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The non-interventional approach to papillary thyroid microcarcinomas. An "active surveillance" dilemma

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ABSTRACT

Background: Recent studies suggest that papillary-thyroid-microcarcinomas (PTMi) and follicular-variant-papillary-thyroid-cancers (FVPTC) are less aggressive overall. Our observations argue against.
Objectives: To assess whether PTMi and FVPTC are indeed low-risk and could be safely followed without intervention.
Methods: We prospectively collected data of subjects with PTC on pathology post-thyroidectomy. Odds ratios (OR) were calculated with Fisher's exact test and differences between means were calculated using Mann Whitney's test.
Results: 696 met inclusion-criteria; 436 had macrocarcinomas (PTMa) and 260 had PTMi. PTMa were statistically significantly more likely to present multifocal [44.0% vs.28.1%], with extrathyroidal extension [22.1% vs.3.4%], lymph nodes involvement [25.5% vs.8.8%] and local invasion [3.1% vs.0.4%] ($p < 0.05$ for all), but not with distant metastasis [3.4% vs.1.3%, $p > 0.05$]. Therefore, PTMi measuring down to 0.01 cm, harbored aggressive features. We also identified 174 cases with FVPTC and 522 subjects with non-FVPTC. FVPTC had lower incidence of multifocality [40.1%, vs.60.9%], extrathyroidal extension [8.6% vs.17.4%] and lymphatic involvement [5.2% vs.24.0%], but not distant metastasis or local invasion [$p > 0.05$ for all]. Therefore, FVPTC measuring down to 0.5 cm, also harbored aggressive features.
Conclusions: PTMi and FVPTC aggressive features are substantial enough to require careful evaluation, independent of their original tumor size before defaulting to just "active surveillance."

1. Introduction

Since thyroid cancer is associated with great survival rates, it is being paralleled to prostate cancer for its "benign" behavior [1]. Among the different forms of thyroid cancer, the most common is Papillary Thyroid Cancer (PTC), comprising approximately 87.4% of all thyroid cancer cases. The continuous rise in the availability of point of care ultrasound examination of the thyroid gland, led to a steep rise in the identification of thyroid nodules, over the past decades, with only a fraction of them (7–14%) being malignant [2]. The marked increase in the prevalence of thyroid cancer in the population consisted of an increase in large tumors (macrocarcinomas = tumors > 1 cm in largest diameter) and small tumors (microcarcinomas = tumors < 1 cm in largest diameter); however, microcarcinomas' incidence rose faster, reaching 39% of all newly diagnosed thyroid cancer cases [2–4]. The aggressiveness of PTC is thought to depend to some extent on the tumor's pathological stage and a large part of staging is tumor size. To that, the 2015 ATA thyroid nodules and differentiated thyroid cancer guidelines states that: "an active surveillance management approach can be considered as an alternative to immediate surgery in patients with very low risk tumors (e.g., papillary microcarcinomas without clinically evident metastases or local invasion, and no convincing cytologic evidence of aggressive disease)" [5]. Macrocarcinomas on the other hand, have a more aggressive behavior compared to microcarcinomas, and this has been shown by multiple studies [6–9]. However, none revealed a totally indolent behavior for microcarcinomas [10 as an example].

The main therapy for PTC tumors diagnosed by cytology, is surgery. Patients with very low risks can be offered an active surveillance strategy, since mortality rates have been reported to be < 1%, loco-

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Table 1
Comparison of the features of aggressive behavior between the histological findings of papillary thyroid microcarcinomas and macrocarcinomas.

	PTMa N/Total (%)	PTMi N/Total (%)	OR (95% CI) P value	Smallest tumor presenting with this feature
Multifocality	166/377 (44.0%)	64/228 (28.1%)	2.02 (1.42–2.87) < 0.0001	0.10 cm (trifocal)
Extrathyroidal extension	84/380 22.1%	8/231 3.5%	7.91 (3.75–16.7) < 0.0001	0.30 cm
Local invasion	12/383 (3.1%)	1/231 (0.4%)	7.44 (0.96–57.6) 0.0381	0.70 cm
Lymphatic spread	111/435 (25.5%)	23/259 (8.8%)	3.52 (2.18–5.68) < 0.0001	0.01 cm (3 cases with a maximum of 11 out of 28 lymph nodes)
Metastatic disease	13/386 (3.4%)	3/232 (1.3%)	2.66 (0.75–9.44) 0.189	0.10 cm (metastasis to the skeleton)

Abbreviations: PTMa, papillary thyroid macrocarcinomas; PTMi, papillary thyroid microcarcinomas.

regional recurrence rates 2%–6%, and distant recurrence rates 1%–2% [11–13]. Moreover, follicular variant PTC (FVPTC), a subtype of PTC with less aggressive behavior, was recently reclassified as a benign lesion named Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features, when fully encapsulated [14]. Since both microcarcinomas and FVPTC incidences rose dramatically in recent years, FVPTC becoming the most common subtype of the disease [4], there is need for concrete understanding of the risks associated with different therapeutic versus surveillance strategies. Furthermore, the ascertainment bias of over-diagnosing thyroid cancer with ultrasound has allowed for potential unintentional risk underestimation. We performed the present study to assess whether papillary thyroid microcarcinomas (PTMi) and FVPTC are indeed low-risk and could be safely followed without intervention.

2. Methods

2.1. Subjects selection

Our Thyroid Multidisciplinary Clinic is in a tertiary referral academic center, where patients with thyroid nodules are evaluated clinically and registered in a prospectively collected database. Data collection consists of clinical, laboratory, radiological, cytological and histological data for 18 years (1996–2014, USA single institution study). For this study, we extracted data from subjects diagnosed with papillary thyroid cancer by surgical pathology, after undergoing total thyroidectomy. We collected data on thyroid pathology, consisting of the largest tumor size, focality, presence of extrathyroidal extension, capsular invasion, lymphatic or distant metastasis (all features of aggressiveness). In addition, we gathered data on patients' age, gender, preoperative TSH measurement, need for I-131 therapy and/or re-operation. We excluded subjects with multiple synchronous thyroid cancers of different histology, those exposed to neck radiation anytime during their lifetime, those with a family history of PTC in a first degree relative, and those operated on their thyroid gland prior to the enrollment in the study.

Institutional Review Board approval was obtained prior to the initiation of the study, and all subjects signed informed consent to be part of this study.

2.2. Statistical analysis

Our subjects were divided into two groups: those with a primary tumor smaller than 1 cm in the largest diameter (microcarcinomas - PTMi) and those with a primary tumor equal to - or larger than 1 cm in largest diameter (macrocarcinomas - PTMa). The incidence of the features of tumor aggressiveness, split by tumor size were compared and the odds ratios (OR) were calculated with Fisher's exact test. For categorical variables, differences between means were calculated using Mann Whitney's test. P values < 0.05 were considered statistically significant.

3. Results

We reviewed data for 2711 subjects who underwent a total thyroidectomy; 1937 subjects met the exclusion criteria: 233 subjects were excluded due to the presence of thyroid cancers of histology other than papillary thyroid cancer; an additional 1714 subjects were excluded due to the presence of benign disease by histology; 78 subjects were excluded due to incomplete data. In the end, 696 subjects with papillary thyroid cancer were included in our analysis, out of whom 436 had macrocarcinomas (PTMa) and 260 had microcarcinomas (PTMi). PTMa were found more commonly in males (n = 126/181, 69.6%) compared to females (n = 310/515, 60.2%) for an OR of 1.53 with a 95% CI of 1.05–2.18 and a p value of 0.0257. Surprisingly, subjects with a PTMa were younger than those with a PTMi (45.5 ± 16.2 vs. 50.0 ± 14.7 years of age, $p < 0.001$). The features of aggressive behavior of the two subgroups were compared, and the data is presented in Table 1. The smallest tumor presenting with any feature of aggressive disease was as small as 0.01 cm in largest diameter (Table 1 and Fig. 1).

In addition, we compared the incidence of Follicular Variant Papillary Thyroid Cancer (FVPTC) among subjects with PTMa (FV PTMa) and PTMi (FV PTMi), and found that there was no statistically significant difference [FV PTMa n = 115/436 (26.4%), FV PTMi n = 59/260 (22.7%), OR 1.22, 95% CI 0.88–1.53, p = 0.32]. Subjects with FV PTMa had a statistically *insignificant* smaller tumor size, compared to the ones without the FV type (2.3 ± 1.4 cm vs. 2.5 ± 1.4 cm, p = 0.08). Tumor size was not significantly different among subjects with FV and other forms of PTMi (0.47 ± 0.25 cm vs. 0.44 ± 0.25 cm, p = 0.49).

When we compared the features of aggressive tumor behavior between PTMa and PTMi, in the absence of FV papillary thyroid cancer, we found that PTMa have a higher incidence of tumor multifocality [(PTMa n = 120/270 (44.4%), PTMi n = 45/173 (26.0%), OR 2.28, 95% CI 1.50–3.45, $p < 0.0001$], extrathyroidal extension [PTMa n = 70/273 (25.6%), PTMi n = 8/176 (4.5%), OR 7.24, 95% CI 3.39–15.5, $p < 0.0001$], local invasion [PTMa n = 11/276 (4.0%), PTMi n = 1/176 (0.6%), OR 7.26, 95% CI 0.93–56.8, p = 0.034] and lymph node involvement [PTMa n = 104/321 (32.4%), PTMi n = 21/200 (4.2%), OR 4.09, 95% CI 2.46–6.80, $p < 0.0001$], but not distant metastasis [PTMa n = 9/279 (3.2%), PTMi n = 2/177 (1.1%), OR 2.92, 95% CI 0.62–13.7]. Instead, when we compared the two subgroups in the presence of FV papillary thyroid cancer diagnosis, PTMa were found to have a higher incidence of extrathyroidal extension (PTMa n = 14/107 (13.1%), PTMi n = 0/55 (0.0%), OR 17.2, 95% CI 1.01–294.4, p = 0.0027], but not tumor multifocality [PTMa n = 43.0%), PTMi n = 19/55 (34.5%) OR 1.43, 95% CI 0.73–2.81, p = 0.3155], local invasion [PTMa n = 1/107 (0.9%), PTMi n = 0/55 (0.0%), OR 56, 95% CI 0.06–39.0, $p > 0.99$], lymph node involvement [PTMa n = 7/114 (6.1%), PTMi n = 2/59 (3.4%), OR 1.86, 95% CI 0.37–9.28,

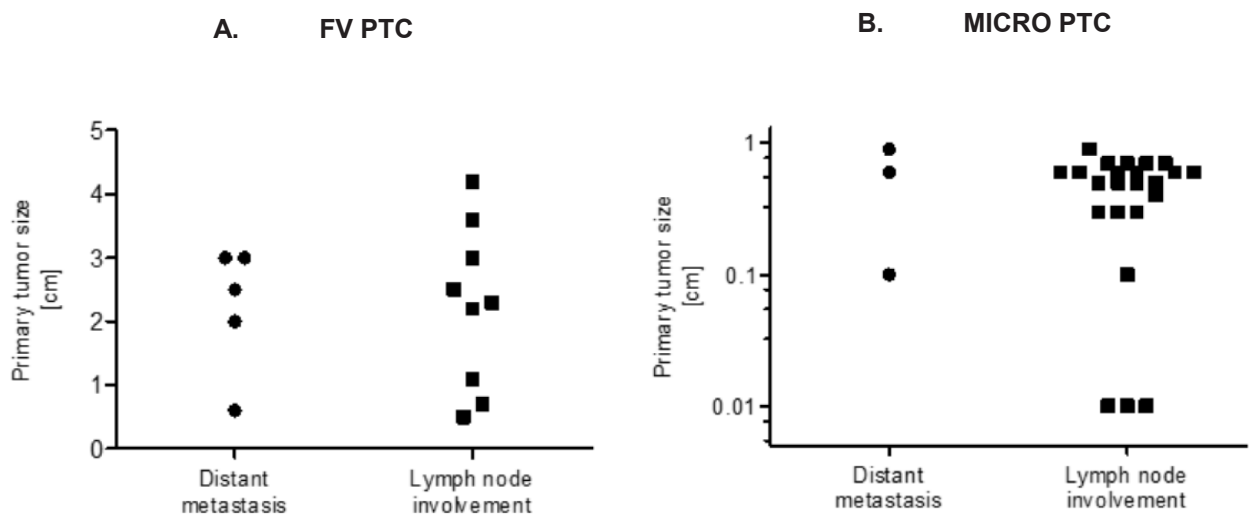

Fig. 1. A. Primary tumor size, in patients with Follicular Variant Papillary Thyroid Cancer presenting with distant metastasis or lymphatic spread. **B.** Primary tumor size in patients with papillary thyroid microcarcinomas of any histological type, presenting with distant metastasis or lymphatic spread.

p = 0.7199] or distant metastasis [PTMa n = 4/107 (3.4%), PTMi n = 1/55 (1.8%), OR 2.09, 95% CI 0.23–19.2, p = 0.6626].

Next, we compared the features of tumor aggressiveness between subjects with FVPTC and those without this subtype of PTC (non-FVPTC). We identified 174 cases with FVPTC and 522 subjects with PTC of the classic type or other variants (non-FVPTC). The mean tumor size was not statistically significantly different in FVPTC (1.6 ± 1.4 cm) compared to non-FVPTC (1.8 ± 1.5 cm), p = 0.0547. Compared to other forms of PTC, FVPTC had lower incidence of multifocality [n = 65/162, (40.1%), compared to n = 270/443 (60.9%), OR 0.43, 95% CI 0.30–0.62, p < 0.0001], extrathyroidal extension [14/162 (8.6%) compared to 78/449 (17.4%), OR 0.45, 95% CI 0.25–0.82, p = 0.0070] and lymphatic involvement [n = 9/173 (5.2%) compared to 125/521 (24.0%), OR 0.17, 95% CI 0.09–0.35, p < 0.0001]. No statistically significant difference was found for local invasion [FVPTC n = 1/162(0.6%), compared to 12/452 (2.7%), OR 0.23, 95% CI 0.03–1.77, p = 0.20] and distant metastasis [FVPTC n = 5/162 (3.1%) compared to 11/456 (2.4%), OR 1.29, 95% CI 0.44–3.77, p = 0.5786].

Finally, we compared the features of tumor aggressiveness between subjects with FVPTC and those without this subtype of PTC based on tumor size. These data are presented in Table 2.

4. Discussion

4.1. Microcarcinomas

Papillary thyroid cancer (PTC) has being paralleled to prostate cancer for its "benign" behavior [1], given its low risk of disease-specific mortality when compared with other forms of thyroid cancer and other cancers. In the years past, PTC staging included primary tumor size in patients older than 45 years of age, given the assumption that smaller tumors are less likely to cause morbidity and mortality [5]. Interestingly, studies from Japan revealed already in 2003, that tumors smaller than 1 cm in largest diameter (microcarcinomas), which were followed without surgery for up to 10 years, tended to grow in a clinically significant manner in 15.9% of patients [15,16]. In patients choosing surveillance over surgery, only 1.2–3.4% developed lymph node metastasis in the lateral neck compartments, but in the subgroup operated on, up to 50.5% had lymphatic involvement [15,16], In addition, even microcarcinomas with sonographic suspicion of tracheal or recurrent laryngeal nerve involvement, did not lead to poor outcomes with observation alone, if they were smaller than 7 mm in size [17]. During a follow up of 9.9 years, only 1 out of 148 patients died of thyroid cancer, when a microcarcinoma was the tumor of origin, and in that case the tumor had already presented with lymph node involvement with poor differentiation, while patients without lymph node involvement had excellent prognosis [18]. On the other hand, observational data from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute suggested that total thyroidectomy conferred a survival benefit in elderly patients with papillary thyroid microcarcinoma, but the study was limited by selection bias [19]. The presence of BRAF V600E mutation seemed to play a significant role, doubling the recurrence rates in these tumors [20]. Mutations in the telomerase reverse transcriptase (TERT) promoter gene were identified in 4.7% of papillary microcarcinomas, without any effect on features of tumor aggressiveness [21], while another study did not find such mutations in tumors which progressed on surveillance alone [22]. The specific role of mutations in the N-, K- or H-ras genes on tumor aggressiveness in microcarcinomas, remains to be elucidated as of yet. An additional study found that the presence of poor vascularity and "strong" calcifications correlated significantly with non-progressive disease over time [23]. It is clear that the biology of these tumors and their microenvironment are likely to be as or more important than just "size" at assessing risk but more studies are needed.

In the present study we reviewed the features of aggressive tumor behavior in papillary microcarcinomas and compared them with those of tumors larger than 1 cm in maximal diameter (macrocarcinomas) in a sample of 696 consecutive patients with papillary thyroid cancer. Our results are in agreement with previous studies, suggesting a less aggressive behavior of papillary thyroid microcarcinomas, compared to macrocarcinomas at all levels. Unfortunately, though, we cannot conclude that microcarcinomas are really indolent, since distant metastasis were found in a percentage of our patients and they originated from tumors as small as 0.1 cm in largest diameter. Lymphatic spread was also present in 8.8% of patients and it was found in tumors as small as 0.01 cm in largest diameter. Also, extrathyroidal extension was present in a tumor as small as 0.3 cm in largest diameter. These findings are consistent with previous findings from multiple studies, where metastatic lesions [24,25], lymph node involvement [26] and poor outcomes [27] occurred even in the absence of a primary intrathyroidal tumor, especially in the presence of tall cell variant histopathology. These observations imply that papillary thyroid microcarcinomas are not to be underestimated. It is obvious that the biology of a tumor cannot be

Table 2
Comparison of the features of aggressive behavior between the histological findings of papillary thyroid microcarcinomas and macrocarcinomas.

	Subtype	PTMa n	PTMi n	Smallest FV tumor presenting with this feature
Multifocality	FV	46/107	19/55	0.2 cm
	Non-FV	120/165	150/278	
	OR (95% CI)	0.28 (0.17–0.47)	0.45 (0.25–0.82)	
	P value	< 0.0001	0.0116	
Extrathyroidal extension	FV	14/107	0/55	1.0 cm
	Non-FV	70/273	8/176	
	OR (95% CI)	0.44 (0.23–0.82)	0.18 (0.01–3.14)	
	P value	0.0087	0.2035	
Local invasion	FV	1/107	0/55	1.0 cm
	Non-FV	11/276	1/176	
	OR (95% CI)	0.23 (0.03–1.78)	1.05 (0.04–26.3)	
	P value	0.1916	> 0.99	
Lymphatic spread	FV	7/114	2/59	0.50 cm
	Non-FV	104/321	21/200	
	OR (95% CI)	0.14 (0.06–0.30)	0.30 (0.07–1.32)	
	P value	< 0.0001	0.1187	
Metastatic disease	FV	4/107	1/54	0.60 cm
	Non-FV	9/279	2/177	
	OR (95% CI)	1.17 (0.35–3.87)	1.62 (0.14–18.2)	
	P value	0.7598	0.5577	

Abbreviations: PTMa, papillary thyroid macrocarcinomas; PTMi, papillary thyroid microcarcinomas.

determine by a tumor size at diagnosis. Our suggestion in the case of such a diagnosis is at least to screen for lymph node involvement with ultrasound guided fine needle aspiration neck mapping in the pre- and immediate post-operative period. On the long-run, follow up with regular ultrasound examinations alone and monitoring of thyroglobulin concentration and thyroglobulin antibodies titers would be appropriate, but the interval for this intervention need to be established, based on further research work.

4.2. Follicular variant of papillary thyroid cancer

Follicular variant of papillary thyroid cancer (FVPTC) is a subtype of papillary thyroid cancer, characterized by the presence of a follicular growth pattern of the tumor, along with nuclear features of papillary thyroid cancer (PTC) [28]. This tumor type has had a rapidly growing incidence, playing a major role on the steep rise in thyroid cancer incidence of the last decades [4]. This tumor type has been found in several studies to be associated with a more favorable prognosis compared to the classical form of PTC overall, especially so, when fully encapsulated [28,29]. This led to an update of the Guidelines issued by the American Thyroid Association in 2015 [5], to incorporate a name change for this tumor, which is currently called Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) [14]. This recent change was based on a retrospective study comparing the outcomes between two groups of patients: 109 cases of non-invasive FVPTC compared to 101 cases with classical form of PTC, followed for more than 10 years. The study noted that all patients with encapsulated FVPTC were alive, without evidence of tumor recurrence, as compared to poorer outcomes in the invasive form of the disease. This was consistent with findings from previous studies [30,31], even though cases with metastatic disease have been described in that subgroup of patients as well [32]. Despite these data, in our clinical practice at a large tertiary care referral center, we identified several patients with FVPTC presenting with aggressive tumor behavior. In order to ascertain whether this tumor type deserves a downgrading attention, we studied a large number of PTC cases of both FV and classical form to compare their histopathological features of tumor aggressiveness. Our findings imply that small and large FV tumors could present with significant features of tumor aggressiveness, even though to a lesser extent compared to the classical variant. Therefore, the identification of a small, fully encapsulated tumor of the FV subtype allow for a less intensive follow up, but these tumors should be cared for with the usual interventions [33] when not fully encapsulated. In addition, a clear statement should be made as to the malignant potential of incompletely encapsulated tumors of this variant, so that public and physicians' awareness is raised.

5. Conclusion

Papillary thyroid cancer is the most common form of thyroid cancer, but due to its benign course as compared with other solid tumors, clinicians tend to be overly optimistic about its outcome. Since the smaller tumors (microcarcinomas) and the ones consisting of follicular variants are believed to be even so benign as to minimize care, the risk of leaving untreated patients with distant or local metastasis is now potential and requires specialty journals to raise immediate attention of all providers involved with thyroid cancer care.

Declarations of interest

None.

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