension in 12. In the other five patients (3%), laryngeal nerve palsy was accidental.

Definitive hypoparathyroidism was observed in four patients (3%) among whom one had had two neck surgeries, first for thyroidectomy and then for neck LN dissection.

Postablation TBS results

The TBS showed foci of uptake outside the thyroid bed considered persistent disease in 33 patients (22%), located in neck LN only, neck LN and lungs, and lungs only in 19, seven, and seven patients, respectively. Foci of uptake in LN metastases were therefore detected in 26 patients and were located in the central, lateral, and both compartments in 15, seven, and four patients, respectively. Overall, 39 foci were detected, 17 being located in the lateral compartment and 22 in the central compartment. Among the 22 central foci, 18 were located behind the sternoclavicular joint (Fig. 1).

Prognostic factors for persistent disease

Prognostic factors for persistent disease are shown in Table 2. Univariate analysis showed that older age, larger tumor size, higher number of metastatic LN, higher number of ECE-LNs, and central location of the metastatic LN were significantly associated with persistent disease. The numbers of LN metastases and ECE-LNs were closely linked. However, the number of ECE-LNs and tumor size were independent prognostic factors for persistent disease. When the tumor size was smaller than 4 cm with 10 or fewer metastatic LN or three or fewer ECE-LNs, the frequency of persistent disease ranged from 10 to 13% (Table 3). Of note, patients with five or fewer metastatic LNs disclosed a frequency of persistent disease of 7%. When the tumor size was smaller than 4 cm with more than 10 metastatic LNs or more than three ECE-LNs or when tumor size was 4 cm or more without any of these LN criteria, the frequency of persistent disease ranged from 20 to 45%. In contrast, when the tumor size was 4 cm or more, with more than 10 metastatic LNs or more than three ECE-LNs, the frequency of persistent disease reached 75%. Interestingly, persistent disease was not found in any of the 26 patients without involvement of the central compartment, whereas it occurred in 27% of the 122 patients with central LN metastases.
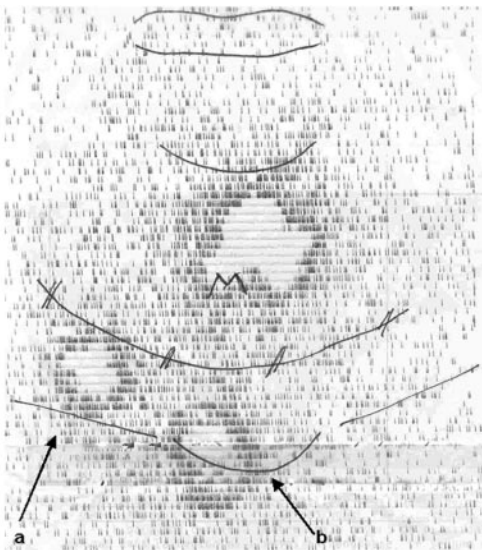

FIG. 1. Persistent disease on a postablation TBS: one focus of uptake is located in the right lateral compartment (a) and the other one behind the right sternoclavicular joint corresponding to a retrovascular LN metastasis (b).

TABLE 2. Risk factors for persistent disease

	Persistent disease: yes/total	Univariate analysis		Multivariate analysis 1[a]		Multivariate analysis 2[a]	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age (yr)							
<45	24/85 (28%)	1 (ref)		1 (ref)		1 (ref)	
≥45	9/63 (14%)	0.4 (0.2–1.0)	0.05	0.6 (0.2–1.7)	0.3	0.6 (0.2–1.5)	0.3
Sex							
Male	12/38 (32%)	1 (ref)					
Female	21/110 (19%)	0.5 (0.2–1.2)	0.11				
Tumor size (mm)[b]							
≤20	12/78 (15%)	1 (ref)		1 (ref)	0.06	1 (ref)	0.03
20–40	13/51 (25%)	1.8 (0.8–4.4)	<0.001	1.5 (0.6–3.8)		1.6 (0.6–4.0)	
>40	8/18 (44%)	4.4 (1.4–13.4)		2.9 (0.8–10.2)		3.4 (1.0–11.3)	
Bilaterality							
No	16/78 (21%)	1 (ref)					
Yes	17/70 (24%)	0.4 (0.1–2.1)	0.5				
Multifocality							
No	11/57 (19%)	1 (ref)					
Yes	22/91 (24%)	1.3 (0.9–1.6)	0.06				
Extension beyond the thyroid capsule							
No	13/76 (17%)	1 (ref)					
Yes	20/72 (28%)	1.9 (0.8–4.1)	0.12				
Number of metastatic LN						Nt	
≤5	5/72 (7%)	1 (ref)		1 (ref)	<0.001		
6–10	7/36 (19%)	3.2 (0.9–11.0)	<0.0001	3.1 (0.9–10.7)			
>10	21/40 (53%)	14.8 (4.9–44.5)		11.3 (3.6–35.1)			
Number of ECE-LN				Nt			
0	10/83 (12%)	1 (ref)				1 (ref)	
1–3	5/28 (18%)	1.6 (0.5–5.1)	<0.01			1.6 (0.5–5.2)	0.01
>3	18/37 (49%)	6.9 (2.7–17.4)				5.4 (2.1–14.3)	
Central LN metastases							
No	0/26	1 (ref)	c				
Yes	33/122 (27%)	c					
Lateral LN metastases							
No	5/39 (13%)	1 (ref)					
Yes	28/109 (26%)	2.4 (0.8–6.6)	0.10				

ECE-LN, Lymph node metastases with ECE; ref, reference; NS, not statistically significant; Nt, not tested.
[a] Multivariate analysis 1 included age, tumor size, and the number of metastatic LN; multivariate analysis 2 included age, tumor size, and the number of ECE-LN.
[b] Unknown tumor size for one patient.
[c] Not estimable.

Prognostic factors for recurrent disease

The 115 patients with a normal postablation TBS were followed up for a mean of 8 yr (range 0.1–16; median 8 yr). The patient whose follow-up was less than 1 yr was excluded from further analysis.

The Tg/TSH at 6–12 months, available in 100 patients, was undetectable and detectable in 72 (63%) and 28 (24%) cases, respectively. Of note, the Tg level was less than 10 μg/liter in 16 of the 28 patients with detectable Tg level. In the remaining 15 patients, either the recovery test was less than 80% (nine) or the Tg measurement was not performed (six).

Recurrences occurred in eight patients (7%) after a mean follow-up of 4.7 yr (range 1–7). Five- and 10-yr disease-free survivals were 96% (CI 93–99%) and 91% (CI 86–97%), respectively. Recurrence occurred in neck LNs, lungs, and both lungs and thyroid bed in six, one, and one case, respectively. In these patients, the Tg/TSH level at 6–12 months was elevated in five patients, undetectable in two, and could not be measured because of interferences in one. The recurrences were found by neck palpation, diagnostic ^{131}I TBS, and ultrasonography in six, one, and one case, respectively.

Prognostic factors of recurrence are shown in Table 4. Univariate analysis showed that the numbers of metastatic LNs and ECE-LNs and the Tg/TSH level were prognostic factors of recurrence. The frequency of recurrence was similar in patients with either initial central (8%) or lateral (9%) LN metastases. The number of ECE-LNs was the only independent risk factor of recurrence. The 10-yr recurrence rate was 2% in patients with three or fewer ECE-LNs and 38% in patients with more than three ECE-LNs. In case of undetectable Tg/TSH level, when the number of ECE-LNs was three or fewer or the number of LN metastases was 10 or fewer, the frequency of recurrence was 2–3% (Table 3). In the patients with undetectable Tg/TSH level with more than 10 LN metastases or more than three ECE-LNs, the frequency of recurrence ranged from 12 to 14%. In contrast, in patients with detectable Tg/TSH level and either more than three ECE-LNs or more than 10 metastatic LNs, the frequency of recurrence was 44 and 27%, respectively.

Survival

After a mean follow-up of 8 yr (range 0.1–16; median 8), nine patients died, one from distant metastases of thyroid

TABLE 3. Frequency of persistent disease according to the number of ECE-LN and metastatic LN and to tumor size and frequency of recurrent disease according to Tg/TSH level and the number of ECE-LN and metastatic LN

	ECE-LN ≤ 3	LN metastases ≤ 10	ECE-LN >3	LN metastases >10
Persistent disease[a]				
Tumor size ≤ 40 mm	13/101 (13%)	10/98 (10%)	11/28 (39%)	14/31 (45%)
[95% CI]	[8–21]	[5–18]	[23–57]	[29–62]
Tumor size > 40 mm	2/10 (20%)	2/10 (20%)	6/8 (75%)	6/8 (75%)
[95% CI]	[6–51]	[6–51]	[41–93]	[41–93]
Total	15/111 (14%)	12/108 (11%)	17/36 (47%)	20/39 (51%)
[95% CI]	[8–21]	[6–18]	[32–63]	[36–66]
Recurrent disease[b]				
Tg/TSH level				
Undetectable	1/65 (2%)	2/66 (3%)	1/7 (14%)	0/6
[95% CI]	[0.3–8]	[1–10]	[3–51]	
Elevated	1/19 (5%)	2/17 (12%)	4/9 (44%)	3/11 (27%)
[95% CI]	[1–25]	[3–34]	[19–73]	[10–56]
Total	2/84 (2%)	4/83 (5%)	5/16 (31%)	3/17 (18%)
[95% CI]	[1–8]	[2–12]	[14–56]	[6–41]

Tg/TSH, Tg level measured 6 to 12 months after initial treatment after L-T$_4$ withdrawal.
[a] One patient with persistent disease excluded because of unknown tumor size.
[b] Fourteen patients with unknown Tg/TSH level and one patient with a follow-up shorter than 1 yr excluded.

cancer 3 yr after initial surgery and eight from unrelated causes. The patient who died of thyroid cancer had an initial normal TBS. Ten-year disease-specific survival rate was 99% (CI 97–100%).

Discussion

A reliable prognostic classification is needed in PTC patients to adapt initial therapy and follow-up schemes to the risks of persistent and recurrent disease. According to the recent pTNM classification, patients with a minimal extrathyroidal tumor extension and/or LN metastases belong to the same stage I group when under 45 yr and stage III or IV otherwise. However, the respective impact on prognosis of LN metastases and minimal extrathyroidal tumor extension has not been properly documented. Mainly because pathological subtype, initial neck surgery, and ^{131}I administration differs between patients (2, 5, 8, 10, 14, 19). Because we routinely perform a total thyroidectomy with a complete selective LN dissection, we were able to precisely evaluate the prognostic impact of the LN status. Furthermore, because all patients received ^{131}I ablation and because ^{131}I uptake in thyroid remnants was low on the TBS, we could accurately visualize uptake foci outside the thyroid bed and therefore distinguish persistent disease from recurrent disease.

From an epidemiological standpoint, our study shows that LN involvement remains frequent whereas major extrathyroidal tumor extension is rare in PTC patients without distant metastases at presentation. Indeed, except for 12 patients with LN metastases and laryngeal nerve extension, tumor extension to subcutaneous soft tissue, larynx, or trachea was not found in this series. Furthermore, we showed that minimal extrathyroidal extension is strongly linked to LN metastases because 89% of the tumors with minimal extrathyroidal extension were associated with LN metastases. Both surgical and pathological procedure standardizations are in fact critical to understand discrepancies between studies. We found lateral LN metastases in 74% of our patients and skipping metastases (ipsilateral LN metastases without central LN metastases) in 12%, in accordance with previous series (24). These findings highlight the importance of routine ipsilateral dissection. Our complication

rate (6%) was concordant with other series on similar patients (25–27).

This study, being retrospective, is subject to biases. Furthermore, because thyroid cancer is rare, the numbers of patients included and events are low. However, we showed, in accordance with others, that the extent of LN involvement is a risk factor of persistent and recurrent disease (11, 12).

This study is the first to show that the risk for persistent disease (22%) is a critical point, being much higher than the risk for recurrent disease (8%). It allows us to distinguish four risk levels for persistent disease according to the location of LN metastases, the number of metastatic LNs, the number of ECE-LNs, and the tumor size: 1) a low risk (0–7%) in patients without central compartment LN metastases or five or fewer metastatic LNs; 2) a medium risk (5–21%) in patients with 10 or fewer metastatic LNs and three or fewer ECE-LNs and a tumor size of 4 cm or less; 3) a high risk (23–62%) in patients with more than 10 metastatic LNs or more than three ECE-LNs and a tumor size of 4 cm or less; and 4) a very high risk (41–93%) in patients with either more than 10 metastatic LNs or more than three ECE-LNs and a tumor size larger than 4 cm. Because of the small numbers of patients, the risks of persistent disease are overlapping between groups. However, according to these results, and taking into account recent results on second cancer induced by ^{131}I administration (28), we may question the routine administration of ^{131}I in patients whose initial treatment included total thyroidectomy with central and ipsilateral neck LN dissection and whose pathological results showed the absence of central compartment LN metastases or a low number (less than five) of metastatic LNs.

Despite a low number of recurrences, two risk levels for recurrent disease can be distinguished according to the Tg/TSH level at 6–12 months and the number of ECE-LNs and metastatic LNs: 1) a low risk (0.3–10%) in patients with undetectable Tg level, less than three ECE-LNs, and less than 10 metastatic LNs; and 2) a high risk (44%; 95% CI 19–73%) in patients with elevated Tg level and more than three ECE-LNs. Patients with either an elevated Tg level or more than 10 metastatic LNs or more than three ECE-LNs seem to have an intermediate risk of relapse, but risk group classification is limited by the low num-

TABLE 4. Risk factors of recurrence (one patient excluded because of follow-up shorter than 1 yr)

	No. of recurrences	Univariate analysis		Multivariate analysis 1[a]		Multivariate analysis 2[a]	
		RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Age (yr)							
<45	4/60 (7%)	1 (ref)					
≥45	4/54 (7%)	1.2 (0.3–4.7)	0.8				
Sex							
Male	2/26 (8%)	1 (ref)					
Female	6/88 (7%)	0.9 (0.2–4.6)	0.9				
Tumor size (mm)							
≤20	2/65 (3%)	1 (ref)					
20–40	4/39 (10%)	3.1 (0.6–17.0)	0.2				
≥40	2/10 (20%)	7.1 (1.0–51)					
Bilaterality							
No	6/63 (10%)	1 (ref)	0.3				
Yes	2/51 (4%)	0.4 (0.1–2.1)					
Multifocality							
No	5/46 (8%)	1 (ref)	0.2				
Yes	3/68 (4%)	0.4 (0.1–1.6)					
Extension beyond thyroid capsule							
No	2/62 (3%)	1 (ref)	0.11				
Yes	6/52 (12%)	3.7 (0.7–18.1)					
No. of metastatic LN						Nt	
≤5	2/66 (3%)	1 (ref)		1 (ref)			
6–10	2/29 (7%)	2.1 (0.3–14.8)	0.5	1.8 (0.2–12.8)	0.5		
>10	4/19 (21%)	6.7 (1.2–36.7)	<0.03	3.8 (0.6–24.2)	0.2		
No. of ECE-LN							
0	1/72 (1%)	1 (ref)		Nt		1 (ref)	
1–3	1/23 (4%)	2.7 (0.2–43.6)	0.5			2.5 (0.2–40.3)	0.5
>3	6/19 (32%)	24.3 (2.9–202)	<0.01			17.6 (2.0–155)	<0.01
Tg/TSH							
Undetectable	2/72 (3%)	1 (ref)		1 (ref)		1 (ref)	
Elevated	5/28 (18%)	6.2 (1.2–38)	0.03	4.6 (0.8–27.2)	0.09	2.9 (0.5–15.7)	0.57
Unknown	1/14 (7%)	2.7 (0.2–30)	0.42	2.6 (0.2–29.2)	0.4	1.6 (0.1–18.5)	0.16
Central LN metastases							
No	1/24 (4%)	1 (ref)					
Yes	7/89 (8%)	2.0 (0.2–16.3)	0.5				
Lateral LN metastases							
No	1/34 (3%)	1 (ref)	0.3				
Yes	7/81 (9%)	3.0 (0.4–23.8)					

ref, Reference; Nt, not tested; Tg/TSH, Tg level measured 6–12 months after initial treatment following L-T$_4$ withdrawal.
[a] Multivariate analysis 1 included the number of metastatic LN and Tg/TSH; multivariate analysis 2 included the number of ECE-LN and Tg/TSH.

ber of events. These results are concordant with a study from Toubeau *et al.* (29), who found a 3% risk of recurrence in case of undetectable Tg level and no LN metastases and a 40% risk of recurrence in case of detectable Tg level and/or LN metastases. Follow-up schemes could therefore be modulated by initial prognostic factors. Because most recurrences are located in the neck, we suggest to focus follow-up on patients with elevated Tg/TSH level at 6–12 months and more than three ECE-LN or more than 10 metastatic LN by combining neck ultrasonography and serum TSH stimulated Tg determination (30–32). On the contrary, in patients with an undetectable Tg level and three or fewer ECE-LNs and 10 or fewer metastatic LNs, a simplified follow-up protocol based on serum Tg determination and clinical examination should be considered, according to recent recommendations (33, 34). In patients with elevated Tg level and no other risk factor of recurrence, follow-up should be focused on the serum TSH stimulated Tg slope as suggested by Baudin *et al.* (35).

This study shows that the pTNM classification is not adapted to assess the risk for persistent or recurrent disease. In fact, the pTNM classification does not take into account the extent of LN involvement. Furthermore, the pTNM classification separates pretracheal and paratracheal LN metastases (pN1a) from lateral and mediastinal LN metastases (pN1b). In this study, persistent disease was seen only in patients with central LN metastases, and 73% of LN foci of uptake on postablation TBS were located in the central compartment. These results suggest that either a complete central compartment dissection is difficult to achieve or that central LN metastases reflect a more aggressive disease. We therefore suggest that the pN1a classification refers to patients with isolated lateral LN metastases. Furthermore, in accordance with some previous reports (2, 3, 10, 14), but not all (5, 6, 8, 19), our results were not related to the age of the patients, suggesting that the same treatment and follow-up protocols should be applied to all age groups. Finally, minimal extrathyroidal extension was closely related to the presence of LN metastases and did not appear to be an independent prognostic factor for persistent or recurrent disease, suggesting that, when present, it does not justify a stage upgrading.

Our results also show that the current pTNM classification is not relevant enough for the evaluation of specific survival. In the present series, despite the selection of the patients and even though 42% of them belonged to stages III-IV, the 10-yr disease-specific survival rate was 99%. This excellent survival is close

to the survival rate reported for stage I-II patients (6, 22). Other criteria such as histopathological subtypes should be taken into account for the evaluation of prognostic factors of survival.

In conclusion, our study demonstrates the excellent 10-yr survival rate of PTC patients with LN metastases and/or minimal extrathyroidal extension. The risk of persistent and recurrent disease is, however, high. We propose a classification, based on a standardized neck LN dissection, dedicated to the risk of persistent and recurrent disease, taking into account the location of LN metastases, the numbers of metastatic LNs and ECE-LNs, the tumor size, and the Tg level obtained after TSH stimulation at 6–12 months. Minimal extrathyroidal tumor extension, which is closely linked to the presence of LN metastases, has no prognostic influence. This classification could help clinicians for the decision of radioiodine administration and the modulation of follow-up modalities. Indeed, further studies are requested to validate these criteria.

Acknowledgments

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