Papillary Thyroid Microcarcinomas: A Comparative Study of the Characteristics and Risk Factors at Presentation in Two Cancer Registries

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Context: Papillary thyroid microcarcinoma (PTMC) is an indolent neoplasia, often asymptomatic and discovered incidentally. Some PTMCs, however, exhibit a more aggressive behavior, frequently recur, and can even cause cancer-related death.

Objective: The aim of this study was to evaluate the prevalence of PTMCs and the associated risk factors at presentation in 2 thyroid cancer registries from areas with different genetic and environmental characteristics.

Design and Patients: We conducted a retrospective, observational study of all incident cases of PTMCs recorded over a 5-year period in the Sicilian Regional Registry for Thyroid Cancer (SRRTC) and in the Surveillance Epidemiology and End Results (SEER) US registry.

Setting: The study took place at an academic hospital.

Results: The incidence of PTMCs was much higher in Sicily (1777 PTMC diagnosed in 2002–2006; age-standardized incidence rate for the world population [ASRw] = 5.8 per 100 000) than in the United States (14 423 PTMC in the period 2004–2008; ASRw = 2.9 per 100 000). Within the SRRTC, a significantly higher incidence was observed in the volcanic area (ASRw = 10.4 vs 4.6 in the rest of Sicily). In Sicily, the female to male ratio was higher, and PTMC patients were younger. In both registries, a significant inverse correlation was observed between age and tumor size. Young patients (≤45 y) exhibited a higher frequency of nodal metastases.

Conclusions: PTMC incidence is twice as high in Sicily compared with the United States, and within Sicily, the incidence is twice as high in the volcanic area. In young patients, PTMCs are larger at presentation and exhibit more risk factors. In both registries, more than 35% of PTMCs exhibited 2 or more risk factors, suggesting that they may require surgery and follow-up similar to that of larger carcinomas. (***J Clin Endocrinol Metab*** **98: 1427–1434, 2013)**

Thyroid microcarcinomas, ie, thyroid cancers smaller than 1 cm in diameter, have become a public health issue due to the continuous worldwide increase of thyroid cancer incidence, with microcarcinomas representing nearly 50% of all thyroid cancers. Microcarcinoma is a definition based on size, with no information on the tumor biology. Most thyroid microcarcinomas exhibit indolent behavior and require neither aggressive treatment nor in-

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Abbreviations: ASRw, age-standardized incidence rate for the world population; CI, confidence interval; PTMC, papillary thyroid microcarcinoma; SEER, Surveillance Epidemiology and End Results; SRRTC, Sicilian Regional Registry for Thyroid Cancer; US, ultrasound.

tensive follow-up, as indicated by recent guidelines (1, 2). For these tumors, the risk of overdiagnosis (ie, the identification of small tumors that will never cause health problems) is a strong possibility. Overdiagnosis carries the risk of overtreatment, with a consequent burden of potential complications, patient distress, and economic costs (3).

However, at an early stage, also aggressive tumors will appear as microcarcinomas. When undertreated, these microcarcinomas can progress with extrathyroid extension, lymph node invasion, and distant metastases. Eventually, these cancers exhibit an increased recurrence rate as well as the potential for cancer-related death (4, 5).

It is therefore important to identify which microcarcinomas are likely to progress and recur when treated with a more conservative clinical approach. A series of clinical parameters, including characteristics of both the microcarcinoma (size, multifocality, histological variants, vascular or capsular invasion, lymph node metastases, and rare distant metastases) and the host (age, gender, previous irradiation, and ethnicity), have been proposed for stratifying the risk level and defining a risk-adapted algorithm for a rational approach to thyroid microcarcinoma treatment and follow-up (6, 7).

To verify the prevalence of the above-mentioned risk factors and to determine whether these risk factors are similarly distributed and associated in different environmental and ethnic settings, we analyzed 2 thyroid cancer registries from geographic areas that are different in terms of ethnicity, environment, and lifestyle. The large microcarcinoma series of the Sicilian Regional Registry of Thyroid Cancer (SRRTC, Sicily, Italy) and that of the Surveillance Epidemiology and End Results (SEER, United States) were analyzed for a similar 5-year period. Because of the heterogeneous distribution of thyroid cancer incidence in Sicily, with a doubled incidence in the volcanic area of Catania (8), SRRTC data were analyzed both with and without cases from the province of Catania.

Patients and Methods

All of the papillary thyroid microcarcinomas (PTMCs; ≤10 mm in diameter) from the SRRTC were retrospectively selected in the 5-year period 2002–2006. Case recruitment procedures for the SRRTC have been described previously (8) and are based on pathology diagnoses. Papillary microcarcinomas represented 98.0% (1777 of 1814) of all microcarcinomas diagnosed in Sicily in the study period.

Data from the National Cancer Institute's SEER 18 registry were analyzed after selecting all new cases of PTMCs in the 5-year period 2004–2008 using the International Classification of Disease for Oncology (ICD-O-3) codes 8050, 8052, 8260, 8340–8344, and 8450. Papillary microcarcinomas represented 98.3% (14 423 of 14 671) of all microcarcinomas registered in the SEER in the study period.

The following parameters were analyzed because they were available in both registries: histotype, age at diagnosis (≤45 vs >45 y), gender, extent of surgery (total or near-total thyroidectomy vs hemithyroidectomy), tumor size (≤6 mm vs >6 mm maximum diameter), extrathyroid extension (including both minimal and large extrathyroid invasion), multifocality (including both uni- and bilateral cancer foci), and TNM category classified according to the 7th edition of the American Joint Committee on Cancer, Cancer Staging Manual (9).

Six patients from the SRRTC series who were missing the information regarding age at diagnosis were excluded from the study.

Because a much higher incidence of thyroid cancer is present in the volcanic area of Sicily (8), the Sicilian cohort of microcarcinoma patients was subdivided into microcarcinomas from residents in the province of Catania (volcanic area, approximately 1 million inhabitants; n = 675 PTMCs) and residents from the rest of Sicily (approximately 4 million inhabitants; n = 1102 PTMCs).

Statistical analysis

Quantitative data are shown as the mean ± SD, whereas numbers and percentages are provided for qualitative data. Percentages were compared using the χ^2 test, and the *t* test was used for continuous variables. Pearson's correlation coefficient was calculated to investigate the relationship between age at diagnosis and tumor size by plotting the 5-year age intervals and the mean tumor diameter at each interval. Age-standardized incidence rate for the world population (ASRw) and the 95% confidence intervals (CIs) were calculated for both male and female patients (10). Data are expressed as the number of new diagnoses per 100 000 persons per year. All tests were 2-sided, and a P value < 0.05 was considered statistically significant. Data from the SEER refer to the last release (April 2012, based on the November 2011 submission) and were obtained through the SEER*Stat software version 7.0.9. Statistical analyses were performed with SPSS software, version 13.0 for Windows (SPSS Inc, Chicago, Illinois).

Results

SRRTC patients

In the 5-year period between 2002 and 2006, 1777 patients with PTMCs were diagnosed in Sicily, a Mediterranean island with approximately 5 million inhabitants (n = 5 003 262 residents in 2004 according to the Italian Institute for Statistics; http://demo.istat.it/pop2004/index.html). PTMCs represent 51.7% of all thyroid cancers diagnosed in Sicily during that period, with an ASRw of 5.8 per 10^5 inhabitants (95% CI = 5.2–6.4), 9.5 per 10^5 in females and 1.8 per 10^5 in males (Table 1).

The clinical and histopathological features of the PTMCs are presented in Table 2.

Table 1. ASRw for All Thyroid Cancers and Papillary Microcarcinomas According to Residence

	All Sicily	Catania Province	Sicily Without Catania	SEER
Total thyroid cancers				
Both genders	11.0 (10.2–11.8)	18.4 (16.1–20.8)	8.8 (8.0–9.6)[a]	8.9 (8.8–9.0)[c]
F	17.4 (15.9–18.9)	29.5 (25.4–33.6)	13.9 (12.4–15.4)[a]	13.4 (13.3–13.6)[c]
M	4.2 (3.5–4.9)	6.5 (4.5–8.5)	3.4 (2.7–4.1)[a]	4.3 (4.2–4.4)[d]
Papillary microcarcinomas				
Both genders	5.8 (5.2–6.4)	10.4 (8.6–12.2)	4.6 (4.0–5.2)[a]	2.9 (2.8–3.0)[c]
F	9.5 (8.4–10.6)	17.0 (13.8–20.2)	7.5 (6.4–8.6)[a]	4.6 (4.5–4.6)[c]
M	1.8 (1.3–2.3)	3.3 (1.9–4.7)	1.5 (1.0–2.0)[b]	1.1 (1.0–1.2)[c]

Abbreviations: F, female; M, male. Data are expressed as ASRw (95% CI).

[a] $P < .01$ vs Catania province cohort.

[b] $P < .05$ vs Catania province cohort.

[c] $P < .01$ vs all Sicily cohort.

[d] Not significant vs All Sicily cohort.

Age and gender

The mean age at diagnosis was 49.4 ± 13.2 years. The female-to-male ratio was 5.4:1.0. This ratio was significantly higher in patients younger than 60 years (5.8:1.0) than it was in older patients (4.1:1.0; $P = .03$). PTMCs were diagnosed before the age 45 years in 693 cases (39.0%), with a similar proportion in the 2 genders (Table 2).

Tumor size

The mean PTMC size was 5.5 ± 3.0 mm. There were 679 (38.2%) tumors larger than 6 mm in maximum diameter (7–10 mm). The prevalence of larger (>6 mm) PTMCs was similar in males (101 of 279; 36.2%) and in females (578 of 1498; 38.6%; $P = .46$).

The average tumor size was significantly higher in younger patients (up to 45 y old, corresponding to 39% of the studied cohort) than in older subjects (5.9 ± 3.0 vs 5.3 ± 2.9 mm, respectively; $P < .0001$). A significant inverse relationship was observed between tumor size and age at diagnosis ($r = -0.63$; $P = .011$) (Figure 1A).

Extent of primary tumor

Lymph nodes were removed in 456 of 1777 (25.7%) patients on the basis of either primary tumor characteristics (multifocality, capsule invasion and/or extrathyroid extension) or the presence of suspicious lymph nodes during a presurgery ultrasound (US) cervical scan. These criteria, however, were not used in all surgeries and were rarely used in incidental cases. Lymph node metastases

Table 2. Clinical and Histopathological Features of Both SRRTC and SEER PTMC Patients

Parameters at Diagnosis	SRRTC (n = 1777)	SEER (n = 14 423)	*P* Value
Gender, F/M [ratio]	1498/279 [5.4]	11 743/2680 [4.4]	.003
Age (mean ± SD), y	49.4 ± 13.2	50.6 ± 13.9	<.001
Age ≤ 45 yr	693 (39.0)	5287 (38.3)	.04
F	589 (39.3)	4586 (39.1)	.74
M	104 (37.3)	701 (26.2)	<.0001
Tumor size (mean ± SD), mm	5.5 ± 3.0	5.4 ± 3.0	.06
Tumor > 6 mm	679 (38.2)	5524 (38.3)	.96
F	578 (38.6)	4466 (38.0)	.69
M	101 (36.2)	1058 (39.5)	.30
Lymph nodes (N1)	125 (27.4)[a]	1628 (28.9)[a]	.52
F	96 (25.4)[b]	1092 (23.8)[b]	.49
M	29 (37.2)	536 (50.8)	.03
Extrathyroid extension	134 (7.5)	900 (6.2)	.04
F	113 (7.5)	678 (5.8)	.008
M	21 (7.5)	222 (8.3)	.73
Multifocality	462 (26.0)	4834 (33.5)	<.0001
F	382 (25.5)	3876 (33.0)	<.0001
M	80 (28.7)	958 (35.7)	.01

Abbreviations: F, female; M, male. Data are expressed as number (percentage) unless otherwise specified.

[a] Percentage calculated in the 456 patients of the SRRTC and in the 5637 of the SEER in whom lymph nodes were removed.

[b] *P* value = .04 and <.0001 with respect to males of SRRTC and SEER, respectively.

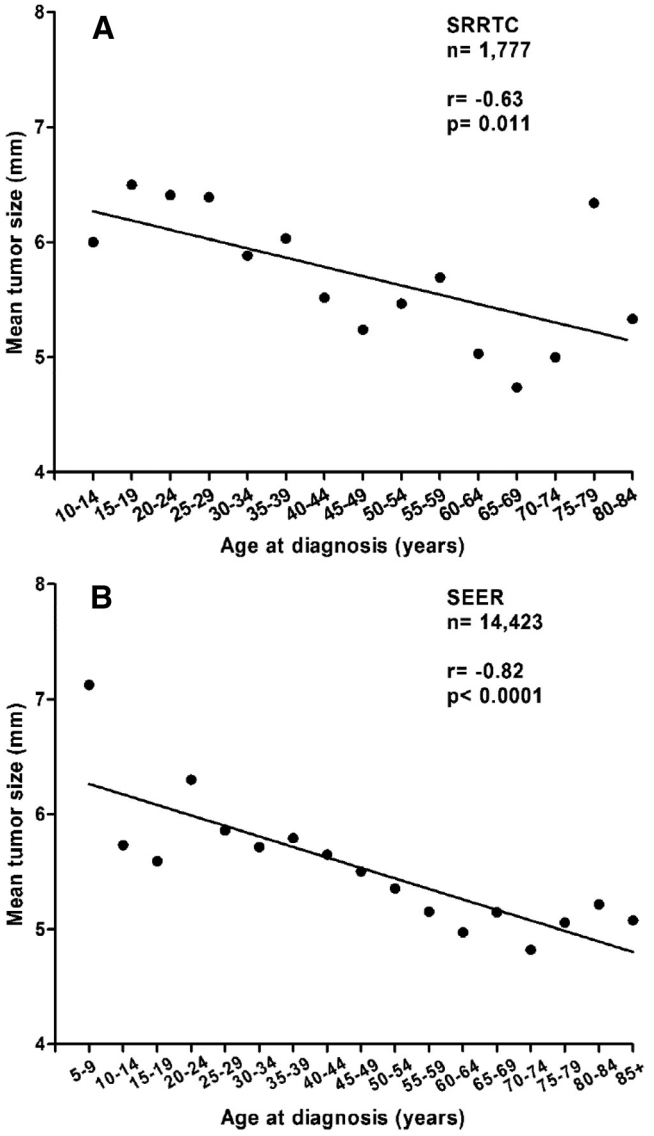

Figure 1. Relationship between microcarcinoma size and patient age at diagnosis.

were observed in 125 patients (27.4% of subjects underwent lymph node excision). Positive lymph nodes were more frequent in male than in female patients (37.2 vs 25.4%; $P = .04$) (Table 2) and in larger PTMCs (>6 mm) (32.5 vs 21.6% in smaller tumors; $P = .011$). PTMCs in young patients (≤45 y), after adjusting for tumor size, had a higher risk of nodal metastases than did tumors in older patients (odds ratio = 2.4; 95% CI = 1.5–3.7; $P < .0001$).

Extrathyroid extension was observed in 134 patients (7.5%), with no significant difference between genders (Table 2). Extrathyroid extension was more frequent in larger (>6 mm) PTMCs (13.5 vs 3.8% in 1- to 6-mm PTMCs; $P < .0001$). Lymph nodes were excised in 402 of 1643 (24.5%) T1 PTMCs and in 54 of 134 (40.3%) T3 PTMCs. Lymph node positivity was observed in 23.9% of T1 patients and in 53.7% of T3 patients.

Table 3. Clinical and Histopathological Features of PTMCs in Patients Living in the Province of Catania or in the Rest of Sicily

	Catania	Sicily Without Catania	*P* Value
Age (mean ± SD), y	49.6 ± 13.1	49.3 ± 13.1	.62
Female/male ratio	5.6	5.3	.74
Tumor size (mean ± SD), mm	5.6 ± 3.0	5.5 ± 2.9	.40
>6 mm (%)	39.4	37.5	.42
Lymph nodes (N1) (%)	30.6[a]	25.3[a]	.24
Extrathyroid extension (%)	8.7	6.8	.14
Multifocal (%)	28.7	24.3	.045

[a] Percentage of N1 cancers among patients who underwent lymph node excision (n = 183 in Catania; n = 273 in the rest of Sicily).

Total or near-total thyroidectomy was performed in 1642 (92.4%) patients, and only 135 (7.6%) patients were treated with hemithyroidectomy. The availability of all thyroid tissue for pathological examination in over 90% of cases made possible an accurate evaluation of multifocality. Multifocality was observed in 462 of 1777 (26.0%) patients, with a slightly higher prevalence, not statistically significant, in males (28.7 vs 25.5%; $P = .27$). Lymph node involvement was much higher in multifocal than in nonmultifocal microcarcinomas (40.7 vs 19.7%, respectively; $P < .0001$). Moreover, multifocality occurred more frequently in both larger (>6 mm) and extrathyroidal PTMC (31.7 and 53.0%, respectively) with respect to smaller (≤6 mm) and intrathyroidal PTMCs (22.5 and 23.8%, respectively; $P < .0001$ for both differences).

The volcanic area

PTMC incidence was much higher in the volcanic area of Catania (ASRw = 10.4 per 10^5; 95% CI = 8.6–12.2) than in the rest of Sicily (ASRw = 4.6 per 10^5 inhabitants; 95% CI = 4.0–5.2) (Table 1). When comparing PTMCs occurring in residents of the volcanic area of Catania to the rest of Sicily, a higher percentage ($P = .045$) of multifocal PTMCs was present in the volcanic area (Table 3). No significant difference was observed for the other parameters, although microcarcinomas in the volcanic area had a tendency to be larger and more frequently exhibited nodal involvement and extrathyroid extension (Table 3).

Comparison between Sicilian and SEER thyroid microcarcinoma patients

In the 5-year period between 2004 and 2008, 14 423 PTMCs were recorded in the SEER 18 registry. The incidence rate (ASRw) was 2.9 per 10^5 inhabitants (95% CI = 2.8–3.0), which is significantly lower ($P < .01$) than the rate in Sicily, even after excluding the volcanic area (Table

1). The different incidence between the 2 registries was mainly due to the higher incidence in Sicily of PTMC in patients younger than 60 years. The clinical and histopathological features at diagnosis are summarized in Table 2.

Age and gender

The mean age at diagnosis was significantly higher in the SEER cohort. This age difference was mainly due to the male gender: male patients ≤ 45 years represented 37.3% of the PTMC cases in Sicily relative to 26.2% in the US cases ($P < .0001$). No difference between SRRTC and SEER was observed in the percentage of young (≤45 y) female patients with PTMC (Table 2).

The female to male ratio in the United States (4.4:1.0) was significantly lower than in Sicily ($P = .003$). As in Sicily, however, the female prevalence was higher in patients younger than 60 years (5.2:1.0) compared with older patients (2.8:1.0) ($P < .0001$).

Tumor size

The average PTMC size was similar between the SEER and SRRTC cohorts (Table 2). The percentage of PTMCs larger than 6 mm (38.3%) was similar to that of Sicily, with no difference between the 2 genders ($P = .17$).

As in Sicily, the mean tumor diameter was greater in young patients (≤45 y) (5.7 ± 3.0 vs 5.2 ± 3.0 mm in older patients; $P < .0001$). In addition, the Pearson's correlation analysis confirmed the inverse relationship between tumor diameter and age at diagnosis in the SEER series ($r = -0.82$; $P < .0001$; Figure 1B). Again, the average tumor diameter was significantly higher in both males and females younger than 60 years (males, 5.6 ± 3.0 mm; females, 5.5 ± 3.0 mm) compared with older patients (males, 5.1 ± 3.0 mm; females, 5.0 ± 3.0 mm; $P < .0001$ with respect to younger patients of the same gender).

Extent of primary tumor

Lymph node involvement was observed in 1628 of 14 423 (11.3%) patients. This percentage was calculated on the assumption that all T1 PTMCs in which node excision was not performed were node negative. The calculated percentage of involved lymph nodes may be biased by different selection criteria because the surgical approach to the evaluation of lymph node metastases was heterogeneous, and different criteria were used both between and within the 2 areas studied. However, when the percentage of cervical node positivity was calculated among the number of cases in which lymph nodes were excised, very similar percentages were observed in the SEER and SRRTC cohorts (Table 2).

As in Sicily, positive lymph nodes in the SEER cohort were more frequent in male than in female patients (50.8 vs 23.8%, respectively; $P < .0001$) and in larger PTMCs (34.9 vs 23.6% in PTMCs smaller than 7 mm; $P < .0001$). After adjusting for tumor size, PTMCs in young patients (≤45 y) exhibited a higher risk of nodal metastases than did PTMCs in older patients (odds ratio = 1.26; 95% CI = 1.12–1.42; $P < .0001$).

Extrathyroid extension was significantly less frequent in US patients than in Sicilian patients (6.2 vs 7.5%, respectively; $P = .04$). Extrathyroid extension was more frequent among male patients than among female patients (8.3 vs 5.8%; $P < .0001$) (Table 1) and, as in Sicily, in larger PTMCs (11.3 vs 3.2% in 1- to 6-mm microcarcinomas; $P < .0001$). Lymph node involvement was more frequent in T3 tumors (63.5%) relative to T1 tumors (24.0%). The percentage of T1 cancers with lymph node involvement in the SEER cohort was similar to that observed in Sicily, but the percentage of T3 tumors with lymph node involvement was higher than in Sicily.

Multifocality was present in 4834 (33.5%) patients, a significantly higher percentage than in Sicily. Lymph node involvement, as in Sicily, was much higher in multifocal PTMCs (37.4% of patients with excised cervical nodes) than in PTMCs without multifocality (21.9%). Multifocality was more frequently observed in both larger (>6 mm) and extrathyroidal PTMCs (42.0 and 55.3%, respectively) with respect to smaller (≤6 mm) and intrathyroidal PTMCs (28.9 and 32.6%, respectively; $P < .0001$ for both differences).

The percentage of PTMC patients having 2 or more than 2 risk factors was higher in the SEER cohort (42.7 vs 37.8% in Sicily; Table 4), despite the lower PTMC incidence in the United States with respect to Sicily.

Discussion

Curative intent is the advisable aim for cancer patients, even when the cancer has indolent progression, because malignant evolution can change with time. However, PTMCs have recently been considered a disease requiring in

Table 4. PTMC Stratification on the Basis of the Number of Risk Factors at Presentation in 2 Cancer Registries

No. of Risk Factors	SRRTC (n = 1777)	SEER (n = 14 423)	*P* Value
None	438 (24.7)	3181 (22.0)	.014
1	667 (37.5)	5086 (35.3)	.06
2	405 (22.8)	3652 (25.3)	.02
3 or more	267 (15.0)	2504 (17.4)	.015

Data are expressed as number (percentage).

most cases minimal or no intervention (11). Based on their frequent incidental discovery (12–14) and the high prevalence of occult PTMCs at autopsy (15), it has even been suggested that PTMCs represent a normal phenomenon and not cancer (16). It is well recognized, however, that a certain proportion of PTMCs have an unfavorable outcome that includes not only cancer-related death (very low, approximately 0.5%) (17, 18) but also recurrent disease, with follow-up costs and the burden of worry and distress for patients and their families. Because PTMCs do not represent a homogeneous entity, risk-adapted management is the most rational approach to these tumors. To stratify PTMCs according to the risk for progression and/or recurrence, a number of risk factors have been identified (7, 19).

A recent study based on the SEER cohort analysis indicates that 2 or more than 2 risk factors at presentation should prompt more aggressive treatment of PTMCs to prevent cancer-related mortality (7). Our study follows similar criteria, but the risk factors analyzed are partially different from those considered by Yu et al (7), who also analyzed the impact of ethnicity and the presence of distant metastases, 2 parameters that are not included in our study because the Sicilian population is ethnically homogeneous and distant metastases in PTMC are very rare (only 91 of 18 445 or 0.5% in the series of Yu et al) and are not recorded in the SRRTC. In our analysis, however, we included the evaluation of 2 additional risk factors (tumor size and multifocality) that may be relevant when stratifying PTMCs for the risk of recurrence. Our study indicates that, using the 6 above-mentioned risk factors at presentation as surrogate indicators of outcome, in both registries at least 1 of 3 PTMCs requires extensive surgical treatment (total or subtotal thyroidectomy with cervical node excision when appropriate) to avoid or reduce the risk of recurrence. In some cases, when many risk factors are present, radioiodine treatment may also be advisable. The percentage of PTMC patients having 2 or more risk factors is higher in the SEER cohort, despite a lower PTMC incidence with respect to the SRRTC cohort.

A novel finding of the present analysis is that young age ($\leq$45 y) is a negative factor in PTMC patients because it is more frequently associated with other negative prognostic factors than is older age. American Thyroid Association (ATA) guidelines (Ref. 1, Location key B8) suggest near-total or total thyroidectomy for older patients (>45 y) with a < 1-cm thyroid nodule suspected for malignancy at cytology. Because both the SRRTC and the SEER cohorts indicate that young patients, on average, have larger PTMCs, with more frequent extrathyroid extension and lymph node metastases even after correcting for tumor size, we believe that extensive thyroid surgery should also be recommended for young patients. Microcarcinomas, therefore, may have a different behavior than macrocarcinomas that more frequently exhibit adverse outcomes in patients older than 45 years (20, 21) because risk factors at presentation, predictive of a higher recurrence rate, are more frequent in PTMCs occurring at a young age.

Microcarcinoma size is a well-recognized risk factor frequently associated with all other negative prognostic factors, including lymph node metastases, extrathyroid extension, and multifocality. Tumor size, therefore, follows a continuous negative trend, with smaller PTMCs exhibiting better prognosis than larger (>6 mm) PTMCs, and carcinomas $\leq$ 10 mm having a better outcome than 10- to 15-mm and 10- to 20-mm cancers (5, 22). Small size alone ($\leq$6 mm), however, is not a guarantee of low risk. In both registries, a significant number of PTMCs $\leq$ 6 mm had 2 or more associated risk factors (17.1% in SRRTC and 21.2% in SEER), a feature predicting unfavorable outcomes (7).

Lymph node involvement in both studied cohorts was lower than that reported in most series of microcarcinomas from a single center (23). This result is the probable consequence of the registry recruitment characteristics that aggregate data obtained using varied surgical approaches to metastatic lymph node detection. Most surgeons, in fact, do not proceed to central compartment lymph node excision after an incidental microcarcinoma discovery or after a PTMC is diagnosed before surgery because the microcarcinoma risk level is not assessed. Among patients with T1 PTMC who underwent lymph node dissection, more than 20% exhibited metastatic lymph nodes. The assumption that T1 microcarcinomas, when not explored at surgery, do not have lymph node involvement likely results in the underestimation of the true rate of local PTMC metastases in the SEER.

When comparing data from the 2 registries, the higher PTMC incidence in Sicily is characterized by a younger age at presentation and more frequent extrathyroid extension (Table 2). The percentage of lymph node involvement is difficult to judge because of the heterogeneous and poorly defined selection criteria for lymph node excision. Multifocality, however, is significantly more frequent in the United States. This finding may be dependent on the more zealous search for cancer foci by the US pathologists but could also depend on genetic cancer characteristics or influences of environmental factors. According to the ATA guidelines (Ref. 1, recommendation 32), multifocality should no longer be considered a risk factor requiring radioiodine as adjuvant therapy when all cancer foci are smaller than 10 mm. Whether prophylactic lymph node excision is appropriate for multifocal PTMCs is not defined. In accordance with recent observations indicating

that multifocality is associated with more frequent recurrence (4, 24, 25), our data from the analysis of both registries also confirm that multifocality is frequently associated with larger cancer size, lymph node metastases, and extrathyroid invasion. Multifocality, therefore, should be considered an important risk factor when evaluating the overall risk stratification of PTMCs, and postsurgical radioiodine ablation should be considered for patients having a multifocal microcarcinoma with a tumor maximum diameter > 6 mm, young age ($\leq$45 y), and male gender, even when no data are available on lymph node status.

Our study has an important limitation because it does not include follow-up analyses, and risk factors at presentation are only surrogate indicators of the real outcome of the cancer. The evaluation of these risk factors at presentation by surgeons and pathologists has a significant subjective component and can be influenced by their expertise and accuracy. Clinicians that assist thyroid cancer patients, however, have to rest upon these factors to decide treatment and follow-up intensity. We thought it would be interesting, therefore, to compare large series of microcarcinomas in 2 independent areas and evaluate similarities and differences. The large number of observations (over 16 000 PTMCs), in fact, may compensate for variability of individual/regional observations for better defining the prevalence of PTMCs that are at risk of progression and recurrence. On the other hand, the feasibility of prospective studies on microcarcinoma outcome is low because PTMCs would require decades of follow-up due to the indolent behavior of these tumors. The future molecular characterization of PTMC biology (26, 27) should overcome the uncertainty regarding the risk of progression and, consequently, will better indicate the most appropriate treatment for PTMCs in terms of cost/benefit. At present, based on the clinical characteristics at presentation (concordant in 2 large registries), PTMC risk stratification should suggest total thyroidectomy in at least 1 of 3 PTMCs, specifically in the case of larger microcarcinoma size and in young, male patients. Moreover, a careful assessment of cervical lymph node involvement is required in these patients when the cancer exhibits extrathyroid extension and/or is multifocal.

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