World Scientific Research Journal (WSRJ) ISSN: 2472-3703
www.wsr-j.org

Clinical Application of Thyroid Nodule Imaging Diagnosis System in Macau Public Medical System

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Abstract: Objects: Thyroid nodules are common diseases. Ultrasound is highly sensitive and specific in the diagnosis of thyroid nodules and has no invasion and radiation. It has become an important imaging diagnostic method for thyroid nodules. The 2016 American Thyroid Association (ATA) Management Guidelines, 2014 British Thyroid Association (BTA) Guidelines for the Management of Thyroid Cancer and 2017 American Radiology College Thyroid Imaging Reporting and Data System (TIRADS) are the main guidelines for the diagnosis of thyroid nodules. The purpose of this study is to provide a more comprehensive and unified scheme for the diagnosis of thyroid nodules in Macao's public medical system by comparing the above three guidelines. Method: 558 thyroid nodules from 530 patients with thyroid nodules were classified by TI-RAD, BTA and ATA, and compared with pathological findings for diagnostic analysis. Result: There were 558 thyroid nodules from 526 patients in this study. 26 nodules were malignant (4.7%) and 532 nodules were benign (95.3%). According to the guidelines of ATA, BTA and TI-RADS, the respective performances are calculated as follows: ATA: sensitivity – 96.2 %, specificity- 94%, positive predictive value – 43.9% and negative predictive value- 99.8%. BTA: sensitivity – 88.5 %, specificity- 93.1%, positive predictive value – 38.2% and negative predictive value- 99.4%. TI-RADS: sensitivity – 92.3 %, specificity- 95.1%, positive predictive value – 47.4% and negative predictive value- 99.6%. The curve values of ROC under the three guidelines are as follows: ATA: AUC- 0.81, BTA: AUC-0.824, TI-RADS- AUC-0.849. And there is no significant difference in statistics. Conclusion: In this study, ATA, BTA and TI-RADS had good sensitivity and negative predictive value in the diagnosis of benign and malignant thyroid nodules. Therefore, the three guidelines can be appropriately and reasonably used as the criteria in Macao's public health system.

1. INTRODUCTION

Thyroid nodules are a common clinical problem. According to literature, thyroid nodules affect more than two-thirds of the general population [1, 2]. About 7-15% of these people are definitely proven to be thyroid cancer. The etiology may be related to age, sex, radiation exposure history, family history and other factors [3, 4]. Since about 90% of thyroid nodules are benign in nature, it is essential to correctly classify the malignant risk of nodules, while avoiding a large number of unnecessary invasive operations and/or operations.

Thyroid ultrasound is a widely accepted imaging modality for the preliminary assessment of thyroid nodules. In addition to being widely used to stratify the risk of malignant thyroid nodules, it also helps to determine whether the nodules require fine needle aspiration biopsy (FNAB). There are many reliable literatures for the differential diagnosis of benign and malignant thyroid nodules [5-11]. Because the risk of malignant tumors assessed by ultrasound is not determined by a single ultrasound predictor, it should be assessed by combining ultrasound features. For example, hypoechoic, distinct hypoechoic, lobulated or irregular shape, microcalcification and higher than broad shape. These are the sonographic manifestations of malignant tumors [12-15]. According to the risk of malignant lesions, thyroid nodules have several classification systems. The American Thyroid Association (ATA) and the British Thyroid Association (BTA) published guidelines for the classification of thyroid nodules by ultrasound. The Thyroid Imaging Reporting and Data System (TI-RADS) was also published by the American Radiological Society [16-18]. The purpose of this study is to compare the accuracy of three guidelines in the diagnosis of malignant lesions.

2. METHODS

From April 2016 to December 2017, 558 thyroid nodules underwent ultrasound-guided fine needle biopsy in the Department of Radiology, Centro Hospitalar Conde de São Januário. We retrospectively analyzed the causes of puncture biopsy of these thyroid nodules. Sex and age, cytological and histopathological results of patients were collected from electronic medical records and case records of hospitals. In this study, pathological cytological diagnosis was widely classified according to the Bethesda System for Reporting Thyroid Cytopathology [19]. The categories are as follows: I: non-diagnostic; II: benign; III: atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); IV: follicular neoplasm or suspicious for a follicular neoplasm; V: suspicious for malignancy; or VI: malignant. These nodules were classified according to the latest ATA guidelines, BTA guidelines and TIRADS classification (see the appendix). These three ultrasound risk stratification systems are shown in the appendix. This study was approved by the Hospital Ethics Committee.

IBM SPSS 25.0 software was used for data analysis. Chi-square test was used to compare the coincidence of TI-RADS classification results with pathological results and the difference of ultrasound signs between benign and malignant thyroid nodules. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of TI-RADS in the diagnosis of benign and malignant thyroid nodules were calculated. According to the classification of ATA, BTA and TI-RADS, the ROC curve was constructed and the area under the curve was calculated. The area under the ROC curve was tested by Z test. Then three ROC curves were analyzed by MedCalc software. $P < 0.05$ was considered to have statistical significance.

Exclusion criteria: Pathological findings could not be confirmed, past thyroidectomy history, hyperthyroidism or hypothyroidism, non-thyroidism origin of cervical mass.
This study was independently stratified by two radiologists in our hospital. They assessed each thyroid nodule stratified according to ATA, BTA and TI-RADS guidelines.

3. RESULTS

A total of 558 thyroid nodules from 526 patients were included in this study. In this study, the proportion of women was 86%, while that of men was 14%. The average age of the patients was 55.5±13.3 years. In our study, According to TIRADS classification, the malignant detection rates of categories 3, 4 and 5 were 2.4%, 15.7% and 88.5respectively ($P < 0.001$) (Table 1). The malignant rate of ATA was 3.9% extremely low suspicion, 5.8% low suspicion, 38.8% medium suspicion and 71.4% high suspicion. There was a significant difference between different types ($P < 0.001$). The malignant rates of BTA group were U2 3.7%, U3 7.1%, U4 24.8% and U5 70% respectively ($P < 0.001$) ((table 1). We found that the pathological results were significantly correlated with the three rating systems ($P < 0.05$), so the three rating systems were significantly correlated with the pathological results.
The diagnostic performance of the guidelines includes sensitivity, specificity, positive predictive rate and negative test predictive rate as follows: ATA classification: sensitivity 96.2%, specificity 94%, PPV 43.9% and NPV 99.8%. BTA classification: sensitivity 88.46%, specificity 93%, PPV 38.2% and NPV 99.4%. TI-RADS classification: sensitivity 92.31%, specificity 95.1%, PPV 47.4% and NPV 99.6% (table 2).
In particular, the C index of the model compares different ultrasound classification systems. The C index of TI-RADS was the highest (0.849 (95% CI: 0.817-0.878), followed by BTA (0.824 (95% CI: 0.790-0.855). The C index of the system proposed by ATA was the lowest (0.810 (95% CI: 0.774-0.841). There was no significant difference in C index between TI-RADS, ATA and BTA. Their P values were 0.64(TI-RADS versus BTA), 0.75(BTA versus ATA) and 0.14(ATA versus TI-RADS), respectively (Figure 1).

Table 1. Malignant rate and recommended malignant rate of thyroid nodules based on ATA, BTA and ACR TI-RADS ultrasonography

Classification	Total no. of cases(n=558)	No. (%)		Malignancy rate (%)	Recommended malignancy rate (%)
		Benign(n=532)	Malignant(n=26)		
ACR TI-RADS					
TR3	405	404	1	0.2	4.8%
TR4	127	126	2	1.6	9.1%
TR5	26	3	23	88.5	35%
BTA					
Benign (U2)	268	267	1	0.4	
Intermediate(U3)	139	138	1	0.7	
Suspicious(U4)	121	118	3	2.5	
Malignant(U5)	30	9	21	70	
ATA					
Very low suspicion	255	254	1	0.4	<3
Low suspicion	172	171	1	0.6	5-10
Intermediate suspicion	103	99	4	3.9	10-20
High suspicion	28	8	20	71.4	>70-90

Table 2. Diagnostic accuracy of the three US classification systems

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ACR TI-RADS	92.31	95.1	99.6	47.4
BTA	88.46	93	99.4	38.2
ATA	96.2	94	99.8	43.9

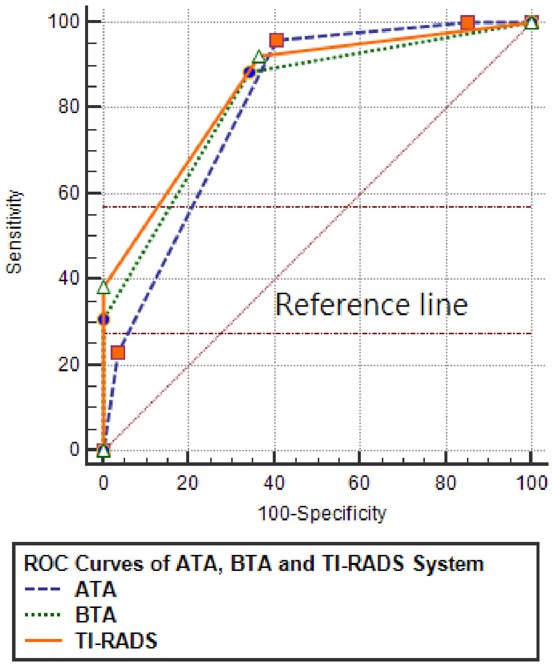

Figure 1. Receiver operating characteristic (ROC) curve was used to diagnose high-risk malignant nodules in cytology. The area under the ROC curve (AUC) of three classification systems is shown in the figure. The AUC values of ATA: AUC-0.81, BTA: AUC-0.824, TI-RADS-AUC-0.849. There was no significant difference in statistics (P > 0.05).

4. DISCUSSION

Thyroid nodules are common surgical diseases. At present, ultrasonography is the most important and sensitive imaging examination in the diagnosis of thyroid nodules. It is difficult to judge the benign and malignant thyroid nodules because of the complexity of the sonographic features of thyroid nodules and the confusion of the sonographic features of benign and malignant nodules. In addition, there are no clear criteria for the diagnosis of thyroid nodules. At the same time, there are subjective differences in each doctor's description of ultrasound images, and the level of diagnosis is also quite different, which seriously affects the clinician's judgment and diagnosis of the lesions. Therefore, there are many kinds of thyroid nodule image classification system. Among them, the American Thyroid Association (ATA), the British Thyroid Association (BTA) and the TI-RADS system of the American Radiological Society are mostly used by radiologists. The use of these classification systems has greatly improved the communication between clinicians and radiologists and helped to standardize clinical practice. But how to choose the best scheme is a difficult problem when facing different classification systems. In this study, we compared the accuracy of all ATA, BTA and ACR-TI-RADS US classifications for thyroid nodules based on the FNA results of 558 thyroid nodules. The malignant rate of our study is 4.6%, which is lower than 16-20% in foreign studies [20-22]. However, in the three stratified systems, the malignant rate of the highest risk levels (ATA-high suspicious, BTA-U5 and TI-RADS-TR5) was more than 70%. Therefore, the above three systems have high detection rate of malignant thyroid nodules at high risk. In C statistical analysis, the highest AUC value of TI-RADS was 0.849, while the AUC values of BTA and ATA were 0.824 and 0.810, respectively. These results indicate that the three grading systems are also very high for the malignant detection of thyroid nodules. However, there was no significant difference between the three groups in statistics ($P > 0.05$). The results are different from those of some foreign literatures [23-25]. This study compared the diagnostic accuracy of three established risk classification guidelines for thyroid nodules. The sensitivity, specificity and negative predictive rate of the three indicators were more than 90%. Among them, the sensitivity and negative predictive value of ATA guidelines were the highest. The positive predictive value (PPV) of the three diagnostic systems exceeded 30%, and TI-RADS was the highest, reaching 47.4%. Although the three grading systems have a high rate of malignant diagnosis of thyroid nodules, one case was diagnosed as benign by BTA and papillary thyroid cancer by pathology. Therefore, the results of our study suggest that three rating systems, BTA, ATA and TI-RADS, are highly sensitive and negative predictors for ultrasound diagnosis of thyroid nodules. It is an important diagnostic and screening tool.

The main limitation of this study is a retrospective study. Risk factors such as radiation exposure history, family history, gender and age were not analyzed. Although this study was conducted independently by two radiologists, each case was analyzed. However, two recent studies have reported errors in observer-to-observer correlation to influence the pattern of sonograms used to identify nodules [26, 27]. The pathological results of this study are related to Bethesda cytological system. Although some of the cases in this study were confirmed by pathology after surgical resection. But most of them are based on cytology. Therefore, some cases may be false negative result and cause bias [28, 29].

In conclusion, the TI-RADS stratified rating published by ACR and the recently revised ATA and BTA guidelines have high sensitivity and NPV in the diagnosis of thyroid cancer. These three systems are feasible in clinical application and have good negative predictive value. They can be used as alternatives for patients who need FNA. Although the sensitivity and negative predictive value of the three classification systems are high. In this study, we found that the reason why many thyroid nodules were punctured was the size of nodules (>2cm). Recent studies have shown that the size of thyroid nodules is not directly related to malignancy [25]. At the same time, we found that quite a few of these nodules were classified as TR2 in ACR TI-RADS and U2 in BTA. However, the malignancy rates at all levels are not specified in the BTA rating. Therefore, we summarize three thyroid nodule rating systems and conclude that ACR TI-RADS has better clinical applicability and US-FNA indications.

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APPENDIX

The TIRADS, BTA and ATA classification categories

TI-RADS classification	
TR1 (0 points)	Benign
TR2 (2 points)	Not suspicion
TR3 (3 points)	Mildly suspicion
TR4 (4 – 6 points)	Moderately suspicion
TR5 (> 7 points)	High suspicion
Score = Composition + Echogenicity + Shape + Margin+ Echogenic foci	
Composition	
Cystic or almost completely cystic	0 points
Spongiform	0 points
Mixed cystic and solid	1 point
Solid or almost completely solid	2 points
Echogenicity	
Anechoic	0 points
Hyperechoic or isoechoic	1 point
Hypoechoic	2 points
Very hypoechoic	3 points
Shape	
Wider than tall	0 points
Taller than wide	3 points
Margin	
Smooth	0 points
Ill-defined	0 points
Lobulated or irregular	2 points
Extra-thyroidal extension	3 points
Echogenic foci	
None or large comet- tail artifacts	0 points
Macrocalcification	1 point
Peripheral calcification	2 points
Punctate echogenic foci	3 points
BTA classification	
U1 (normal)	Normal thyroid gland
U2 (benign)	(a) halo, iso-echoic / mildly hyper-echoic (b) cystic change +/- ring down sign (colloid) (c) micro- cystic / spongiform (d & e) peripheral egg shell calcification (f) peripheral vascularity.
U3 (intermediate/equivocal)	(a) homogenous, hyper-echoic (markedly), solid, halo (follicular lesion). (b) possible hypo-echoic, equivocal echogenic foci, cystic change (c) mixed/central vascularity.
U4 (suspicious)	(a) solid, hypo-echoic (compare with thyroid) (b) solid, very hypo-echoic (compare with muscle) (c) disrupted peripheral calcification, hypo-echoic (d) lobulated outline
U5 (Malignant)	(a) solid, hypo-echoic, lobulated / irregular outline, micro-calcification. (b) solid, hypo-echoic, lobulated/irregular outline, globular calcification (c) intra-nodular vascularity

	(d) shape (taller >wide) (AP>TR) (e) characteristic associated lymphadenopathy
ATA classification	
Benign	Purely cystic nodules (no solid component)
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or extrathyroidal extension (ETE), or taller than wide shape
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension (ETE), or taller than wide shape
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension (ETE)