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Original Article

Hashimoto's thyroiditis elicits decreased diagnostic efficacy of thyroid nodule ultrasound-guided fine needle aspiration

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Abstract: Background: False negative (FN) or false positive (FP) results of thyroid ultrasound-guided fine needle aspiration (US-guided FNA) cause missed diagnosis of thyroid cancer or unnecessary thyroidectomy. Purpose: To explore the impact of Hashimoto's thyroiditis (HT) on the diagnostic efficacy of US-guided FNA and to analyze the differences in diagnostic efficacy between US-guided FNA and thyroid ultrasonography (US) in patients with HT. Method: Medical records were reviewed retrospectively. Patients with and without Hashimoto's thyroiditis (HT) were included in the exposure and non-exposure group, respectively. Results: HT was not an independent risk factor for thyroid cancer. The percentage of undetermined results of US-guided FNA (Bethesda I, III, IV) in the exposure group was significantly higher. The US-guided FNA's diagnostic sensitivity, specificity, and accuracy were significantly lower, and FP rate (FPR) and FN rate (FNR) were higher in the exposure group. In the exposure group, US tended to give higher diagnostic sensitivity, accuracy, PPV, NPV, and lower FPR and FNR. Receiver operating characteristic (ROC) curve analysis showed that, in the exposure group the diagnostic efficacy of thyroid US was significantly higher than of US-guided FNA. Conclusion: HT tends to cause undetermined results and elicit lower diagnostic performance of US-guided FNA. In patients with HT, the diagnostic efficacy of thyroid US is, at least, not inferior to US-guided FNA.

Keywords: Thyroid cancer, ultrasonography, fine needle aspiration, diagnostic efficacy

Introduction

The incidence of thyroid cancer has been rapidly increasing. It is estimated that about 52,070 new cases (3.0% of all new cancer cases) will be diagnosed and about 2,170 deaths from thyroid cancer (0.4% of all cancer deaths) will happen in United States in 2019 [1]. Although patients with differentiated thyroid cancer (DTC) which comprises the vast majority of all thyroid cancers have excellent prognosis compared with most carcinomas [2], their quality of life (QoL) after thyroidectomy can be significantly decreased [3]. Moreover, decrease in QoL is, to some extent, correlated with complications after thyroidectomy, such as transient or permanent recurrent laryngeal nerve palsy, parathyroid gland dysfunction [4, 5], hypocalcemia, and hypomagnesemia [6]. Additionally, acute hypothyroidism induced by thyroid hormone withdrawal after thyroidectomy has been reported to correlate with diminished QoL and increased brain functional connectivity [7]. Overdiagnosis of thyroid cancer has been proposed to be occurring recently and attracted wide attention [8]. Hence, accurate diagnosis of thyroid cancer is indispensable in order to avoid missed diagnosis or unnecessary thyroidectomy.

Ultrasound guided fine needle aspiration (US-guided FNA) is a highly effective diagnostic method, that can obviate unnecessary surgery for thyroid lesions and avoid overtreatment of benign disease [9]. It is highly recommended when clinically indicated [10]. However, some factors tend to influence the diagnostic efficacy of US-guided FNA, such as nodule size [11], concurrent of Hashimoto's thyroiditis (HT) [12], and operator's experience [13, 14]. HT is one of

the most common thyroid disorders, and its incidence is on the order of 0.3-1.5 cases per 1,000 population per year [15]. It has been reported that HT is a risk factor for DTC [16, 17]. Moreover, it seems that HT exerts an influence on diagnostic efficacy of US-guided FNA by presenting as goiter or nodules with confusing ultrasonic characteristics [12, 15]. However, whether HT can alter the diagnostic efficacy of US-guided FNA remains controversial, and research on this is limited, thus more studies remain to be conducted.

Currently, we explored the relationship between HT and thyroid cancer and analyzed the variation in diagnostic efficacy of US-guided FNA between patients with and without HT. We also compared the diagnostic performance of thyroid ultrasonography (US) and nodular US-guided FNA in patients with HT. Hence, whether HT is present should be taken into account when managing thyroid nodules.

Method

Patients and clinical data acquisition

The protocols in this study were approved by the Ethics Committee of Xiangya Hospital, Central South University (Changsha, China). We reviewed patients' medical records from January 2016 through April 2018 in our hospital. The inclusion criteria are the following: patients with complete records, including US-guided FNA biopsy report, thyroid US report before US-guided FNA, surgical histology (all reports were from our hospital). The exclusion criteria are: patients without complete records; thyroid US report was after US-guided FNA; no formal thyroid US report; patient records without a clear correlation between nodule location, cytology, and surgical histology; and patients with an incidental thyroid cancer defined as a malignancy found outside the nodule of interest. Patients with nodules equal to or smaller than 10 mm would receive US-guided FNA when the following conditions were met: nodule location was close to the thyroid capsule, trachea, or nerve; or the patient had a family history of thyroid cancer. If a patient had more than one biopsy for the same nodule, the FNA performed immediately before the surgery was used in our analysis. Clinical data, including age, sex, and surgical histology which was classified as benign or malignant, nodule number, and the characteristics of nodule US are shown in **Table 1**. Nodule size was described in terms of maximum diameter. Clinical history and thyroid US reports were carefully matched to thyroid FNA cytology and surgical pathology reports in all patients. Patients with HT were selected as the exposure group. In the non-exposure group, nodules were selected randomly by SPSS (v. 19; SPSS/IBM) from patients without HT. The ratio of the number of cases in exposure and non-exposure group was 1 to 2.

FNA technique and categorization

Thyroid FNA at our center was performed under US guidance and by the same clinical team. All FNA performers received certification and support from the cytology and ultrasound technician. The final FNA results were verified by at least one experienced cytopathologist. Our FNA reports generally include an assessment of adequacy, cellularity, selection of a diagnostic result category, and an additional treatment suggestion. Cytology results were recorded as nondiagnostic or unsatisfactory (ND/USF) (Bethesda I), benign (Bethesda II), atypical (atypia of undetermined significance [AUS] or follicular lesion of undetermined significance [AUS/FLUS]) (Bethesda III), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) (Bethesda IV), suspicious for malignancy (SM) (Bethesda V), or malignancy (Bethesda VI) according to the Bethesda System for Reporting Thyroid Cytopathology [18]. All results were reviewed and verified by at least two authors.

Statistical analysis

For assessment of US-guided FNA diagnostic efficacy, thyroid nodules with FN/SFN, SM, or malignant FNA results that were found to be malignant at the time of surgery were considered true positive results. Likewise, nodules with ND/USF, benign, or AUS/FLUS FNA results that were ultimately found to have cancer within the biopsied nodule were considered false negative results. Nodules with ND/USF, benign, or AUS/FLUS FNA and benign surgical pathology results were considered to be true negative FNA results, and nodules with FN/SFN, SM, or malignant FNA results, but benign pathology, were classified as false positive results. Continuous data were presented as medians with interquartile ranges (25% and 75%) if they were not normally distributed (as determined

Table 1. Clinical characteristics and uni- and multivariate analysis between benign and malignant groups

-		Benign Frequency/%	Malignancy Frequency/%	Uni-P	Multi-P	OR (95% CI)
Gender	Male	5/21.7	18/78.3	0.219	-	-
	Female	31/35.2	57/64.8			
Age	> 50	11/44.0	14/56.0	0.16	0.214	-
	≤ 50	25/29.1	61/70.9			
Echogenicity	Equal or high	5/55.6	4/44.4	0.11	0.304	-
	Nonuniform	4/57.1	3/42.9			
	Low	27/28.4	68/71.6			
Morphology	Regular	22/43.1	29/56.9	0.026	0.029	2.69 (1.11, 6.52)
	Irregular	14/23.3	46/76.7			
Border	Clear	23/40.4	34/59.6	0.067	0.72	-
	Unclear	13/24.1	41/75.9			
Cal-	None	19/42.2	26/57.8	0.011		
	Micro-Cal	13/21.7	47/78.3		0.045	2.52 (1.02, 6.22)
	Macro-Cal	4/66.7	2/33.3			
CDFI	None	18/45.0	22/55.0	0.067	0.172	-
	Little	4/36.4	7/63.6			
	Much	14/23.3	46/76.7			
Invasion	No	34/31.8	73/68.2	0.594	0.464	-
	Yes	2/50.0	2/50.0			
Aspect ratio	≤ 1	29/35.4	53/64.6	0.267	0.522	-
	> 1	7/24.1	22/75.9			
CLN	Invisible	24/39.3	37/60.7	0.162	0.32	-
	Visible	9/28.1	23/71.9			
	Enlargement	3/16.7	15/83.3			
Solid	No	5/62.5	3/37.5	0.11	0.074	-
	Yes	31/30.1	72/69.9			
HT	No	19/25.0	57/75.0	0.014		
	Yes	17/48.6	18/51.4		0.013	0.31 (0.13, 0.78)
Age		46 (34, 51)	42 (36, 49)	0.376	-	-
Diameter		8 (6, 19)	8 (6, 13)	0.574	-	-

Cal- Calcification, CDFI Color doppler flow imaging, CLN Cervical lymph node, HT Hashimoto's thyroiditis.

by the Shapiro-Wilk test), and groups were compared using the Wilcoxon rank-sum test. Categorical data were analyzed using chi-square test (Fisher's exact test). Odds ratio value was calculated by logistic regression analysis. Data were analyzed using SPSS (v. 19; SPSS/IBM) for Windows. A two-sided *p*-value < 0.05 was considered significant.

Results

Clinical characteristics and risk factors for thyroid cancer

816 patients with 976 nodules (35 from patients with HT and 941 from patients without HT) met inclusion criteria. 76 nodules were randomly selected into a non-exposure group by SPSS (v. 19; SPSS/IBM) from non-exposure cases according to established principles. Finally, there were 111 nodules (23 from males and 88 from females) included in this study, 35 in the exposure group and 76 in the non-exposure group. The median age of all patients was 43 (quartiles 35 and 50). The nodule US features and the diagnosis in histopathology are shown in **Table 1**. For these 111 nodules, 4.5% were diagnosed as ND/USF with malignancy rate of 40.0%, 22.5% as benign with malignancy rate of 40.0%, 14.4% as AUS/FLUS with malignancy rate of 50.0%, 1.8% as FN/SFN

Table 2. Comparison of diagnostic efficacy of US-guided FNA in thyroid cancer between groups of patients with or without HT

-	SS	P	SP	P	PPV	P	NPV	P	FPR	P	FNR	P	A	P
No HT	93.0%	< 0.001	52.6%	0.008	85.5%	0.399	71.4%	0.177	14.5%	0.008	28.6%	< 0.001	82.9%	0.001
HT	11.1%		94.1%		66.7%		50.0%		33.3%		50.0%		47.4%	

SS Sensitivity, SP Specificity, PPV Positive predictive value, NPV Negative predictive value, FPR False positive rate, FNR False negative rate, A Accuracy.

with malignancy rate of 50.0%, 14.4% as SM with malignancy rate of 62.5%, and 42.3% as malignant with malignancy rate of 93.6%.

The malignancy rate for each nodular ultrasonic characteristic between benign and malignant was compared by univariate analysis (**Table 1**). The results showed that the malignancy rate for nodules with irregular morphology or microcalcification was significantly higher (P = 0.026 compared with nodules with regular morphology and P = 0.011 compared with nodules with macrocalcification or without calcification). On the contrary, nodular malignancy rate in patients with HT was significantly lower than those without HT (51.4% vs. 75.0%, P = 0.014). Multivariate analysis showed irregular morphology (OR = 2.69, 95% CI 1.11-6.52), and microcalcification (OR = 2.52, 95% CI 1.02-6.22) were independent risk factors for malignancy, but not for HT (OR = 0.31, 95% CI 0.13-0.78) (**Table 1**).

Comparison of diagnostic efficacy of US-guided FNA in patients with and without HT

First, we compared the differences in clinical characteristics between the exposure and non-exposure group. No difference was found between these two groups (Supplementary Table 1). The differences in distribution of US-guided FNA cytology between the exposure and non-exposure group were analyzed. US-guided FNA cytology was divided into undetermined (Bethesda I, III, IV), suspicious (Bethesda V), and determined (Bethesda II and VI). In the exposure group, the percentage of undetermined was significantly higher than in the non-exposure group (37.1% vs. 13.2%, P = 0.004). The percentage of the suspicious or determined tended to be lower in the exposure group than in non-exposure group (8.6% vs. 17.1%, P = 0.234; 54.3% vs. 69.7%, P = 0.113).

After that, the diagnostic efficacy of US-guided FNA between exposure and non-exposure group was analyzed and compared. As shown in **Table 2**, compared with the exposure group, the diagnostic sensitivity and accuracy in non-exposure group significantly improved and the FPR and FNR decreased (P < 0.05). Although the diagnostic specificity in the non-exposure group decreased, the corresponding Youden Index remarkably increased (0.456 vs. 0.052). The diagnostic PPV and NPV in non-exposure group tended to be higher than exposure group, although the differences were not significant (85.5% vs. 66.7%, P = 0.399; 71.4% vs. 50.0%, P = 0.177).

Difference in diagnostic efficacy between US and US-guided FNA among patients with HT

Since the diagnostic performance of US-guided FNA was significantly lower in the exposure group, we compared the diagnostic efficacy between US and US-guided FNA. According to our previous analysis, age younger than 50 years (OR = 2.09, 95% CI 1.45-3.03), hypoechogenicity (OR = 3.31, 95% CI 1.84-5.97), irregular morphology (OR = 1.75, 95% CI 1.22-2.52), microcalcification (OR = 2.13, 95% CI 1.46-3.12), and nodular aspect ratio > 1 (OR = 1.83, 95% CI 1.07-3.12) were recognized as independent risk factors for malignancy. Based on ROC curve analysis (**Figure 1**), a screening test by US was considered as positive when the nodule of interest occurred with three or more risk factors. Compared with US-guided FNA, US tended to show higher diagnostic accuracy (71.4 vs. 47.4 P = 0.167) (**Table 3**). Also, the diagnostic sensitivity, PPV, NPV, and Youden Index tended to be higher, while the diagnostic FPR and FNR tended to be lower in US than in US-guided FNA. Additionally, ROC curve analysis showed that US had significant higher diagnostic efficacy than US-guided FNA (P = 0.042, **Figure 2**).

Discussion

The incidence of thyroid cancer rapidly increased from 2000 to 2012 [19]. One of the

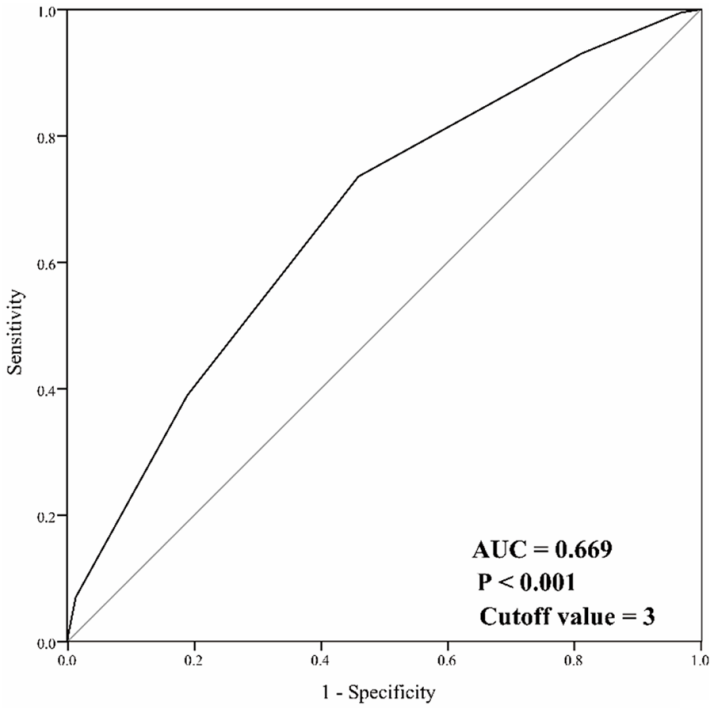

Figure 1. ROC analysis to show Predictive value of risk factors recognized by multivariate analysis for thyroid cancer.

important reasons is health screening, such as thyroid US. Indeed, US plays an increasingly important role in thyroid cancer diagnosis. American Thyroid Association Management Guidelines recommend thyroid sonography with survey of the cervical lymph nodes should be performed in all patients with known or suspected thyroid nodules [10]. Many papers have reported diagnostic value of US for thyroid cancer [10, 20], as some nodular ultrasonic characteristics, such as solid component, hypoechogenicity, micro-lobulated or irregular margins, microcalcifications, and taller-than-wide shape, have been reported to be closely correlated to thyroid cancer [21, 22]. In the current study, only nodular morphology and microcalcifications were found to be independent risk factors for thyroid cancer. This is presumably associated with sample selection. This current study is a cohort study, in which 35 target cases (patients with HT) are included in the exposure group and about twice the number of cases in the target group are selected randomly by SPSS as the non-exposure group. The results from analysis of all cases (816 patients with 976 nodules) are consistent with other studies [21, 22]. Additionally, some studies have shown that HT predisposes patients to the development of thyroid cancer [16, 23]. However, in our study, HT was not a risk but a protective factor for thyroid cancer. Hence, the association between HT and thyroid cancer is still controversial and remains to be explored further.

US-guided FNA is an indispensable pre-surgery diagnostic method with really high diagnostic accuracy, sensitivity, and specificity [9, 10]. It significantly contributes to obviate unnecessary thyroidectomy. However, unnecessary thyroidectomy for benign nodular lesion or missed diagnosis of thyroid cancer often happens due to false positive or false negative results of US-guided FNA. Previous studies have reported that FNR and FPR can be up to 19.7% and 17.0% [24-26]. Some strategies have been proposed to improve the diagnostic efficacy of US-guided FNA, such as detecting gene mutation [27]. Previous studies have shown the relationship between thyroid tumorigenesis and $BRAF^{V600E}$ mutation [28]. In addition, microRNA (miRNA) [29] and Long Noncoding RNA (LncRNA) [30] are also involved with thyroid cancer, so detecting certain miRNA or LcnRNAs may play a potential role in diagnosis of thyroid cancer. For nodules with Bethesda III or IV results, repeat US-guided FNA has some effect [31]. Moreover, variation in diagnostic accuracy of US-guided FNA can be caused by sample selection and some other factors, such as technique, specimen processing, interpretative issues [32], operator's experience [13], and the characteristics of nodule itself, like nodule size [33]. Moreover, Gao et al. [12] pointed that the diagnostic value of US-guided FNA for HT-negative nodules was significantly higher compared with HT-positive nodules, and HT was the only one risk factor for the increased FNR. In the current study, the percentage of undetermined results of US-guided FNA (including Bethesda I, III, and IV) in patients with HT significantly increased, which suggests HT decreases the diagnostic efficacy of US-guided FNA. Furthermore, we compared the diagnostic value of US-guided FNA in patients with and without HT and found that in patients without HT, US-guided FNA for

Table 3. Difference in diagnostic efficacy in thyroid cancer between US and US-guided FNA among patients with HT

-	SS/%	P	SP/%	P	FPR/%	P	FNR/%	P	Accuracy/%	P	PPV/%	NPV/%
US	77.8	< 0.001	64.7	0.125	30.0	0.125	26.7	< 0.001	71.4	0.167	70.0	73.3
FNA	11.1		94.1		33.3		50.0		47.4		66.7	50.0

US Ultrasonography, FNA US-guided fine needle aspiration.

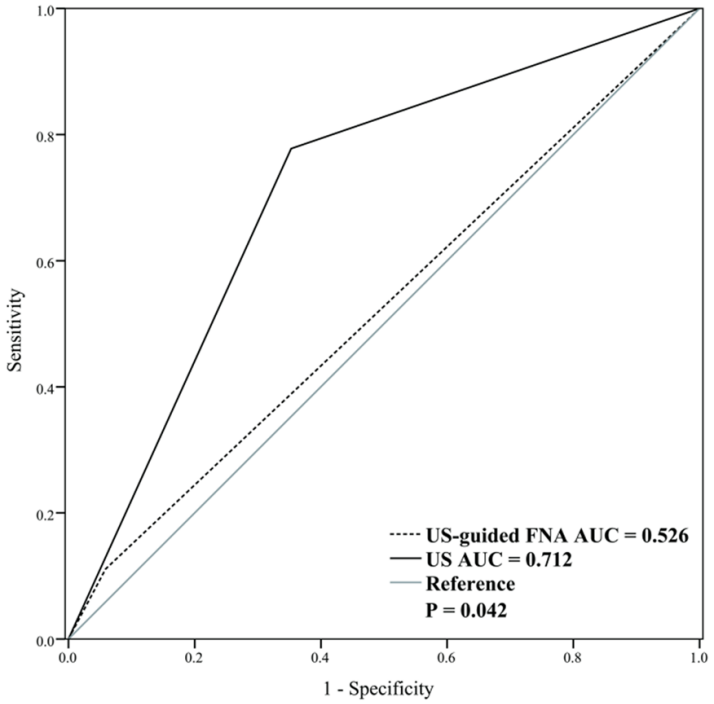

Figure 2. Comparison of diagnostic efficacy in thyroid cancer between US and US-guided FNA by ROC analysis among patients with HT.

thyroid cancer had significant higher diagnostic sensitivity, accuracy, and lower FNR and FPR. Also, the PPV and NPV tended to be higher in patients without HT. All these results prove that HT has a potential impact on the diagnostic performance of US-guided FNA. It has been found that goiter and pseudonodules have some similarities with cancerous nodules [15] and they have some ultrasonic characteristics in common like hypo-echogenicity [34]. On the other hand, fibroblastic proliferation in HT lesion may contribute to the sonographic changes [35]. All those likely participate in forming the basis of decreased diagnostic efficacy of US-guided FNA in patients with HT.

Thyroid US is sensitive and cost-effective diagnostic tool for thyroid cancer and has been recommended to be used to determine a pretest probability of malignancy to identify the patients, who are most likely to benefit from biopsy and further analysis [36]. Experts have established several diagnostic systems of thyroid US, such as various TIRADS systems [37, 38] and ATA US categories [10], in order to improve its diagnostic performance. Since in patients with HT the diagnostic efficacy of US-guided FNA significantly decreased, we questioned whether there was any difference in diagnostic efficacy between thyroid US and US-guided FNA for such a special population. In the current study, we adopted US categories that were determined according to the number of thyroid cancer risk factors (malignancy was diagnosed when the nodule of interest is with 3 or more risk factors and otherwise the nodule was diagnosed as benign by US). After comparison, we found that there was no significant difference in diagnostic accuracy between these two diagnostic tests. However, the diagnostic efficacy in thyroid US are significant higher according to ROC curve analysis. It needs to be mentioned that we do not use TI-RADS system to analyze the diagnostic efficacy of thyroid US because we found the area under curve (AUC) from ROC curve analysis was larger when adopting US categories (AUC = 0.712 for US categories vs. AUC = 0.691 for TI-RADS system, P = 0.021. Data not shown). We also compared the diagnostic efficacy of thyroid US and US-guided FNA by adopting TI-RADS system as the assessing method for thyroid US. No significant difference was found (AUC = 0.691 for thyroid US vs. AUC = 0.526 for US-guided FNA, P = 0.165. Data not shown). All these results show that the diagnostic efficacy of thyroid US is, at least, not inferior to US-guided FNA in patients with HT.

In our study, we systematically performed statistical analysis. Compared with studies with

hundreds of samples, our sample size is a bit small, although such a sample size is in accordance with statistical principles, based on which the sample size is estimated to be 33. However, Yu et al [39] have shown that sampling error is a minor cause for false-negative FNAs, which supports that our results have important reference significance that HT has a potential impact on the diagnostic efficacy of US-guided FNA. In addition, our previous analysis has shown the impact of nodular size on the diagnostic efficacy of US-guided FNA. However, in the current study, we do not focus on nodular size, which may change the influence of HT on the diagnostic efficacy of US-guided FNA. Hence, further studies remain to be implemented.

Conclusion

Hashimoto's thyroiditis indeed has an important impact on the diagnostic efficacy of US-guided FNA. It increases the percentage of undetermined results of FNA (Bethesda I, III, and IV) and decreases the diagnostic performance of US-guided FNA. In patients with HT, the diagnostic efficacy of US-guided FNA is, at least, not superior to thyroid US.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Comparison of clinical characteristics between HT and No-HT group

-		No HT Frequency/%	HT Frequency/%	P
Gender	Male	18/78.3	5/21.7	0.256
	Female	58/65.9	30/34.1	
Echogenicity	Equal or high	6/66.7	3/33.3	0.081
	Nonuniform	2/28.6	5/71.4	
	Low	68/71.6	27/28.4	
Morphology	Regular	34/66.7	17/33.3	0.706
	Irregular	42/70.0	18/30.0	
Border	Clear	39/68.4	18/31.6	0.991
	Unclear	37/68.5	17/31.5	
Cal-	None	29/64.4	16/35.6	0.705
	Micro-Cal	42/70.0	18/30.0	
	Macro-Cal	5/83.3	1/16.7	
CDFI	None	26/65.0	14/35.0	0.722
	Little	7/63.6	4/36.4	
	Much	43/71.7	17/28.3	
Invasion	No	73/68.2	34/31.8	1
	Yes	3/75.0	1/25.0	
Aspect ratio	≤ 1	55/67.1	27/32.9	0.595
	> 1	21/72.4	8/27.6	
CLN	Invisible	41/67.2	20/32.8	0.922
	Visible	22/68.8	10/31.3	
	Enlargement	13/72.2	5/27.8	
Solid	Mix	6/75.0	2/25.0	1
	Solid	70/68.0	33/32.0	
Age		42.6 ± 9.8	42.6 ± 11.1	0.991
Diameter		8.2 (6.9, 14.5)	7.0 (5.0, 11.0)	0.147

HT group: nodules from patients with HT. No-HT group: nodules from patients without HT.