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# Utility of Preoperative Ultrasonography in Transferred Patients with Suspicious Malignancy on Ultrasonography-Guided Fine-Needle Aspiration Cytology of Thyroid Nodules: A Single-Center Retrospective Study

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**Background:** This study aimed to assess the utility and characteristics of preoperative ultrasonography (US) in patients transferred to referral hospitals from local clinics with a diagnosis of malignancy on US-guided fine-needle aspiration cytology of thyroid nodules.





**Material/Methods:** From January 2018 to June 2018, 109 transferred patients underwent preoperative US in our hospital for suspected thyroid malignancy on cytological analysis after US-guided fine-needle aspiration of thyroid nodules in local clinics. Preoperative US was performed by a single radiologist in all patients. Among them, 6 were excluded from the study because of refusal of thyroid surgery. Preoperative US and histopathological results were compared in all patients.

**Results:** After thyroid surgery, pathological examination revealed papillary thyroid carcinoma (PTC) (n=98), follicular adenoma (n=1), and nodular hyperplasia (n=4). Of the 103 patients, 91 exhibited suspicious US findings on the preoperative US, whereas 12 did not. In the 91 patients with suspicious US findings, PTC (n=90) and follicular adenoma (n=1) were confirmed after thyroid surgery. In the 12 patients with no suspicious US findings, PTC (n=8) and nodular hyperplasia (n=4) were confirmed after thyroid surgery. On repeat analysis of the cytological slides of the 4 nodular hyperplasia cases from the local clinics, Bethesda category II (n=1) and III (n=3) were determined.

**Conclusions:** In the transferred patients with a malignant cytology, preoperative US might be helpful to detect false-positive cytology cases.

**MeSH Keywords:** **Neoplasms • Preoperative Care • Thyroid Nodule • Ultrasonography**

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## Background

The main role of thyroid ultrasonography (US) is to detect thyroid nodules and to assist with the decision on further management (reassurance, US follow-up, or biopsy) [1,2]. In patients with a suspicious thyroid malignancy on cytological analysis, US is the most popular preoperative diagnostic tool for the evaluation of tumor stage, nodal stage, multifocality, and bilaterality [1]. US-guided fine-needle aspiration is used worldwide for the diagnosis of thyroid nodules, and it is safe and accurate [1,2]. The diagnostic accuracy of US-guided fine-needle aspiration cytology of thyroid nodules has progressively increased over time. Until the 1990s, only 30–65% of the aspirates that were considered suspicious for cancer were actually proved to be cancerous [3]. In the 2000s, the malignancy rate of thyroid nodules with a malignant cytology exceeded 90% [4,5]. In the Bethesda classification, the malignancies of Bethesda categories V and VI are 50–75% and 97–99%, respectively, if noninvasive follicular thyroid neoplasm with papillary-like nuclear features is considered as malignancy [6]. Nevertheless, a false-positive or -negative cytology is a significant problem in the management of thyroid nodules. To overcome this limitation, a combined approach of US diagnosis and cytological analysis has been recommended [4,7,8]. However, discordance between US and cytological diagnosis is not rare, and decisions with regard to appropriate management in these cases are difficult [4,7,8]. Furthermore, operator dependency should be considered in both diagnostic methods.

In our country (South Korea), numerous physicians or radiologists with variable degrees of experience perform US diagnosis or US-guided fine-needle aspiration of thyroid nodules. Thus, diagnostic accuracy of US or cytological diagnosis can be different depending on the operators or institutions. Many patients who have undergone US-guided fine-needle aspiration of thyroid nodules and have been diagnosed with malignancy on cytological analysis in local clinics are transferred to referral centers for thyroid surgery. However, the diagnostic accuracy of cytological analysis in local clinics may be different. This leads to the dilemma of whether surgery should be performed immediately in these transferred patients with a malignant cytology.

To the best of our knowledge, no previous study has investigated the diagnostic accuracy and utility of preoperative US in patients transferred to referral centers from local clinics with a cytological diagnosis of malignancy. Thus, this study aimed to evaluate the utility of preoperative US in patients with known malignant thyroid nodules in a referral medical center and to assess whether preoperative US prevents unnecessary surgery in these patients, through a retrospective analysis of US and histopathological findings.

## Material and Methods

### Study population

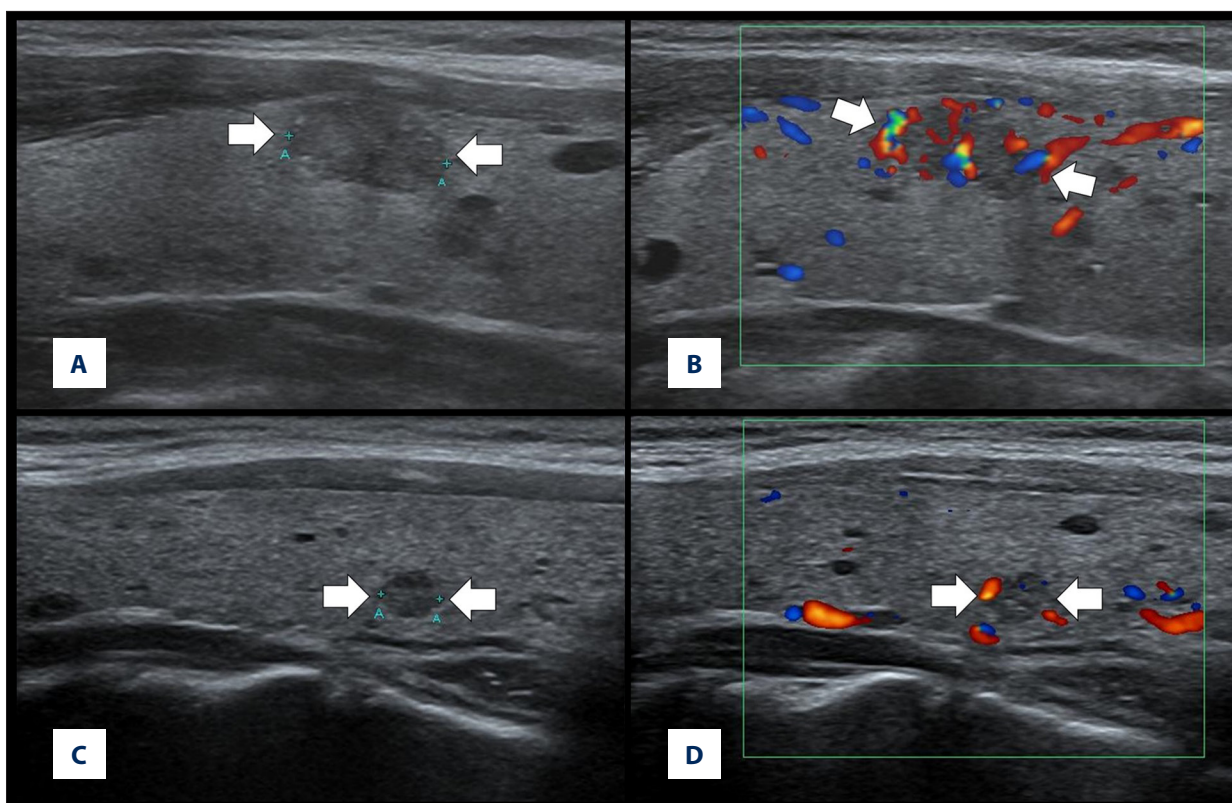
This study was approved by the Busan Paik Hospital institutional review board (IRB 18-0169). Given the retrospective nature of the investigation and the use of anonymized patient data, the requirement for informed consent was waived. Many patients with suspected thyroid malignancy on cytological analysis are transferred for thyroid surgery to our hospital from local clinics, as our hospital is a referral medical center. From January 2018 to June 2018, 109 transferred patients (87 female patients and 22 male patients with a mean age of  $47.3 \pm 12.0$  years; range, 18–75 years) underwent preoperative thyroid US by a single radiologist at our hospital as they exhibited malignant findings on US-guided fine-needle aspiration cytology that was performed in local clinics. Among them, 6 patients were excluded as the patients refused thyroid surgery in our hospital. Ultimately, 103 patients (83 females and 20 males with a mean age of  $47.5 \pm 12.1$  years; range, 18–75 years) were investigated.

### Preoperative ultrasonography

All patients underwent preoperative thyroid US performed by a single radiologist with 15 years of experience in thyroid US. High-resolution ultrasound scanners (iU 22, Philips Medical Systems, Bothell, WA, USA; and Aplio 400, Toshiba Medical Systems, Tokyo, Japan), with a 5–12 MHz and an 8–15 MHz linear probe, respectively, were used. One of the 2 US instruments was randomly used for each patient.

The radiologist was not blinded to the clinico-cytological information from local clinics, and US features of known malignant thyroid nodules were investigated by real-time US. For each nodule, composition (solid [no obvious cystic component], partially cystic [with a cystic component], or cystic [no solid component]), echogenicity (isoechoic, hypoechoic, or hyperechoic), margin (smooth, spiculated/microlobulated, or poorly defined), calcification (no calcification, microcalcification, macrocalcification, or mixed calcification [both micro- and macrocalcifications]), and orientation (parallel [when the anteroposterior diameter of the nodule was equal to or less than its transverse or longitudinal diameter] or non-parallel [when the anteroposterior diameter of the nodule was longer than its transverse or longitudinal diameter on a transverse or longitudinal plane]) were determined by the same radiologist [7,9].

On the basis of real-time US features, each thyroid nodule was classified into a Korean Thyroid Imaging Reporting and Data System (K-TIRADS) category by the same radiologist, as follows: category 2 (benign), 3 (low suspicion), 4 (intermediate suspicion), and 5 (high suspicion) [9]. In terms of US diagnosis,



**Figure 1.** A 43-year-old female patient who underwent total thyroidectomy for papillary thyroid carcinoma (PTC) in both thyroid lobes. Longitudinal gray scale (A) and color Doppler (B) sonograms of the right thyroid lobe obtained before thyroid surgery show a solid thyroid nodule with hypoechogenicity, a microlobulated margin, microcalcifications, a parallel orientation, and mixed vascularity (arrows) (6.4×10.9×13.0 mm, K-TIRADS category 5, classic type). After total thyroidectomy, this nodule was determined as being the primary PTC. Longitudinal gray scale (C) and color Doppler (D) sonograms of the left thyroid lobe obtained before thyroid surgery show a small thyroid nodule with similar US features (arrows) (4.4×4.5×4.8 mm, K-TIRADS category 5, classic type). This nodule was determined as being the satellite PTC.

K-TIRADS categories 4 and 5 were classified as malignant, whereas K-TIRADS categories 2 and 3 were classified as benign. In K-TIRADS, suspicious US features include microcalcification, spiculated/microlobulated margin, and nonparallel orientation [9].

### Pathological analysis

All patients underwent thyroid surgery in our hospital. All histopathological slides were reviewed by a single pathologist with 15 years of experience in thyroid pathology, according to the criteria of the World Health Organization International classification of thyroid tumors [10]. The pathologist retrospectively reviewed the histopathological slides while blinded to the US findings. The subtypes of papillary thyroid cancer (PTC) include classic, follicular variant, tall cell variant, oncocyctic variant, columnar variant, hobnail variant, solid variant, Warthin-like variant, and diffuse sclerosing variant. In cases wherein no thyroid malignancy was found after thyroid surgery, cytological slides were rented from local clinics, and the same pathologist retrospectively reviewed the cytological slides.

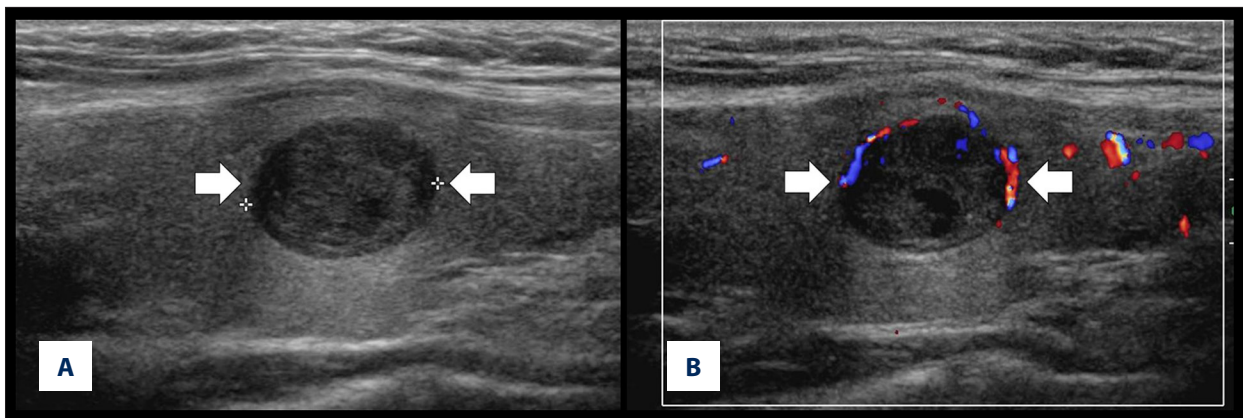
### Statistical analysis

The data were tested for normality using the Kolmogorov-Smirnov test. The age of the patient and size of the thyroid nodule at the time of diagnosis were expressed as mean±standard deviation (SD). To evaluate the differences in thyroid nodules, we used the independent *t* tests for continuous variables and Pearson's  $\chi^2$  test or Fisher's exact test (for small cell values) for categorical variables. All statistical analyses were performed with statistical software (SPSS, version 24.0, IBM Corp., Armonk, NY, USA), and  $P<0.05$  was considered statistically significant.

### Results

Of the 103 thyroid nodules with a malignant cytology in 103 patients, 102 were solid and 1 was partially cystic. Preoperative US diagnosed these nodules as K-TIRADS category 2 (n=0), 3 (n=12), 4 (n=22), and 5 (n=69). The mean largest diameter of these nodules was 9.9±6.4 mm (range, 3.0–34.7 mm). The





**Figure 2.** An 18-year-old female patient who underwent hemithyroidectomy for follicular adenoma in the right thyroid lobe. Longitudinal gray scale (A) and color Doppler (B) sonograms of the right thyroid lobe obtained before thyroid surgery show a solid thyroid nodule with hypoechoogenicity, a smooth margin, no calcifications, a parallel orientation, and peripheral vascularity (arrows) (10.0×14.2×14.9 mm, K-TIRADS category 4). After right hemithyroidectomy, this nodule was confirmed as being follicular adenoma.

nodules were located in the right lobe (n=51), left lobe (n=44), and isthmus (n=8). The types of thyroid surgery included total thyroidectomy (n=32), hemithyroidectomy (n=69), and isthmusectomy (n=2). PTC (n=98), follicular adenoma (n=1), and nodular hyperplasia (n=4) were confirmed on pathological examination. Among the 90 PTCs, the subtypes included classic (n=79), follicular variant (n=8), tall cell variant (n=2), and oncocyctic variant (n=1). On the basis of the pathological results, 31 patients (30.1%, 31 out of 103 patients) had multiple PTCs, whereas 67 patients had a solitary PTC. Among the 31 patients with multiple PTCs, 19 patients (18.4%, 19 out of 103 patients) exhibited bilaterality. The T stage was T1a in 69 patients, T1b in 20 patients, T2 in 8 patients, T3a in 1 patient, T3b in 0 patients, T4a in 0 patients, and T4b in 0 patients. The N stage was N0 in 68 patients, N1a in 24 patients, and N1b in 6 patients.

Of the 103 patients, 91 patients (72 females and 19 males with a mean age of 47.4±12.3 years; range, 18–75 years) exhibited suspicious findings on preoperative US: K-TIRADS category 2 (n=0), 3 (n=0), 4 (n=22), and 5 (n=69). PTC (n=90) and follicular adenoma (n=1) were confirmed on pathological examination. All 90 PTC cases exhibited suspicious US findings on preoperative US, and this corresponded to the malignant cytological diagnosis in the local clinic (Figure 1). In the follicular adenoma case, K-TIRADS category 4 was determined on preoperative US (Figure 2). Patient age and sex, nodule size and location, K-TIRADS category, and pathology according to concordance or discordance between preoperative US in our hospital and cytological analysis in local clinics are compared in Table 1. K-TIRADS and pathology exhibited statistically significant differences ( $P<0.0001$ ), whereas the other parameters did not exhibit any significant differences ( $P>0.05$ ).

Of the 103 patients, 12 patients (11 female and 1 male, mean age of 48.6±11.0 years; range, 25–64 years) exhibited no suspicious findings on preoperative US: K-TIRADS category 2 (n=0), 3 (n=12), 4 (n=0), and 5 (n=0). However, these patients underwent thyroid surgery because of the malignant cytological diagnosis from the local clinics. After thyroid surgery, PTC (n=8) (Figure 3) and nodular hyperplasia (n=4) (Figure 4) were confirmed on pathological examination. In these patients, a single pathologist from our hospital also retrospectively reviewed the cytological slides that we rented from the local clinics. In the repeat cytological analysis, Bethesda categories II (n=1) and III (n=3) were determined in the 4 patients with nodular hyperplasia, whereas Bethesda categories IV (n=5) and V (n=3) were found in the 8 patients with PTC.

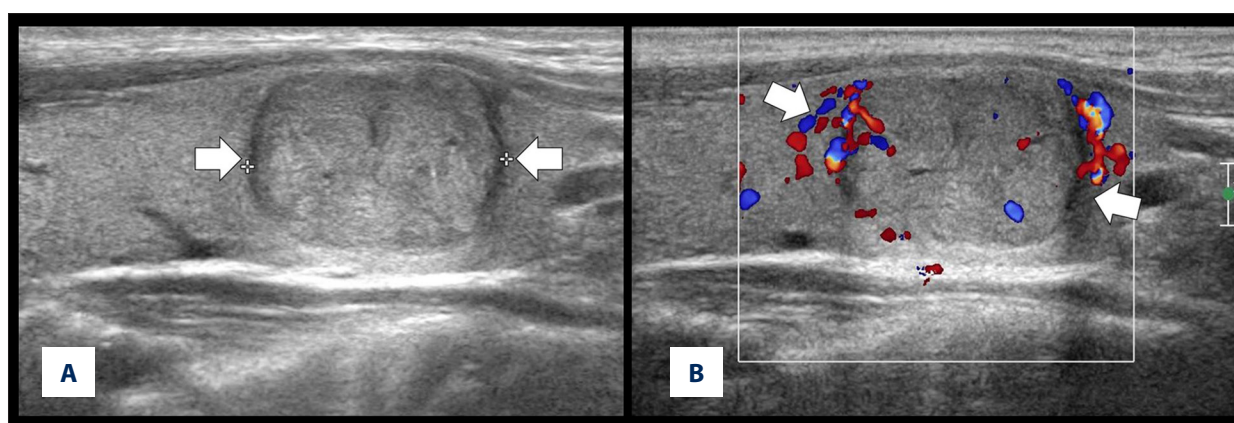
## Discussion

Fine-needle aspiration is the most accurate method for evaluating thyroid nodules, while thyroid US aids decision-making about whether fine-needle aspiration is indicated [1]. In several studies, a combination of thyroid US and cytological result may be helpful in the decision-making process for thyroid nodules [4,7,8]. Nevertheless, false-positive cases are unavoidable in US and cytological diagnoses of thyroid nodules [11–13]. In transferred patients, in particular, US and cytological diagnosis are performed at 2 different institutions and thus there would be differences in terms of patient management compared to that in a single institution. Thus, routine re-reviewing of the cytology at the referred institution may be necessary for appropriate patient management. However, re-reviewing of the cytology may involve costs and time. To our knowledge, no guidelines regarding re-reviewing of the cytology of thyroid nodules in the referred institutions have been

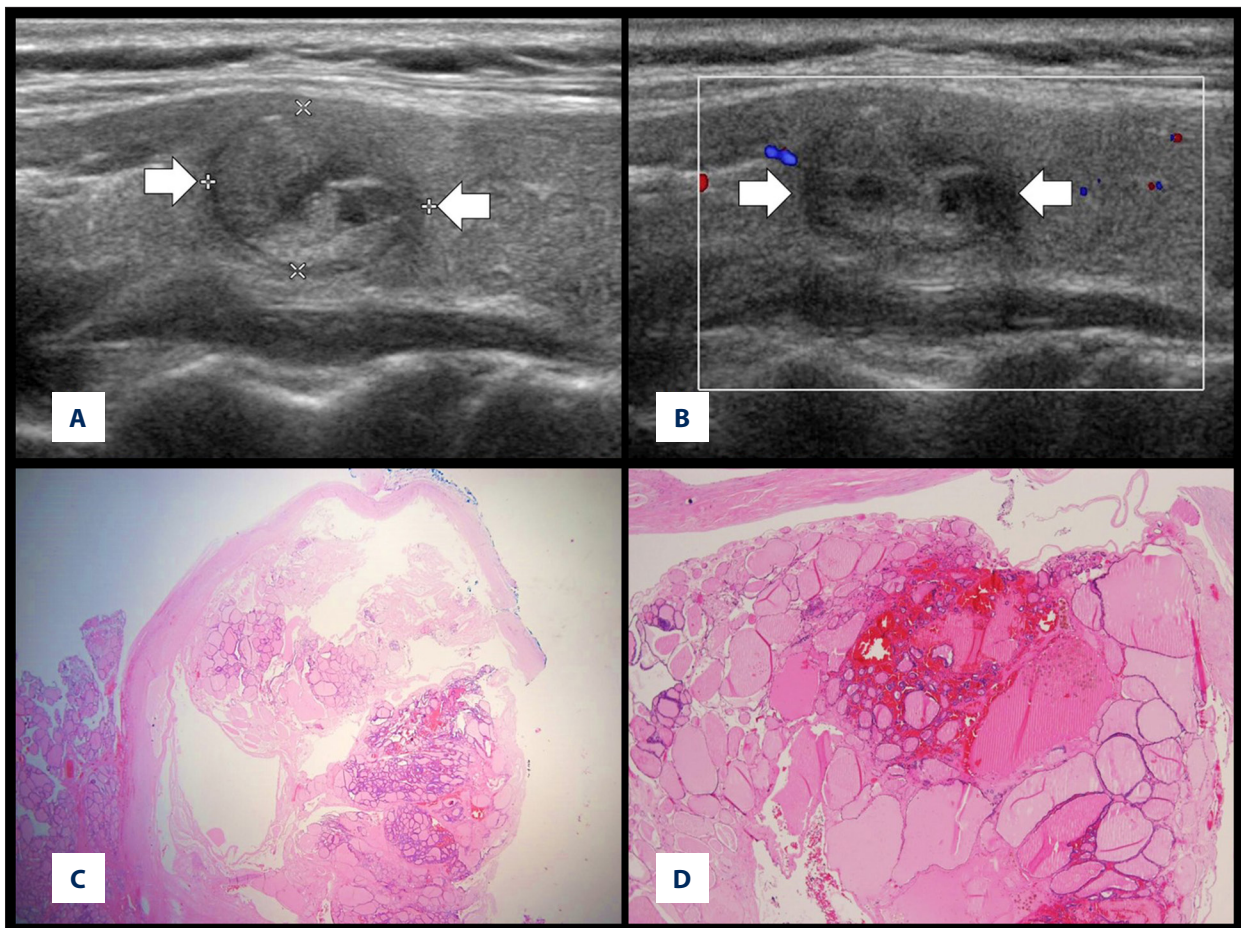
**Table 1.** Comparison of demographics and characteristics according to concordance or discordance between preoperative US in our institution and cytological analysis in local clinics.

Items	Concordance (n = 91)	Discordance (n = 12)	P value
Age (yr)	47.4±12.3	48.6±11.0	0.734
Sex			0.453
Female	72 (86.7)	11 (13.3)	
Male	19 (95)	1 (5)	
Size (mm)	9.3±5.8	14.7±8.6	0.057
Location			0.542
Right	45 (88.2)	6 (11.8)	
Left	38 (86.4)	6 (13.6)	
Isthmus	8 (100)	0	
K-TIRADS category			<0.0001
3	0	12 (100)	
4	22 (100)	0	
5	69 (100)	0	
Pathology			<0.0001
PTC	90 (91.8)	8 (8.2)	
Follicular adenoma	1 (100)	0	
Nodular hyperplasia	0	4 (100)	

Data presented in parentheses are percentage of each item. K-TIRADS – Korean Thyroid Imaging Reporting and Data System; PTC – papillary thyroid carcinoma.



**Figure 3.** A 45-year-old female patient who underwent total thyroidectomy for papillary thyroid carcinoma (PTC) in the right thyroid lobe. Longitudinal grayscale (A) and color Doppler (B) sonograms of the right thyroid lobe obtained before thyroid surgery show a solid thyroid nodule with isoechoogenicity, a smooth margin, no calcifications, a parallel orientation, and peripheral vascularity (arrows) (13.9×16.6×20.2 mm, K-TIRADS category 3). After total thyroidectomy, this nodule was confirmed as being the solitary PTC.



**Figure 4.** A 48-year-old female patient who underwent hemithyroidectomy for nodular hyperplasia in the right thyroid lobe. Longitudinal gray scale (A) and color Doppler (B) sonograms of the right thyroid lobe obtained before thyroid surgery show a partially cystic thyroid nodule with predominant isoechoogenicity, a smooth margin, no calcifications, a parallel orientation, and scanty vascularity (arrows) (11.3×12.9×15.3 mm, K-TIRADS category 3). After right hemithyroidectomy, this nodule was confirmed as showing nodular hyperplasia. After a single cytopathologist at our hospital reviewed the cytological slides from a local clinic, this case was diagnosed as Bethesda category III (not shown). After hemithyroidectomy, the right thyroid lobe shows a well-circumscribed nodule with marked cystic change, stromal fibrosis, and degeneration (hematoxylin and eosin stain, 10×) (C). This nodule is composed of variably sized dilated follicles with hemorrhage (hematoxylin and eosin stain, 100×) (D).

established. Herein, we attempted to compare the diagnostic accuracy of preoperative US and cytological analysis in transferred patients.

In the present study, 91 transferred patients (88.3%) exhibited concordant results between preoperative US in our hospital and cytological analysis in local clinics. However, 12 patients (11.7%) with no suspicious findings in the preoperative US (i.e., K-TIRADS category 3) underwent thyroid surgery because of malignant cytological diagnosis obtained from the local clinic. Among them, 8 exhibited PTC after thyroid surgery, whereas 4 exhibited nodular hyperplasia. We believe that unnecessary thyroid surgery could have been avoided if a careful review and comparison between preoperative US at referral

hospitals and cytological analysis at local clinics had been performed. Thus, re-analysis of cytological slides from local clinics should be performed when preoperative US in transferred patients exhibits no suspicious findings. In these patients, when no malignant cytology is determined in the cytological re-analysis, repeat biopsy or simple US follow-up may be recommended, rather than thyroid surgery. However, if a malignant cytology is determined in the cytological re-analysis, the scheduled thyroid surgery can be performed. To establish guidelines for this issue, large-scale studies are required.

This study has several limitations that should be considered. First, the sample size was small. Second, all cytological slides from the local clinics were not reviewed, except in the 4 cases



with nodular hyperplasia. Furthermore, we did not investigate whether the malignant cytology was of Bethesda category V or VI. Third, some of the patients did not undergo thyroid surgery. These patients were excluded from the study, and sampling bias might have occurred. Finally, detailed US data in the local clinics such as K-TIRADS category, multiplicity, bilaterality, tumor stage, and nodal stage were not investigated because only some US images of thyroid nodules with a malignant cytology were available for the patients. Therefore, we could not compare the features, such as multifocality, tumor stage, and nodal stage based on investigations at our hospital and those at the local clinics.

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## Conclusions

We believe that preoperative US may be helpful to detect false-positive cytology cases in patients transferred to referral centers from local clinics with a diagnosis of malignancy on cytological analysis. In these patients, preoperative US should focus not only on preoperative staging (including multifocality, bilaterality, tumor stage, and nodal stage) but also on the possibility that the lesion may not be malignant.

## Conflicts of interest

None.