Preoperative Ultrasonographic Features of Papillary Thyroid Carcinoma Predict Biological Behavior

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Background: Although ultrasound (US) features of papillary thyroid carcinoma (PTC) are well established, little is known regarding biological behavior according US features. We investigated whether there was a difference in biological behavior between PTCs that did and did not meet malignant US criteria.

Patients and Methods: We retrospectively reviewed clinical records and histological and US findings of the index tumors in 488 patients who underwent surgery for PTC. Benign-looking PTC (B-PTC) was defined as showing none of the accepted US criteria for malignancy. Malignant-looking PTCs (M-PTCs) and B-PTCs were compared in terms of patients' age, sex, tumor size, histological subtype, multifocality, lymph node (LN) metastasis, extrathyroidal extension, stage, recurrence, and distant metastasis.

Results: B-PTCs accounted for 74 (15%) of all 488 PTCs. Mean tumor size was not significantly different between the groups, with 1.10 cm for M-PTC and 1.11 cm for B-PTC ($P = .947$). Univariate and multivariate analysis indicated that M-PTC more frequently had LN metastasis, extrathyroidal extension, and a higher stage than B-PTC (all $P < .05$). The results were significant in tumors $\geq$1.0 cm, whereas there were no significant differences in tumors $<$1 cm. As the number of malignant US features increased, multifocality, extrathyroidal extension, LN metastasis, and a higher stage were more likely.

Conclusion: PTCs that did not meet malignant US criteria had better prognostic indicators than PTCs that met US criteria. Therefore, US features at the time of diagnosis can serve as a useful tool for predicting biological behavior in PTC. **(*J Clin Endocrinol Metab* 98: 1476–1482, 2013)**

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer and accounts for 70% to 90% of well-differentiated thyroid malignancies (1–5). Many authors have reported ultrasound (US) criteria for use in differentiating benign from malignant thyroid lesions, and the specific US findings of PTC are well established (6–11). As a result, preoperative thyroid US has significantly facilitated the accurate evaluation of PTC. However, we occasionally encounter benign-looking masses on US that were found to have malignant histology after surgery. Because these PTCs lack accepted US criteria for malignancy, the diagnosis can be missed or delayed on US evaluation.

PTC generally displays an indolent clinical course and is known to have a favorable prognosis despite 15% to 30% local and regional recurrence (12–15). However, some cases show clinicopathological features that predict a more progressive course and suggest poorer prognosis. Tumor size, patient age, extrathyroidal extension, lymph node (LN) metastasis, and distant metastasis are recognized as prognostic factors of PTC (16–21). Fortunately, the identification of tumor features associated with good

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Abbreviations: B-PTC, benign-looking PTC; CI, confidence interval; FNA, fine-needle aspiration; LN, lymph node; M-PTC, malignant-looking PTC; OR, odds ratio; PTC, papillary thyroid carcinoma; TNM, tumor node metastasis; US, ultrasound.

prognosis may allow patients to defer surgery and alleviate their concerns about cancer.

To our knowledge, no reports have been published to date evaluating the previously identified biological behavior associated with US features of PTC. We hypothesized that PTC that is benign-looking on US at the time of diagnosis may have better biological behavior than PTC that is obviously malignant. We investigated whether there was a difference in biological behavior between PTCs that did and did not meet malignant US criteria.

Patients and Methods

Patients

Institutional Review Board approval was obtained for this retrospective study, and informed patient consent was waived. From March 2006 to December 2006, 544 patients (mean age, 47 years; range, 16–71 years) underwent total (n = 519) or hemithyroidectomy (n = 25) with or without LN dissection for PTC in our institution. All patients (n = 544) who underwent surgery were preoperatively diagnosed as PTC after fine-needle aspiration (FNA) for several reasons including suspicious US findings (n = 318), a request from the patient or physician (n = 168), or symptomatic mass (n = 58). There was no guideline of nodule size for FNA in our institution at that time. We performed FNA for any nodule in all patients referred for FNA except when the nodule showed definite benign findings such as cystic, predominantly cystic, or spongiform appearance. The largest or the most suspicious one was aspirated if there were multiple nodules.

In our institution, lateral neck dissection is indicated only when there is metastatic PTC diagnosed preoperatively. We excluded 37 patients who did not have preoperative US performed at our institution. Eleven patients who did not undergo follow-up US for at least 18 months and eight patients who had incidentally identified PTC after surgery for a benign lesion were also excluded. Finally, 488 patients were included in the study sample for statistical analysis. We retrospectively reviewed clinical records, histological reports, and initial and follow-up US images of index tumors.

After surgery, cervical US to evaluate the thyroid bed and cervical nodal compartments was performed at 6 months and then annually for 5 years (mean follow-up period, 60 months; range, 18–71 months). Some patients underwent neck computed tomography (CT) scan (n = 42), positron emission tomography/CT scan (n = 54), or both (n = 25) to evaluate the recurrence during the follow-up period. Most of the patients (n = 435, 80%) underwent radioiodine scan with diagnostic or therapeutic dose after surgery.

Image analysis

We used the HDI 5000 (Advanced Technology Laboratories, Bothell, Washington) or the LOGIQ700 ultrasound scanners (GE Medical Systems, Milwaukee, Wisconsin) equipped with 12- to 5-MHz linear-array transducers. Thyroid US was performed for preoperative evaluation by 1 of 4 board-certified radiologists or 1 of 4 senior residents. Both longitudinal and transverse scans were obtained using gray-scale. However, color Doppler scan was not routinely obtained, which was available in 106 (21.7%) of 488 patients. All US images were retrospectively reviewed by 2 board-certified radiologists until consensus was reached, one (S.J.H) of whom was involved in the original US studies, whereas the other (N.S.Y.) was not. At the time of the review, readers were blinded to the exact histologic subtype of the PTC. Malignant-looking PTCs (M-PTCs) were defined as those showing at least 1 accepted sonographic criterion: taller than wide shape, marked hypoechogenicity, microcalcifications, and infiltrative border (22, 23). Benign-looking PTCs (B-PTC) were defined as tumors without any of the accepted US criteria. Patients with M-PTCs and B-PTCs were then compared in terms of patient age, patient sex, tumor size, histological subtype, multifocality, LN metastasis, extrathyroidal extension, stage, recurrence, and distant metastasis. We also evaluated these prognostic factors according to tumor size ($<$1.0 and $\geq$1.0 cm). We investigated how many worrisome US findings were correlated with prognostic factors and which features were correlated with poor prognostic findings.

Histopathology

Histopathology was evaluated by pathologic reports. Index tumors were assessed for tumor node metastasis (TNM) staging, using the American Joint Committee on Cancer/International Union Against Cancer pathologic TNM classification criteria (24).

Histological subtypes were divided into two categories: not aggressive and aggressive (25–27). The not aggressive subtype included classic, follicular, and oncocytic variants (28). Tall cell, columnar cell, diffuse sclerosing, solid, and insular variants of PTC were defined to be aggressive subtypes.

Statistical analysis

Patients with B-PTCs and M-PTCs were compared according to patients' age and tumor size using Wilcoxon's 2-sample test. Patients' gender, multifocality, extrathyroidal extension, LN metastasis, stage, tumor recurrence, and histological subtype in 2 groups were compared using the χ^2 test or Fisher's exact test. Associations between M-PTCs and prognostic factors were evaluated by using logistic regression analysis. With adjustment for all variables, multiple logistic regression analysis was performed to determine independent predictors of M-PTCs from prognostic factors. We further analyzed that prognostic factors between groups (0, 1, 2, 3, and 4) according to the number of malignant US findings were compared using logistic regression analysis. Each US feature was compared with the presence and absence of prognostic factors using χ^2, Fisher's exact test, and logistic regression. The prediction powers of each US feature for poor prognostic factors (extrathyroidal extension, LN metastasis, and a high stage) were assessed using area under the curve (AUC) and compared using Delong's method. The risk for recurrence of prognostic factors was assessed using Fisher's exact test, χ^2 test, and logistic regression. All statistical analyses were performed with SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina) and a P value $< .05$ was considered to indicate a statistically significant difference.

Results

The clinical characteristics of B-PTCs and M-PTCs are shown in Table 1. B-PTCs accounted for 74 (15.2%) of

Table 1. Univariate Analysis of Clinical characteristics of Patients With B-PTCs and M-PTCs[a]

Characteristics	B-PTCs	M-PTCs	Total	*P* Value
Number	74 (15.2)	414 (84.8)	488	
Sex (male/female)	14/60	71/343	488	.712
Mean age, y	45 (17–73)	47 (13–80)		.905
Tumor size, cm	1.11 (0.3–2.5)	1.10 (0.2–7.5)		.947
Tumor size				
<0.5 cm	7 (9.4)	48 (11.6)	55	
0.5–1.0 cm	38 (51.4)	198 (47.8)	236	
>1.0 cm	29 (39.2)	168 (40.6)	197	
Histologic subtype				1.000
Not aggressive	74 (100.0)	410 (99.0)	484	
Aggressive variant	0 (0.0)	4 (1.0)	4	
Multifocality	18 (24.3)	147 (35.5)	165	.089
Extrathyroidal extension	29 (39.2)	266 (64.3)	295	<.001
LN metastasis	21 (28.4)	190 (45.9)	211	.005
Central	21 (28.4)	185 (44.7)	206	
Lateral	2 (2.7)	45 (10.9)	47	
AJCC TNM stage				.019
I	50 (67.6)	218 (52.7)	268	
II	0 (0)	0 (0)	0	
III	21 (28.4)	139 (33.6)	160	
IV	3 (4.1)	57 (13.8)	60	
Distant metastasis	0	0	0	
Recurrence	1 (1.4)	21 (5.1)	22	.226
LN dissection	59 (79.7)	372 (89.9)		.024
Radioiodine therapy	60 (81.1)	375 (90.6)		.015
Total thyroidectomy	72 (97.3)	408 (98.6)		.348
Lobectomy	2 (2.7)	6 (0.4)		
Follow–up, mo	64 (39–70)	60 (18–71)		

Abbreviation: AJCC, American Joint Committee on Cancer.

[a] Results are shown as number (percent) or mean (range).

488 PTCs (Figure 1), and M-PTCs were 414 (84.8%) of 488 based on US features (Figure 2). Univariate analysis indicated that M-PTC showed a significantly higher proportion of patients with LN metastasis and extrathyroidal extension than B-PTC (45.9% vs 28.4%, $P = .005$; 64.3% vs 39.2%, $P < .001$). Preoperatively, US-detected suspicious LN metastasis was found in 68 (13.9%) of 488 patients. Pathological metastasis was confirmed in 56 (82.4%) of 68 patients. Preoperative central LN metastasis on US was detected in 2 (9.5%) of 21 B-PTC metastatic patients and 54 (29.1%) of 185 M-PTC metastatic patients, whereas lateral LN metastasis was depicted in 0 (0%) of 2 B-PTC metastatic patients and 42 (93.3%) of 45 M-PTC metastatic patients. A significant extrathyroidal extension with pT4a which invaded trachea and nerve was identified in only 3 patients with M-PTC. A higher stage (III and IV) disease was significantly more common in patients with M-PTC than in those with B-PTC. The 74 patients with B-PTC included classic type (n = 68) and follicular variant (n = 6). B-PTC had no aggressive variant. Classic (n = 394), follicular variant (n = 15), oncocytic variant (n = 1), diffuse sclerosing variant (n = 2), and solid variant (n = 2) were observed in M-PTC patients. Patients' age irrespective of subgroup (<45 or ≥45 years), multifocality, and histological subtype were similar between the 2 groups.

The mean follow-up periods for B-PTC and M-PTC patients were 64 and 60 months, respectively. Surgical extent was not different between two groups. Although a higher proportion of M-PTC patients underwent LN dissection and radioiodine therapy compared with B-PTC patients, recurrence was identified in 21 (5.1%) of M-PTC patients and only 1 (1.4%) of the B-PTC patients ($P = .226$). There were no cases of distance metastasis in any patients.

The clinical characteristics of B-PTCs and M-PTCs according to tumor size are shown in Table 2. Extrathyroidal extension and LN metastasis were more significantly common in M-PTC than in B-PTC. The results were significant in tumors of 1 cm or larger, whereas there were no significant differences in tumors smaller than 1 cm.

Table 3 demonstrates the results of multivariate analysis for biological behavior in B-PTC and M-PTC patients. Analyzed variables after adjustment included extrathyroidal extension, LN metastasis, and TNM stage. Odds ratios (ORs) of LN metastasis [OR = 2.236; 97.5% confidence interval (CI) = 1.286–3.888; $P = .0043$], extrathyroidal extension (OR = 2.784; 97.5% CI= 1.674–4.628; $P < .0001$), and a higher stage (OR = 2.842; 97.5% CI =

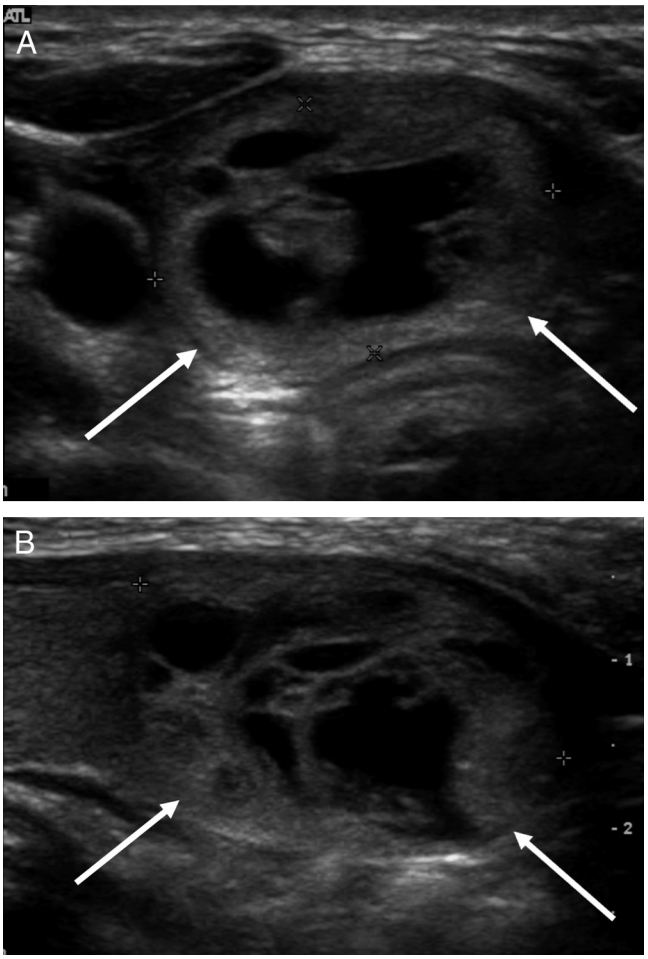

Figure 1. A 21-year-old woman with B-PTC. Transverse (A) and longitudinal (B) ultrasonograms show a 2.7-cm well-defined and isoechoic nodule (arrows) in the right thyroid gland, which was diagnosed as PTC by US-guided FNA. She underwent total thyroidectomy without central LN dissection. A pathologic report revealed a 2.2-cm PTC without extrathyroidal extension.

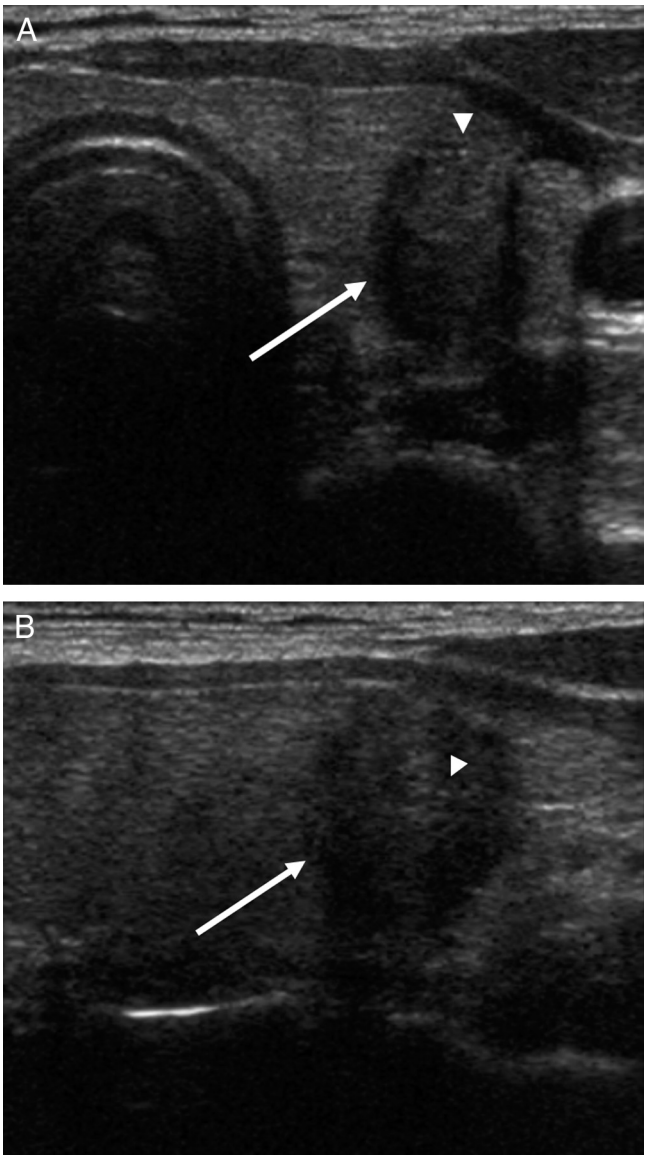

Figure 2. A 40-year-old woman with M-PTC. Transverse (A) and longitudinal (B) ultrasonograms show a 1.1-cm irregular hypoechoic nodule (arrow) with a few microcalcifications (arrowhead). Extrathyroidal extension and central LN metastasis were revealed on a pathologic report after total thyroidectomy with central LN dissection.

1.481–5.453; $P = .0017$) were significantly higher in M-PTC than B-PTC based on multivariate analysis. These factors were also significant in ≥1-cm tumors.

Of 488 nodules, there were nodules having 0 (n = 74, 15.2%), 1 (n = 35, 7.2%), 2 (n = 129, 26.4%), 3 (n = 184, 37.7%), or 4 (n = 66, 13.5%) of 4 US criteria for malignancy. As the number of malignant US features in nodules increased, advanced age ($P = .028$), multifocality ($P = .002$), extrathyroidal extension ($P < .001$), LN metastasis ($P = .007$), a higher stage ($P < .001$), and receiving radioiodine therapy ($P < .007$) were more likely. In a multivariate analysis, a greater number of suspicious US findings was independently associated with multifocality (OR = 1.253; 95% CI = 1.06–1.482; $P = .008$), extrathyroidal extension (OR = 1.38; 95% CI = 1.171–1.625; $P < .0001$), LN metastasis (OR = 1.246; 95% CI = 1.04–1.492; $P = .017$), and a high stage (OR = 1.341; 95% CI = 1.076–1.671; $P = .009$).

A taller than wide shape was correlated with a higher stage ($P = .009$). Nodules with marked hypoechogenicity showed a high frequency of extrathyroidal extension ($P = .005$) and a higher stage ($P = .006$). Microcalcifications and infiltrative border were associated with extrathyroidal extension ($P = .036$ and $P < .001$, respectively) and LN metastasis ($P < .001$ and $P < .001$, respectively). However, there was no statistically significant difference in comparison of each US finding that could predict poor prognostic factors using Delong's method.

Of the 106 patients with color Doppler scan, 53 (50%) nodules showed increased vascularity, whereas the remaining nodules (50%) showed no vascularity.

Table 2. Univariate Analysis of Clinical Characteristics of Patients With B-PTCs and M-PTCs According to Tumor Size

Size	Number (%)	Age		Histologic Subtype		Multifocality	Extrathyroidal Extension	LN Metastasis	AJCC TNM Stage		Recurrence
		< 45 y	≥45 y	Not Aggressive	Aggressive				Low (I or II)	High (III or IV)	
All											
B-PTCs	74 (100.0)	31 (41.9)	43 (58.1)	74 (100.0)	0 (0.0)	18 (24.3)	29 (39.2)	21 (28.4)	50 (67.6)	24 (32.4)	1 (1.4)
M-PTCs	414 (100.0)	154 (37.2)	260 (62.8)	410 (99.0)	4 (1.0)	147 (35.5)	266 (64.3)	190 (45.9)	218 (52.7)	196 (47.3)	21 (5.1)
P value		.443		1.000		0.089	<.001	.005	.018		.226
<1.0 cm											
B-PTCs	45 (60.8)	18 (58.1)	27 (62.8)	45 (60.8)	0 (0.0)	8 (44.4)	16 (55.2)	10 (47.6)	30 (60.0)	15 (62.5)	0 (0.0)
M-PTCs	246 (59.4)	88 (57.1)	158 (60.8)	246 (60.0)	0 (0.0)	76 (51.7)	141 (53.0)	85 (44.7)	138 (63.3)	108 (55.1)	4 (19.0)
P value		1.000		NA		.148	.051	.308	.374		1.000
≥1.0 cm											
B-PTCs	29 (39.2)	13 (38.2)	16 (37.2)	29 (39.7)	0 (0.0)	10 (55.6)	13 (44.8)	11 (37.9)	20 (40.0)	9 (37.5)	1 (100.0)
M-PTCs	168 (40.6)	66 (42.9)	102 (39.2)	164 (40.0)	4 (100.0)	71 (48.3)	125 (80.6)	105 (67.7)	80 (36.7)	88 (44.9)	17 (81.0)
P value		1.000		1.000		1.000	<.001	.018	.101		1.000

Abbreviations: AJCC, American Joint Committee on Cancer; NA, not available.

In our study, the risk for recurrence was independently associated with LN metastasis (OR = 4.362; 95% CI = 1.226–15.521; $P = .022$) and larger tumor size (OR = 1.769; 95% CI = 1.175–2.665; $P = .006$).

Discussion

Although PTCs usually carry a favorable prognosis, some tumors are progressive and become life-threatening for patients (12–15). It is useful to identify patients with poor prognosis using easily accessible parameters. Because US is already used as a preoperative diagnostic tool, US features could serve as important differentiating factors and may be very helpful in predicting the clinical outcomes and appropriate management of patients. Although follicular thyroid cancers that frequently have an oval to round shape with a thick and irregular halo but do not have microcalcifications on US are different from PTCs (29), PTC may be predicted by certain sonographic signatures and combinations of features. Moreover, recent advances in the resolution of US have permitted the qualitative evaluation of carcinoma as the technique of choice for tumor staging (6–11). In this study, however, 74 of the 488 PTC patients (15.2%) lacked US findings typical of PTC and thus failed to be diagnosed with malignant nodules on their initial US evaluation. In our results, about 15.2% of all PTCs may be missed when using US for diagnosis.

Table 3. Multivariate Analysis of Biological Behavior Between M-PTCs and B-PTCs

Factors	OR	CI	*P* Value
All tumors			
Extrathyroidal extension	2.784	1.67–4.63	<.001
LN metastasis	2.236	1.29–3.89	.0043
High stage (III or IV)	2.842	1.48–5.45	.0017
≥1.0-cm tumors			
Extrathyroidal extension	5.03	1.936–13.067	<.001
LN metastasis	3.337	1.267–8.786	.0106
High stage (III or IV)	3.91	1.292–11.833	.0116

Evaluation of the extent of intranodular vascularity of thyroid nodules that are suspicious by ultrasonic criteria is useful in distinguishing benign from malignant nodules (30), However, some investigators suggested that vascularity itself or a combination of vascularity and gray-scale US features was not as useful as the use of suspicious gray-scale US features alone for predicting thyroid malignancy (31). In our study, vascularity was identified in half of the PTCs available. It seems that the application of color Doppler helps differentiate relatively large nodules with a lack of overt malignant features because the assessment of vascularity might be limited in nodules smaller than 1 cm.

In a recent study, spongiform appearance and isoechogenicity were suggested as US indicators for benign nodules, because only 1 of 360 malignant nodules demonstrated this appearance (8). They also reported that although some malignant nodules were ultimately diagnosed, they showed either a predominantly cystic appearance that is strongly predictive of benignity or hyperechogenicity or isoechogenicity, which were considered atypical US features of PTC. These atypical B-PTCs occurred more often than expected. We note that PTC US features at the time of diagnosis have not been described as biological behavior. Numerous studies in the past have suggested factors that may influence the recurrence of PTC. Historically, prognostic variables have included advanced age; aggressive histologic subtypes including tall cell variant, solid variant, insular variant, columnar cell variant, and diffuse sclerosing variant; larger tumor size; and presence of extrathyroidal extension and metastasis (22, 27, 32).

Interestingly, the biological characteristics of B-PTCs differed significantly from those of M-PTCs in our study. Fukushima et al (33) evaluated the difference in biological

characteristics between patients with medullary thyroid carcinoma who have typical findings of thyroid carcinoma and those diagnosed with follicular tumor or benign nodule on US. They reported that the latter showed an excellent prognosis like our results. Although the tumor size of M-PTCs was similar to that of B-PTCs, M-PTC patients had a greater frequency of each extrathyroidal tumor extension, LN metastasis, and a high stage (III or IV), which have been described as significant prognostic factors of PTC. Furthermore, as the number of malignant US features increased, multifocality, extrathyroidal extension, LN metastasis, and a higher stage were more likely. These findings strongly suggest that B-PTC has a more indolent character than M-PTC, although our follow-up period of mean 60 months was relatively short. Only 1 patient (1.4%) with B-PTC had a tumor recurrence, whereas 21 patients (5.1%) with M-PTC had recurrence. This difference was not statistically significant, despite the potential clinical significance. The risk of recurrence was higher in patients with LN metastasis or larger tumor size in the present study.

The rate of PTC misdiagnosis as a benign nodule by US and FNA has been reported to be 3.9% (67 cancers in 1730 patients) (34). Ito et al (34) also reported that none of these patients showed clinicopathological features reflecting biologically aggressive behaviors such as preoperatively detected LN metastasis, massive extrathyroidal extension, and advanced age with the exception of larger tumor size. These studies show that B-PTCs may be sometimes encountered and neglected in clinical practice. However, it is likely an unavoidable problem, although meticulous US examination with experience is critical to limit this problem. As the result of the Ito study with large tumor size, some cases of B-PTCs seen on US were shown not to consist solely of PTC, but rather to have a malignant focus beside or within a benign nodule (such as nodular hyperplasia). Finally, this type of malignancy has the potential to become a tiny micro-PTC, in which the ultimate size is different from that seen on initial US; this carcinoma has an excellent prognosis. B-PTCs carried good prognostic factors in our study, even though B-PTCs had the potential for delayed diagnosis. As such, patients with B-PTC might be reassured and allowed to schedule elective procedures rather than urgent ones based upon the US features.

We routinely evaluated the presence of LN metastasis on preoperative US in all patients. However, we usually focused on LNs of the lateral compartment that could alter surgical extent. In this study, pathological metastasis was confirmed in 56 (82.4%) of 68 US-detected patients. LN metastasis on preoperative US was not mentioned in 155 (73.4%) of 211 patients. However, lateral LN metastasis was depicted in 0 (0%) of 2 B-PTC patients and 42 (93.3%) of 45 M-PTC patients. The reason for a high false-negative US of LN metastasis was that central micrometastatic nodes that did not appear abnormal preoperatively with US were common because nearly routine central neck dissection was performed. Another was that the main interest of the radiologists who performed preoperative US examination was the LNs of the lateral compartment that could change surgical extent and not the central LN, since it was going to be dissected.

Our prognostic factors according to tumor size were significant in groups with $\geq$1 cm only. This reflects that the comparison of smaller PTCs as the basis of US features has no effect on prognostic factors because most tumors smaller than 1 cm are likely to have an excellent prognosis.

The major limitation of our study is that we analyzed clinical records, imaging findings, and pathological data retrospectively. This retrospective approach could have prevented us from identifying important US findings that give a clue to diagnosis in real time, which might have influenced the evaluation of the investigators. In addition, although 15.2% of PTCs were classified as B-PTCs in our result, this may be an underestimate because investigators reviewed images knowing that malignancy was part of the inclusion criteria. As a result, they may have been biased toward identifying malignant features. Recurrence or metastasis may also be underreported because some patients had relatively short follow-up periods of as little as 18 months. The diagnostic accuracy of US criteria is also dependent on tumor size (8). The mean tumor sizes of M-PTCs and B-PTCs in our study were small (about 1 cm) and may have limited our evaluation of tumor characteristics on preoperative thyroid US.

In conclusion, we demonstrated significant differences in biological characteristics between patients with PTC who have typical findings of thyroid carcinoma and those that appeared consistent with benign nodules on US. PTCs that did not meet malignant US criteria have better biological behaviors than PTCs that did, including extrathyroidal extension, LN metastasis, and advanced stage. Therefore, US features at the time of diagnosis can serve as a useful tool to predict biological behavior in PTC.

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