Evaluation of Diagnostic Efficiency of Ultrasound Features on Malignant Thyroid Nodules in Chinese Patients

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Background: The aim of this study was to evaluate the efficacy of ultrasonic features in predicting the malignancy of thyroid nodules in a group of Chinese patients.

Methods: In all, 762 patients with thyroid nodules (424 malignant and 338 benign) underwent ultrasound (US) check and surgery between March 2011 and July 2014 at Peking University First Hospital were identified. Univariate and receiver operating characteristic (ROC) analyses were performed to calculate the sensitivity, specificity, negative and positive predictive values of each US feature, and the accuracy of their combinations for prediction of malignancy.

Results: Patients with malignant nodules were younger and without obvious risk history than those in the benign group (P < 0.001, P = 0.93). No individual US sign was fully predictive of a malignant lesion. The Youden indexes of irregular margins and hypoechogenicity were the first and second highest in all US features, which were 51.9% and 45.2%, respectively. The sensitivity of solid components (89.7%) and hypoechogenicity (89.2%) and the specificity of taller-than-wide shape (98.5%) and microcalcifications (90.6%) were the first and second highest in all US features. Intranodular flow on a color Doppler examination was a weak predictor of malignancy. Under ROC analysis excepting intranodular flow, the 95% confidence interval (CI) of areas under the curves of hypoechogenicity and irregular margins with any one of the US features were overlapped that of five-feature combinations (95% CI: 0.850–0.901).

Conclusions: We should be alert with taller-than-wide shape and microcalcifications. Intranodular flow was a weak predictor of malignancy. According to Youden indexes and ROC analysis, irregular margins and hypoechogenicity combined with solid component or taller-than-wide shapes or microcalcifications have a high predicative value for malignant thyroid nodules in Chinese patients.

Key words: Malignancy; Thyroid Nodules; Ultrasonography

INTRODUCTION

Thyroid nodules are a common clinical finding and occur in approximately 10–70% of the general adult population and are more common in women, the elderly, and patients with a family history of thyroid disorders. Malignant transformation of thyroid nodules occurs in only 5–10% of patients depending on age, gender, history of radiation exposure, and family history of cancer. In a survey of ten large cities in China, the prevalence of thyroid nodules ranged from 10.2% to 18.6% and the incidence of thyroid cancer had increased from 1.78/100,000/year to 6.56/100,000/year from 1998 to 2009. In this study, the incidence of thyroid nodules in 2009 was approximately 10.09/100,000 in females and 3.11/100,000 in males. Moreover, thyroid ultrasounds (US) have become a popular extension of the physical examination in China, and other Asian countries such as Korea, so there was an increase in the incidence of thyroid nodules being identified as a result of the use of US. It is an essential public health concern to find an accurate and cost-effective method in China for accurate diagnosis and detection of suspicious thyroid nodules.

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Thyroid US is the major diagnostic modality for the detection of thyroid nodules and has a major role in excluding the presence of malignancy. Several US features such as hypoechogenicity, irregular margins, solid component, microcalcifications, taller-than-wide shape, and intranodular vascularity have been identified as major predictors of malignancy in thyroid nodules. Although previous research agrees that these features are important for predicting malignancy risk, there is still some controversy. It is well known that malignant US features can have different predictive values for the grading of the malignancy depending on nodule characteristics. Currently, there are few Chinese studies regarding the effectiveness of US in malignant thyroid nodules and no definite guideline based on Chinese evidence-based study. In this study, we analyzed the US data compared with pathology results of 762 patients who underwent surgery in our hospital. The aim of the current study was to evaluate the effectiveness of US in predicting malignant thyroid nodules.

**Methods**

**Study population and data collection**

We consecutively enrolled patients with thyroid nodules who underwent surgery and had a pathological diagnosis between March 2011 and July 2014 at our hospital. A total of 762 patients with thyroid nodules (424 malignant and 338 benign) were included. The present study was a retrospective medical record based cohort study approved by our hospital’s ethics committee. All subjects were de-identified so no need for written consent.

Thyroid gray-scale and color Doppler US LOGICOQ GRQE9 (General Electric Company, Fairfield, CT, USA) was performed. The main sonographic criteria evaluated for each nodule included the following: composition, echogenicity, taller-than-wide, margins, calcifications, and vascularity. The composition was classified as solid, cystic, or mixed. Echogenicity was classified as hyperechogenicity, isoechochogenicity, and hypoechogenicity in comparison with normal thyroid tissue. The taller-than-wide shape was defined as the ratio of anteroposterior dimension to transverse dimension than 1. Nodule margins were described as well circumscribed or poorly circumscribed (irregular). Microcalcifications were defined as <2 mm. Macrocalcifications were defined as larger than 2 mm. The vascularity of each nodule on color Doppler US was classified as absent, peripheral, or central vascularity; however, when a nodule showed both peripheral and central vascularity, it was classified as having central vascularity. Each US was reanalyzed using the same classifications by one experienced sonographist.

Histological examination was paraffin wax embed after surgery and was interpreted by thyroid cytopathologists. Cytopathology was reported as benign, indeterminate (follicular or Hurthle cell neoplasm), suspicious for malignancy, or malignant according to The Bethesda System for Reporting Thyroid Cytopathology.

**Statistical analysis**

Univariate analysis was performed to determine the risk of malignant thyroid nodules. Student’s t-tests were calculated for continuous variables, such as age and tumor size. Chi-square tests and Fisher’s exact test were employed for categorical variables such as gender, pathologic diagnosis, echo texture, calcification, vascularity, and margins. All tests were two-sided, and \( P < 0.05 \) was considered statistically significant. The level of discrimination was estimated using the area under the receiver operating characteristic curve (AUC). Univariate analysis and receiver operating characteristic (ROC) curve calculations were performed in SPSS 18.0 (International Business Machines Corporation, Armonk, NY, USA). The Youden index was calculated using the formula \((\text{sensitivity} + \text{specificity}) - 1\).

**Results**

Seven hundred and sixty-two patients were enrolled in the study, of which 570 were women and 192 were men. Four hundred and twenty-four malignant thyroid carcinomas were identified, of which 410 were papillary carcinomas, 4 were follicular carcinomas, 8 were medullary carcinomas, and 2 were anaplastic carcinomas. Another 338 benign thyroid nodules were also identified. The mean age of patients in the malignant group was 45.1 ± 11.6 years, and the mean age of the benign group was 51.3 ± 11.9 years (\( P < 0.0001 \)). The majority of malignant nodules was found in patients between 45–60 years (43.6%) and 18–45 years (46.5%). Only 14.4% patients had traditional risk factors. The ratio of females to males was approximately 3:1 in malignant

| Items                          | Malignant n (%) | Benign n (%) | \( P \)   |
|-------------------------------|-----------------|--------------|----------|
| Number                        | 424             | 338          |          |
| Age, years, mean (SD)         |                 |              |          |
| <18                           | 45.1 (11.6)     | 51.4 (11.9)  | <0.0001  |
| 18–<45                        | 3 (0.7)         | 2 (0.6)      |          |
| 45–<60                        | 197 (46.5)      | 93 (27.5)    |          |
| >60                           | 183 (43.2)      | 163 (48.2)   |          |
| Gender                        |                 |              |          |
| Male                          | 111 (26.2)      | 87 (24.2)    | 0.528    |
| Female                        | 313 (73.8)      | 251 (75.8)   |          |
| Family and individual history |                 |              |          |
| None                          | 363 (85.6)      | 298 (88.2)   | 0.928    |
| Thyroid disease               |                 |              |          |
| Thyroid carcinoma             | 33 (7.8)        | 25 (7.4)     |          |
| Other cancer                  | 6 (1.4)         | 4 (1.2)      |          |
| Head and neck irradiation     | 16 (3.8)        | 8 (2.4)      |          |
| Thyroid disease with thyroid carcinoma | 1 (0.2) | 1 (0.3)    |          |
| Thyroid disease with other cancer | 2 (0.5)    | 0 (0)       |          |
| Thyroid carcinoma with other cancer | 2 (0.5) | 0 (0)       |          |

SD: Standard deviation.
group; however, no difference was observed in the benign group \((P = 0.53)\) [Table 1].

According to our study, no individual US sign is fully predictive of a malignant lesion. The features of US including sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value were calculated [Table 2]. The Youden indexes of irregular margins and hypoechogenicity were the first and second highest in all US features (51.9% and 45.2%, respectively). The Youden indexes of solid component, microcalcifications, and intranodular vascularity were 36.6%, 35.4%, and 14.6%, respectively. The specificity of taller-than-wide shape was 98.5%, but the Youden index was only 15.2% because of low sensitivity.

ROC analyses were performed on each US feature and their combinations, except intranodule flow [Figure 1]. The AUC for the combination of five US features was the largest, which was 0.876 [95% confidence interval [CI], 0.850–0.901, Table 3]. The 95% CI of AUCs of hypoechogenicity and irregular margins with any other feature were overlapped that of five features combinations.

**DISCUSSION**

It is well accepted in the current literature that patients with a nodular thyroid should be evaluated if they meet the following criteria: male gender, preexisting autoimmune disease, history of head and neck irradiation, elderly, or have a family history of thyroid disease. Baier *et al.* evaluated the US data and the clinical and laboratory characteristics of 944 patients with thyroid nodules and noted an association between malignant solid component nodules and patients younger than 45 years.\(^{[13]}\) Age is one of the criteria to evaluate malignancy in the UICC/AJCC system, which uses 45 years as the cutoff point.\(^{[14]-[16]}\) In the current study, we found that the average age of patients with malignant nodules was 45 years without obvious risk factors and the percentage of malignant nodules among 18–45 years patients was almost as much as that among 45–60 years patients. Therefore, doctors should pay more attention to abnormal US features.

According to the 2015 American Thyroid Association Guideline Task Force, solid component hypoechoic nodules with one or more of the following features had over 70–90% risk of malignancy: irregular margins, microcalcifications, taller-than-wide shape, and rim calcifications.\(^{[17]}\) However, in our study, irregular margins and hypoechogenicity had a higher predictive value than solid component and hypoechogenicity. For the prediction of malignancy, the sensitivity of solid component in our study was low. Azizi *et al.* found that solid nodules had a statistically insignificant increased risk of malignancy (73.3% of malignant and 66.0% of benign nodules were solid components; odds ratio \([OR]\), 1.4; 95% CI, 0.9–2.3).\(^{[18]}\) D’Souza *et al.* reported similar results (65.4% of cancers and 59.2% of benign nodules were solid components; \(OR\), 1.3; 95% CI, 0.5–3.1).\(^{[19]}\)

| Ultrasonic features | Carcinoma case, \(n\) (%) | Benign case, \(n\) (%) | Youden index (%) | Specificity (%) | Sensitivity (%) | PPV (%) | NPV (%) |
|---------------------|--------------------------|------------------------|-----------------|----------------|----------------|---------|---------|
| Irregular margins   | 306 (72.2)               | 67 (19.8)              | 51.9            | 79.8           | 72.1           | 82.0    | 69.1    |
| Hypoechogenicity    | 380 (89.6)               | 147 (43.4)             | 45.3            | 55.6           | 89.7           | 72.2    | 80.7    |
| Solid component     | 378 (89.1)               | 178 (52.7)             | 36.6            | 47.4           | 89.2           | 68.5    | 77.3    |
| Microcalcifications | 175 (41.3)               | 30 (8.9)               | 35.4            | 90.6           | 44.8           | 85.8    | 56.2    |
| Taller-than-wide shape | 71 (16.8)            | 5 (1.5)                | 15.3            | 98.5           | 16.8           | 93.4    | 48.0    |
| Intranodular vascularity | 202 (47.6)        | 75 (22.7)              | 14.6            | 68.8           | 45.8           | 67.9    | 52.0    |

PPV: Positive predictive value; NPV: Negative predictive value; US: Ultrasound.
Moon et al. found that solid components were not helpful for distinguishing malignant nodules from benign ones.\textsuperscript{[28]} Solid components are not considered as good predictors of malignancy as shown by previous US studies.\textsuperscript{[21,22]} Therefore, this consideration should be included in the establishment of our new guideline.

Despite the subjective variations in margin interpretation, an irregular margin is a useful marker of malignancy with high accuracy, specificity, and PPV.\textsuperscript{[23]} A previous meta-analysis reported that irregular margins were a strong predictor of malignancy (OR, 7.2; specificity, 79.6%).\textsuperscript{[24]} After the multivariate analysis, border irregularity as observed by US and the Bethesda IV category was able to accurately predict malignancy in 76.9% of the thyroid nodules with indeterminate cytology.\textsuperscript{[25]} The present study highlights the predictive value of intranodule flow as low, which is supported by previous studies.\textsuperscript{[26,27]} The limitation of our study is its retrospective design; however, this was controlled for by reevaluation of the ultrasonographic features.

In conclusion, we should be alert with taller-than-wide shape and microcalcifications. Intranodular flow was a weak predictor of malignancy. According to the Youden indexes and ROC analysis, irregular margins and hypoechogenicity combined with solid component or taller-than-wide shapes or microcalcifications have a high predicative value for malignant thyroid nodules in Chinese patients.

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Conflicts of interest
There are no conflicts of interest.

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