Retrospective Analysis of 255 Papillary Thyroid Carcinomas ≤ 2 cm: Clinicohistological Features and Prognostic Factors

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Key Words

Papillary thyroid carcinoma · Microcarcinoma · Thyroid cancer

Abstract

Background: Papillary thyroid carcinoma (PTC) is the most common thyroid cancer. The widespread use of neck ultrasound (US) and US-guided fine-needle aspiration cytology is triggering an overdiagnosis of PTC. **Objective:** To evaluate clinical behavior and outcomes of patients with PTCs ≤ 2 cm, seeking for possible prognostic factors. **Methods:** Clinical records of cases with histological diagnosis of PTC ≤ 2 cm followed at the Endocrine Department of Instituto Português de Oncologia, Lisbon between 2002 and 2006 were analyzed retrospectively. **Results:** We identified 255 PTCs, 111 were microcarcinomas. Most patients underwent near-total thyroidectomy, with lymph node dissections in 55 cases (21.6%). Radioiodine therapy was administered in 184 patients. At the last evaluation, 38 (14.9%) had evidence of disease. Two deaths were attributed to PTC. Median ($\pm$ SD) follow-up was 74 ($\pm$ 23) months. Multivariate analysis identified vascular invasion, lymph node and systemic metastases significantly associated with recurrence/persistence of disease. In addition, lymph node involvement was significantly associated with extrathyroidal extension and angioinvasion. Median

($\pm$ SD) disease-free survival (DFS) was estimated as 106 ($\pm$ 3) months and the 5-year DFS rate was 87.5%. Univariate Cox analysis identified some relevant parameters for DFS, but multivariate regression only identified lymph node and systemic metastases as significant independent factors. The median DFS estimated for lymph node and systemic metastases was 75 and 0 months, respectively. **Conclusions:** In the setting of small PTCs, vascular invasion, extrathyroidal extension and lymph node and/or systemic metastases may confer worse prognosis, perhaps justifying more aggressive therapeutic and follow-up approaches in such cases.

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Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy. The widespread use of neck ultrasound (US) has led to the identification of small asymptomatic thyroid nodules with indeterminate clinical relevance [1]. Moreover, US-guided fine-needle aspiration cytology is triggering an overdiagnosis of PTC, with the associated risks and harms of overtreatment [1, 2]. It is estimated that 49% of the rising incidence of thyroid carcinomas consist of cancers measuring 1 cm or smaller and 87% consist of cancers measuring 2 cm or smaller [2].

The clinical course of small PTCs is generally favorable, especially when smaller than 1 cm (papillary thyroid microcarcinoma, PTMC) [3, 4]. Nonetheless, a few cases may behave aggressively [5]. Identification of predictors of relapse or potential to spread has not been well established yet [5].

We performed a retrospective analysis of a series of 255 patients with PTCs ≤ 2 cm, aiming to evaluate their clinical behavior and outcomes and to seek for possible prognostic factors, in order to tailor treatment to individual needs.

Materials and Methods

We reviewed the clinical records of patients with PTC followed at the Endocrine Department of Instituto Português de Oncologia, Lisbon (a tertiary referral center) between 2002 and 2006. Patients were identified through the South Regional Cancer Register and the database of our department. Clinical records of 255 cases with histological diagnosis of PTC ≤ 2 cm were analyzed retrospectively.

In all cases, the histological slides were reviewed by experienced pathologists from our institution. Seventy-nine (31.0%) patients were diagnosed incidentally after surgery for benign thyroid disorders, herein designated incidental PTCs; 159 (62.3%) patients had preoperative fine-needle aspiration cytology suggestive of thyroid malignancy (nonincidental PTCs). In 17 cases, the reason why surgery was performed was unknown. For assessment of risk recurrence the three-level stratification proposed by the American Thyroid Association was used [2].

Follow-up was based mainly on TSH-suppressed thyroglobulin and cervical US. Response to initial therapy was defined as NED (no evidence of disease – suppressed thyroglobulin <1 ng/ml, negative neck US), as BED (biochemical persistent disease – suppressed thyroglobulin ≥ 1 ng/ml in the absence of structural disease), as SED (structural persistent disease – locoregional or distant metastases) and as recurrence (biochemical or structural disease identified after a period of NED).

All data and statistical tests were carried out using SPSS (version 20.0, SPSS, Inc., Chicago, Ill., USA). Descriptive statistics were used to summarize the data; χ^2 analysis and Fisher's exact test were used for categorical variables. Student's *t* test was used to compare continuous variables. Univariate and multivariate logistic regressions, Kaplan-Meier method and univariate and multivariate Cox models were carried out to recognize prognostic variables. A *p* value <0.05 was considered statistically significant.

Results

The study included 255 patients with PTC ≤ 2 cm; 111 (43.5%) were PTMCs. Their clinicopathological characteristics are summarized in table 1. Most of the patients underwent near-total thyroidectomy (97.6%), associated

Table 1. Clinicopathological characteristics of the 255 small PTCs

Clinicopathological characteristics	PTC ≤ 2 cm (n = 255)
Patient age at diagnosis, years	
Average (range)	47 (9–85)
≤ 45 years	116 (45.5%)
>45 years	139 (54.5%)
Female gender (ratio female:male)	215 (84.3%) (5.4:1)
Family history of thyroid cancer	15 (5.9%)
Type of diagnosis	
Incidental PTC	79 (31.0%)
Nonincidental PTC	159 (62.3%)
Unknown	17 (6.7%)
PTC size	
≤ 1.0 cm	111 (43.5%)
1.1–2.0 cm	144 (56.5%)
Average size, cm	1.23 $\pm$ 0.5
Variant	
Classic variant	154 (60.4%)
Follicular variant	81 (31.8%)
High-risk variants ¹	20 (7.8%)
Multifocality	98 (38.4%)
Bilaterality	73 (28.6%)
Extrathyroidal extension	78 (30.6%)
Vascular invasion	36 (14.1%)
Positive surgical margin	33 (12.9%)
Lymph node metastases	73 (28.6%)
Distant metastases	6 (2.4%)
PTC risk classification [5]	
Low risk	124 (48.6%)
Intermediate risk	108 (42.4%)
High risk	23 (9.0%)

¹ High-risk PTC variants: 13 tall-cell; 3 trabecular; 2 solid; 2 diffuse sclerosing.

with lymph node dissections in 55 cases (21.6%). Eighty-four patients (32.9%) were operated in the Head and Neck Surgery Department of our institution. The remaining 171 patients underwent surgery at other hospitals and were then referred for postoperative follow-up and eventual radioactive iodine (RAI) therapy at our institution. Postoperative complications were seen in 47 (18.5%) patients (definitive hypoparathyroidism in 30 patients, dysphonia in 15 and both in 2). RAI was administered in 184 (72.2%) patients and of these 46 (25.0%) had more than one RAI therapy. Reoperations due to locoregional recurrence were performed in 29 cases. Median ($\pm$ SD) follow-up was 74 ($\pm$ 23) months. At the last evaluation, 38 (14.9%) had evidence of disease, 14 (36.8%) of which with BED and the remaining 24 with SED (63.2%). Two deaths were attributed to PTC (cases staged as T3N1bM1 and T4bNxMx).

Table 2. Descriptive data, univariate and multivariate analysis for clinical and histopathological characteristics using recurrence/persistence of disease as end point

Characteristics	NED (n = 217)	Recurrence/ persistence of disease (n = 38)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Patient age at diagnosis								
≤45 years	98 (45.2%)	18 (47.4%)	1.00			1.00		
>45 years	119 (54.8%)	20 (52.6%)	0.92	0.46–1.83	0.801	1.55	0.53–4.50	0.426
Gender								
Female	187 (86.2%)	28 (73.7%)	1.00			1.00		
Male	30 (13.8%)	10 (26.3%)	2.23	0.98–5.05	0.055	2.67	0.79–9.03	0.114
Type of diagnosis								
Incidental PTC	75 (37.1%)	4 (11.1%)	1.00			1.00		
Nonincidental PTC	127 (62.9%) missing 15 cases	32 (88.9%) missing 2 cases	4.72	1.61–13.88	0.005	1.25	0.28–5.53	0.773
PTC diameter								
≤1.0 cm	98 (45.2%)	13 (34.2%)	1.00			1.00		
1.1–2.0 cm	119 (54.8%)	25 (65.8%)	1.58	0.77–3.26	0.212	1.90	0.61–5.95	0.271
Classic variant								
No	86 (39.6%)	15 (39.5%)	1.00			1.00		
Yes	131 (60.4%)	23 (60.5%)	1.01	0.49–2.04	0.985	0.96	0.31–2.99	0.950
Multifocality								
No	141 (65.0%)	16 (42.1%)	1.00			1.00		
Yes	76 (35.0%)	22 (57.9%)	2.55	1.27–5.15	0.009	1.13	0.25–5.19	0.876
Bilaterality								
No	162 (74.7%)	20 (52.6%)	1.00			1.00		
Yes	55 (25.3%)	18 (47.4%)	2.65	1.31–5.37	0.007	1.33	0.27–6.48	0.728
Extrathyroidal extension								
No	163 (75.1%)	14 (36.8%)	1.00			1.00		
Yes	54 (24.9%)	24 (63.2%)	5.18	2.50–10.71	0.000	1.49	0.45–4.91	0.511
Vascular invasion								
No	198 (91.2%)	21 (55.3%)	1.00			1.00		
Yes	19 (8.8%)	17 (44.7%)	8.44	3.81–18.66	0.000	5.02	1.60–15.69	0.006
Positive surgical margin								
No	196 (90.3%)	26 (68.4%)	1.00			1.00		
Yes	21 (9.7%)	12 (31.6%)	4.31	1.90–9.77	0.000	3.33	0.80–13.85	0.098
Lymph node metastases								
No	173 (79.7%)	9 (23.7%)	1.00			1.00		
Yes	44 (20.3%)	29 (76.3%)	12.67	5.59–28.70	0.000	17.72	4.67–67.34	0.000

OR = Odds ratio; 95% CI = 95% confidence interval.

Descriptive data and univariate/multivariate analysis of clinical and histopathological features according to recurrence/persistence of disease are presented in table 2. Vascular invasion and lymph node metastases were significantly associated with recurrence/persistence of disease. In addition, lymph node involvement was associated with extrathyroidal extension and angioinvasion by multivariate analysis (table 3).

Median ($\pm$ SD) disease-free survival (DFS) was estimated as 106 ($\pm$ 3) months and the 5-year DFS rate was 87.5% (fig. 1a). Univariate Cox analysis identified several

factors relevant for DFS, but multivariate Cox regression only identified lymph node and systemic metastases as independent factors with hazard ratios estimated at 6.61 (2.48–17.66) and 4.82 (1.69–13.79), respectively (online suppl. table 1, www.karger.com/doi/10.1159/000369133). The mean ($\pm$ SD) DFS estimated for lymph node involvement was 75 ($\pm$ 6.5) months (fig. 1b).

Concerning size, larger PTCs (1.1–2.0 cm) had more frequently high-risk histological variants (11.8 vs. 2.7%; $p = 0.01$), multifocality (41.0 vs. 35.1%; $p = 0.34$), extrathyroidal extension (38.9 vs. 19.8%; $p = 0.00$), vascular

Table 3. Descriptive data, univariate and multivariate analysis of small PTCs without and with lymph node involvement and clinico-pathological predictors for its occurrence using lymph node disease as end point

Characteristics	Features of PTCs without lymph node disease (n = 182)	Features of PTCs with lymph node disease (n = 73)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Age at diagnosis								
≤45 years	74 (40.7%)	42 (57.5%)	1.00			1.00		
>45 years	108 (59.3%)	31 (42.5%)	0.51	0.29–0.88	0.015	0.60	0.29–1.24	0.170
Gender								
Female	158 (86.8%)	57 (78.1%)	1.00			1.00		
Male	24 (13.2%)	16 (21.9%)	1.85	0.92–3.73	0.086	1.47	0.60–3.61	0.402
Type of diagnosis								
Incidental PTC	72 (39.6%)	7 (9.6%)	1.00			1.00		
Nonincidental PTC	110 (60.4%)	66 (90.4%)	6.93	2.99–16.02	0.000	4.24	1.64–10.93	0.003
PTC diameter								
≤1.0 cm	88 (48.4%)	23 (31.5%)	1.00			1.00		
1.1–2.0 cm	94 (51.6%)	50 (68.5%)	2.04	1.15–3.61	0.015	1.15	0.55–2.43	0.707
Classic variant								
No	83 (45.6%)	27 (37.0%)	1.00			1.00		
Yes	99 (54.4%)	46 (63.0%)	1.38	0.78–2.43	0.268	1.48	0.71–3.11	0.297
Multifocality								
No	122 (67.0%)	35 (47.9%)	1.00			1.00		
Yes	60 (33.0%)	38 (52.1%)	2.21	1.27–3.84	0.005	1.28	0.41–3.98	0.668
Bilaterality								
No	141 (77.5%)	41 (56.2%)	1.00			1.00		
Yes	41 (22.5%)	32 (43.8%)	2.68	1.51–4.79	0.001	1.61	0.48–5.45	0.445
Extrathyroidal extension								
No	148 (81.3%)	29 (39.7%)	1.00			1.00		
Yes	34 (18.7%)	44 (60.3%)	6.60	3.63–12.02	0.000	5.47	2.41–12.40	0.000
Vascular invasion								
No	171 (94.0%)	48 (65.8%)	1.00			1.00		
Yes	11 (6.0%)	25 (34.2%)	8.09	3.72–17.63	0.000	3.38	1.28–8.93	0.014
Positive surgical margin								
No	160 (87.9%)	62 (84.9%)	1.00			1.00		
Yes	22 (12.1%)	11 (15.1%)	1.29	0.59–2.82	0.522	0.44	0.15–1.33	0.147
Distant metastases								
No	179 (98.4%)	70 (95.9%)	1.00			1.00		
Yes	3 (1.6%)	3 (4.1%)	2.56	0.50–12.97	0.257	3.33	0.39–28.47	0.272

OR = Odds ratio; 95% CI = confidence interval.

invasion (18.8 vs. 8.1%; $p = 0.02$), positive surgical margin (16.7 vs. 8.1%; $p = 0.04$) and lymph node involvement (34.7 vs. 20.7%; $p = 0.014$) when compared with PTMCs. By univariate and multivariate analysis we could not confirm poorer prognosis in larger PTCs.

Discussion

In this retrospective study we analyzed the characteristics, outcomes and predictive factors of 255 cases of PTC up to 2 cm. These small PTCs represent a growing prob-

lem in thyroidology because their incidence is rising, mainly resulting from the widespread use of US [2, 6].

Among patients included in the present study, 36.1% were diagnosed following a US performed as a 'routine exam'; 31% were incidental PTCs diagnosed after surgery for benign disorders. A few patients (5.9%) had familial forms of PTC, which is concordant with the overall prevalence of 4.5% estimated from several series [1, 5, 7–9].

In line with previous studies [5, 10–12], we observed that approximately one third of cases presented histological features classically associated with a worse prognosis such as multifocality, bilaterality, extrathyroidal exten-

Fig. 1. DFS Kaplan-Meier curve of 255 PTCs (a) and a DFS curve stratifying for lymph node metastases (b).

sion or lymph node metastases. Angioinvasion and positive surgical margin were noticed in almost one sixth of the patients. The relatively high number of cases with positive surgical margins (12.9%) may be due to the fact that the majority of the patients underwent surgery at different hospitals, most of them without specialized endocrine surgeons. Moreover, the high prevalence of extrathyroidal extension (30.6%) may also contribute to positive surgical margins (extrathyroidal extension prevalence in PTCs with positive and negative surgical margins was 69.7 and 24.8%, respectively; $p = 0.00$).

Contrasting with this high prevalence of aggressive histological features, most patients were in remission after a mean ($\pm$ SD) follow-up of 74 (± 23) months. Five-year DFS rate and cancer-specific mortality rate were estimated at 87.5 and 0.8%, respectively. Since 98% of patients had a near-total thyroidectomy and 72% were offered adjuvant RAI, it is uncertain whether the favorable results were due to the intrinsically indolent behavior of the tumors or to the extent of treatment.

The observation of a high proportion of aggressive histological criteria, especially multifocality, may justify total thyroidectomy as the initial surgical approach not only to decrease recurrences but also to facilitate the follow-up [4, 5, 13]. In contrast, others suggest less invasive approaches such as hemithyroidectomy or even just observation [14–16].

RAI is usually considered based on risk assessment, however, it remains unclear whether ablative RAI is effective in reducing recurrences of small PTCs: Pelizzo et al. [17], Chow et al. [18] and Creach et al. [19] reported lower recurrence rates with RAI after thyroidectomy; in contrast, Baudin et al. [20], Sawka et al. [21] and Scharzt et al. [22] failed to confirm this finding.

Based on a bimodal analysis, we found that lymph node involvement, systemic metastases and angioinvasion were the most important prognostic predictors. The role of lymph node involvement, as relapse predictor, has already been documented for tumors up to 1.5 cm [5, 23]. The results of the present study support the same conclusions for PTCs up to 2 cm. Multivariate analysis identified only extrathyroidal extension and vascular invasion as predictors for lymph node involvement, confirming previous studies [24, 25].

An open question is whether the clinical behavior of tumors ≤ 1 and $>1 \leq 2$ cm may differ significantly. Pellegriti et al. [5] stratified small PTCs in PTMC versus 1.1–1.5 cm and found increased aggressiveness with larger tumors; however, tumor size was not a predictor of recurrence. Similar findings were reported by Arora et al. [12], who found no differences in recurrence rates for PTMCs versus conventional PTCs (>1 cm). Roti et al. [7] excluded an association between size and recurrence. In line with previous studies, the present results, although limited by

the small number of patients and short follow-up, did not support a prognostic value for size. In addition, we found more favorable clinicopathological features, less recurrence rates and higher DFS associated with incidental PTCs, as other studies have also reported [1, 5, 7, 20, 26].

In conclusion, in the setting of PTCs ≤ 2 cm, the presence of vascular invasion, extrathyroidal extension and lymph node and/or systemic metastases may confer more aggressive biological behavior to PTC and worsen the prognosis, perhaps justifying more aggressive therapeutic and follow-up approaches.

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Disclosure Statement

The authors have nothing to disclose.