0021-972X/06/$15.00/0
*Printed in U.S.A.*

The Journal of Clinical Endocrinology & Metabolism 91(6):2171–2178

doi: 10.1210/jc.2005-2372

# Clinical and Histological Characteristics of Papillary Thyroid Microcarcinoma: Results of a Retrospective Study in 243 Patients

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**Context:** The recognition of thyroid microcarcinoma has increased due to the widespread use of ultrasound-guided fine-needle aspiration biopsies.

**Objective:** The objective of this study was to describe histological and clinical characteristics of papillary thyroid microcarcinoma (PTMC) less than or equal to 1 cm.

**Design:** This study was a retrospective cohort.

**Setting:** This study was conducted at a university hospital endocrine clinic.

**Patients:** Over a 9-yr period, 243 consecutive patients with PTMC were studied.

**Results:** PTMC was an incidental finding at surgery in 21.4% of the PTMC cases. There were no differences in the clinical characteristics between those with incidental PTMC and those with suspected thyroid carcinoma. None of the patients with a cancer less than 8 mm had distant metastases, whereas distant metastases were observed in patients with cancers $\geq$ 8 mm ($P \leq 0.05$). Disease-related mortality was not observed.

**Conclusions:** PTMC is prevalent in the population. Among patients with PTMC, tumor size more than 8 mm is associated with more aggressive disease. **(*J Clin Endocrinol Metab* 91: 2171–2178, 2006)**



THE WIDESPREAD USE of thyroid ultrasound (US) has led to the recognition that a large number of healthy subjects have thyroid nodules. It has been reported that the prevalence of thyroid nodules increases with advancing age, being approximately 60% in 80-yr-old subjects (1). More importantly, US-guided fine-needle aspiration biopsies (FNABs) permit the cytological evaluation of nodules smaller than 1 cm. Thus, it is not surprising that it is possible to detect very small thyroid carcinomas, and it is likely that the increasing number of thyroid cancers observed recently in many countries may be, at least in part, due to this diagnostic approach (2, 3). It is possible that the number of small thyroid cancers diagnosed during life will ultimately equal the prevalence of occult thyroid cancer found at autopsy, up to 36% (4).

Thyroid carcinomas less than 1 cm are almost exclusively papillary and are termed papillary thyroid microcarcinoma (PTMC) according to the World Health Organization (5). They are diagnosed after FNAB or incidentally during thyroid surgery for benign thyroid disorders such as Graves' disease and nodular goiter.

The clinical importance of PTMC is debatable. Some authors have observed that PTMCs have a benign behavior and do not progress over a mean follow-up period of 3.8 yr (6). In contrast, other authors have reported cases of PTMC with local lymph node and distant metastases at the time of diagnosis and during follow-up evaluation (7–12). Occasionally, PTMC causes cancer-related death (8, 9, 13, 14).

Recently, Pellegriti *et al.* (15) reported a series of patients with thyroid microcarcinomas, identifying some clinical and histological cancer characteristics present at diagnosis that had prognostic and therapeutic relevance. In this series, the cancers were surprisingly aggressive.

Because PTMC is being diagnosed with increasing frequency, it is important to describe the clinical and histological characteristics that confer cancer aggressiveness. This knowledge will enhance the development of treatment guidelines for a cancer that may reach endemic proportions in the future.

## Patients and Methods

### *Patients*

Between 1993 and 2002, 615 patients were diagnosed and treated for thyroid carcinoma at the Division of Endocrinology of the University of Ferrara, Italy. Among these patients, 243 (39.5%) had a thyroid cancer less than or equal to 1 cm in diameter. These 243 patients included 191 with suspected cancer by FNAB and 52 with incidental PTMC found in 1265 patients operated on for Graves' disease (112 patients) or nodular

**First Published Online February 14, 2006**

Abbreviations: CV, Coefficient(s) of variation; FNAB, fine-needle aspiration biopsy; FT4, free $T_4$; PTMC, papillary thyroid microcarcinoma; Tg, thyroglobulin; TNM, tumor-node-metastasis; US, ultrasound; WBS, whole-body scan.

**JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

goiter. A retrospective examination of the records of patients with PTMC is presented in the present study. The histopathological examination and staging of the cancers were conducted by the same team in the Department of Morbid Anatomy of the University of Ferrara (Italy). Cancers were staged according to the sixth edition of the Cancer Staging Manual (16). The mean age (±SD) of the patients was 51.5 ± 15.1 yr (range, 16–85 yr). Of these patients, 197 were women, and 46 were men. None of the patients had a past history of external x-ray therapy.

### *Management and follow-up*

The patients underwent total thyroidectomy or near-total thyroidectomy in 92 and 8% of the cases, respectively. Before fixation, the whole thyroid gland was cut in 5-mm slices for macroscopic examination to define the dimension of malignant lesions and their multifocality. Neck lymph nodes macroscopically involved were dissected in 39 (13%) patients. Two hundred thirty-five (96%) patients underwent postsurgical treatment with radioiodine [administered dose of $^{131}$I ranged from 50–100 mCi (1.85–3.7 GBq)]. Eight patients were not treated with $^{131}$I because two had manic psychosis, one was on chronic dialysis, one had multiple myeloma, one had hepatic cirrhosis, one had prostate cancer, and two (85 and 83 yr old) had postinfarct ischemic cardiomyopathy. All patients received TSH-suppressive doses of L-$T_4$. Although PTMC is generally a low-risk cancer, external radiotherapy was considered for 24 patients older than 45 yr who underwent surgery before 2001 for invasive PTMC (staged at that time as pT4, according to the fifth edition of Cancer Staging Manual, 1997). Follow-up ranged from 2.4–10.6 yr (median 5.1 yr). All patients were examined at 3 and 6–12 months after the initial treatment and yearly thereafter or more frequently depending on the clinical course. At each visit, the patients had a clinical examination, neck US, and measurement of serum TSH, free $T_4$ (FT4), thyroglobulin (Tg), and Tg antibody concentrations by automated chemiluminescent assays. This approach has recently been suggested by Mazzaferri *et al.* (17) and by Schlumberger *et al.* (18). Patients with undetectable TSH-stimulated serum Tg concentrations with no evidence of neck lymph node metastases at US examination and negative whole-body scan (WBS) were defined as free of disease. Tg assay (Immulite, Diagnostic Products Corp., Los Angeles, CA) had a detection limit of 0.2 ng/ml and a functional sensitivity of 0.9 ng/ml with intra- and interassay coefficients of variation (CV) of 5.3 and 7%, respectively. Serum TSH assay (ACS Centaur, Chiron Diagnostic Corp., East Walpole, MA) had an analytical sensitivity of 0.01 mU/liter with an intra- and interassay CV of 2.4 and 3.2%, respectively. Serum FT4 assay (ACS Centaur, Chiron Diagnostic Corp.) had an analytical sensitivity of 1.29 pmol/liter with an intra- and interassay CV of 5.0 and 5.7%, respectively. Serum Tg antibody assay (Immulite, Diagnostic Products Corp.) had an analytical sensitivity of 2.0 IU/ml with an intra- and interassay CV of 4.2 and 8.7%, respectively.

### *Imaging procedures*

WBSs were performed after radioiodine treatment to visualize local thyroid remnant and lymph node and distant metastases. Six months later, all patients had a repeated WBS after TSH stimulation (withdrawal of $T_4$ or, more recently, use of recombinant human TSH) to evaluate the effect of $^{131}$I therapy on the thyroid remnant or metastases.

Neck US was performed in all patients at each visit during the follow-up period (Toshiba SSA 370 Power Vision 6000 with a 6–12-MHz linear probe, Toshiba, New York, NY). The presence of local and/or distant metastases due to recurrent or persistent disease was diagnosed when the WBS was positive and/or serum Tg concentrations were detectable either during or off TSH-suppressive L-$T_4$ therapy. Because the functional sensitivity of the Tg assay was 0.9 ng/ml, this value was used as a cut-off level. In a few patients with elevated serum Tg concentrations and when clinically necessary, the presence of distant metastases was evaluated by other imaging procedures such as chest x-ray, computed tomography, nuclear magnetic resonance (NMR), and 2-fluoro-2-deoxy-D-glucose positron emission tomography. Recurrence in the neck area was also diagnosed by US-guided FNAB.

### *Statistical analysis*

Statistical analysis of the differences between clinical and histological variables between groups was conducted by $\chi^2$ test or Student's *t* test as appropriate. Statistical analysis of risk factors for the presence of neck lymph node and distant metastases at diagnosis was conducted by a multiple logistic regression analysis employing SYSTAT software, version 5.0 (SYSTAT, Inc., Evanston, IL). The dichotomous variables considered in the analysis were: age at diagnosis (<45 or ≥45 yr), gender, incidental or nonincidental diagnosis, cancer diameter less than 5 mm or more than or equal to 5 mm, bilateral foci, multiple foci, capsular invasion, coexistence of Hashimoto's thyroiditis, coexistence of Graves' disease, and familial or nonfamilial PTMC. Statistical analysis to predict the risk for local recurrence and lymph node and distant metastases during follow-up was not conducted because of the small number of patients with recurrent disease. Results are reported as mean ± SD and range values, as indicated.

## Results

Table 1 reports the clinical and histopathological characteristics at the time of diagnosis of 52 patients with incidental and 191 with suspected PTMC. No significant differences in clinical and histopathological characteristics were observed between the two groups. Patients with incidental PTMC had been operated on for Graves' disease in eight patients, nontoxic nodular goiter in 25 patients, and toxic adenoma in 19 patients. The prevalence of incidental PTMC was 4.1% of the 1265 patients operated upon for benign thyroid diseases. The remaining 191 patients underwent thyroidectomy because a FNAB of a thyroid nodule was diagnostic or suspicious for malignancy and/or clinical evaluation was suspicious for thyroid carcinoma. Among the 191 patients with noninci-

**TABLE 1.** Clinical and histopathological characteristics of patients with nonincidental and incidental thyroid microcarcinomas (PTMCs)

| | Total patients (n = 243) [no. patients (%)] | Patients with incidental PTMC (n = 52) [no. patients (%)] | Patients with nonincidental PTMC (n = 191) [no. patients (%)] | $\chi^2$ test |
|---|---|---|---|---|
| Age > 45 yr | 168 (69) | 32 (62) | 136 (71) | NS |
| No. of women | 197 (81) | 46 (88) | 151 (79) | NS |
| Tumor diameter > 5 mm | 157 (65) | 35 (67) | 122 (64) | NS |
| Tumor diameter < 5 mm | 86 (35) | 17 (33) | 69 (36) | NS |
| Bilateral | 45 (19) | 6 (11) | 39 (20) | NS |
| Multifocality | 78 (32) | 10 (19) | 68 (36) | NS |
| Extrathyroidal extension | 42 (17) | 8 (15) | 34 (18) | NS |
| Total thyroidectomy or near-total | 243 (100) | 52 (100) | 191 (100) | NS |
| $^{131}$I therapy | 235 (96) | 52 (100) | 183 (96) | NS |
| Lymph node metastases at diagnosis | 32 (13) | 2 (4) | 30 (16) | NS |
| Distant metastases at diagnosis | 4 (1.6) | 0 | 4 (2) | NS |
| Familial thyroid cancer | 13 (5.3) | 5 (9.6) | 8 (4.2) | NS |

NS, Not significant.

dental thyroid carcinoma, 18% were referred to our clinic for further evaluation of palpable thyroid nodules or enlarged neck lymph nodes, 28% for thyroid nodules detected by neck ultrasonography conducted for other reasons, and 54% because of a family history of thyroid disease and/or presence of altered laboratory test results (TSH, FT4, and thyroid peroxidase antibodies). In these patients, US examination revealed thyroid nodules.

The mean diameter of the cancers was 0.6 ± 0.3 cm (range, 0.1–1.0 cm). The mean diameter of incidental (52 patients) and suspected (191 patients) cancer was 0.55 ± 0.26 and 0.56 ± 0.27 cm, respectively. The histopathological types of the cancers and associations with other thyroid diseases are reported in Table 2. A single focus of PTMC was found in 165 patients (68%), whereas in 78 patients (32%), the tumor was multifocal. Thirty-three patients (13.5%) had multiple tumoral foci in one thyroid lobe, whereas 45 of the 78 patients with multifocal PTMC had bilateral disease. The mean tumor size of multiple foci was 3 mm (range, 0.3–5 mm).

Thirteen patients (5.3%) had familial thyroid cancer because papillary carcinoma was identified in two members of the same family. In two of these patients (a father and his son), medullary thyroid carcinoma was also detected at histological examination, and subsequent genetic analysis revealed a RET proto-oncogene mutation, indicating a familial medullary thyroid carcinoma. Pathology revealed that 175 patients (72%) had a PTMC confined to the thyroid, and 68 (28%) had thyroid capsular invasion with muscle and/or adipose tissue infiltration. These 68 patients were treated as follows: 53 were treated with $^{131}$I, 10 with $^{131}$I and external radiotherapy, one with external radiotherapy only, and four were not treated.

Thirty-two patients (13.2%), 25 women and seven men, had lateral-cervical lymph node metastases, and four had pulmonary and mediastinal node metastases. Eighteen patients with lateral-cervical lymph node metastases were treated with $^{131}$I and external radiotherapy, one with external radiotherapy only, and 13 with $^{131}$I only. All patients with distant metastases (1.6%) were treated only with $^{131}$I.

A total of 34 patients had neck node and/or distant metastases at the time of diagnosis. The prevalence of neck lymph node and distant metastases at diagnosis did not differ between men and women. All the patients with neck node and/or distant metastases had a preoperative diagnosis of thyroid cancer by FNAB.

**TABLE 2.** Histological types of the tumors and associated thyroid diseases

| Histological variant of tumor | No./% patients |
|---|---|
| Classic papillary | 194/79.8 |
| Follicular variant papillary (PTMC vF) | 32/13.1 |
| Sclerosing variant papillary (PTMC vS) | 12/5.0 |
| Tall cells variant papillary (PTMC tc) | 2/0.8 |
| Oncocytic variant papillary (PTMC vO) carcinoma | 2/0.8 |
| Follicular carcinoma (FTC) | 1/0.4 |
| Associated thyroid diseases | |
| Hashimoto thyroiditis | 64/26.3 |
| Multinodular goiter | 39/16.0 |
| Single foci of nodular hyperplasia | 15/6.2 |
| Graves' disease | 14/5.8 |
| Follicular adenoma | 11/4.5 |
| Familial medullary carcinoma | 2/0.8 |

The clinical and histological characteristics of patients with nodal and/or distant metastases are reported in Table 3. Thirty-two patients with thyroid cancer with a diameter more than or equal to 5 mm, and two with a diameter less than 5 mm had lymph node metastases ($P < 0.01$). None of the patients with a cancer less than 8 mm had distant metastases, whereas distant metastases were observed in patients with cancers more than or equal to 8 mm ($P \leq 0.05$) (Fig. 1). The tumor-node-metastasis (TNM) classifications of the 243 patients with PTMC are reported in Table 4.

Patients with familial PTMC cases had a similar prevalence of multifocality, bilaterality, capsular invasion, and lymph node metastases compared with patients without a family history of PTMC. Familial cases did not have distant metastases at the time of the initial diagnosis.

By multivariate analysis, the diagnosis of PTMC in patients with suspected cancer correlated with the presence of neck lymph node metastases ($P < 0.03$) as did the presence of the follicular variant of PTMC ($P < 0.04$). The presence of Hashimoto's thyroiditis correlated ($P < 0.03$) with the absence of neck lymph node metastases, *i.e.* patients with Hashimoto's thyroiditis had a 3-fold lower probability of having neck lymph node metastases.

### *Clinical findings during the follow-up of the patients*

After thyroidectomy, the mean follow-up period was 4.4 ± 2.9 yr (range, 2.4–10.6 yr; median, 5.1 yr). Patients classified as T1N0M0 were disease free 1 yr after $^{131}$ I treatment, and no recurrence has as yet been observed. Sixty patients classified as T3N0M0 were disease free 3 yr after $^{131}$I or $^{131}$I plus eternal radiotherapy treatment.

Among the 32 patients with neck lymph node metastases at the time of diagnosis, 28 were disease free 2 yr after the initial treatment. One patient, T1N1aM0, and one patient, T3N0M0, had local recurrence and neck lymph node metastases 8 and 13 months after the initial surgery and $^{131}$I therapy, respectively. The two patients classified at diagnosis as T3N1aM0 had neck lymph node metastases 9 and 18 months, respectively, after surgery and $^{131}$I treatment. These four patients with relapsing or persistent disease during follow-up, and the four patients with distant metastases at diagnosis were disease free 4 yr after thyroidectomy followed by multiple treatments with larger doses of $^{131}$I. Table 5 summarizes the clinical and histological characteristics of the four patients who had neck lymph node metastases during follow-up. Three of these patients had classic papillary microcarcinoma, and one had a follicular variant of microcarcinoma. The cancer diameter was more than or equal to 8 mm in these four patients. The prevalence of lymph node metastases during follow-up was significantly higher ($P \leq 0.05$) in patients whose cancers were more than or equal to 8 mm than in those with cancers less than 8 mm (Table 5). At the time of diagnosis in these four patients, capsular invasion was observed in all, and multiple and bilateral foci were observed in three cases. These four patients had elevated serum Tg concentrations (18–38 ng/ml, negative TgAb) after thyroidectomy and off L-$T_4$ suppressive therapy and before $^{131}$I treatment.

**TABLE 3.** Characteristics of the patients with lymph node and distant metastases at diagnosis

| Patient no. | Age (yr) | Sex | Tumor histology | Tumor diameter (mm) | Multifocal/ bilateral | Capsular extension | Extrathyroid extension | Lymph metastasis | Distant metastases | Tg (ng/ml) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 31 | F | PTMC | 10 | − | + | − | + | − | 12 |
| 2 | 59 | F | PTMC | 8 | + | + | + | + | − | 18 |
| 3 | 61 | F | PTMC | 7 | + | + | + | + | − | 9 |
| 4 | 46 | M | PTMC | 6 | + | + | + | + | − | 21 |
| 5 | 42 | F | PTMC | 10 | − | + | + | + | − | 16 |
| 6 | 56 | F | PTMC | 10 | + | + | + | + | − | 13 |
| 7 | 70 | F | PTMC vS | 10 | − | − | − | + | − | 19 |
| 8 | 73 | F | PTMC | 9 | − | − | − | + | − | 9 |
| 9 | 45 | F | PTMC | 7 | + | + | + | + | − | 23 |
| 10 | 37 | F | PTMC | 6 | + | + | + | + | − | 29 |
| 11 | 42 | M | PTMC vS | 8 | − | − | − | + | − | 32 |
| 12 | 35 | F | PTMC | 9 | + | + | − | + | − | 17 |
| 13 | 47 | F | PTMC vF | 7 | + | + | + | + | − | 18 |
| 14 | 59 | M | PTMC vS | 10 | − | + | − | + | − | 32 |
| 15 | 27 | F | PTMC | 7 | + | − | + | + | − | 14 |
| 16 | 23 | F | PTMC | 4 | − | − | − | + | − | 19 |
| 17 | 31 | F | PTMC | 10 | + | + | + | + | − | 38 |
| 18 | 54 | F | PTMC vF | 10 | − | + | + | + | − | 23 |
| 19 | 52 | M | PTMC vS | 6 | + | + | + | + | − | 18 |
| 20 | 65 | F | PTMC tc | 9 | + | + | − | + | − | 29 |
| 21 | 54 | F | PTMC | 7 | + | − | + | + | − | 20 |
| 22 | 38 | F | PTMC | 2 | + | − | + | + | − | 20 |
| 23 | 31 | M | PTMC | 8 | + | + | + | + | − | 12 |
| 24 | 67 | F | PTMC | 7 | + | + | − | + | − | 10 |
| 25 | 52 | F | PTMC vS | 8 | + | + | − | + | − | 10 |
| 26 | 39 | F | PTMC | 9 | − | + | + | + | − | 24 |
| 27 | 69 | F | PTMC vF | 7 | − | + | + | + | − | 16 |
| 28 | 65 | M | PTMC | 7 | + | + | + | + | − | 18 |
| 29 | 52 | F | PTMC vS | 6 | + | + | − | + | − | 18 |
| 30 | 38 | M | PTMC | 9 | + | + | − | + | − | 21 |
| 31 | 47 | F | PTMC vS | 8 | + | + | + | + | Lung | 40 |
| 32 | 54 | F | PTMC vF | 9 | + | − | + | − | Mediastin | 28 |
| 33 | 25 | F | PTMC | 9 | + | − | + | − | Mediastin | 25 |
| 34 | 24 | F | PTMC | 10 | + | − | + | + | Lung | 26 |

M, Male; F, female; Tg, TSH-stimulated serum Tg concentrations after thyroidectomy and before $^{131}$I treatment; vS, sclerosing variant; vF, follicular variant; tc, tall cells variant.

Lymph node metastases concentrated $^{131}$I in only one patient, whereas in the other three patients, lymph node metastases were detected by neck US examination and confirmed by fine-needle aspiration cytology and/or Tg measurement in the needle washing fluid. Surgical removal of neck lymph node metastases was carried out in two patients (patients 1 and 4 of Table 5).

None of the patients with familial PTMC had recurrent disease during follow-up. Among the eight patients with concomitant illnesses not treated with $^{131}$I, capsular invasion was present in five and multiple and bilateral foci in two and one patients, respectively, and one had neck lymph node metastases at surgery. One of these patients was treated with external x-ray therapy. Of these eight patients, two died from other concomitant, unrelated diseases, whereas the other six are alive without clinical or diagnostic evidence of recurrent disease. Among the 24 patients treated with external x-ray therapy, six were T3N0M0, three were T3N1bM0, two were T3N1aM0, 11 were T1N1aM0, and two were T1N1bM0. One of these patients had recurrent disease during follow-up.

The presence of neck lymph node and distant metastases

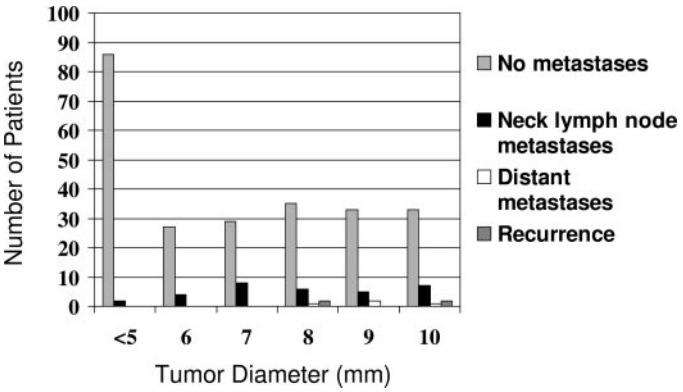


FIG. 1. Associations between microcarcinoma diameter and presence of neck lymph nodes at diagnosis, distant metastases at diagnosis, and recurrence.

**TABLE 4.** TNM staging of the tumors (according to Ref. 16)

| Tumor staging at diagnosis | Patient no./% |
|---|---|
| T1N0M0 | 148/60.9 |
| T1N0M1 | 2/0.8 |
| T1N1aM0 | 17/6.9 |
| T1N1aM1 | 1/0.4 |
| T1N1bM0 | 7/2.9 |
| T3N0M0 | 61/25.1 |
| T3N1aM0 | 2/0.8 |
| T3N1aM1 | 1/0.4 |
| T3N1bM0 | 4/1.6 |

**TABLE 5.** Characteristics of patients who showed, by US examination and FNAB, recurrence or lymph node metastases during follow-up

| Patient no. | Age (yr) | Sex | Tumor histology | Tumor diameter (mm) | Multifocal | Bilateral | Capsular extension | TNM staging | $^{131}$I WBS | Tg (ng/ml) | US exam and FNAB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 41 | F | PTMC | 8 | + | − | − | T1N1aM0 | Negative | 18 | + |
| 2 | 50 | F | PTMC | 8 | + | + | + | T3N0M0 | Negative | 29 | + |
| 3 | 46 | F | PTMC | 10 | + | − | + | T3N1aM0 | Positive | 21 | + |
| 4 | 45 | F | PTMC vF | 10 | − | − | + | T3N1aM0 | Negative | 16 | + |

TSH-stimulated Tg values were obtained after thyroidectomy and before $^{131}$I treatment. $^{131}$I WBS results were obtained during follow-up (8–18 months after thyroidectomy). F, Female; vF, follicular variant.

at the time of diagnosis and the recurrence or persistence of disease (data reported in Tables 5 and 6) were more common in patients with cancers more than or equal to 8 mm ($P < 0.01$).

## Discussion

Since the introduction of US-guided FNAB, a progressive increase in the prevalence of PTMC has been observed among all patients with papillary carcinoma, from 12% before 1980 to 25% after 1990 (9). Furthermore, a higher prevalence of cancers less than or equal to 5 mm compared with those 5–10 mm was found from 1996–2001 than from 1990–1996 (19). These observations suggest that the diagnosis of PTMC will increase in the general population.

In the present study, we report the findings in 243 patients with PTMC. They represented 39.5% of all patients with thyroid cancer in our institution between 1993 and 2002. This prevalence of PTMC among all patients with thyroid cancer was higher than that observed in some studies (9, 20, 21), where the prevalence of PTMC was determined only in patients who were operated upon for suspicion of papillary thyroid cancer. Incidental PTMC was diagnosed in 21.4% of our patients with PTMC, considerably lower than previously reported prevalence rates of 38–91% (7, 8, 13, 15, 19, 22, 23). Finally, the prevalence of incidental PTMC in all patients thyroidectomized for benign thyroid disease was 4.1%, a value lower than that reported in other studies (24, 25). These different findings are probably due to different populations but also to the different use and skill of US thyroid examination and US-guided FNAB. US-guided FNAB is very sensitive in the diagnosis of thyroid cancer, but one study reported that 40% of patients operated on for thyroid cancer did not have a FNAB (21).

It is debatable whether total/near total thyroidectomy or lobectomy is the appropriate treatment for patients with microcarcinoma of the thyroid, although we have suggested that the former may be preferable (26). By a recent meta-analysis, the benefit of $^{131}$I administration for thyroid remnant ablation is also unclear in patients with low-risk thyroid carcinoma (27), but we have recommended total/near total thyroidectomy followed by $^{131}$I administration for remnant ablation in patients with PTMC. This therapeutic approach enhances the use of TSH-stimulated Tg measurements as an early and specific marker of disease persistence or recurrence.

Most series of patients with PTMC have reported low cancer recurrence rates (7, 13, 14, 19, 28, 29), although this finding has not been universal (8, 9, 15). Disease-related mortality has occasionally been observed (8, 9, 13, 14). In the present study, we found that multiple foci and neck lymph node metastases were observed more frequently in patients with suspected PTMC identified preoperatively by FNAB than in incidental cancers. We cannot easily explain this finding because other clinical and histological variables, such as age, gender, cancer size, and bilateral foci prevalence did not differ between the two groups of patients. However, patients with suspected cancer might have had a delayed diagnosis. Recently, Pellegriti *et al.* (15) reported that suspected PTMC had a higher rate of multiple but not bilateral foci, neck lymph node metastases, or distant metastases than incidental cancers. Baudin *et al.* (7) also reported an increased prevalence of multifocal and bilateral foci of cancer in suspected than in incidental PTMC. In several recent studies (7, 9, 15), multiple foci have been observed in only 32–40% of the cases, a value similar to that observed in the present study; other studies have reported even lower prevalence rates (10–20%) (8, 14, 19).

Multifocality was originally considered to be an expression of intrathyroidal metastases. However, the observations that different intrathyroidal tumor foci have different RET/PTC gene rearrangements (30), and independent clonal origins (31) suggest that they may arise as distinct cancers. The presence of multiple foci may not indicate increased aggressiveness. Some studies have reported a similar prevalence of multifocality (32–40%), but a different frequency of lymph node metastases (13–43%) (7, 9, 15). Other studies have reported that the occurrences of multifocality and lymph node metastases were similar (10–12% and 9–13.4%, respectively)

**TABLE 6.** Tumor diameter and presence of neck lymph node or distant metastases

| Tumor diameter (mm) | Total patients (n = 243) (no. of patients/%) | Patients with lymph node metastases (n = 32) (no. of patients/%) | Patients with distant metastases (n = 4) (no. of patients/%) | Patients with recurrence (*n* = 4) (no. of patients/%) |
|---|---|---|---|---|
| <5 | 86/34 | 2/0.8 | 0/0 | 0/0 |
| 6 | 27/11 | 4/1.6 | 0/0 | 0/0 |
| 7 | 29/12 | 8/3.3 | 0/0 | 0/0 |
| 8 | 35/15 | 6/2.5 | 1/0.4 | 2/0.8 |
| 9 | 33/14 | 5/2.1 | 2/0.8 | 0/0 |
| 10 | 33/14 | 7/2.9 | 1/0.4 | 2/0.8 |

(14, 19). In the present report, multifocality was observed in 32% of the cases, whereas lymph node metastases were found in only 13%. Cancer size does not seem to explain the varying prevalence of neck lymph node metastases because all studies in different series except one (15) included only patients with cancers no larger than 1 cm. These findings suggest that it is difficult to predict the aggressiveness of microcarcinoma at the time of diagnosis.

During follow-up, we have observed only four patients (1.7%) who had recurrent or persistent disease, and none experienced cancer-related mortality. Furthermore, the patients with neck lymph node and distant metastases at the time of diagnosis were all apparently cancer free at the time of the last follow-up visit. The low recurrence/persistence rate of the disease observed in the present series of patients is similar to that reported in some studies (13, 14, 19, 28, 29) but not in others that found persistent or recurrent disease in 6–14.4% of the patients (8, 9, 15).

It is not clear whether the presence of lymph node metastases at the time of diagnosis is a risk factor for the recurrence or persistence of disease because series of patients with a similar prevalence of lymph node metastases at diagnosis had elevated (9, 15) or low (7, 8) rates of recurrent/persistent disease. More recently, Wada *et al.* (29) reported lymph node metastases at diagnosis in 64% of patients and recurrence in only 0.5%.

Cancer size does not seem a convincing explanation for the different recurrence/persistence rate of disease in the different studies because almost all studies included only patients with cancers less than or equal to 1.0 cm (7–9, 28). In patients with cancers larger than 1 cm, a close relationship between cancer size and aggressiveness has been demonstrated (15). The relative risk of cancer death increased 1.4-fold for each 1-cm increment in the size of the cancer (8). Mazzaferri and Young (20) reported no recurrence in patients with papillary thyroid cancer less than or equal to 1.5-cm diameter, whereas in those with larger cancers the recurrence rate was closely correlated ($r = 0.82$) with cancer size. Pellegriti *et al.* (15) observed that cancers with a diameter more than 1 cm were more aggressive as defined by the presence of multiple, bilateral foci, extrathyroidal invasion, and lymph node metastases, than those with a smaller diameter. Chow *et al.* (9) have reported that the incidence rate of local and lymph node recurrence in patients with PTMC did not differ between patients with cancers less than or equal to 5 mm compared with those more than 5 mm. Pelizzo *et al.* (19) did not mention any difference in aggressiveness between patients with PTMC whose tumors had a diameter greater than 5 mm compared with those smaller than 5 mm. In the present study, we have observed that patients with cancers more than or equal to 8 mm but less than or equal to 1 cm had higher cancer aggressiveness, arbitrarily defined by the presence of neck lymph node and distant metastases at the time of diagnosis and recurrent disease during follow-up, than patients with smaller cancers. However, cancer size more than or equal to 8 mm but less than or equal to 1 cm was not an independent risk factor for aggressiveness using a multivariate logistic analysis.

In the present study and in a previous report (15), familial PTMC did not confer increased tumor aggressiveness as suggested in an earlier study (32).

Concomitant Graves' disease was present in only eight patients with PTMC in this series (3.2%), a value lower than previously observed (12%) (15). Furthermore, we did not observe increased cancer aggressiveness in these patients, similar to one study (33) but not another earlier study (34). However, it is not clear whether the presence of serum TSH receptor-stimulating antibodies for a longer period of time in patients with PTMC might induce higher cancer aggressiveness. In contrast, the presence of Hashimoto's thyroiditis significantly reduced the risk of lymph node metastases at diagnosis, as reported earlier (35).

A possible protective effect of iodine deficiency on cancer recurrence has been suggested (15). However, the present findings and an earlier study (19), both carried out in areas of near-adequate iodine intake, had recurrence rates of 2%, lower than the reported rate in the study from an iodine-deficient area (15). Furthermore, a very recent autopsy study reported the prevalence of PTMC in iodine-deficient and -sufficient areas to be 4.9 and 4.5%, respectively (36).

The optimal treatment of PTMC is still debatable. One study observed that patients with proven PTMC followed for a mean period of 3.8 yr did not have any evidence of disease progression (6). Most physicians would suggest that their patients with PTMC undergo some type of thyroidectomy. Partial thyroidectomy has been carried out in 65.3–99.7% of 2869 patients reported in three different series (13, 14, 29). However, in these series, 88% of the patients were thyroidectomized for benign thyroid disease with an incidental diagnosis of PTMC.

Total/near total thyroidectomy was carried out in 69–95% of 2587 patients reported in six series of patients (7–9, 15, 19, 28). In these series, PTMC was an incidental finding in 38–67.3% of the patients. Surprisingly, in these studies, recurrence of disease was observed in 1–25% of the cases, a value higher than that reported in those patients who underwent partial thyroidectomy (1.3–2.3%) (13, 14, 29). In the present study, total/near total thyroidectomy was carried out in all patients, including those with a diagnosis of incidental PTMC.

It is unclear whether $^{131}$I treatment after thyroidectomy is effective in reducing the recurrence rate of PTMC. In the study of Pelizzo *et al.* (19), patients who underwent $^{131}$I treatment for PTMC did not have cancer recurrence, whereas tumor recurred in 2% of those not so treated. In the study of Chow *et al.* (9), patients not treated with $^{131}$I after thyroidectomy had a recurrence rate of 9.8%, whereas those who were treated had a lower recurrence rate of 3.7% ($P < 0.05$). In contrast, Baudin *et al.* (7) found that $^{131}$I treatment did not affect the recurrence rate in PTMC. Similarly, a recent meta-analysis by Sawka *et al.* (27) did not find a significant salutary effect of $^{131}$I ablation of thyroid remnants in patients with low-risk well-differentiated thyroid carcinoma. In our study, almost all patients were treated with $^{131}$I, with a recurrence rate of 1.7%. In three series of patients (13, 14, 29) treated by partial thyroidectomy and not receiving $^{131}$I therapy, the recurrence rate was similarly only 1.3–2.3%.

Disease-related mortality was not observed in the present study. In four previous case series, the mortality rate was less

than 0.4%. In two of these series, patients underwent partial thyroidectomy without $^{131}$I treatment (13, 14), and in two other series, patients were treated with total/near total thyroidectomy in most followed by $^{131}$I treatment in 10 and 67.5% of the patients, respectively (8, 9).

It is likely that in the near future molecular studies will be able to discriminate aggressive PTMC from those with an indolent clinical course. At present, it has been reported that RET/PTC rearrangement is present in micropapillary thyroid carcinoma (37), but this finding does not seem to be a sign of cancer aggressiveness (38). In contrast, RET/PTC3-positive papillary thyroid carcinoma has a more aggressive behavior (39). Recently, it has been reported that lymph node metastases of papillary cancer are accompanied by a new BRAF mutation, different from that observed in the matched primary thyroid cancer, confirming the progression model of cancer where metastatic foci have a new mutational event (40).

In view of different predictive factors of cancer aggressiveness observed in the many reported studies and the lack of randomized studies, including the present one, concerning the optimal treatment of PTMC, we suggest that total/near total thyroidectomy followed by $^{131}$I treatment is a safe therapeutic approach and certainly improves the diagnostic accuracy of serum Tg concentrations during follow-up.

## Acknowledgments

We thank Dr. Giuseppe Gilli (Department of Health Physics, S. Anna Hospital, Ferrara, Italy) for the statistical analysis.

Received October 28, 2005. Accepted February 6, 2006.

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This work was supported by grants from the Italian Ministry of University and Scientific and Technological Research (MIUR 2002067251-003), Fondazione Cassa di Risparmio di Ferrara, and Associazione Ferrarese dell'Ipertensione Arteriosa to the University of Ferrara. This work was also supported by National Institutes of Health Grant 1 K23 DK064611.

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