

## CLINICAL STUDY

# Scoring system for predicting recurrences in patients with papillary thyroid microcarcinoma

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## Abstract

**Context:** Papillary thyroid microcarcinomas (PMC) defined as tumors  $\leq 10$  mm in diameter (including pT1a and pT3 according to the latest pTNM classification) have good prognosis, although recurrence is possible. Clinicians are interested in using a scoring system for predicting recurrences.

**Objective:** To identify the prognostic factors for recurrence in patients with PMC and to develop a scoring system based on lymph node involvement, multifocality, and sex. To determine the impact of extrathyroidal invasion (ETI) and a threshold value for analyzing multifocality.

**Methods:** Single-center retrospective study of a cohort of 1669 patients with PMC managed from 1960 to 2007. The Kaplan–Meier survival rate and prognostic factors of events were analyzed using log-rank tests and uni- and multivariate Cox model-based analyses. A scoring system was proposed.

**Results:** Sixty-eight recurrences were observed. Initial lymph node metastases ( $P=0.0001$ ), multifocality ( $P=0.05$ ), and male sex ( $P=0.01$ ) were significantly associated with recurrence, although there was a period effect (after 1990). PMC size was not a significant variable. Our scoring system allows us to separate patients into three risk groups according to their recurrence-free probability. For PMC Nx patients, total foci size of multifocal tumors  $> 20$  mm was significantly associated with recurrence ( $P<0.0001$ ). Radioiodine (RAI) ablation was associated with better outcome only in PMC with ETI.

**Conclusion:** Our scoring system classifies recurrence risk. In PMC Nx patients, multifocality is important in planning therapeutic strategies. Recurrence probability of pT3 PMC appears lower if RAI ablation is performed.

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## Introduction

Over the past 30 years, there has been a significant rise worldwide in the incidence of papillary thyroid microcarcinoma (PMC) (1), i.e. thyroid carcinoma  $< 10$  mm in diameter (2). The last pTNM classification does not recognize PMC as a specific entity. They are included in the pT1a carcinoma category when the tumor is confined to the thyroid and in the pT3 category (called 'micro pT3') when minimal extrathyroidal invasion (ETI) is present (i.e. extension to the sternothyroid muscle or perithyroid soft tissues) (3). The overall prognosis of PMC is excellent, although locoregional recurrence (LRR) and the development of distant metastases have been known to occur (3–7 and  $< 1\%$  respectively) (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15).

PMC prognosis depends on the initial clinicopathological presentation. Clinicians are interested in using a scoring system to accurately predict recurrence risk and manage patients accordingly (16). The presence of neck lymph node involvement and multifocality are known to

be factors of poor prognosis. In contrast, a unifocal microcarcinoma pT1a presents no cause for concern (16, 17). However, other clinicopathological situations have prognostic significance that is less clearly specified in the guidelines (18, 19), such as Nx PMCs that are incidentally diagnosed after total or partial thyroidectomy for presumably benign disease and therefore have not undergone lymph node dissection. In such cases, the clinician is faced with the issue of multifocality, which is present in up to 48% of cases (20). However, there is no medical data concerning the threshold beyond which multifocality is associated with a higher risk of recurrence. Another unresolved issue is the prognostic impact of small ETI for PMC on the recurrence risk and as a result the relevance of radioiodine (RAI) ablation in such cases.

The aims of this study were to determine recurrence-free probability, identify prognostic factors for recurrence, and develop a simple scoring system enabling the clinician to assess the risk of recurrence. Prognostic factors such as lymph node involvement, ETI, tumor

size, sex, multifocality, and RAI treatment were analyzed in a large cohort of 1669 patients with PMC treated at a single institution. Multifocality was studied specifically in pT1a Nx PMCs, which are a common issue for physicians. Prognosis of the pT3 PMC subgroup was also specifically studied. We found that initial lymph node metastases, multifocality, and male sex were the three major prognostic factors for relapse. By assigning scoring points for each factor, patients are divided into three risk groups according to their recurrence-free probability. In patients with multifocal pT1a Nx PMC (pT1a (m) Nx), the sum of all foci > 20 mm was a significant predictor of recurrence. RAI ablation was associated with reduced risk of recurrence only in pT3 PMC.

## Patients and methods

### Patients

Patient information was obtained from a database and from medical records. Of the 6416 patients with differentiated thyroid carcinoma that were treated and followed at the Department of Nuclear Medicine at the Groupe Hospitalier Pitié-Salpêtrière from 1960 to 2007, 1758 patients (308 men and 1450 women) were affected by PMC.

Histological data were obtained from the initial pathology reports. Of the 1758 patients with PMC, 106 were classified initially as having follicular carcinoma. Owing to the rarity and the diagnostic pitfalls of this follicular type, histology slides or reports of the 106 cases were reviewed by a single experienced pathologist: 12 were true, minimally invasive follicular carcinoma (diagnosis based on capsular effraction and/or vascular invasion without typical nuclear features of papillary carcinoma) and were excluded. In the same way, two cases were excluded due to tumor size > 10 mm, two cases were a 'not otherwise specified' histological type, one case was a medullary carcinoma, and 62 cases did not have slides available. So, finally, of the 106 cases, 27 were papillary PMC, which in most

cases were a follicular variant of papillary carcinoma and were kept in our final series.

Furthermore, 10 (0.6%) PMC patients with distant metastases at diagnosis were also excluded. Metastases were located as follows: lung metastases (eight patients), bone metastases (one patient), and mediastinal lymph node involvement (one patient). These metastases were detected by cytological or histological analysis or by abnormal iodine uptake after therapeutic whole-body scan (WBS).

The final series included 1669 patients. Their characteristics are presented in Tables 1 and 2. The mean age of the patients at initial diagnosis was  $47.2 \pm 13.1$  years. The mean size of the initial tumor was  $6.2 \pm 2.9$  mm. Multifocality was accurately assessed in the subgroup of 236 patients with pT1a (m) Nx PMC, with recording data regarding the number of foci, the total foci size, and the bilaterality. In this subgroup, the number of foci ranged from 2 to 11 (mean: 2.6) and the total foci size ranged from 2 to 53 mm (mean: 9.7 mm). The total foci size was between 21 and 53 mm in six patients. Among pT1a (m) Nx carcinomas, 41% were discovered incidentally at the pathological examination.

### Initial treatment and follow-up

Patient follow-up data were obtained from the database, medical records, town council registers, and periodic correspondence with patients or their referring physicians. Initial treatment is presented in Tables 1 and 2. Until 1990, the decision to carry out RAI ablation depended on the result of the diagnostic WBS performed 6 weeks after surgery. For the last two decades, the indication for RAI ablation has been discussed on a regular basis in a multidisciplinary staff meeting at our hospital, and iodine therapy has been indicated for tumors with extension beyond the thyroid capsule (pT3 or pT4) and in patients with lymph node involvement (N1) or distant metastases (M1). A suppressive dose of L-thyroxine (L-T<sub>4</sub>) treatment is initially prescribed only for patients who have received an ablative <sup>131</sup>I dose.

**Table 1** Patients' characteristics according to the initial lymph node status.

	N0 (n=418)	Nx (n=962)	N1 (n=289)	Total (n=1669)
Sex, male	53 (12.7%)	148 (15.6%)	88 (30.4%)	289 (17.3%)
Age ≥ 45 years	237 (56.7%)	596 (15.4%)	117 (40.5%)	950 (57%)
Total or near-total thyroidectomy	411 (98.3%)	924 (96%)	287 (99.3%)	1622 (97.2%)
Lobectomy	7 (1.7%)	38 (4%)	2 (0.7%)	47 (2.8%)
Initial cervical node surgery <sup>a</sup>	418 (100%)	0	261 (90.3%) <sup>b</sup>	679 (40.7%)
Radioiodine ablation of thyroid remnants	368 (88%)	659 (68.5%)	281 (97.2%)	1308 (78.4%)
Tumor size ≤ 5 mm	82 (19.6%)	369 (38.3%)	56 (19.4%)	507 (30.4%)
Multifocality	141 (33.7%)	258 (26.8%)	118 (40.8%)	517 (31%)
Vascular invasion	12 (2.9%)	34 (3.5%)	26 (9%)	72 (4.3%)
ETI (pT3)	53 (12.7%)	65 (6.7%)	57 (19.7%)	175 (10.5%)
Period of initial diagnosis earlier than 1990	96 (23%)	199 (20.7%)	113 (39.1%)	408 (24.4%)

ETI, extrathyroidal invasion.

<sup>a</sup>Includes modified radical lymph node dissection and limited lymph node excision.

<sup>b</sup>Lymph node metastasis discovered incidentally during pathological examination of the thyroid.

**Table 2** Patients' characteristics according to the presence of ETI.

	pT1 (n=1494)	pT3 (n=175)	Total (n=1669)
Sex, male	257 (17.2%)	32 (18.3%)	289 (17.3%)
Age ≥ 45 years	848 (56.8%)	102 (58.3%)	950 (57%)
Total or near-total thyroidectomy	1448 (97%)	174 (99.4%)	1622 (97.2%)
Lobectomy	46 (3%)	1 (0.6%)	47 (2.8%)
Initial cervical node surgery <sup>a</sup>	571 (38.2%)	108 (61.7%)	679 (40.7%)
Radioiodine ablation of thyroid remnants	1137 (76.1%)	171 (97.7%)	1308 (78.4%)
Tumor size ≤ 5 mm	495 (33.1%)	12 (6.8%)	507 (30.4%)
Multifocality	444 (29.7%)	73 (41.7%)	517 (31%)
Vascular invasion	56 (3.7%)	16 (9.1%)	72 (4.3%)
Initial cervical lymph node metastases (N1)	232 (15.5%)	57 (32.6%)	289 (17.3%)
Undetermined lymph node status (Nx)	897 (60%)	65 (37.1%)	962 (57.6%)
No lymph node metastases (N0)	365 (24.4%)	53 (30.3%)	418 (25%)
Period of initial diagnosis earlier than 1990	386 (25.8%)	22 (12.6%)	408 (24.4%)

<sup>a</sup>Includes modified radical lymph node dissection and limited lymph node excision.

Changes in the follow-up of patients with PMC took place during the study period. Ultrasonography and, if necessary, fine-needle aspiration biopsy have been progressively included in follow-up since 1990 in combination with the recombinant human TSH-stimulated thyroglobulin test (21). Currently, the follow-up protocol consists of regular clinical examinations, serum thyroglobulin level measurement, detection of anti-thyroglobulin antibodies (systematically performed since its availability in 1981), and neck ultrasonography. WBS under TSH stimulation (i.e. withdrawal of T<sub>4</sub> or, more recently, the use of recombinant human TSH) is no longer performed systematically to check the efficiency of thyroid remnant ablation.

### Definition and diagnosis of recurrence

Events were analyzed retrospectively. Events that were considered recurrent included the following:

- LRR, defined as a thyroid bed, soft tissue, or cervical lymph node recurrence of an initially treated PMC. The diagnosis of LRR was assessed by histological analysis at surgery or by fine-needle aspiration biopsy or by a positive <sup>131</sup>I cervical uptake anywhere in the neck after <sup>131</sup>I diagnostic (11.1 MBq) or therapeutic (3.7 GBq) dose.
- Isolated and repeatedly elevated serum thyroglobulin levels (> 10 ng/ml after T<sub>4</sub> withdrawal) that justified the administration of a second therapeutic dose of <sup>131</sup>I.
- Distant metastases assessed by cytological or histological analysis or by iodine uptake after diagnostic or therapeutic WBS.

Among patients who experienced recurrence, we analyzed the result of the 6-month checkup after initial treatment. We distinguished between patients whose 6-month checkup was normal (i.e. normal clinical examination, undetectable thyroglobulin level, and normal ultrasonography) and those whose 6-month checkup was abnormal (suspicious thyroglobulin level

and/or ultrasonography interpreted according to previous RAI ablation).

Residual Tg levels, suspicious neck ultrasonography, or imaging at 6-month checkup after initial treatment, which did not lead to a proven locoregional event or distant metastases or the second administration of <sup>131</sup>I therapeutic dose, were not considered as events in the statistical analysis of prognostic factors for recurrence. Patients who were retreated by surgery or <sup>131</sup>I within 6 months of the initial treatment were not considered to have a recurrence.

### Definition of end point status

At end point, patients were considered as follows:

- cured if serum thyroglobulin levels (when available) were under 2 ng/ml after withdrawal of L-T<sub>4</sub> (or under 2.5 ng/ml before 1984) or, more recently, under 1 ng/ml after the use of recombinant human TSH or undetectable on L-T<sub>4</sub> therapy or when there was no iodine uptake after diagnostic WBS and/or normal neck ultrasonography,
- to have progressive disease if serum thyroglobulin levels increased significantly between two assays or if morphological imaging (CT scan and PET scan) was abnormal,
- to have a stable disease if they did not match the definition of cured but if serum thyroglobulin levels were stable between the last two assays or if the tumor volume was stable on morphological imaging.

### Statistical analysis

The main criterion of the study is the time to recurrence, defined as the difference between the date of recurrence treatment and the date of the treatment. We considered the date of recurrence to be the date of recurrence treatment, with this date corresponding to a standardized reliable proof of recurrence for all patients. Follow-up time was defined as the date of death or the

date of the last news from survivors. Patients with no observed recurrence before the end of follow-up were considered as censored at this date. The following potential prognostic factors were studied: age at primary tumor diagnosis, sex, period of initial diagnosis (before or after 1990), initial tumor size (mean  $> 5$  or  $\leq 5$  mm), invasion of the initial tumor (multifocality, ETI, and vascular invasion), initial lymph node metastases, complete initial surgery (total or near-total thyroidectomy vs lobectomy), initial cervical lymph node surgery (modified radical lymph node dissection or limited lymph node excision vs no lymph node surgery), initial RAI therapy, and RAI dose. For patients with pT1a (m) Nx tumors, the following variables were also studied: number of foci, the sum of the largest sizes of all foci, and bilaterality of the foci. Taking the hypothesis that tumor foci are spherical (volume:  $4/3 \pi r^3$ ), the total volume of the tumor foci was calculated and the prognostic value of the total volume was evaluated. The prognostic value of each variable was studied in the total series as well as in pT1a (m) Nx DTMC subset and according to the presence of ETI. The relationships between each potential risk factor and time to recurrence were described using the Kaplan–Meier estimation method and tested first using log-rank tests. In a second step, multivariate Cox models were built using stepwise regressions. Variables with  $P$  values  $< 0.20$  in univariate analyses were entered into the step-wise regressions, and variables significant with a  $P$  value  $< 0.05$  with the Wald test were retained in the final models. All tests were two-sided, with a  $P$  value  $< 0.05$  considered significant. Computations were performed using the SAS V9 statistical package. A simplified prognostic classification was derived from the final Cox model obtained from data with treatment year after 1990. In order to build the classification, Kaplan–Meier recurrence-free probability functions were estimated for each of the eight configurations obtained from the three binary variables defining the final model, and configurations of variables with near recurrence probability functions were grouped into three prognostic classes. Finally, a simple scoring system was built in order to classify the final prognostic groups.

## Results

### Recurrences and outcome

In our study, the mean follow-up time was  $6.5 \pm 6.7$  years (range: 1 month–37.9 years; median: 4.7 years). Sixty-eight recurrences (4.1%) were observed. Of these 68 recurrences, 16 occurred in patients whose 6-month checkup was normal (i.e. normal clinical examination, undetectable thyroglobulin level, and normal ultrasonography) whereas the other 52 occurred in patients whose 6-month checkup was abnormal. Prognostic factors for recurrence (univariate and multivariate analysis) were

analyzed taking into recurrences, 56 (3.3%) were locoregional and two were lung metastases. A second therapeutic dose of  $^{131}\text{I}$  was administered in ten cases (0.6%) based on isolated and repeatedly elevated serum thyroglobulin levels. The maximal time period between initial treatment and diagnosis of recurrence was 15 years. The recurrence-free probability at 5, 10, and 20 years was 95.2% (confidence interval (CI): (94%; 96.5%)), 93.5% (CI: (91.9%; 95.5%)), and 92.2% (CI: (91%; 94.4%)) respectively.

At the end point, 1526 patients (91.4%) were cured, 18 patients (1%) had progressive disease, and 42 patients (2.5%) had stable disease. Eighty-three patients (5%) were lost in follow-up, and 38 patients (2.3%) died, although none as a result of their thyroid cancer.

### Prognostic factors for recurrence of the 1669 patients

Prognostic factors for recurrence (univariate and multivariate analysis) were analyzed taking into account

**Table 3** Prognostic factors for recurrence (univariate analysis).

Variable	10-Year recurrence cumulative incidence probability (S.D.)	P value
Age at diagnosis		0.024
$\geq 45$ years	0.05 (0.01)	
$< 45$ years	0.08 (0.01)	
Sex		<b><math>&lt; 0.0001</math></b>
Male	<b>0.12 (0.02)</b>	
Female	<b>0.05 (0.01)</b>	
Surgical procedure		0.29
Lobectomy	0.18 (0.08)	
Near-total thyroidectomy	0.04 (0.02)	
Total thyroidectomy	0.07 (0.01)	
Initial cervical node surgery		<b>0.001</b>
No dissection	<b>0.05 (0.01)</b>	
Lymph node dissection	<b>0.09 (0.01)</b>	
Radioiodine ablation of thyroid remnants		0.96
Yes	0.06 (0.01)	
No	0.10 (0.04)	
Tumor size		0.070
$\geq 5$ mm	0.08 (0.01)	
$< 5$ mm	0.04 (0.01)	
Multifocality		<b>0.007</b>
Yes	<b>0.10 (0.02)</b>	
No	<b>0.05 (0.01)</b>	
Vascular invasion		0.46
Yes	0.03 (0.02)	
No	0.07 (0.01)	
Capsular invasion		0.26
Yes	0.08 (0.02)	
No	0.06 (0.01)	
Initial cervical lymph node metastases		<b><math>&lt; 0.0001</math></b>
Yes	<b>0.19 (0.03)</b>	
No	<b>0.04 (0.01)</b>	
Initial diagnosis year		0.94
$< 1990$	0.06 (0.01)	
$\geq 1990$	0.06 (0.01)	

Significant values are in bold.

an interaction period effect. Univariate analysis is shown in Table 3. We chose 1990 as a transitional year as this year is the beginning of the routine use of neck ultrasound for monitoring patients. Significant prognostic factors for recurrence in the multivariate analysis (Table 4) were lymph node metastases, multifocality, and male sex. Considering the interaction period effect, we found an interaction for lymph node metastases, which had more important prognostic significance after 1990 (hazard ratio (HR)=7.5 (1.4–28.9)) than before (HR=3.2 (1.6–6.1)). On the other hand, we found no interaction between multifocality and male sex.

ETI did not appear as an independent variable as it was significantly associated with recurrence in the univariate analysis but not in the multivariate analysis. It is notable that ETI and lymph node metastases are interrelated ( $P<0.0001$ ). Indeed, 57 out of 175 (32.6%) pT3 PMC patients presented with initial lymph node metastases vs 232 out of 1494 (15.5%) pT1a PMC ( $P<0.0001$ ). Patient age, the size of the PMC, or the RAI ablation appeared to be not significant variables associated with recurrence in the multivariate analysis.

### Scoring system

The score was designed to permit risk stratification with available information at initial presentation for patients diagnosed most recently, i.e. 1990 (this year corresponds to the beginning of the regular use of ultrasound).

Points were attributed to three significant prognostic factors: sex (female=0, male=1), multifocality (absent=0, present=1), and lymph node metastasis (absent=0, present=3). Patients were then divided into three risk groups according to their recurrence-free probability (Fig. 1; Table 5).

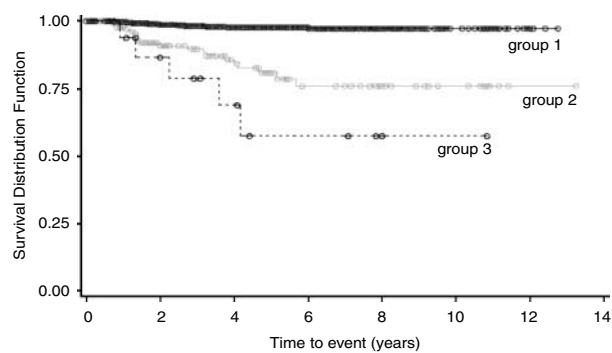
The low-risk group corresponds to the score 0, 1, or 2, i.e.:

- PMC N0 or Nx, unifocal or multifocal, in a female or
- PMC N0 or Nx, unifocal or multifocal, in a male.

The intermediate-risk group corresponds to the score 3 or 4, i.e.:

**Table 4** Prognostic factors for recurrence (multivariate analysis).

Variables	Hazard ratio (95% CI)	P value
Sex		
Female	1	0.010
Male	2.0 (1.2; 3.2)	
Multifocality		
No	1	0.051
Yes	1.6 (1.0; 2.6)	
Initial cervical lymph node metastases		
No	1	0.001
Yes, before 1990	3.2 (1.6; 6.1)	
Yes, after 1990	7.5 (4.3; 13.1)	



**Figure 1** Time to event stratified by three group score: group 1 (black line), group 2 (gray line), and group 3 (dotted line).

- PMC N1, unifocal or multifocal in a female or
- PMC N1, unifocal in a male.

The high-risk group corresponds to the score 5, i.e. PMC N1, multifocal in a male. It is noticeable that in the low-risk group, out of the 29 events observed, 10 (34.5%) occurred in patients whose 6-month checkup was normal (i.e. normal clinical examination, undetectable thyroglobulin level, and normal ultrasonography). In the intermediate-risk group, out of the 31 events observed, 21 (80.6%) occurred in patients whose 6-month checkup was already abnormal. In the high-risk group, the eight events observed occurred after an abnormal 6-month checkup. As expected, pT3 PMC were much more frequent in the high-risk group (Table 5).

### Prognostic factors for recurrence in patients presenting with pT1a (m) Nx PMC

In the group of patients with pT1a (m) Nx PMC, the total foci size of a multifocal cancer was a significant predictor for prognosis ( $P=0.009$ ; HR: 1.2 (1.05–1.4)), with the threshold of a total foci size  $>20$  mm significantly associated with risk of recurrence ( $P=0.03$ ). Surprisingly, bilaterality, the number of foci, or the threshold of total foci size  $>10$  mm was not significantly associated with an increased risk of recurrence. As shown in Fig. 2, the recurrence-free probability of pT1a (m) Nx PMC with a total foci size  $>20$  mm was worse than for those  $<20$  mm ( $P=0.03$ ). Moreover, our analysis of the total volume of the tumor foci in patients with pT1a (m) Nx tumors showed that this variable was also significantly linked to prognosis ( $P<0.0001$ ).

### Recurrence-free probability and prognostic factors for recurrence depending on the presence of ETI

The recurrence-free probability of patients with pT3 PMC was 89.8% (CI: (83.9%, 95.6%)) at 10 years and was statistically different from those with pT1a PMC



**Table 5** Final scoring system for patients diagnosed since 1990.

Recurrence risk	Patients	pT3 PMC	Score	10-Year recurrence probability (95% CI)
Low	1085	105 (9.7%)	0, 1, or 2	2.7% (1.3–4.1%)
Intermediate	153	39 (25.5%)	3 or 4	24% (13.7–34.3%)
High	23	9 (39.1%)	5	42.6% (12.7–72.5%)

( $P=0.02$ ). In patients presenting with micro pT3 carcinoma, the only variable significantly associated with absence of recurrence (multivariate analysis) was RAI ablation dose ( $P<0.002$ ; HR: 0.97 (0.95–0.99)), which averaged 3.2 GBq (range: 0–4.1 GBq).

## Discussion

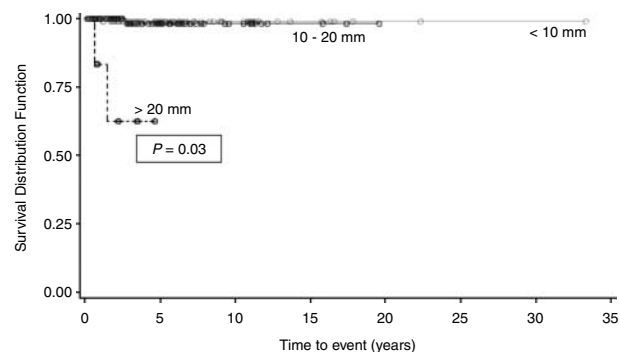
Owing to the dramatic worldwide increase in PMC commonly diagnosed fortuitously after thyroidectomy, clinicians are faced with the challenge of detecting those that are potentially aggressive and managing these efficiently. Although in most cases the outcome is favorable, PMC at diagnosis can present with signs of invasion associated with recurrence risk such as lymph node metastasis (17.3%), ETI (10.7%), multifocality (31%), and even distant metastasis in our series (0.6%). The latest guidelines enable the clinician to stratify the patients according to these factors (18, 19). Nevertheless, frequent incidental detection of PMC implies no neck lymph node dissection, which makes the risk stratification of these patients difficult. Moreover, the evaluation of the degree of multifocality and its management is not sufficiently addressed by the guidelines.

In our retrospective study on a large series of PMC, we started to investigate the predictors for relapse in order to build a scoring system that would accurately predict a patient's postoperative outcome. Most recurrences in papillary thyroid cancer occur within the first 5 years (22, 23). In our work, the median follow-up is 4.7 years. It should be noted that approximately a quarter of our patients (23%) were followed for more than 10 years, which is a reliable period to detect recurrence. Bearing in mind these considerations, our work proposes interesting data that, we feel, will be useful to the clinician.

First, lymph node metastases, multifocality, and male sex were significantly associated with recurrence risk in the multivariate analysis. Overall, our data are consistent with the findings of many others (4, 5, 8, 10, 11, 12, 13, 15, 23, 24, 25, 26, 27).

Secondly, to develop this scoring system, we had to take into account the heterogeneity of the management of patients attending our center over a very long period namely from 1960 to 2007. We chose 1990 as a turning point because this year marks the start of the

routine use of cervical ultrasound. The analysis highlighted a period effect that we took into consideration as the time of diagnosis could have an impact on the prognosis. Consequently, on the basis of our Cox step-wise regression analysis, the scoring system was developed solely for patients whose diagnosis of cancer had been made since 1990. Lymph node metastases appeared to have greater prognostic significance after 1990 than before while multifocality and male sex had no interaction with the period. Our data allow classification of patient recurrence risk using simple criteria available at initial presentation, i.e. lymph node status, multifocality, and male sex. Compared with the ETA and ATA guidelines of stratification risk, our scoring system offers additional benefits (18, 19). First, it clarifies the degree of risk of Nx PMC patients. These patients fall into the low-risk group as did most patients in our series. Indeed, the low-risk group represents 65% of our patients with a 10-year recurrence probability of 2.7% (1.3–4.1%) compared with significantly higher risk in the intermediate and high-risk groups: 24 (13.7–34.3%) and 42.6% (12.7–72.5%) respectively. More precisely, the 10-year recurrence probability for patients with N0 DTMC (3.1% (0.9–5.3%)) was statistically not different from those of patients with Nx DTMC (3.9% (2–5.8%)) but both were significantly better than those of the N1 DTMC group (18.7% (13.1–24.2%)). This is naturally reassuring for the patient who has not had neck dissection. Therefore, we focused on the analysis of multifocality in a group of patients with pT1a (m) Nx PMC. We found that multifocality is a prognostic factor for recurrence (HR=1.6) as asserted in other publications (5, 13, 23, 28). Recently published guidelines (18, 19) highlight that PMC patients without lymph node metastasis (N0) presenting with multifocal pT1a with a total foci size  $\leq 10$  mm are at low risk and so RAI therapy is not recommended. Data regarding the relevance of this 10 mm threshold are lacking. Our results clearly show that when total foci size reaches 20 mm or more, there is a higher risk for recurrence.



**Figure 2** Time to event for pT1a Nx patients for multifocal DTMC with total foci size < 10 mm (gray line), between 10 and 20 mm (black line), and > 20 mm (dotted line).

However, it is not higher when total foci size is 10 mm. For pT1a (m) Nx PMC, when all foci are <20 mm, our data suggest that RAI ablation may not be recommended (instead of the 10 mm threshold currently recommended). The recommendation remains a hypothesis in the absence of a prospective study comparing the outcome of RAI-treated groups (with total foci tumor size more than 20 mm) vs a nontreated group. Out of caution, we studied the total volume of the tumor foci rather than tumor size. Our results once again showed that there was a close relationship between the total volume of a multifocal pT1a Nx tumor and the risk of recurrence. This result suggested that the total volume is a reliable predictor of recurrence that should be taken into account when evaluating the prognosis of PMC. It further showed that progress remains to be made in creating efficient tools that estimate tumor mass.

Secondly, the model highlights the prognostic significance of the patient's sex. Male sex appeared to be a significant risk factor, although this is attenuated when the tumor is strictly unifocal with no lymph node involvement. In our classification, female patients with N1 PMC fell into the intermediate-risk group, such as in the ATA guidelines (whatever the gender), whereas the ETA guidelines classified them as high risk.

It is noteworthy that in our study, most recurrences occurred in patients whose 6-month checkup after the initial treatment was abnormal (the eight events of the high-risk group and the 25 events out of 31 in the intermediate-risk group). It is difficult to judge how far this may be due to the aggressive behavior of the disease and/or an incomplete initial treatment especially regarding the lymph node dissection procedure. This makes the recent concept based on the delayed risk stratification that integrates the results of the 6- to 12-month control after initial treatment all the more interesting (29, 30, 31, 32). Lastly, we focused on the high-risk group patients. Besides the impact of well-established poor prognosis on the presence of lymph node metastases, we wanted to accurately study the role of ETI whose impact on PMC prognosis has not been well established so far. ETI is recognized as a risk factor for recurrence of carcinoma >10 mm, but this point is still being debated for PMC, as some authors report that ETI is a predictive factor of adverse outcome (33, 34), while others do not (4, 5, 10, 15, 35, 36). One can assume that the minimal ETI of a PMC that is located on the edge of the gland could have a weaker prognostic impact than that of the ETI of a macrocarcinoma developing at the center of the gland and finally invades peripheral soft tissue. In our study, the presence of ETI did not appear to be an independent predictive factor for recurrence in the entire cohort, as it was significantly associated with relapse in the univariate analysis but not in the multivariate one. Surprisingly, in the pT3 PMC group, lymph node metastases were not associated with recurrence. These results are probably due to the fact that ETI and lymph node metastases are

interrelated, as suggested both by our statistical analysis and by other authors (26). Furthermore, in this pT3 PMC group, the ablative dose of  $^{131}\text{I}$  was the only variable significantly associated with a lower risk of recurrence. Although RAI remnant ablation was not significantly associated with recurrence in our entire series of PMC patients or in several other studies (37, 38), it may be mandatory for patients with pT3 PMC. Ideally, this needs to be confirmed in a prospective study comparing the two therapeutic options (RAI ablation or abstention).

In conclusion, although relapse is rare in patients with PMC, clinicians should pay particular attention to lymph node status, multifocality, male sex, and to a lesser extent to ETI when predicting recurrence. Our scoring system will help physicians accurately predict patients' recurrence risk at initial presentation. This will produce better management decisions tailored on an individual basis, although ideally it needs to be tested on a larger scale. Our study should reassure patients with pT1a Nx PMC regarding the absence of lymph neck dissection. Such patients with multifocality presenting with a total foci size <20 mm may also warrant less aggressive therapeutic and follow-up strategies. Further studies need to be carried out regarding the pathological significance of ETI specifically for pT3 PMC.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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