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Ultrasound Echogenicity of Papillary Thyroid Cancer Is Affected by Tumor Growth Patterns and Tumor Fibrosis

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Abstract. *Background/Aim: The association between preoperative ultrasound (US) echogenicity and histopathological characteristics of papillary thyroid cancer (PTC) has been rarely investigated is not well characterized. This study evaluated a relationship between the clinical characteristics of PTC, histopathological phenomena including tumor growth patterns (TGPs) and tumor fibrosis (TF), and US echogenicity. Patients and Methods: In total, 170 patients with PTC (<2 cm) underwent total thyroidectomy with central neck dissection. Demographics, US echogenicity, tumor size, extra-thyroidal extension (ETE), lymph node metastasis (LNM) within the central and lateral neck, TGPs, and TF percentage were reviewed. Results: Patients with TGP II (encapsulated growth with partial pericapsular extension) and III (infiltrative growth) were more frequently burdened by ETE and lateral neck LNM compared to patients with TGP I (encapsulated growth with a well-defined cystic or solid characteristic). Older age was significantly deterministic of TGP III, and male gender and higher TF percentage were independent risk factors for lateral neck LNM. TGP III and TF were independent determining factors for marked hypoechogenicity on US. Conclusion: PTC with TGP II and III and higher tumor fibrosis exhibited more aggressive clinicopathologic behaviors. TGP III and TF were determinants for marked hypoechogenicity.*

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Key Words: Papillary thyroid cancer, ultrasonography, tumor growth pattern, tumor fibrosis, metastasis.

Metastasis of papillary thyroid cancer (PTC) to the cervical nodes is considered quite common; indeed, occult metastasis has been found to occur in 50-60% of cases (1, 2). Although the clinical significance of nodal metastasis and the efficacy of elective neck dissection are uncertain, lymph node (LNM) metastasis to the neck is associated with an increased risk of regional recurrence (3-5) and a higher rate of distant metastasis (6). Ultrasound (US) is the most commonly used diagnostic tool for preoperative staging of PTC. Preoperative tumor characteristics on US, such as tumor size, echogenicity, and tumor contact with capsule, are of considerable prognostic value (7). Notably, marked hypoechogenicity is reported to be predictive of LNM within the central compartment, especially in papillary thyroid microcarcinoma (8).

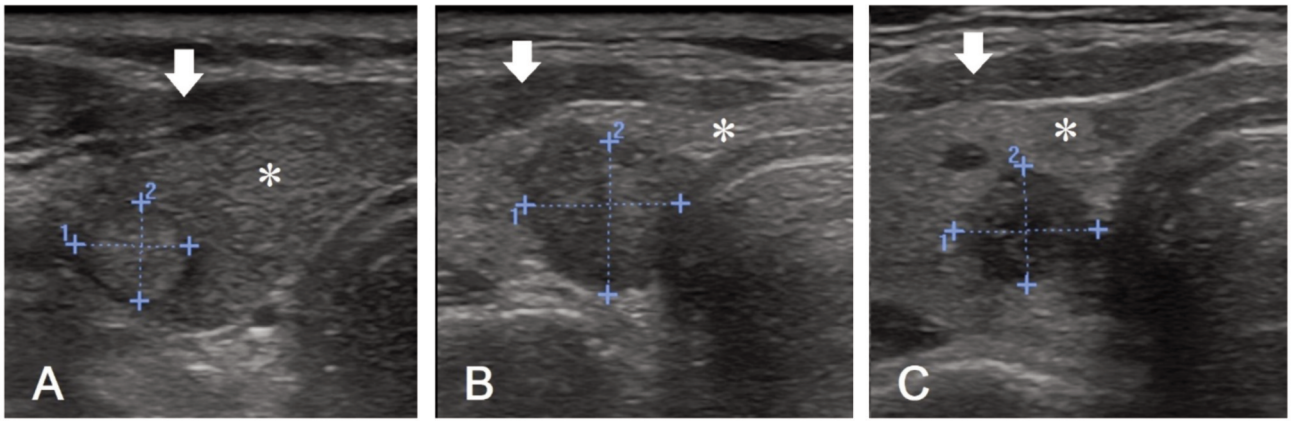

Figure 1. *Three kinds of echogenicity demonstrated by ultrasound imaging. (A and B) The thyroid nodules (area defined by blue crosses) demonstrate the same echogenicity as the normal thyroid tissue (asterisks) (A) and the strap muscle (arrows) (B), which were recorded as isoechoic and hypoechoic. (C) The thyroid nodule with a well-defined spiculated margin in the right thyroid gland shows decreased echogenicity compared to the surrounding strap muscle (arrow), and it was recorded as marked hypoechoic.*

Diligent efforts have been made to ascertain predictive factors for LNM and recurrence based on histopathological characteristics of the tumor. Factors predictive of an aggressive tumor behavior include: i) loss of cellular polarity and cohesiveness, ii) hobnail feature, iii) invasive tumor growth, and iv) lateral tubular growth (9-14). Invasive tumor growth patterns (TGPs) with an infiltrative tumor border are regarded to be predictive of LNM in PTC (13). Tumor fibrosis (TF), superficial tumor location, and intraglandular tumor spread/multifocality combined with the *BRAF* mutation can be used in a molecular-pathologic risk stratification model for a better prediction of aggressive tumors (15).

Although several investigations have been conducted regarding US characteristics as well as tumor histopathology as predictive indicators of aggressive tumor behavior, such as in LNM, there are only a few reports associating the preoperative US echogenicity and histopathological characteristics of the tumor. In this study, we aimed to evaluate the effect of TGPs and TF on the clinical behavior of PTC and analyze the relationship between these two histopathological characteristics and US echogenicity for a better preoperative understanding of the tumor's behavior and management.

Patients and Methods

Study population. Between March 2007 and April 2009, 537 patients diagnosed with PTC underwent surgery at our institution. We collected information of 170 patients with a primary tumor size of less than 2 cm. Revisional cases, tumor size over 2 cm, and histologic variants other than conventional PTC were excluded. All patients underwent near-total or total thyroidectomy with routine central-compartment neck dissection based on the 2006 guidelines of the American Thyroid Association (16). If multiple thyroid tumors were observed on the preoperative US, paratracheal lymph node dissection was performed on the side where the largest tumor was located. Preoperative assessment for cervical LNM included a high-resolution US scan, fine needle aspiration cytology, and a computerized tomography (CT) scan. If there was preoperative evidence of LNM in the lateral neck by preoperative US-guided fine-needle aspiration, lateral compartment dissection was performed. This study was approved by the Pusan National University Hospital Research Ethics Review Board, who granted a waiver of consent for access to clinicopathological records from each participant (H-2003-016-089). All study methodologies were carried out under the guidelines and regulations of the Pusan National University Hospital Research Ethics Review Board.

Ultrasound assessment. The examination was performed by an experienced endocrinologist (SSK) using a US scanner (Vivid i; GE Healthcare, Milwaukee, WI, USA) equipped with a 10- to 13-MHz linear probe. Echogenicity of the tumor was evaluated and categorized as i) isoechogenicity, ii) hypoechogenicity, and iii) marked hypoechogenicity. We defined marked hypoechogenicity as decreased echogenicity compared to that in the surrounding strap muscle. The thyroid nodules demonstrating the same echogenicity as that of the strap muscle and the normal thyroid tissue were recorded as hypoechoic and isoechoic (Figure 1) (17).

Histopathological evaluation including TGPs/TF. Pathologic data of tumor size, extrathyroidal extension (ETE), and LNM in the central and lateral neck were reviewed. TGPs and TFs were retrospectively measured by an experienced head and neck pathologist (DHS). Three kinds of TGPs were defined: i) a well-defined encapsulated growth with a cystic or solid characteristic, ii) an encapsulated growth with partially pericapsular tumor extension, iii) an infiltrative tumor growth (stellate and spiculated margin) (Figure 2). TF was estimated by the percentage of a fibrotic area within the tumor (Figure 3).

Statistical analysis. The χ^2 test or Fisher exact test was used to rule out the role of chance in any associations between pathologic parameters and LNM. Factors related to US echogenicity were

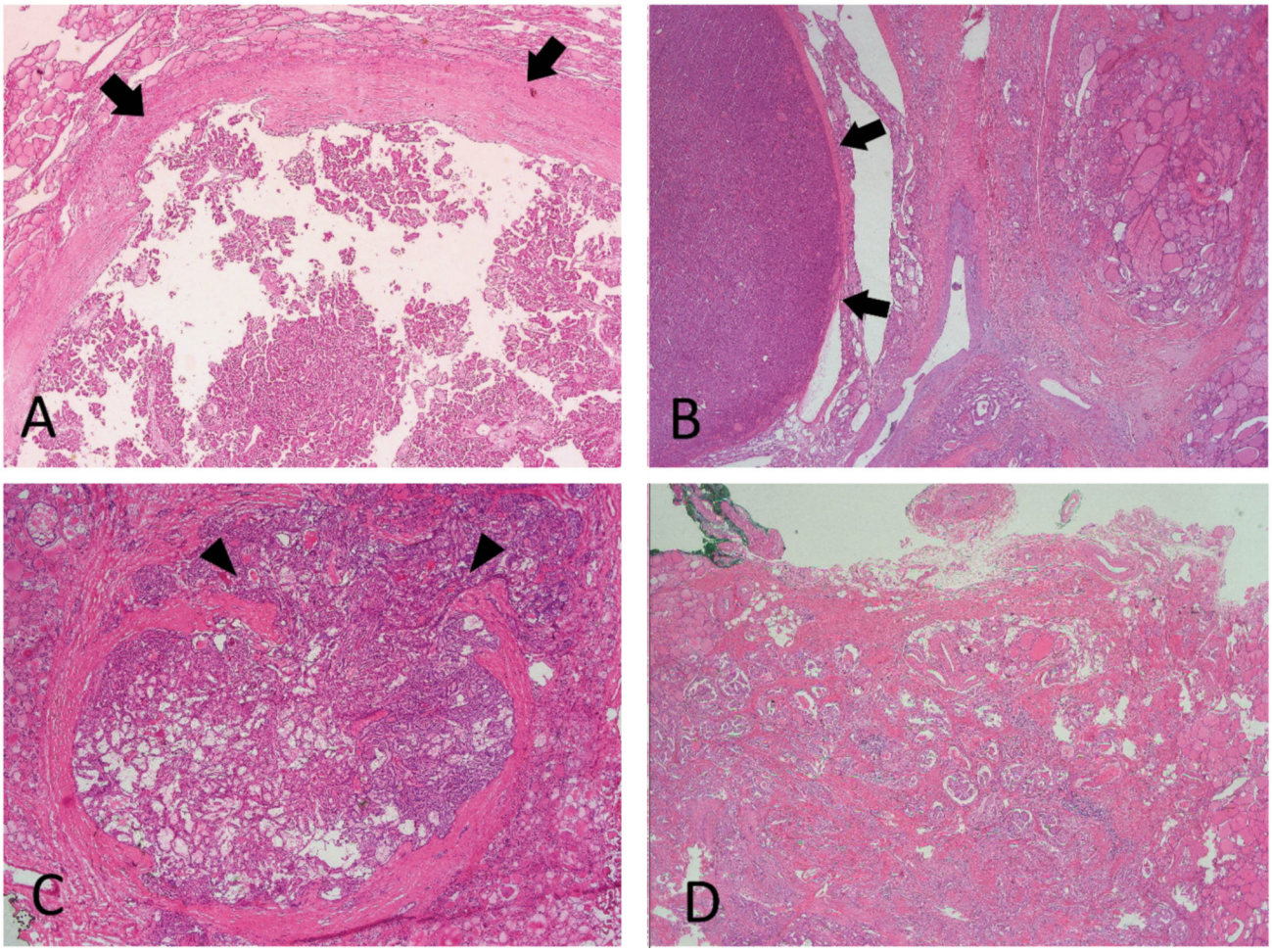

Figure 2. *Tumor growth patterns. By definition, tumor growth pattern I describes a well-defined encapsulated growth (arrow) with a cystic or solid characteristic (A and B). An encapsulated growth with a partially pericapsular tumor extension (arrowhead) is growth pattern II(C), while an infiltrative tumor growth (stellate and spiculated margin) (D) is growth pattern III. (Hematoxylin & Eosin staining, original magnification ×40).*

analyzed using logistic regression analysis. Statistical analysis was performed using the IBM SPSS Statistics for Windows, version 18.0 (IBM Corp., Armonk, NY, USA). Null hypotheses of no difference were rejected if *p*-Values were less than 0.05, or, equivalently, if the 95% confidence intervals (CIs) of risk point estimates excluded 1.

Results

Patient Demographics. Of the 170 patients who underwent surgery for thyroid cancer during the study period, 147 (86%) were female and 23 (14%) were male. The mean age was 50.2 years (range=23-80 years) and the mean size of the primary tumors was 1.24 cm (range=0.2-1.9 cm). Postoperative transient hypocalcemia and temporary vocal fold paresis were noticed in 61 (36%) and 6 patients (3.5%), respectively; however, all of them recovered completely within six months, and there was no permanent hypocalcemia or permanent vocal fold paresis. Nodal involvement in the central and lateral neck occurred in 95 (56%) and 23 (13.5%) cases, respectively. Three kinds of TGPs, namely TGP I, II, and III, were observed in 15 (9%), 99 (58%), and 56 cases (33%), respectively. Mean TF percentage was 28.6 (0-90%). Iso- or hypoechogenicity and marked hypoechogenicity were measured in 80 (47%) and 90 (53%) of cases, respectively (Table I).

Clinicopathologic characteristics by TGPs/TF. TGPs II and III had more frequent ETE than TGP I (I=13.3%, II=63.6%, and III=66.1%; $p<0.005$). The incidence of lateral neck LNM increased with a higher TGP (I=0%, II=12.1%, III=19.6%) (Table II). In multivariate analysis, only the patient age was the significant determining factor for TGP III [$p=0.043$, odds ratio (OR)=1.057] (Table III). There were no significant differences in age, gender, tumor size, or central LNM affecting TF.

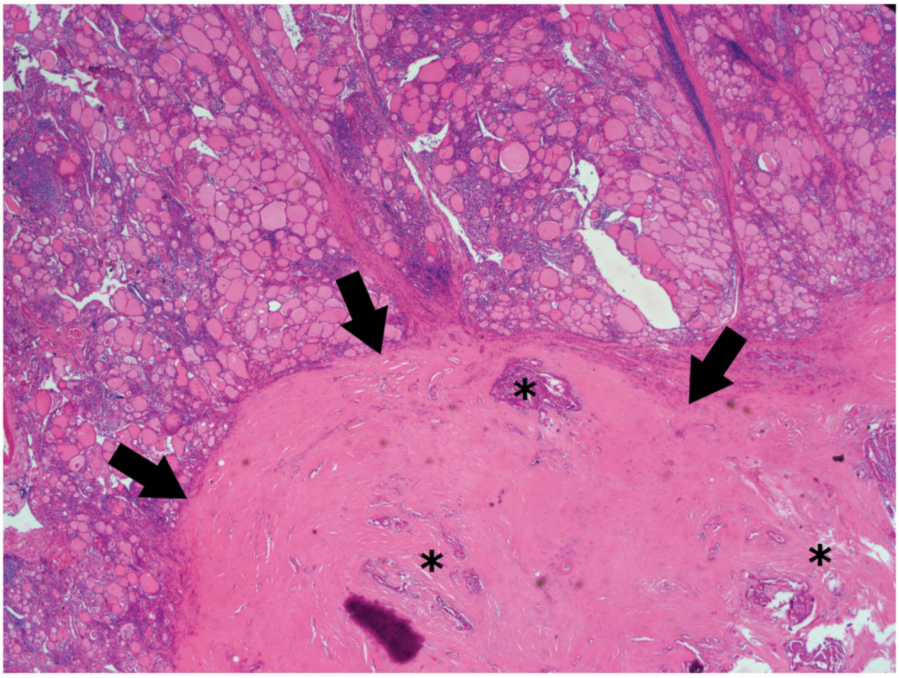

Figure 3. *Intratumoral fibrosis. Multiple tumor foci of PTC (asterisks) are entrapped in dense collagenous fibrosis (arrows), the border of which is well demarcated from the surrounding thyroid tissue. (Hematoxylin &Eosin staining, original magnification ×40).*

LNM by clinicopathological characteristics and TGPs/TF. Tumor size was the significant risk factor for LNM in the central compartment in the multivariate analysis (p=0.007, OR=5.036). This was also the significant factor for lateral neck LNM in the univariate analysis, but the role of chance could not be ruled out in the multivariate analysis. Male gender and a higher percentage of TF were significant risk factors for lateral neck LNM in the multivariate analysis (p=0.015, OR=3.827; p=0.040, OR=1.025) (Table IV).

US echogenicity by clinicopathological characteristics and TGPs/TF. Patient age, gender, and tumor size did not exhibit any significance with respect to the type of US echogenicity; however, TGP II/III and TF were the determining factors for the US marked hypoechogenicity in the univariate analysis. In the multivariate analysis, only TGP III and TF had significance (p=0.033, OR=4.838; p=0.049, OR=1.020) (Table V).

Table I. *Demographics and clinical characteristics of the 170 patients.*

Age at diagnosis, years	50.2±10.9 (23-80)[a]
Gender	
Female	147 (86%)
Male	23 (14 %)
Tumor size, mm	7.4±3.6 (2-20)[a]
Extrathyroidal extension	
Present	102 (60%)
Absent	68 (40%)
Nodal involvement	
Central neck metastasis	95 (56%)
Lateral neck metastasis	23 (13.5%)
Tumor growth patterns[b]	
I	15 (9%)
II	99 (58%)
III	56 (33%)
Tumoral fibrosis (%)	28.6±18.3 (0-90)[a]
Ultrasound echogenecity	
Iso- or hypoechogenicity	80 (47%)
Marked hypoechogenicity	90 (53%)

[a]Mean±standard deviation (range). [b]I: A well-defined encapsulated growth with a cystic or solid characteristic; II: an encapsulated growth with partially pericapsular tumor extension; III: an infiltrative tumor growth.

Discussion

Many studies have been conducted to predict the aggressive behavior of PTC by histopathological analysis. Prominent hobnail features, loss of cohesiveness, and polarity are noted for tumor aggressiveness and LNM (9-12, 14). Tumor border is also a significant prognostic element of the aggressive behavior in PTC (18-20). Jung *et al*., have reported that the infiltrative tumor border is a strong predictive factor for LNM (13). Moreover, lateral tubular growth and intraglandular disseminations are noted as significant risk factors for LNM (19). Tumor fibrosis is known to be associated with poor prognosis by increased tumor recurrence and distant metastasis

Table II. *Clinical characteristics by tumor growth patterns and tumor fibrosis.*

	No. Patients				
	Tumor growth pattern				
Variables	I	II	III	*p*-Value	Tumor fibrosis (%)
No. of patients	15	99	56		170
Age, years[a]	46.4±10.5	49.6±10.6	52.4±11.2	0.675	–
Gender					
Male	1/15 (6.7%)	15/99 (15.2%)	7/56 (12.5%)	0.649	26.7±13.2[a]
Female	14/15 (93.3%)	84/99 (84.8%)	49/56 (87.5%)		28.9±19.0[a]
Tumor size[a]	7.9±3.4	7.4±3.3	7.2±4.2	0.777	–
Extrathyroidal extension	2/15 (13.3%)	63/99 (63.6%)	40/56 (66.1%)	0.000*	–
Central neck metastasis	6/15 (40%)	59/99 (60%)	30/56 (53.6%)	0.335	26.9 *vs*. 30.0[b]
Lateral neck metastasis	0/15 (0%)	12/99 (12.1%)	11/56 (19.6%)	NA[c]	27.6 *vs*. 35.4[b]

NA: Not applicable. [a]Mean±standard deviation. [b]Mean of TF in no metastasis group *vs*. metastasis group. [c]Estimation of *p*-Value is implausible, because there are no occurrences of lateral neck metastasis in patients having a type I tumor growth pattern. *Statistically significant.

Table III. *Logistic regression analysis of clinicopathological factors affecting tumor growth patterns.*

Tumor growth pattern[a]		Univariate			Multivariate		
		OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
II	Age	1.027	0.977-1.080	0.291	1.029	0.979-1.082	0.259
	Gender	0.400	0.049-3.272	0.393	0.398	0.048-3.275	0.392
	Tumor size	0.707	0.181-2.764	0.618	0.608	0.149-2.473	0.487
III	Age	1.053	1.001-1.111	0.047	1.057	1.002-1.116	0.043
	Gender	0.500	0.057-4.414	0.533	0.500	0.056-4.488	0.536
	Tumor size	0.588	0.135-2.560	0.479	0.452	0.099-2.057	0.304

OR: Odds ratio; CI: confidence interval. [a]The reference category is tumor growth pattern I.

in colorectal and oral cavity cancer (21, 22). Also, extensive fibrosis in PTC can predict a more aggressive tumor behavior, such as regional or distant metastasis (15, 23).

Our study demonstrated that more aggressive growth patterns more frequently result in ETE and LNM within the lateral compartment. Multivariate analysis revealed that older age, one of the well-known prognostic factors of PTC, was a significant determinant for the most aggressive histological pattern, namely, TGP III. Furthermore, male gender and TF were significant independent risk factors for lateral neck LNM.

US is a powerful tool for the diagnosis of thyroid malignancy and the prediction of LNM, even though it is not widely used in the detection of central neck LNM due to its lower relative accuracy compared to its accuracy in detecting lateral neck LNM and ETE (24-27). Nevertheless, it has been reported that the US echogenicity of a tumor can be a predictive factor for the ETE and central neck LNM (7). Others have shown cases of PTC with LNM in the lateral compartment with US hypoechogenicity or marked hypoechogenicity in preoperative evaluation, which means there was no lateral neck LNM in PTC with isoechogenicity (8).

To the best of our knowledge, only a few studies have focused on the relationship between preoperative US echogenicity, tumor histological characteristics, and clinical manifestations such as regional LNM. Wang *et al*., have analyzed the associations of ultrasonographic margin status of PTC with histopathological parameters (28). It was noted that half of the malignant nodules had a well-defined boundary on the US and the remaining half had an ill-defined border. Well-defined boundaries on the US were associated with well-defined histological margins, with or without the presence of an intact fibrous pseudo-capsule. Half of the malignant nodules with ill-defined boundaries on the US exhibited infiltration into the surrounding thyroid tissue, whereas the remaining half with ill-defined boundaries presented with irregular histological margins rather than infiltration (28).

Table IV. *Logistic regression analysis of clinicopathologic factors and TGPs/TF for central and lateral lymph node metastasis (LNM).*

	Central LNM						Lateral LNM					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age	0.989	0.962-1.017	0.440	0.977	0.948-1.008	0.143	1.028	0.986-1.072	0.187	1.018	0.975-1.064	0.410
Gender	1.570	0.627-3.930	0.335	1.420	0.537-3.752	0.480	3.582	1.280-10.021	0.015	3.827	1.291-11.343	0.015
Tumor size, mm	5.119	1.752-14.956	0.003	5.036	1.562-16.233	0.007	3.120	1.091-8.923	0.034	2.703	0.851-8.589	0.092
ETE	2.010	1.078-3.750	0.028	1.406	0.683-2.894	0.355	2.067	0.771-5.543	0.149	1.358	0.459-4.015	0.580
TGP												
I	1			1			NA[a]			NA[a]		
II	2.212	0.730-6.702	0.160	1.908	0.534-6.821	0.320	NA[a]			NA[a]		
III	1.731	0.543-5.515	0.354	1.650	0.423-6.445	0.471	NAa			NA[a]		
TF	1.009	0.992-1.027	0.285	1.406	0.683-2.894	0.355	1.020	1.001-1.042	0.061	1.025	1.001-1.049	0.040

OR: Odds ratio; CI: confidence interval; ETE: extrathyroidal extension; TGP: tumor growth pattern; TF: tumor fibrosis; NA: not applicable. [a]Estimation of odds ratios and CIs are implausible, because there are no occurrences of lateral LNM in patients having type I of tumor growth pattern.

Table V. *Logistic regression analysis of clinicopathological factors and TGPs/TF for US echogenicity.*

	Iso- or hypoechogenicity	Marked hypoechogenicity	Univariate			Multivariate		
No. of patients	80	90	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age	50.7±9.9	49.9±11.8	0.993	0.966-1.021	0.639	0.988	0.959-1.018	0.427
Gender								
Female	67/80 (83.7%)	80/90 (88.9%)	1			1		
Male	13/80 (16.3%)	10/90 (11.1%)	0.644	0.266-1.563	0.331	0.650	0.260-1.626	0.357
Tumor size, mm	7.8±3.9	7.0±3.2	0.536	0.225-1.278	0.159	0.590	0.239-1.457	0.252
TGP								
I	12/80 (15.0%)	3/90 (3.3%)	1			1		
II	47/80 (58.7%)	52/90 (57.8%)	4.426	1.179-16.653	0.028	3.268	0.818-13.048	0.094
III	21/80 (26.3%)	35/90 (38.9%)	6.667	1.687-26.393	0.007	4.838	1.133-20.660	0.033
TF, %	24.5±13.5	32.3±21.2	1.026	1.007-1.046	0.007	1.020	1.010-1.040	0.049

OR: Odds ratio; CI: confidence interval; TGP: tumor growth pattern; TF: tumor fibrosis.

In this study, we investigated the relationship between aggressive histological features, such as TGPs and TF, and clinical manifestations, such as LNM in the central and lateral neck. Univariate analysis revealed that TGP II/III and the percentage of TF were the significant factors determining US marked hypoechogenicity, while in the multivariate analysis, TGP III and TF were the significant determinants of marked hypoechogenicity. Taken together, it can be reasonably inferred that tumors exhibiting more invasive TGPs and a higher percentage of TF, which may be associated with more frequent ETE and lateral neck LNM, can have a marked hypoechogenicity on the preoperative US.

The limitations of this study are the lack of i) a large number of cases and ii) long-term follow-up data for regional recurrences or distant metastasis. Despite this, based on the relationship between US echogenicity, histological tumor behavior, and clinical manifestations, this study can provide a more comprehensive understanding of the tumor behavior of PTC concerning the preoperative US echogenicity. This information can be used in personalized treatment strategies for men or older patients.

In conclusion, tumors with more invasive TGPs had more frequent ETE and lateral neck LNM. Older age was the significant determinant for an aggressive growth pattern, while male gender and a higher percentage of TF were significant independent risk factors for the lateral neck LNM. Marked hypoechogenicity of the tumor on US was significantly affected by TGPs and TF. Therefore, it is thought that PTC

with marked hypoechogenicity can have a more aggressive tumor behavior and lead to advanced clinical staging. As such, it can be used as a more personalized and optimized treatment strategy in the treatment of PTC by offering a preoperative prediction of tumor behavior.

Conflicts of Interests

The Authors declare no competing interests.

Authors' Contributions

YSL, JCL and IJK conceived and designed the study. YSL, SMS, SSK and DHS analyzed the data. YSL and BJL drafted the manuscript. All Authors revised the article for important intellectual content, reviewed the data and their analyses and approved this article.

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