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Original Article
Risk for malignancy of thyroid nodules based on ultrasound imaging characteristics

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Abstract: To correlate ultrasound imaging characteristics of thyroid nodules with the relative importance of these features in predicting risk for malignancy, we retrospectively analyzed the patients who underwent thyroid ultrasound imaging from June 2012 to September 2014. Thyroid cancers were identified by Department of Pathology, Renmin Hospital of Wuhan University. A total of 933 patients with 1362 thyroid nodules defined by ultrasound examinations, including 340 diagnosed as having thyroid cancer. For hypoechoic nodules four ultrasound nodule characteristics-microcalcifications (OR=27.954; 95% CI 18.119, 43.128; P<.0.001), central vascularity (OR=5.841; 95% CI 4.162, 8.197; P<0.001), ill-defined or speculated margins (OR=3.034; 95% CI 2.227, 4.135; P<0.001) and cervical lymphadenopathy (OR=22.981; 95% CI 13.045; 40.483, P<0.001)-were the only findings associated with the risk of thyroid cancer. If none of abnormal ultrasound imaging characteristic the risk of cancer was less than 20% as Grade I. If 1 characteristic is used as an indication for ultrasound except microcalcifications, the risk of cancer was in Grade II (20%-50%). If 2 characteristics were required for ultrasound imaging included only had microcalcifications, Grade III (50%-80%) was presented. If 3 or more suggestive ultrasound characteristics were contained, it would have the grade IV (>80%). Thyroid ultrasound imaging could be used to identify patients who have a low risk of cancer to reduce unnecessary and excessive treatment and biopsy.

Keywords: Thyroid nodules, ultrasound imaging

Introduction

Thyroid nodule is a common clinical problem and the incidence of thyroid nodules has increased with the recently increasing use of thyroid ultrasonography (US) in China [1]. Several previous studies have demonstrated that thyroid nodules are found in 4-8% of the general population with palpation, in 19-67% of patients with the use of US and 96%-98.4% of patients by Fine-needle aspiration (FNA) [2-5]. Indeed, as compared with FNA, thyroid US has been the crucial diagnosis method of thyroid nodules as the advantage of being a noninvasive procedure and giving immediate information. Yet the clinical importance of thyroid nodules lies in the detection of malignancy, the great majority of nodules are benign, less than 5% of them being malignant [6, 7]. For the small sample sizes many studies are limited to analysis the association between the ultrasound imaging characteristics of thyroid nodules and the risk of thyroid cancer [8-10]. This ascertainment bias will overestimate the risk of cancer associated with the accuracy of ultrasound imaging. This study aimed to determine the ultrasound imaging characteristics that are associated with cancer and to use this information to develop a standardized diagnosis system for interpreting thyroid ultrasound imaging.

Materials and methods

Patients

We retrospectively studied the data from 933 patients with 1362 nodules from June 2012 to September 2014 at Renmin Hospital of Wuhan University, China. All patients preoperatively were diagnosed with thyroid nodule by US and were assessed for clinical, laboratory and US variables. All patients underwent surgery, and the final diagnosis was based on the results of

Table 1. Histologic findings of the study cancers

Type	Cancers, No. (%) (n=340)
Papillary	335 (98.53%)
Follicular	3 (0.89%)
Medullary	1 (0.29%)
Anaplastic	1 (0.29%)
Not specified	0

histopathologic examination of resected thyroid gland tissue. Routine hematoxylin eosin staining and immunohistologic examination were performed. Clinical variables included age and gender. Laboratorial variables involved TSH levels as the baseline. From the total sample 11 patients were excluded because they lacked complete information for statistical analysis.

Characterizations of US examinations

GE Healthcare color Doppler US (Model: Vivid E9, Norway) and a superficial probe (Model: 4C-D, 7.5-10 MHz) were used for standard US. Nodule number, diameters (cm), volume, echogenicity, margin (well, ill-defined or speculated defined), type of calcification and vascularization pattern (type II: absence of blood flow; type II: peripheral vascular flow; type III: Central vascular flow.) were evaluated by using standard US. The echogenicity of the nodules was classified into four categories: hypoechogenicity, isoechogenicity, hyperechogenicity and mixed echogenicity. Calcification within the nodule was classified into three categories (type I: absence of calcification, type II: Coarse or Rim calcifications, type III: Microcalcifications), Microcalcification was defined as hyperechoic spots less than 2 mm. Shape was assessed as the ratio of anteroposterior (A) to transverse (T) dimensions (A/T≥1 or <1). Cervical lymphadenopathy was defined as irregular shape, A/T>1, disorders of leather/medulla ratio.

Statistical analysis

All statistical analyses were performed with SPSS 17.0 statistical software. For the Single-Predictor analysis, data was analyzed by using χ^2 test or Fisher's exact test to categorical variables, and the non-parametric test (Mann-Whitney) to quantitative variables of the two groups (P<0.05). We performed single-predictor modeling to assess the association between specific ultrasound imaging characteristics and malignancy generalized estimating equations. For variables that were statistically significant in the single-predictor model, we calculated diagnostic accuracy statistics (sensitivity, specificity, likelihood ratios and predictive values). For the multivariate analysis, a logistic regression model was applied to data, using the predictors of malignancy that was statistically significant in the single-predictor analysis. The risk of cancer (predictive values) associated with each definition of an abnormal ultrasound imaging interpretation was calculated.

The positive predictive value (PPV) was the risk of cancer for a patient who was found to have abnormal ultrasound images. For definition of abnormal ultrasound images result, we calculated the grades of malignancy on the basis of the risk of cancer.

Results

A total of 933 patients with 1362 thyroid nodules received ultrasound examinations during the study period, including 340 nodules diagnosed as thyroid cancer (**Table 1**). There were 710 women and 223 men with a mean age of 51.46 years (range: 14-77 years). The cancers were diagnosed 1 day to 1 month after clinical, serum level of TSH, ultrasound examinations. There were no significant differences in gender (P=0.14), serum TSH levels (hypothyroidism P=0.271, hyperthyroidism P=0.275) and number of nodules (2-3 P=0.275; >4 P=1.00) between the two groups, but Patient's age was more than 45 years old was an independent clinical significant predictor of malignancy (P=0.026), **Table 2**.

Single-predictor modeling results

Several ultrasonography images were significantly associated with the risk of cancer (**Table 3**; **Figure 1**). Microcalcifications had the strongest association with cancer; 55.88% of cancer nodules vs 4.01% of benign nodules had microcalcifications (OR=5.028 P<0.001). Cervical lymphadenopathy also was suggestive feature of malignancy (OR=5.027, P<0.001). Nodule size, central vascularity, margins, shape, echogenicity and coarse or rim calcifications were also each significantly associated with malig-

Table 2. Characteristics of Patients Included in the Study

Characteristic	Benign n=654 (%)	Malignancy n=279 (%)	P
Age			
<20	4 (0.6%)	6 (1.8%)	0.377
20-45	145 (22.2%)	96 (28.2%)	Reference
>45	505 (77.2%)	238 (70.0%)	0.026
Sex			
Male	147 (22.5%)	76 (27.0%)	
Female	507 (77.5%)	203 (73.0%)	0.14
TSH level			
Normal	531 (81.2%)	207 (74.2%)	Reference
Hypothyroidism	57 (8.7%)	39 (14.0%)	0.271
Hyperthyroidism	66 (10.1%)	33 (11.8%)	0.275
No. of nodules			
1	416 (63.6%)	167 (59.9%)	Reference
2-3	231 (35.3%)	109 (39.1%)	0.275
>4	7 (1.1%)	3 (1.1%)	1.00

nancy, but the magnitude of association was smaller, with ORs ranging from 1.1 to 2.9. Simple isoechoic nodules, mixedechoic nodules, equal or hyperechoic nodules and peripheral vascularity were not associated with the risk of cancer.

Multiple-predictor modeling results in hypoechoic nodules

A multiple logistic regression analysis was performed to determine independent US predictors for malignancy in hypoechoic nodules. Four nodule characteristics were significantly associated with the risk of cancer in the multiple-predictor modeling: microcalcifications (OR=27.954; 95% CI 18.119, 43.128; P<.0.001), central vascularity (OR=5.841; 95% CI 4.162, 8.197; P<0.001), ill-defined or speculated margins (OR=3.034; 95% CI 2.227, 4.135; P<0.001), and cervical lymphadenopathy (OR=22.981; 95% CI 13.045, 40.483, P<0.001) (Data not shown).

The risk of cancer with the several definitions of abnormal ultrasound images was given in **Table 4**. Microcalcifications had the highest risk of cancer, 61.13% (95% CI 55.18%, 66.84%) as a single predictor. If 2 abnormal ultrasound imaging characteristics were included, the sensitivity (SN) would be lower, with SNs ranging from 52% to 69%, and the risk of cancer (RC) with those would be higher, with RCs ranging from 64% to 75%. Included 3 or 4 abnormal characteristics would be the most specific definition of abnormal ultrasound images, however, this definition would detect only a proportion of cancer (SNs, 54.67%-69.42%) but would have high risks of cancer (80.57%-95.76%). Compared with existing guidelines that recommend biopsy of all thyroid nodules greater than 5 mm, this more stringent rule requiring 2 or more abnormal characteristics to prompt biopsy would reduce unnecessary biopsies while thyroid cancer maintained a low malignancy of cancer in patients.

Predictive values: grades analysis in hypoechoic nodules

The risk of thyroid cancer in hypoechoic nodules based on the ultrasound images reached grades analysis in **Table 5**, (grade I: the risk <20%, grade II: 20%-50%; grade III: 50%-80%, grade IV: >80%). Microcalcifications were the most predictive characteristic and had reached the grade III, others just reached the grade II. If 2 characteristics were required to define ultrasound images as abnormal, the risk of cancer would reach the grade III, whereas 3 or more suggestive ultrasound characteristics would have the grade IV.

Discussion

Although thyroid nodules are common, most (98.4%) are benign, attach great importance to diagnosis of malignance that nodules should be sampled to reduce overtreatment [7]. Age in thyroid nodule patients is identified as an independent predictor for malignancy with >45 years old (P<0.001), which agree with the Baier et al study [11]. In recent studies TSH levels as a predictor of malignancy has been discussed so that the serum TSH levels might be related to increasing the risk of malignancy [12]. However, both hypothyroidism and hyperthyroidism have no significant difference by two groups (P=0.06, P=0.543). Patients with multiple thyroid nodules have the same risk for malignancy as those with solitary nodules.

Traditionally, a predominantly solid component is regarded as being suggestive of a malignant nodule rather than a benign nodule [13]. The predominantly solid is defined as the hyp-

Table 3. Comparison of sonographic characteristics between benign and malignancy nodules

Characteristic	Benign n=1022 (%)	Malignancy n=340 (%)	Odds Ratio (95% CI)	P
Size				
≤1 cm	147 (14.38%)	88 (25.88%)	1 (reference)	
1-2	413 (40.41%)	141 (41.47%)	1.471 (1.183, 1.730)	0.001
>2 cm	462 (45.21%)	111 (32.65%)	1.933 (1.528, 2.445)	<0.001
Margins				
Smooth	814 (79.65%)	198 (58.24%)	1 (reference)	
Ill-defined	208 (20.35%)	142 (41.76%)	1.353 (1.235, 1.484)	<0.001
Vascular flow				
I	480 (46.97%)	116 (34.12%)	1 (reference)	
II	429 (41.97%)	67 (19.71%)	0.931 (0.883, 0.981)	0.009
III	113 (11.06%)	157 (46.18%)	1.924 (1.663, 2.227)	<0.001
Shape				
A/T<1	910 (89.04%)	167 (49.12%)	1 (reference)	
A/T≥1	112 (10.96%)	173 (50.88%)	2.867 (2.400, 3.426)	<0.001
Echogenicity				
Isoechoic	50 (4.89%)	6 (1.76%)	1 (reference)	
Hypoechoic	583 (57.05%)	283 (83.24%)	1.326 (1.198, 1.469)	=0.001
Mixed	318 (31.11%)	47 (13.82%)		0.812
Normal/Hyperechoic	71 (6.95%)	4 (1.18%)		0.415
Calcifications				
No	755 (73.87%)	91 (26.77%)	1 (reference)	
Microcalcifications	41 (4.01%)	190 (55.88%)	5.028 (3.706, 6.643)	<0.001
Coarse or Rim	226 (22.12%)	59 (17.35%)	1.125 (1.056, 1.200)	<0.001
Cervical lymph nodes				
Normal	996 (97.46%)	208 (61.18%)	1 (reference)	
Enlargement	26 (2.54%)	132 (38.82%)	5.027 (3.534, 7.150)	<0.001

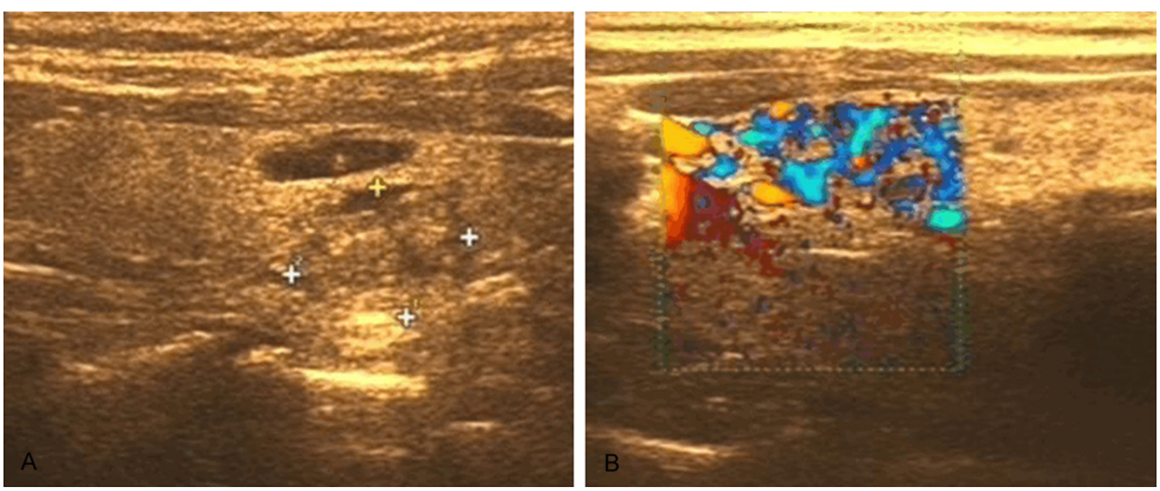

Figure 1. Transverse sonographic image of thyroid nodules. A. Nodules with microcalcifications, A/T>1, speculated margin, heterogeneous echotexture of solid portion. This nodule was classified as PTC. B. Nodules with central vascularity. This nodule was classified as PTC.

oechoic nodule by US, only the hypoechoic echogenicity have statistical difference (OR= 1.326, P=0.001). So the hypoechoic nodules were systematically accessed in our study.

Table 4. Multiple-predictor modeling results of abnormal ultrasound imaging characteristics in hypoechoic nodules

Characteristic	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Likelihood Ratio (95% CI)		Risk of Cancer (%, 95% CI)
			Present	Absent	
Single					
M1	51.03 (44.56, 57.47)	68.19 (64.54, 71.68)	1.60 (1.36, 1.89)	0.72 (0.63, 0.82)	36.47 (31.34, 41.83)
C1	84.80 (79.13, 89.44)	83.36 (80.30, 86.12)	5.10 (4.26, 6.10)	0.18 (0.13, 0.25)	61.13 (55.18, 66.84)
V1	63.86 (56.82, 70.49)	70.69 (67.22, 74.00)	2.18 (1.87, 2.54)	0.51 (0.42, 0.62)	37.94 (32.76, 24.72)
L1	87.70 (80.53, 92.95)	76.31 (73.09, 79.33)	3.70 (3.20, 4.28)	0.16 (0.10, 0.26)	37.81 (32.14, 43.74)
Double					
M1C1	58.87 (53.56, 64.04)	85.49 (82.13, 88.43)	4.06 (3.23, 5.10)	0.48 (0.42, 0.55)	73.85 (68.32, 78.87)
M1V1	52.76 (47.61, 57.86)	83.06 (79.41, 86.29)	3.11 (2.50, 3.88)	0.57 (0.51, 0.64)	71.02 (65.36, 76.24)
M1L1	58.54 (52.90, 60.21)	82.15 (78.68, 85.26)	3.28 (2.68, 4.01)	0.50 (0.44, 0.58)	65.37 (59.51, 70.90)
C1V1	65.29 (59.52, 70.75)	83.80 (80.52, 86.72)	4.03 (3.29, 4.94)	0.41 (0.35, 0.49)	67.14 (61.33, 72.58)
C1L1	82.42 (77.20, 86.88)	88.18 (85.34, 90.63)	6.97 (5.57, 8.72)	0.20 (0.15, 0.26)	74.56 (69.07, 79.53)
V1L1	68.54 (62.60, 74.06)	83.28 (80.04, 86.18)	4.10 (3.37, 4.99)	0.38 (0.32, 0.45)	64.66 (58.79, 70.23)
Triple					
M1C1V1	54.67 (49.94, 59.33)	94.83 (92.94, 96.33)	10.56 (7.63, 14.62)	0.48 (0.43, 0.53)	86.93 (82.43, 90.62)
M1C1L1	59.85 (54.80, 64.74)	89.66 (86.56, 92.25)	5.79 (4.39, 7.64)	0.45 (0.40, 0.51)	82.69 (77.76, 86.91)
C1V1L1	69.42 (64.40, 74.12)	93.82 (91.35, 95.77)	11.24 (7.94, 15.92)	0.33 (0.28, 0.38)	89.05 (84.81, 92.43)
M1V1L1	54.81 (49.89, 59.66)	87.75 (84.36, 90.64)	4.47 (3.44, 5.82)	0.52 (0.46, 0.58)	80.57 (75.47, 85.01)
ALL	55.53 (51.00, 60.00)	96.82 (94.51, 98.34)	17.45 (9.94, 30.62)	0.46 (0.42, 0.51)	95.76 (91.71, 97.79)

M1: ill-defined or lobulated margins. V1: III central vascularity. C1: microcalcifications. L1: enlargement of cervical lymph node.

Table 5. Grade analysis of risk of cancer based on the abnormal ultrasound imaging characteristics in hypoechoic nodules

Grade	MVCL	Interpretations
I (<20%)	None	M0: smooth margins.
		M1: ill-defined or lobulated margins.
II (20%-50%)	M1 V1 L1	V0: no or peripheral vascular flow;
		V1: central vascularity.
III (50%-80%)	C1 M1V1 M1C1 M1L1	C0: no, coarse or rim calcifications;
	V1C1 C1L1 V1L1	C1: microcalcifications.
IV (>80%)	M1V1C1 M1C1L1	L0: normal cervical lymph nodes.
	V1C1L1 M1V1L1 M1V1C1L1	L1: enlargement of cervical lymph nodes.

M: margins, V: vascular flow, C: calcifications, L: cervical lymph nodes.

Therefore, only the hypoechoic nodule alone cannot be a useful criterion for the differentiation of malignant from benign nodules. Our findings support previous study results [14, 15] that ill-defined margin, microcalcifications, central vascularity and enlargement of cervical lymph node are suggestive for differentiating malignant thyroid nodules from benign ones. We categorized the tumor margin into two subtypes: well-defined smooth and ill-defined margin. Results of our study have suggested that ill-defined nodular margins favor a diagnosis of malignancy. This result conveys the fact that malignant nodules have the marginal infiltration. In our study, the presence of any calcification increased the risk of malignancy by the OR ranging from 1.125 to 5.028. Benign nodules have coarse or rim calcifications, especially with a long disease duration [16], while microcalcifications correspond pathologically to calcified psammoma bodies that are typical of papillary cancer [17, 18]. Microcalcifications have a high predictive value (61.13%) and are statistically significant predictors of malignancy. The hypoechoic nodules with the central vascularity are correlated to thyroid malignancy in our study, which don't agree with currently data in the literature. In our study, The hypoechoic nodules with the central vascularity have OR=5.841 (95% CI 4.162, 8.197) and a high risk of malignancy (37.94%, 95% CI 32.76%, 24.72%). A study [19] evaluates 1083 thyroid nodules, 814 benign and 269 malignant. The central flow is frequently seen in benign nodules and the absence of vascularity is more frequent in malignant nodules. So the relationship between the central vascularity and malignancy require more study. Our data confirm cervical lymphadenopathy are significantly associated with the risk of cancer in hypoechoic nodules (OR=22.981; 95% CI 13.045, 40.483, P<0.001), that is consistent with some study [20]. However, for small nodules cervical lymph nodes seldom have metastatic tumor, the cervical lymph nodes are not appropriate for the small nodules.

Although we find that the size (>2 cm) and shape (A/T≥1) are significantly different between two groups (P<0.001), whereas both of them don't contain in multiple-predictor modeling. For the benign nodules, patients will receive surgery when the nodules are much bigger so that they will induce pressure symptoms or impair appearance that will influence the results. According to the American Thyroid Association (ATA) guideline, a reasonable definition of growth is a 20% increase in the nodule diameter with a minimum increase in two or more dimensions of at least 2 mm, which is roughly a 50% increase in volume [21], whereas some study finds that the rate of tumor growth does not distinguish between malignant and benign thyroid nodules. So for unclear consensus on the definition of nodule growth, so that don't include our study. As the development of ultrasonic technology, a large amount of small malignant tumors is found, then for that shape (A/T≥1) has less specificity.

The grades analysis is obtained by the risk of thyroid cancer in hypoechoic nodules based on the abnormal ultrasound images. We suggest that patients with hypoechoic nodules in grade I/II should keep regular follow-up in that the majority (80%-85%) of papillary carcinomas that comprise most thyroid carcinomas are regarded as low risk malignancies with a 99% survival rate at 20 years after surgery. Patients with hypoechoic nodules in grade III/IV should take the size, patient selection et al into account for further treatment. Regard to the high survival rate of standard total thyroidectomy with adjuvant radioiodine treatment in such low-risk groups [22], some investigators do not recommend further treatment in nodules 1 cm or smaller, even if they have US findings suggestive of a malignancy.

The evaluation of our study is retrospective, then the selection bias is unavoidable. As the evaluation is not in real time, it may have influenced the evaluation of the interpreters. For instance, the relatively more malignancy in our study than expected in daily practice as patients with obviously benign findings at US usually do not undergo biopsy or surgery. Our study aims at determining how to reduce unnecessary and excessive treatment and biopsy. Our study does not provide evidence as to whether the detection of thyroid cancers will lead to improved patient outcomes. The uniform standards for the interpretation of thyroid US would be a first step toward standardizing the diagnosis and treatment of thyroid nodules and confining excessive treatment.

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Disclosure of conflict of interest

None.

Authors' contribution

Original idea by SSR and WQ. WQ and LX designed and conducted the survey and gathered the data. LJJ, WJ and NJ performed statistical analysis, figures, which was reviewed and approved by SSR and CC. All authors read and approved the final manuscript.

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