ROLE OF ULTRASONOGRAPHY AND COLOR DOPPLER IMAGING IN IDENTIFICATION OF THYROID NODULES SUSPICIOUS OF MALIGNANCY FOR FINE NEEDLE ASPIRATION

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ABSTRACT:

Background: *Thyroid nodules are an exceedingly common finding on neck sonography. Ultrasound is the most commonly used imaging technique for the evaluation of thyroid nodules. Fine Needle Aspiration (FNA) of the thyroid is the single most useful diagnostic test for evaluating thyroid nodules.*

Aim of Work: *To investigate the performance of US imaging and color flow mapping in identification of thyroid nodules indicated for FNA to predict thyroid cancer to avoid unnecessary interventions.*

Patients and Methods: *Type of Study: Cross sectional study. Study Setting: The study was conducted at Ain Shams University Hospitals. Study Period: from December 2020 to September 2021. Study Population: Patients undergoing Neck US for thyroid nodules.*

Results: *The correct interpretation of thyroid ultrasound report using the ACR-TIRADS criteria helps to facilitate the identification of highly suspicious nodules. The aggregate risk of malignancy increased as the TIRADS level increased from TR 1 to TR 5 (P-value <0.001). Intranodular vascularity and high resistive indices (RI) were few of the specific signs for malignant thyroid nodules in our study (P-value <0.005).*

Conclusion: *The present study concludes that US features (ACR-TIRADS) along with color and pulse Doppler should be used as first line imaging modality in evaluations of thyroid nodules. An excellent correlation was seen in diagnosis of thyroid lesions between sonography and FNA.*

Keywords: *Ultrasonography, Fine Needle Aspiration*

INTRODUCTION:

Ultrasonography (US) is one of the most widely used imaging technologies in medicine. It is portable, free of radiation risk, and relatively inexpensive when compared with other imaging modalities, such as magnetic resonance and computed tomography the images can be acquired in "real time," thus providing instantaneous visual guidance for many interventional procedures including those for regional anesthesia and pain management[1].

Thyroid nodules are exceedingly common, with a reported prevalence of up to 68% in adults on high-resolution US[2].

Certain features of thyroid nodules on US are consistently predictive of malignancy and are used as criteria for FNA. These criteria have various sensitivity and specificity, but unfortunately none of them alone is sufficient to discard or detect malignancy efficiently[3].

FNA of the thyroid is the single most useful diagnostic test for evaluating which patients with thyroid nodules should undergo surgery [4].

Since about 90% of thyroid nodules are benign, it is crucial to correctly stratify the malignancy risk of the nodules to avoid a huge number of unnecessary invasive procedures and/or surgery, as an improper use of FNA has the risk of increasing healthcare expenditures and even of inappropriately referring patients to surgery in case of indeterminate cytology [5].

Medical professional societies such as the American Thyroid Association (ATA) and American Association of Clinical Endocrinologists have suggested that the initial cytological diagnosis can be postponed until growth of a nodule or a change in its US features is observed. Repeated FNA of nodules with an initial benign cytological diagnosis leads to a final diagnosis of cancer in approximately 2% of cases [6].

PATIENTS AND METHODS:

Type of Study: Cross sectional study.

Study Setting: The study was conducted at Ain Shams University Hospitals.

Study Period: from December 2020 to September 2021.

Study Population: Patients undergoing Neck US for thyroid nodules.

Inclusion criteria: Adults with thyroid nodules of both sexes. With no prior diagnostic workup in the current condition. No sex predilection. Age group: ranges from 18 to 75 years.

Exclusion criteria: Patients with multinodular goiter. Past history of interventions targeting the thyroid gland (surgery, or Radioactive Iodine).

Sampling Method: This study was performed on convenience sample.

Sample Size: Using PASS 11 program for sample size calculation, reviewing results from previous study [5]. showed about 90% of thyroid nodules are benign, regarding, accuracy and reproducibility of ultrasonography classification systems in characterizing cytologically indeterminate thyroid nodules results from previous study[7] showed that US sensitivity and specificity were (89% and 67% respectively), based on these results, a sample size of at least 25 patients will be needed.

Ethical considerations: Informed oral consent explaining the procedure details was obtained from all patients prior to inclusion in the study. The study was conducted according to the stipulations of the Ain Shams University ethical and scientific committee. The privacy of participants and confidentiality of data was guaranteed during the various phases of the study.

Study Tools and procedures: Detailed explanation of the procedure and obtaining an oral consent. All patients were subjected to full history taking prior to scanning.

Thyroid Ultrasound:

Ultrasound of the thyroid gland was performed in an ultrasound machine (Mindray DC-60 exp) using a high-frequency probe (7-10 MHz). Axial and sagittal ultrasound scanning of the thyroid nodules with the head slightly extended was performed. Imaging interpretation of thyroid nodules was done, guided by the American College of radiology (ACR) Thyroid Imaging, Reporting and Data System (TI-RADS) template as follows:

Criteria to confirm the nature of the scanned thyroid nodules (either benign or malignant) included the following:

Fine needle aspiration cytology (FNAC) report.

Thyroid Fine needle aspiration cytology (FNAC):

FNAC was undertaken by a radiologist with ultrasound guidance after the thyroid ultrasound. The procedure was explained carefully to the patient.

The patient was placed in a supine position with head is turned, chin extended, away from the side to be biopsied to allow easier access. The transducer was placed directly over the lesion and the patient was instructed not to swallow or speak during the insertion of the needle.

FNA was performed using a 26-gauge needle attached to a 10 ml syringe. Two to three aspirations were performed on each nodule. Cytology smears were prepared on three to six slides. Slides were fixed immediately in 95% alcohol and sent for cytopathology. A cytology technician confirmed the adequacy of the specimen before being reported by cytopathologists.

Statistical Analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric while with non-parametric distribution were presented as median with inter-quartile range (IQR). Also, qualitative data were presented as number and percentages. Also, the comparison between two groups regarding qualitative data were done by using Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and parametric distribution were done by using Independent t-test while with non-parametric distribution were compared by using Mann-Whitney test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the P-value was considered significant as the following: P-value > 0.05: Non-significant. P-value < 0.05: Significant. P-value < 0.01: Highly significant.

RESULTS:

Table (1): Demonstrating summary of the comparison between benign group and malignant group of the studied cases

		No. = 25
Age	Mean ± SD	48.80 ± 12.53
	Range	26 – 72
Sex	Female	18 (72.0%)
	Male	7 (28.0%)
Side	Right	16 (64.0%)
	Left	9 (36.0%)
Ultrasound		
Nodule Size	Mean ± SD	2.90 ± 0.72
	Range	1 – 4
TIRADS	III	9 (36.0%)
	IV	13 (52.0%)
	V	3 (12.0%)
TIRADS	III	9 (36.0%)
	IV + V	16 (64.0%)
Doppler		
Peak Systolic velocity (PSV	Mean ± SD	23.42 ± 10.58
	Range	8.52 – 43.6
RI	Mean ± SD	0.65 ± 0.08
	Range	0.52 – 0.81
Biopsy		
Biopsy Result	Benign	20 (80.0%)
	Malignant	5 (20.0%)

Table (2): Demonstrating comparison between benign group and malignant group regarding age and sex of the studied cases, and site of the nodule

		Biopsy Results		Test value	P-value	Sig.
		Benign	Malignant			
		No. = 20	No. = 5			
Age	Mean ± SD	46.35 ± 10.97	58.6 ± 14.84	-2.088•	0.048	S
	Range	26 – 65	39 – 72			
Sex	Female	16 (80.0%)	2 (40.0%)	3.175*	0.075	NS
	Male	4 (20.0%)	3 (60.0%)			
Site	Right	13 (65.0%)	3 (60.0%)	0.043*	0.835	NS
	Left	7 (35.0%)	2 (40.0%)			

P-value >0.05: Nonsignificant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *: Chi-square test; •: Independent t-test

Table (3): Demonstrating comparison between benign group and malignant group regarding nodule size and TIRADS score

Ultrasound		Biopsy Results		Test value	P-value	Sig.
		Benign	Malignant			
		No. = 20	No. = 5			
Nodule Size	Mean ± SD	3.00 ± 1.00	3.00 ± 0.00	0.466•	0.645	NS
	Range	1 – 4	2 – 3			
TIRADS	III	9 (45.0%)	0 (0.0%)	14.423*	0.001	HS
	IV	11 (55.0%)	2 (40.0%)			
	V	0 (0.0%)	3 (60.0%)			
TIRADS	III	9 (45.0%)	0 (0.0%)	3.516*	0.061	NS
	IV + V	11 (55.0%)	5 (100.0%)			

P-value >0.05: Nonsignificant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *:Chi-square test; •: Independent t-test

Table (4) Demonstrating comparison between benign group and malignant group regarding PSV and RI of the intranodular vessels

Doppler		Biopsy Results		Test value•	P-value	Sig.
		Benign	Malignant			
		No. = 20	No. = 5			
PSV	Mean ± SD	21.64 ± 9.75	30.55 ± 11.9	-1.755	0.093	NS
	Range	8.52 – 39.5	16.45 – 43.6			
RI	Mean ± SD	0.63 ± 0.07	0.73 ± 0.05	-2.799	0.010	S
	Range	0.52 – 0.81	0.64 – 0.77			

P-value >0.05: Nonsignificant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) •: Independent t-test

ROC curve of US and Doppler as a predictor of malignancy

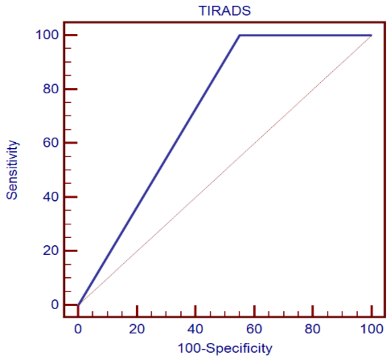

Diagram 1: Graph demonstrating the specificity of the TIRADS

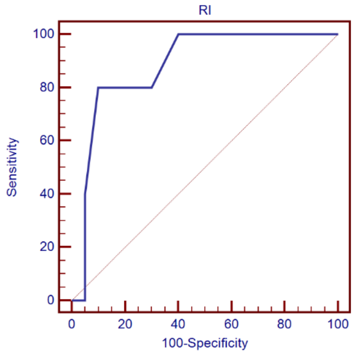

Diagram 2: Graph demonstrating the specificity of the intranodular vessels RI

Table (5): Demonstrating the diagnostic performance of the TIRADS and doppler

Parameter	AUC	Cutoff Point	Sensitivity	Specificity	PPV	NPV
Ultrasound						
TIRADS	0.560	--	100.0	45.0	31.3	100.0
Doppler						
RI	0.880	>0.73	80.0	90.0	66.7	94.7

The previous receiver operating characteristic curve ROC (Diagram 1) shows the high sensitivity of the TIRADS, but also relatively low specificity, as several nodules which were classified as suspicious by the TIRADS turned out to be actually benign.

On the other hand, the other ROC curve (Diagram 2) shows that the RI cutoff point has higher specificity to detect malignant cases -despite the lower sensitivity-, as most of the nodules with higher RI than 0.73, were actually malignant.

DISCUSSION:

Thyroid nodules are a very common clinical problem, and the prevalence of thyroid nodules is 19–68% with the use of high-resolution US. Differentiating malignancy is an important clinical process, as malignancy occurs in 7–15% of detected thyroid nodules depending on various risk factors [8].

The most commonly reported complications of FNA are local pain and minor hematomas; serious ones are rare [9].

Repeated FNA of nodules with an initial benign cytological diagnosis leads to a final diagnosis of cancer in approximately 2% of cases[6].

US risk stratification systems (RSSs) have been developed to reduce the number of unnecessary FNA procedures in patients with thyroid nodules[10].

The efficacy of these RSSs to differentiate benign nodules from the malignant ones according to their ultrasonographic features has been proved by many studies.

American Association of Clinical Endocrinologists, American College of Endocrinology and Associazione Medici Endocrinologi (AACE/ACE/AME), American College of Radiology (ACR-TIRADS), European Thyroid Association (EU-TIRADS), Korean Society of Thyroid Radiology (K-TIRADS), and American Thyroid Association (ATA) were among these developed RSSs.

A critical step in developing the ACR TI-RADS guidelines and all other similar guidelines is stratification of lesions on the basis of their risk of malignancy[11].

The ACR-TIRADS showed superior diagnostic performance compared to other thyroid nodule guidelines and its use has reduced a larger number of unnecessary FNAs [12].

Yet vascularity was not among the TIRADS criteria, which was based only on ultrasonographic features (microcalcifica-tions, hypoechogenicity, microlobulation or irregular margins, and a taller-than-wide shape).

The Doppler criteria remain controversial, mainly because the sensitivity of Doppler is highly dependent on the US equipment and settings, and because the definition of central vascularity has a low interobserver agreement [3].

Individual variations of tissue attenuation, patient movement and lack of cooperation, motions as swallowing or breathing, and pulsations of adjacent arterial structures may affect Doppler US investigation[13].

Nodule vascularity is not part of ACR TI-RADS lexicon, as lesion vascularity has not been found to consistently correlate with papillary thyroid cancer; however, there is an association with follicular cancers [14].

Although many studies considered the nodule vascularity in the detection of malignancy, it was mostly classified into non-vascular, peripheral, central, and mixed vascularity.

The aim of this study is to evaluate the ability of the ultrasonographic features (here ACR-TIRADS was applied) in excluding benign nodules from performing FNA, and the ability of the doppler to refine these results even more.

In order to achieve this, our study included 25 patients with solitary thyroid nodules, who was undergoing FNA. Imaging interpretation was done guided by the ACR-TIRADS template, focusing on their sonographic appearance in relation to their benign or malignant nature.

In addition, our study applied doppler parameters on intranodular vessels (RI & PSV), in order to detect a potential relationship between nodule vascularity and malignancy.

In our study, the ACR-TIRADS showed high diagnostic performance, correctly predicted the nature of thyroid nodules to a large extent, as all of the TIRADS V nodules were malignant. (P-value < 0.001).

In agreement with several studies, this study found a significant relationship between nodule vascularity and malignancy, unlike ***Moon et al. (2010)*** *[15]**; Rosario et al. (2015)*** *[16]**,*** who did not find any relationship between intranodular vascularity and malignancy,

However, this study reported the PSV as an insignificant parameter ($P>0.05$), in agreement with ***Palaniappan et al. (2016)*** *[17]**,*** as well as ***Bhatt et al. (2017)*** *[18]**.*** In contrary to ***Singh et al. (2017)*** *[19]**,*** who reported that the PSV is an important factor in detecting malignancy, and even set a cut-off value (less than 20.4 cm/sec was considered malignant) ***Baş et al. (2021)*** *[20]**; Kalantari (2018)*** *[21]* didn't take the PSV in consideration.

Regarding the RI, this study found that it is a more reliable factor in malignancy detection ($P<0.05$), in agreement with ***Kalantari (2018)****[21]**; Palaniappan et al. (2016)*** *[17]**; Singh et al. (2017)****[19]**.**

This could be attributed to the increased proliferation of malignant cells.

The high central and peripheral RI-PI values noted may be due to stenosis and/or occlusion of arteries due to excess cellular proliferation in malignant nodules *[17]**.**

However, ***Bhatt et al. (2017)****[18]* ***and Tamsel et al. (2007)****[22]* reported no significant association between intranodular

RI and malignancy. They did not determine the sensitivity, specificity, PPV, and NPV.

Our study concluded an RI cutoff value of 0.73, in agreement with ***Palaniappan et al. (2016)[17].*** However, there is disagreement with ***Algin et al (2010)[13]; Kalantari (2018)[21],*** with respect to the RI between the benign and malignant thyroid nodules, as they set a cutoff value of 0.71. Meanwhile, ***Singh et al. (2017)[19]*** set a higher cutoff RI value, at 0.75.

In more recent studies, many authors reported similar findings and concluded that RI value in malignant nodules were higher than in benign nodules.

Conclusion:

The present study concludes that US features (ACR-TIRADS) along with color and pulse Doppler should be used as first line imaging modality in evaluations of thyroid nodules. An excellent correlation was seen in diagnosis of thyroid lesions between sonography and FNA.

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دور الموجات فوق الصوتية والدوبلر الملون في اختيار عقيدات الغدة الدرقية المشتبه بخباثتها لأخذ عينة الإبرة الدقيقة

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نبذة مختصرة

خلفية: تعتبر عقيدات الغدة الدرقية شائعة للغاية في التصوير فوق الصوتي للرقبة. الموجات فوق الصوتية هي تقنية التصوير الأكثر استخدامًا لتقييم عقيدات الغدة الدرقية. إن الشفط بالإبرة الدقيقة للغدة الدرقية هو الاختبار التشخيصي الأكثر فائدة لتقييم عقيدات الغدة الدرقية.

الهدف: للتحقيق في أداء الموجات فوق الصوتية والدوبلر الملون في تحديد عقيدات الغدة الدرقية المشار إليها للتنبؤ بسرطان الغدة الدرقية لتجنب التدخلات غير الضرورية.

المرضى والطرق: نوع الدراسة: دراسة مقطعية. إعداد الدراسة: أجريت الدراسة في مستشفيات جامعة عين شمس. فترة الدراسة: من ديسمبر ٢٠٢٠ إلى سبتمبر ٢٠٢١. مجتمع الدراسة: المرضى الذين يخضعون للكشف بالموجات فوق الصوتية على الرقبة بسبب عقيدات الغدة الدرقية.

النتائج: يساعد التفسير الصحيح لتقرير الموجات فوق الصوتية للغدة الدرقية باستخدام معايير (تي-رادس) على تسهيل تحديد العقيدات المشبوهة للغاية. زاد الخطر الإجمالي للأورام الخبيثة مع زيادة مستوى (تي-رادس) من TR 1 إلى TR 5 (قيمة P <0.001).

كانت زيادة الأوعية الدموية داخل العقيدات ومؤشرات المقاومة العالية للأوعية الدموية بعض من العلامات المحددة للعقيدات الدرقية الخبيثة في دراستنا (P< 0.005).

الاستنتاج: تخلص الدراسة الحالية إلى أنه يجب استخدام معايير(تي-رادس) جنبًا إلى جنب مع الدوبلر الملون كطريقة تصوير أولية لتقييم عقيدات الغدة الدرقية. لوحظ ارتباط ممتاز في تشخيص آفات الغدة الدرقية بين الموجات فوق الصوتية وعينة الابرة الدقيقة.