

Clinical Study

Differences in the Form of Presentation between Papillary Microcarcinomas and Papillary Carcinomas of Larger Size

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Papillary thyroid carcinomas (PTCs) with a diameter ≤ 1 cm are referred to as papillary microcarcinomas (PTMCs). The prognostic factors for PTMCs have not been defined. Different clinical and histopathologic variables were studied in 152 PTCs, including 74 PTMCs and 78 PTCs of larger size. We found that PTMCs are associated with less multifocality ($P = .046$) and bilaterality ($P = .003$), fewer lymphadenectomies ($P < .001$), and a higher rate of incidental tumours ($P < .001$). Moreover, patients with a low aggressive profile were significantly older than the remaining patients (54 ± 13.7 years versus 45.8 ± 13.1 years; $P = .001$). In conclusion PTMCs show significant differences compared to PTCs of larger size in the form of presentation. Furthermore, it is possible that the classic risk factors, which are well validated in PTCs, such as age, must be cautiously interpreted in the current increasing subgroup of PTMCs.

1. Introduction

It has been clearly demonstrated that there is an increasing worldwide incidence of papillary thyroid carcinomas (PTCs). It is uncertain whether this is a real phenomenon, or whether it is due to an increased rate of detection [1]. Practices for management of thyroid diseases have changed over the past few decades. The wide availability of ultrasound (US) and fine needle aspiration biopsy (FNAB) and the improved accuracy of histopathologic examination of surgical specimens have been suggested to be reasons for the increased rate of detection. Moreover, among the new cases, the highest incidence has been observed in the smallest tumors [2]. In the USA, 49% of the increased incidence of PTCs consisted of cancers measuring ≤ 1 cm [3]. In Europe, Leenhardt et al. [4] reported that the proportion of tumors of this size increased from 18.4% between 1983 and 1987 to 43.1% between 1998 and 2001 [4]. Similar results have been confirmed by other authors worldwide [2, 5–8].

PTCs measuring ≤ 1 cm are referred to as papillary thyroid microcarcinomas (PTMCs) [9]. Although PTMCs are not recognized as a specific entity in the tumour, node,

and metastasis (TNM) classification, PTMCs are considered a subset of PTCs that exhibit a more benign behavior. PTMCs usually follow an indolent course and carry an excellent prognosis. Distant metastases and mortality rates are reported to be $< 0.5\%$ for PTMCs [10]. Two large series have recently confirmed the excellent prognosis for PTMCs in long-term followup [5, 11]. Nevertheless, some authors suggest that there exist a subgroup of PTMCs that can be aggressive, requiring therapeutic management similar to larger tumors [12]. Thus, no agreement has been reached about the optimal treatment of PTMCs. In recent years, several clinical and histologic risk factors for aggressiveness have been identified in PTMCs, such as size ≤ 5 mm, multifocality, capsular invasion, tumor extension beyond the parenchyma, lymph node involvement, and the extent of primary surgery [12–17]. In contrast, some studies have failed to identify independent prognostic factors, arguing that to distinguish PTCs on the basis of size alone may be clinically irrelevant [18, 19]. Because PTMCs are being diagnosed with increasing frequency, identification of specific prognostic factors is of outmost importance.

In the present study, we describe the clinical and pathologic presentation of PTMCs, compared with papillary thyroid carcinomas of larger size (LPTCs). We have analyzed the classic risk factors and studied the clinical and histologic characteristics present at the time of diagnosis which were associated with a higher risk of recurrence in PTMCs, such as multifocality, lymph node metastases, and mode of detection (incidental versus nonincidental tumors).

2. Methods

PTMCs were defined as PTCs measuring ≤ 1 cm in greatest diameter. Mode of detection refers to incidental (IPTMCs) or nonincidental tumors (NIPTMCs). IPTMCs were identified in patients undergoing surgery for reasons unrelated to a thyroid malignancy, whereas patients with NIPTMCs underwent thyroidectomy for suspected malignancies. Multifocal disease was defined when >1 focus of PTCs was found in the thyroidectomy specimen. The following clinical variables were considered in the analysis: patient age, mode of detection, and extent of disease. The histopathologic variables after postoperative pathologic examination included the maximum diameter of the primary tumour, multifocality, bilaterality, extrathyroid extension, and lymph node metastases. Patients with PTMCs discovered incidentally, without multifocality, and without lymph node involvement were considered at low risk for developing recurrences. The confidentiality of patient information was absolutely maintained. Data are presented as the mean \pm SD. Statistical analysis was performed by Fisher's exact test for univariate analysis and by Student's t-test to compare continuous variables between groups. All tests were two-tailed. The levels of statistical significance are presented as p values. It was assumed that the observed differences were statistically significant at a $P < .05$ level.

3. Results

Between 2000 and 2009, 152 patients with PTCs were treated in our institution. Among these cases, there were 74 (48.7%) PTMCs and 78 (51.3%) LPTCs.

3.1. Microcarcinoma. The PTMC series included 59 females and 15 males (the female-to-male ratio was approximately 3.9). The mean age at the time of diagnosis was 50.1 ± 13.2 years. Of the 74 cases, 67 (90.5%) underwent total or near-total thyroidectomy, and only 7 (9.5%) underwent lobectomies. The mean tumour size was 5.7 ± 2.6 mm. The pathology reports showed classic variant PTMCs in 64 patients (86%), and follicular variants in 10 patients (14%). Multifocal disease was documented in 26 patients (35.1%). The patients with multifocal disease were younger than patients with a unique focus (45.9 ± 10.2 years versus 52.5 ± 14.2 years; $P = .039$). Contralateral involvement was observed in 7 of 26 patients (27%) with multifocal tumors. Regional lymph nodes were removed in 24 patients (32.4%); of these, 12 (50%) had nodal tumor involvement.

Overall, 72.2% of tumors (52 of 72) presented as IPTMCs (no information was available in 2 cases). In the other 20 cases (27.8%), PTMCs were diagnosed by preoperative US-guided FNABs. In patients with IPTMCs, the indications for surgery were as follows: 29 nontoxic multinodular goiters, 7 toxic multinodular goiters, and 16 solitary nodules. The difference in mean tumour size was statistically significant among the IPTMCs (5 ± 2.3 mm) and NIPTMCs (7.6 ± 2.6 mm; $P < .001$). Multifocality was present in 13 (65%) of 20 patients classified as NIPTMCs, whereas multifocality was present in only 11 (21%) of 52 patients with IPTMCs ($P < .001$).

3.2. Larger Tumours. Tumors >1 cm occurred in 62 females and 16 males (the female-to-male ratio was approximately 3.9). The mean age at the time of diagnosis was 46.2 ± 14.1 years. The primary surgical treatment consisted of total or near-total thyroidectomies in 76 patients and lobectomies in 2 patients. The mean tumor size was 25.21 ± 11.8 mm. The pathology reports showed classic variant LPTCs in 54 patients (69.2%), follicular variant LPTCs in 21 patients (26.9%), and one case each of columnar cell, cribriform-morular variant, and clear cell LPTCs. In this group, multifocality was found in 39 (50%) samples. The age at presentation was not different in patients with and without multifocality. Contralateral involvement occurred in 25 of 39 patients (64%) with multifocal tumours. Lymph node dissection was performed in 60 patients (77%); of these, 36 patients (60%) had nodal tumor involvement.

Only 11 (15.5%) of 71 cases were classified as incidental tumors (no information was available in 7 cases). Of the indications for surgery were as follows: 7 nontoxic multinodular goiters, 3 solitary nodules, and 1 toxic multinodular goiter. Neither tumor size nor multifocality was significantly different among the incidental and nonincidental LPTCs.

3.3. PTMCs versus LPTCs. Table 1 shows the characteristics of both groups. Age and gender were not statistically different between the two groups of patients. However, based on the mode of presentation, patients with IPTMCs were significantly older than patients with incidental LPTCs (51.9 ± 13.5 years versus 41.4 ± 7.95 years; $P = .016$). Moreover, apart from size ($P < .0001$), patients with PTMCs presented with multifocality ($P = .046$) and bilaterality ($P = .003$) less often, fewer lymphadenectomies ($P < .001$), and a higher rate of incidental tumours ($P < .001$). In contrast, in patients in whom the lymph nodes were removed, there were no differences in the frequency of nodal metastases.

3.4. Aggressive Cases. Among all the 152 patients with PTCs, 40 patients (26.3%) in whom PTMCs were discovered incidentally, without multifocality, and without lymph node involvement, were considered at a low risk for developing recurrences. These patients with a low aggressive profile were significantly older than the rest of the patients (54 ± 13.7 years versus 45.8 ± 13.1 years; $P = .001$). Moreover, the low aggressive profile was observed in 28 (36.8%) of 76 patients >45 years of age and in 12 (17.9%) of 67 patients <45 years

TABLE 1: Differences between cases with papillary thyroid microcarcinomas (PTMCs) from those with papillary thyroid carcinomas of larger size (LPTCs).

	PTMC (<i>n</i> = 74)	LPTC (<i>n</i> = 78)	<i>P</i>
Gender (female/male)	15/59 (79.7%/20.3%)	16/62 (79.5%/20.5%)	ns
Age (y)	50.17 ± 13.22	46.29 ± 14.12	ns
Size (mm)	5.7 ± 2.6	25.2 ± 11.8	<.001
Multifocality	26/74 (35.1%)	39/78 (50%)	.046
Lymphadenectomies	24/74 (32.4%)	60/78 (77%)	<.001
Lymph M1	12/24 (50%)	36/60 (60%)	ns
Incidental	52/72 (72.2%)	11/72 (15.2%)	<.001

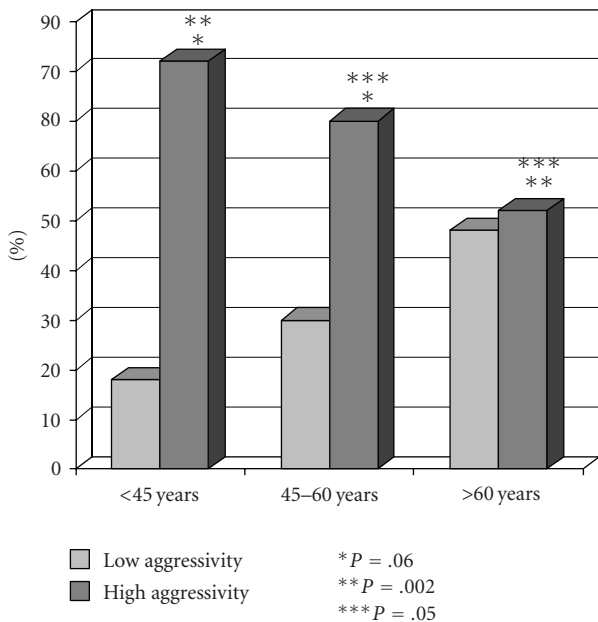


FIGURE 1: Patients with a low aggressive profile are significantly older than patients with a high aggressive profile.

of age ($P = .006$). Finally, patients ≥ 60 years of age had more cases with low aggressiveness compared to patients < 45 years of age ($P = .002$), and to patients between 45 and 60 years of age ($P = .05$). This data is shown in Figure 1.

4. Discussion

PTMC is defined as PTC measuring ≤ 1 cm in size [9]. This variant is also known as occult papillary carcinoma, latent papillary carcinoma, small papillary carcinoma, and papillary microtumor [20]. The current increase in incidence of PTC worldwide is mainly attributed to the corresponding increase in the diagnosis of PTMCs. In most recent series, especially the series that have analyzed cases from the last decade, PTMCs comprise nearly one-half of all the cases of PTCs [2, 3, 8, 21, 22]. Our series confirms this data. PTMCs are considered a subset of PTCs that exhibit a more benign behavior. Distant metastases and mortality rates are reported to be $< 0.5\%$ in patients with PTMCs [10].

Hay et al. [5] reported no difference between the observed number of deaths and the expected number of deaths in a cohort of 900 cases. Appetecchia et al. [23] reported that the outcome of PTMCs was favorable, even in the presence of lymph node metastases and local invasion. In contrast, some authors have suggested that there exist a subset of PTMCs that can be aggressive, requiring therapeutic management similar to larger PTCs [6, 12]. Thus, no agreement has been reached about the optimal treatment of PTMCs. Some authors recommend an aggressive approach to PTMCs, while other authors suggest that no further treatment is needed after lobectomy or thyroidectomy. Moreover, it has even been proposed that observation without surgical treatment is appropriate [24].

Because the number of deaths is very small in patients with PTMCs, in the majority of series authors use the rate of recurrence as a marker of poor clinical outcome. Local and regional lymph node recurrences have been observed with a prevalence rate between 2% and 5.7% [5, 25–27].

In recent years, some specific markers for aggressiveness have been identified [12–17]. Three of the most accepted factors are multifocality, lymph node metastasis, and the mode of diagnosis.

PTMCs frequently present as a multifocal process. Multiple foci are reported in approximately 7%–56% of cases [5, 6, 10, 28]. A number of clinical studies have shown that patients with ≥ 2 foci had a higher recurrence rate and cancer mortality than those with unifocal PTMCs [5, 29]. Baudin et al. [30] reported that only two parameters influenced PTMC recurrences, one of which was multifocality. Moreover, multifocality has been associated with a high incidence of contralateral lobe involvement [31] and is an independent risk factor for metastases [32]. Hence, multifocal PTMCs have been considered to have a poor prognosis. In our series, we have detected a significantly higher rate of multifocality in LPTCs than in PTMCs.

PTMCs also show a high incidence of regional lymph node metastasis, occurring in 12%–64% of patients [6, 25, 33–36]. Wada et al. [37] reported that 64.1% and 44.5% of patients have central and ipsilateral node involvement, respectively, and two-thirds of patients have lymph node metastasis in at least one of the two compartments. It has been described that cases with positive lymph nodes have a higher risk of recurrence [38]. Kim et al. [26] found that lateral cervical node metastasis was the most powerful independent predictor of clinical recurrence. However, other authors have reported that the outcome of PTMCs is favorable, even in the presence of lymph node metastases [5, 23, 37, 39]. Prophylactic neck dissection is not routine in our hospital; node resection was not performed in the incidentally discovered cases. Therefore, the true number of positive lymph nodes is unknown; however, it is interesting to note that among patients in whom lymphadenectomy was performed, the rate of metastasis was not different between PTMCs and LPTCs.

Three circumstances may lead to the detection of a PTMC, as follows, PTMC found at autopsy, PTMC found incidentally in specimens of the thyroid removed for benign thyroid disease, and clinical PTMCs diagnosed before

surgery [40]. Although the prevalence is highly variable, >70% of PTMCs correspond to IPTMCs [10]. It has been suggested that clinical and biological behaviours may differ between IPTMCs and NIPTMCs [41, 42]. Some authors have found that overt tumors are associated with a higher incidence of multicentricity, extrathyroidal involvement, lymphovascular invasion, higher stage, risk of relapse, and death [11, 42–45]. Hence, IPTMCs are associated with a better prognosis, whereas NIPTMCs may have more aggressive behavior. In like manner, we have found significant differences between both modes of presentation in relation to tumor size, multifocality, and age in the group of patients with PTMCs, whereas there were no such differences in tumors >1 cm in size.

Age is considered to be the most important prognostic factor in PTCs and is included in all of the prognostic scoring systems. However, some investigators have failed to show that age affects the outcome of patients with PTMCs [15, 32, 34, 38, 43, 46, 47]. It is interesting to note that in our series, younger age is associated with a higher frequency of specific markers for aggressiveness. Thus, older patients have more IPTMCs without adverse markers, such as multifocality or lymph node metastases. Moreover, the group of patients >60 years of age has a higher incidence of cases with a lower risk of developing later recurrences than the rest of the patients.

In recent years, some of the molecules involved in neoplastic transformation have been explored as markers to assess the biological aggressiveness of PTMC [22, 48]. However, their use is at present not relevant to clinical decision making.

In summary, PTMCs exhibit significant differences in presentation from LPTCs. It is possible that the classic risk factors, which are well validated for PTCs, such as age, must be cautiously interpreted in the current increasing subgroup of PTMCs.

Conflict of Interests

The authors declare that they have no conflict of interests.

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