

Histopathologic Findings Related to the Indeterminate or Inadequate Results of Fine-Needle Aspiration Biopsy and Correlation with Ultrasonographic Findings in Papillary Thyroid Carcinomas

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Index terms:

Thyroid
Ultrasonography
Pathology
Cancer

DOI:10.3348/kjr.2010.11.2.141

Korean J Radiol 2010; 11: 141-148

Received September 4, 2009; accepted after revision October 14, 2009.

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Objective: To determine histopathologic findings related to the indeterminate or inadequate result of fine-needle aspiration biopsy (FNAB) in papillary thyroid carcinomas (PTCs) and to correlate histopathological findings with ultrasonographic features of tumors.

Materials and Methods: We retrospectively reviewed the medical records of FNAB, histopathologic characteristics, and sonographic findings of the solid portion of 95 PTCs in 95 patients. All cases were pathologically confirmed by surgery. Histopathologic characteristics were analyzed for tumor distribution, microcystic changes, fibrosis, and tumor component. We assumed several histopathologic conditions to be the cause of indeterminate or inadequate results of FNAB, including: 1) an uneven tumor distribution, 2) > 30% microcystic changes, 3) > 30% fibrosis, and 4) < 30% tumor component. Ultrasonographic findings of each PTC were evaluated for echotexture (homogeneous or heterogeneous), echogenicity (markedly hypoechoic, hypoechoic, isoechoic, or hyperechoic), and volume of the nodule. We correlated histopathologic characteristics of the PTC with results of the FNAB and ultrasonographic findings.

Results: From 95 FNABs, 71 cases (74%) were confirmed with malignancy or suspicious malignancy (PTCs), 21 (22%) had indeterminate results (atypical cells), and three (4%) were negative for malignancy. None of the assumed variables influenced the diagnostic accuracy of FNAB. Tumor distribution and fibrosis were statistically correlated with ultrasonographic findings of the PTCs ($p < 0.05$). Uneven tumor distribution was related with small tumor volume, and fibrosis over 30% was correlated with homogeneous echotexture, markedly hypoechoic and hypoechoic echogenicity, and small tumor volume ($p < 0.05$).

Conclusion: No histopathologic component was found to correlate with improper results of FNAB in PTCs. In contrast, two histopathologic characteristics, uneven distribution and fibrosis, were correlated with ultrasonographic findings.

Papillary thyroid carcinoma (PTC) is the most common cancer of the thyroid. Fine-needle aspiration biopsy (FNAB) is an established test for the evaluation of thyroid nodules. However, in up to 20% of cases, even repeated aspiration does not yield diagnostic material. In addition, very scant aspirates of borderline adequacy may be a source of diagnostic error. There are several causes of these inadequate results, which include: 1) technical errors and inaccurate methods like a palpation-guided FNAB and 2) cystic changes of the mass (1). Other factors have been reported to influence unsuccessful FNABs, including small nodule size, the

position of the nodule within the thyroid, and the patient's age and body habitus (2, 3). However, except for cystic component there have been no reports about histopathologic characteristics being a factor of indeterminate or inadequate results of FNAB.

Papillary thyroid carcinomas show a variety of sizes, shapes, margins, echotextures, and echogenicities in ultrasonographic investigations. Chan et al. (4) reported that hypoechogenicity, microcalcifications or no calcifications, well-defined margins, and intrinsic hypervascularity were common findings of papillary carcinomas. Tumors with hyperechoic or mixed echo texture, cystic elements, irregular margins, hypovascularity, and coarse or peripheral calcifications were uncommon findings. In addition, there are many reports on ultrasonographic findings of malignant thyroid carcinomas such as marked hypoechogenicity, spiculated margins, taller than wide shape, and calcifications (5, 6). However, there have been few reports that identified the meaning of ultrasonographic findings in correlation with histopathologic characteristics of thyroid nodules (2, 7).

The aim of this study was to determine histopathologic findings related to indeterminate or inadequate result of FNAB in PTCs and to correlate histopathologic findings with ultrasonographic features of the tumor.

MATERIALS AND METHODS

Between September 2008 and January 2009, 306 patients underwent a thyroidectomy, including PTC (n = 221). Of 221 patients, we included 95 who had one PTC in both thyroid glands and had the medical records of FNAB, ultrasonographic findings, and histopathologic findings. We excluded PTCs with inadequate histopathologic findings

due to a previous frozen study during operation and lesions with a greater than 50% cystic portion because the cystic component is a known factor for indeterminate or inadequate results of FNAB.

We retrospectively reviewed the medical records of FNABs, ultrasonographic findings and histopathologic findings of 95 PTCs in 95 patients (75 women, 20 men; age range, 23–73; median age, 48 years). Each case had greater than 90% solid component. This study was approved by the ethics review board of our hospital, and informed consent was waived for this retrospective study.

Real-time ultrasonography and FNAB of thyroid nodules were performed by experienced radiologists using a 5- to 15-MHz transducer. They usually did sufficient to and fro movements of the needle during the FNAB in multiple directions. The images were obtained from axial scans of the thyroid nodule. Several axial images of each thyroid papillary carcinoma were used for the analysis. The location and size of the nodules were recorded and volume was calculated. Cytological diagnoses were classified into one of five categories: 1) malignant (PTC, medullary carcinoma, etc.), 2) suspiciously malignant, 3) indeterminate (atypical cells and follicular neoplasm), 4) negative for malignancy (benign), or 5) inadequate result. We considered the malignant and suspiciously malignant cases as proper FNABs and other results as improper FNABs. After the surgical removal of the nodule, the gross specimen was examined and several histopathologic slices were made according to the axial plane. Histopathologic slices underwent routine paraffin embedding and Hematoxylin & Eosin (H & E) staining. Histopathologic findings corresponding to the ultrasonogram were reviewed via light microscopy by an experienced thyroid pathologist.

The ultrasonographic findings of each PTC were

Table 1. Correlation between Result of Fine-Needle Aspiration Biopsy and Tumor Location and Volume

		PTC	IR
Tumor location	Rt (n = 55)	43 (78%)	12 (22%)
	Lt (n = 39)	27 (69%)	12 (31%)
	Isthmus (n = 1)	1 (100%)	0 (0%)
Position in thyroid gland	Upper (n = 15)	13 (87%)	2 (13%)
	Middle (n = 66)	50 (76%)	16 (24%)
	Lower (n = 13)	7 (54%)	6 (46%)
	Isthmus (n = 1)	1 (100%)	0 (0%)
Volume*	< 0.5 ml (n = 64)	49 (77%)	13 (23%)
	> 0.5 ml (n = 31)	22 (71%)	8 (29%)

Note.— PTC = papillary thyroid carcinoma, IR = improper result of fine-needle aspiration biopsy (atypical cells + negative for malignancy), Rt = right, Lt = left, * Volume = anteroposterior × transverse × longitudinal diameter / 2

Table 2. Correlation between Histopathologic Characteristics and Result of Fine-Needle Aspiration Biopsy

		Total (n = 95)	PTC 71 (75%)	IR 24 (25%)
Distribution	Even (n = 45)	37 (82%)	8 (18%)	
	Uneven (n = 50)	34 (68%)	16 (32%)	
Microcystic change	< 30% (n = 92)	68 (74%)	21 (26%)	
	> 30% (n = 3)	3 (100%)	0 (0%)	
Fibrosis	< 30% (n = 61)	47 (77%)	14 (23%)	
	> 30% (n = 34)	14 (41%)	10 (59%)	
Tumor component	< 30% (n = 11)	9 (82%)	2 (18%)	
	> 30% (n = 84)	62 (74%)	22 (26%)	

Note.— PTC = papillary thyroid carcinoma, IR = improper result of fine-needle aspiration biopsy (atypical cells + negative for malignancy)

evaluated by two radiologists for echotexture, echogenicity, and size by mutual agreement. The echotexture of each lesion was classified as homogeneous or inhomogeneous. The internal echogenicity of the solid portion of the nodule was classified as markedly hypoechoic, hypoechoic, isoechoic, or hyperechoic with respect to the thyroid parenchyma and strap muscle (2, 3). The volume of the nodule was calculated using the measured size (anteroposterior, transverse, and craniocaudal dimension) and categorized as less or greater than 0.5 mL.

Histopathologic characteristics of each papillary carcinoma were analyzed for the cancer distribution, microcystic changes, calcification, fibrosis, and tumor component. The cancer distribution was categorized as 'even' if tumor cells were evenly distributed throughout the mass and as 'uneven' if tumor cells were focally placed and non-tumor components were seen in over one third of the nodule. Microcystic changes were defined in cases where there was a cystic change on microscopy but not on the gross view. These microcystic changes were classified as greater or less than 30%. The fibrosis and the tumor component were also classified as greater or less than 30%. Analyzed histopathologic characteristics were correlated with results of FNABs. We also correlated histopathologic characteristics of PTCs with ultrasonographic findings to identify the significance of ultrasonographic findings. We postulated that following histopathologic characteristics might cause improper FNAB results: 1) an uneven tumor distribution, 2) > 30% microcystic

changes, 3) > 30% fibrosis, and 4) a small tumor component (< 30%). We then tested whether this hypothesis is valid.

Statistical differences between proper and improper results of FNAB were calculated by means of chi-squared test and a *p* value less than 0.05 was considered to indicate statistical significance. A Fisher's exact test for 2 × 2 tables and Pearson chi-square were used to analyze data sets for values that were small.

RESULTS

Of 95 FNABs performed on 95 patients, 71 cases (74%) were malignancy or suspicious malignancy (PTCs), 21 nodules were indeterminate results (atypical cells), and three nodules were negative for malignancy (benign). Therefore, proper results were obtained from 71 cases and 24 cases had improper FNAB.

The results of FNAB, tumor location, and tumor volume are shown in Table 1. The location of PTCs such as the right or left, upper, middle, or lower portion of the gland, and tumor volume did not influence the result of FNAB. Improper results were more common in female patients (20 of 75, 27%) than males (4 of 20, 20%) and in older patients (mean age: proper results, 47.5 years; improper results, 50.6 years). However, the result was not statistically significant.

The relationship between results of the FNABs and histopathologic characteristics is shown in Table 2. There

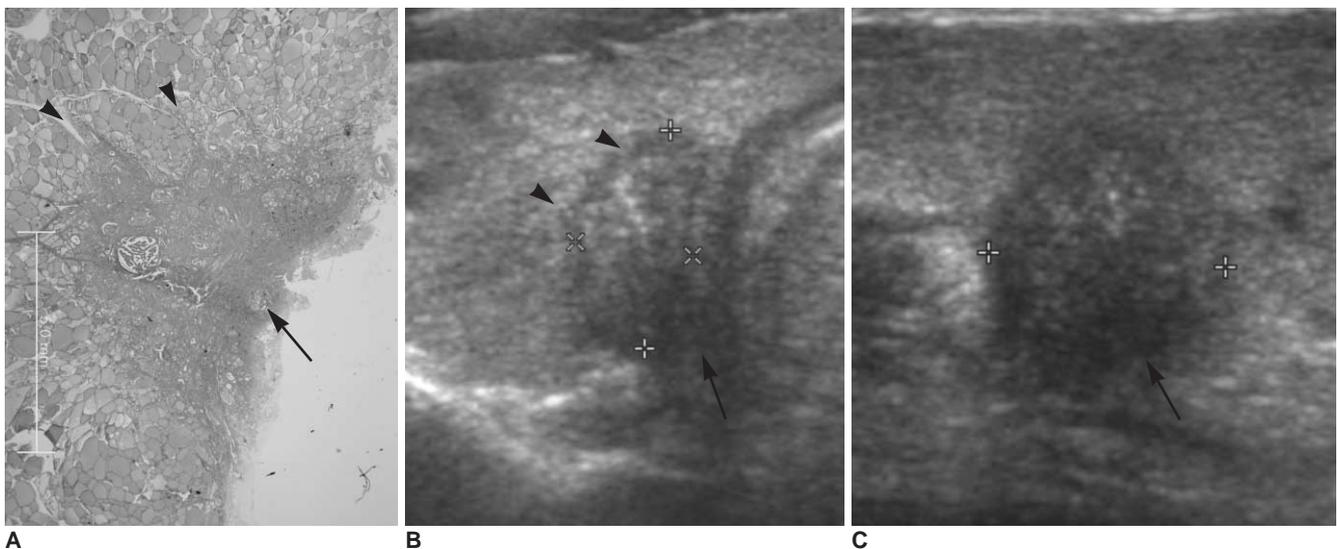


Fig. 1. Histopathologic (A, ×12.5) and ultrasonographic images (B, C) of papillary thyroid carcinoma with uneven distribution and prominent fibrosis of right thyroid gland in 29-year-old male with improper result of fine-needle aspiration biopsy. Uneven distribution of tumor cells, prominent fibrosis (arrows) > 30%, and no microcystic change are seen on histopathologic image (A). Axial (B) and longitudinal (C) ultrasonographic images show heterogeneous echogenicity, markedly hypoechoic or hypoechoic echogenicity (arrows), and spiculated margin (arrowheads). Result of fine-needle aspiration biopsy was indeterminate (atypical cells).

was no statistically significant correlation between results of FNABs and all four assumed histopathologic characteristics. However, nodules with uneven tumor distribution frequently showed improper results on FNABs, although the result was not statistically significant (Fig. 1).

When histopathologic characteristics were correlated with ultrasonographic findings (Table 3), a good correlation was found in tumor distribution and fibrosis: between tumor distribution and tumor volume; between fibrosis and echotexture, echogenicity, and volume. Uneven distribution was predominantly seen in nodules with small volume less than 0.5 mL ($p < 0.05$) (Fig. 2). In addition, an uneven distribution was more frequently seen in nodules with improper FNAB results than in nodules with proper results, although this result was not statistically significant (Table 2). A significant correlation was found between

fibrosis over 30% and homogeneous echotexture, markedly hypoechoic and hypoechoic echogenicity, and small tumor volume less than 0.5 mL ($p < 0.05$) (Fig. 3). No ultrasonographic findings in correspondence with the other two histopathologic characteristics of microcystic change and tumor component were found to be significant.

DISCUSSION

Fine-needle aspiration biopsy is the method of choice for the evaluation of thyroid nodules. However, a non-diagnostic result has been reported in up to 20% of cases, though the success rate has increased with the recent advance of the ultrasonography-guided FNAB (2, 3). Management of the non-diagnostic thyroid nodule is important because the incidence of malignancy among

Table 3. Correlation between Histopathologic Characteristics and Ultrasonographic Findings

		Echotexture		M Hypo	Echogenicity		Hyper	Volume	
		Homo	Hetero		Hypo	Iso		< 0.5 ml	> 0.5 ml
Distribution	Even (n = 45)	19	26	7	25	13	0	24	21
	Uneven (n = 50)	23	27	15	26	9	0	37*	13
Microcystic change	< 30% (n = 92)	41	51	22	49	21	0	60	32
	> 30% (n = 3)	1	2	0	2	1	0	1	3
Fibrosis	< 30% (n = 61)	22	40	8	36	18	0	31	31
	> 30% (n = 34)	20*	13	14 [†]	15 [†]	4	0	29*	4
Tumor component	< 30% (n = 11)	5	6	2	6	3	0	9	2
	> 30% (n = 84)	37	47	20	45	19	0	51	33

Note.— Homo = homogeneous echogenicity, Hetero = heterogeneous echogenicity, M Hypo = marked hypoechogenicity, Hypo = hypoechogenicity, Iso = isoechogenicity, Hyper = hyperechogenicity
 * $p < 0.05$, [†] $p < 0.05$

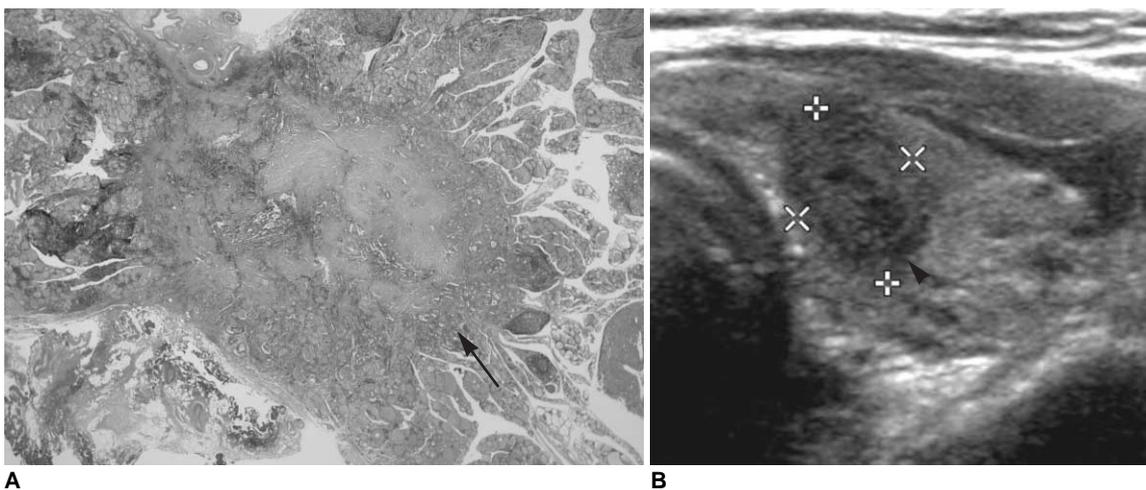


Fig. 2. Histopathologic (A, $\times 12.5$) and ultrasonographic (B) finding of small papillary thyroid carcinoma ($8 \times 5 \times 9$ mm, 0.2 ml) with uneven distribution and prominent fibrosis in left thyroid gland of 50-year-old female. Uneven distribution of tumor cells (A) is seen in nodule. Prominent fibrosis $> 30\%$ (arrow) is represented with hypoechoic and markedly hypoechoic echogenicity (arrowhead) on ultrasonography (B). Result of fine-needle aspiration biopsy is malignancy (papillary carcinoma).

them is 5–10% (1, 8, 9).

There are several causes of these inadequate results, including technical errors and palpation-guided FNA, cystic changes of the mass (1), small nodule size, position of the nodule within the thyroid, and patient age and body habitus (5, 3). However, Alexander et al. (1), reported that the cystic content of each nodule was the only significant and independent predictor of non-diagnostic cytology. In fact, the incidence of initial non-diagnostic FNABs increased with a greater cystic content, from 8% in solid nodules to 36% in nodules with a cystic portion greater than 75%. Age, gender, nodule size, nodule location, and solitary versus multi-nodular status were not found to be predictive factors of a non-diagnostic ultrasonography-guided FNAB. As compared with palpation-guided FNAB, the ultrasonography-guided FNAB showed a very low unsuccessful biopsy rate and was particularly useful for the biopsy of the solid portion in predominantly cystic masses (10). Consequently, cystic components may no longer be an issue for FNABs. In the present study, the location of PTC and gender and age of the patient were not found to be correlated with improper results of FNAB (Table 1). We excluded nodules with a cystic portion greater than 50%.

Papillary thyroid carcinoma volume was classified as less or greater than 0.5 mL (10 mm diameter) and was not found to be a predictor of an inadequate result of FNAB in present study. Similarly, Carmeci et al. (10) also reported that nodule size (average size 1.17 ± 1.1 cm) was not a predictor of an inadequate result of FNAB. Kim et al. (11) reported that ultrasonography-guided FNAB was an effective diagnostic procedure in thyroid nodules with a

maximum diameter less than 5 mm: sensitivity, 87%; specificity, 100%; positive predictive value, 100%; negative predictive value, 82%; and accuracy, 92%. Consistently, Kim et al. (12) also reported that sampling adequacy and efficacy of FNAB of thyroid nodules with maximum diameter below 5 mm were satisfactory, although it was less successful than those of nodules with a maximum diameter larger than 5 mm. Those nodules were smaller than ours. The size of thyroid nodules may not be a predictor of inadequate result of FNAB.

Even FNABs of solid nodules were non-diagnostic in 4–7%, suggesting that a low rate of non-diagnostic specimens is inherent to the procedure itself (2, 10). Some reports have described the histopathologic background as a factor of improper result of FNAB. Carmeci et al. (10) reported that one of two cytologically false negative cases showed a small focus of papillary carcinoma within an adenomatoid nodule. Danese et al. (2) described that two of three false negative cases on ultrasonography-guided FNAB revealed a small papillary carcinoma (3.1×4.3 mm) in a prevalently cystic lesion. However, there have been no reports about histopathologic characteristics causing improper results of FNA in a large population. The current study included 95 PTCs in 95 patients. We assumed four histopathologic characteristics to cause improper results of the FNAB, but these histopathologic characteristics were not significantly correlated with the result of FNABs. However, uneven tumor distribution was more frequently seen in cases with improper results of the FNAB although this result was not statistically valuable. In the present report, many PTCs (64 of 95, 67%) were small (less than 0.5 mL, 10 mm

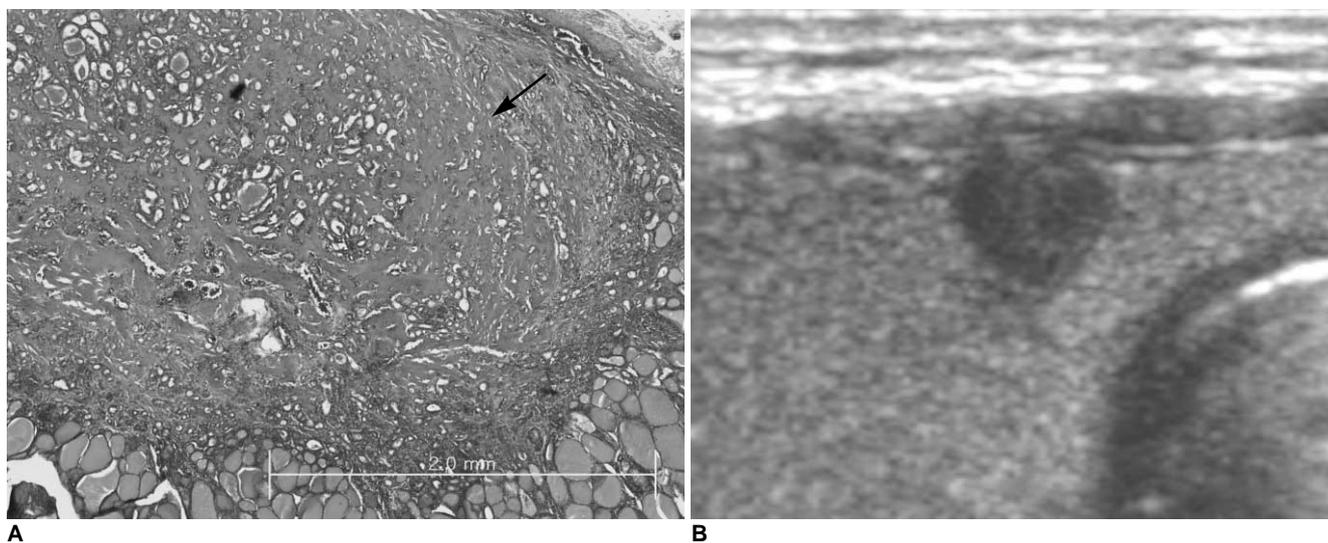


Fig. 3. Histopathologic (A, $\times 12.5$) and ultrasonographic (B) findings of papillary thyroid carcinoma with prominent fibrosis > 30% in right thyroid gland of 28-year-old female. Histopathologic image shows small nodule with uneven tumor distribution and prominent fibrosis (A). Fibrosis (arrow in A) of histopathologic characteristics is represented with homogeneous echotexture and markedly hypoechoogenicity on ultrasonography (B). Result of fine-needle aspiration biopsy is malignancy (papillary carcinoma).

diameter) and we did sufficient to and fro movements of the needle during the FNAB in multiple directions. The uneven distribution effect on improper FNAB results may be less significant in small nodules as compared to large one. The two factors may have contributed to the low sampling error rate and influenced our results.

Various ultrasonographic findings of malignant thyroid

nodules or PTCs have been reported. The findings include a taller-than-wide shape, a spiculated margin, marked hypoechogenicity, micro- or macro-calcification, a well-defined margin, and intrinsic hypervascularity (4-6). To date however, only a limited number of studies have described the results of a comparison between ultrasonographic findings and histopathologic characteristics. A

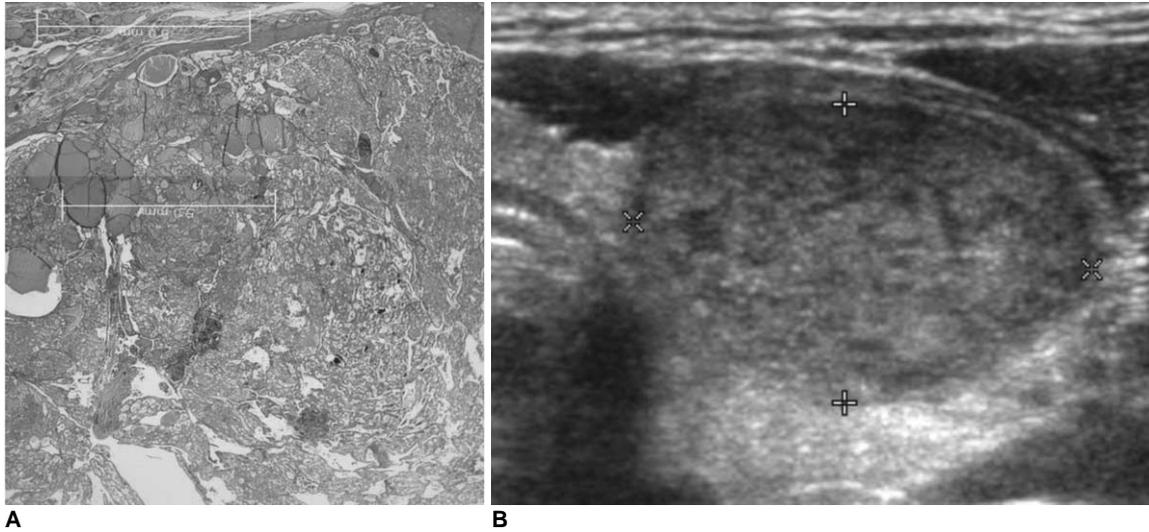


Fig. 4. Histopathologic (A, $\times 12.5$) and ultrasonographic (B) findings of papillary thyroid carcinoma follicular variant with prominent tumor component $> 30\%$ in left thyroid gland of 50-year-old male. Prominent tumor component $> 30\%$ and no fibrosis are seen on histopathologic image (A). These findings are characterized as heterogeneous echotexture and hypoechoic echogenicity on ultrasonography. This mass is larger than 0.5 ml ($16 \times 24 \times 28$ mm, 21.5 ml). Result of fine-needle aspiration biopsy is negative for malignancy (benign).

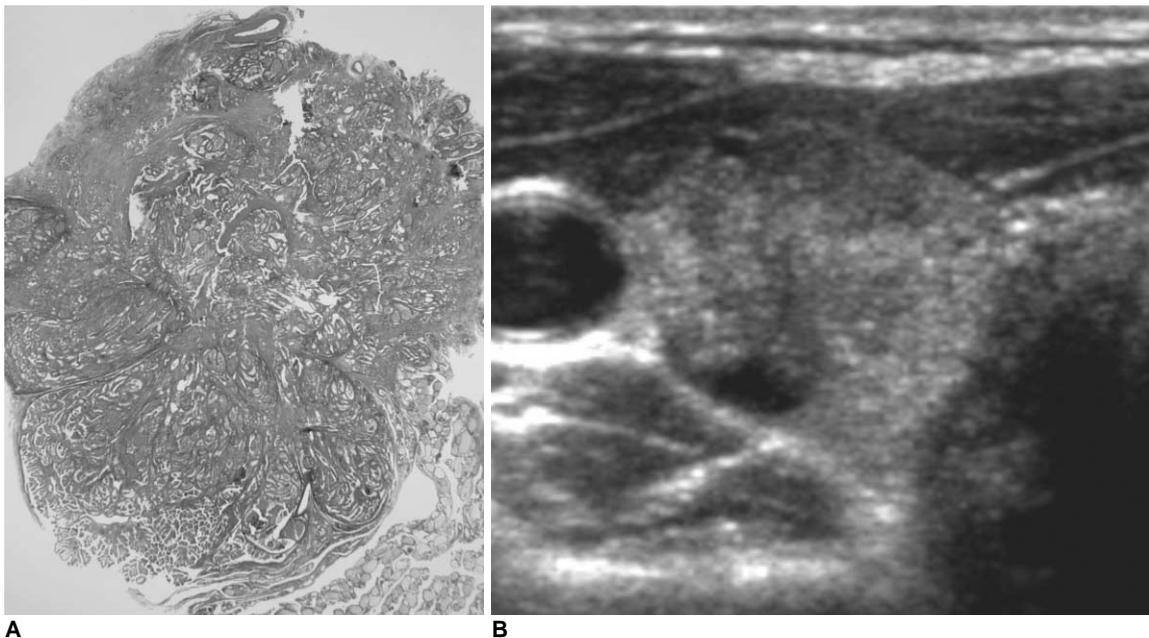


Fig. 5. Histopathologic (A, $\times 12.5$) and ultrasonographic findings (B) of papillary thyroid carcinoma with prominent tumor component ($> 30\%$) in right thyroid gland of 32-year-old male. Histopathologic image shows even tumor distribution and prominent tumor component ($> 30\%$), although some fibrosis $> 30\%$ is seen. No microcystic change is observed. Ultrasonography shows heterogeneous echotexture, isoechogenicity, and ill defined margin. It is larger than 0.5 ml ($12 \times 13 \times 19$ mm, 1.5 ml). Result of fine-needle aspiration biopsy is malignancy (papillary carcinoma).

spiculated margin has also been reported to be indicative of an infiltrated tumor (6). Chen et al. (7) reported that fibrosis showed the lowest echogenicity, enlarged follicles showed the highest echogenicity, and follicular cells and papillary cancer cells showed intermediate echogenicity.

In our study, fibrosis greater than 30% showed a high degree of correlation with homogeneous echotexture, markedly hypoechoic and hypoechoic echogenicity, and small tumor volume (0.5 mL, $p < 0.05$). This result is similar to the report by Chen et al. (7), in that fibrosis showed the lowest degree of echogenicity. However, Chen et al. included both benign and malignant nodules, while we only included PTCs in this study. Chen et al. described that papillary cancer cells showed intermediate echogenicity. We found that the nodules with greater tumor component (over 30%) dominantly showed hypoechogenicity (45 of 84, 54%) (Fig. 4, Table 3) and isoechoogenicity (19 of 84, 23%) (Fig. 5). We classified the echogenicity into four groups (markedly hypoechoic, hypoechoic, isoechoic, and hyperechoic echogenicity), while Chen et al. classified echogenicity into three groups (lowest, intermediate, and high).

Livolsi (13) reported that papillary carcinomas share certain microscopic features. A predominantly papillary pattern is found in 20 to 40% of tumors, a predominantly follicular feature is seen in 15% to 35% of tumors, and equally mixed papillary and follicular features are seen in the remaining tumors. Some reports have described the presence of a correlation between fibrosis and papillary carcinoma. Dense fibrosis is seen in 89% of papillary carcinomas and only 18% of follicular carcinomas (14). Various degrees of intratumoral fibrosis were seen in 67% of the Hashimoto's-associated papillary carcinomas (15). To the best of our knowledge, no reports describing a relation between tumor size (volume) and fibrosis are described in the literature. In our study, fibrosis over 30% was predominantly found in nodules less than 0.5 ml (29 of 33, 88%). We postulate that fibrosis may develop in an early stage of the PTC and is replaced with tumor cells as they grow. However, its pathogenesis is unclear.

This study has some limitations. Our cases were all PTCs. This may have led to the exclusion of PTCs with the false negative result of FNABs. We primarily evaluated histopathologic characteristics as a predictor of improper FNAB results although we evaluated patient age, gender, and PTC location. Hence, all cases were classified into two groups; one having a proper result and the other, an improper result. This was done to eliminate other possible confounding factors that may influence FNAB results such as experience of the radiologist and slight difference in FNAB methods, and difference in other conditions. The

majority of nodules in our cases had a small volume (less 0.5 mL, less than 10 mm in diameter). Our study may be considered an initial attempt to compare ultrasonographic findings and histopathologic characteristics of PTCs. We expect that further studies on this topic we follow.

In conclusion, there is no histopathologic characteristics that explains improper results of FNAB except for a weak correlation found for uneven PTC distribution. The two histopathologic characteristics of the PTCs correlated with ultrasonographic findings. Uneven distribution of PTCs was found to be correlated with small volume (less 0.5 mL), and fibrosis over 30% was found to be correlated with homogeneous echotexture, markedly hypoechoic and hypoechoic echogenicity, as well as small PTC volume (less than 0.5 mL).

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