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Employing the European Thyroid Imaging Reporting and Data System 2017 classification in a malignancy risk stratification system for thyroid nodules at Can Tho Oncology Hospital from 2021 to 2023

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Contributions: VVK, conceptualization; TTHL, data curation and formal analysis; VHN, methodology; PTTH, writing – original draft.

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Informed consent: before study participation, written informed consent was obtained from the patient.

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Abstract
Thyroid nodules are extremely common, accounting for up to 68% of all random ultrasound examinations in adults. They are mostly benign. Early detection of nodules and risk stratification systems (RSS) are critical for guiding monitoring and treatment. The primary methods for managing thyroid nodules are ultrasound and fine-needle aspiration biopsy (FNAB). Thyroid Imaging Reporting and Data Systems (TIRADS) have been developed worldwide, utilizing ultrasound features such as composition, margin, shape, and echogenicity. Many countries have conducted research on the EU-TIRADS classification system, which focuses on key malignant features while remaining easily accessible.
The objectives of this study are to describe imaging characteristics and assess thyroid nodules using the European (EU)-TIRADS 2017 ultrasound system and to compare results to histopathological outcomes and the American College of Radiology (ACR)-TIRADS 2017 systems. The study included patients who had ultrasound findings described using the TIRADS system, underwent surgery, and had histopathological results available. The study used a cross-sectional descriptive methodology.
In examining 435 thyroid nodules in 347 patients, a male-to-female ratio of 1:5, an average age of 44 years, and an average size of 25 mm were found. Comparing EU-TIRADS to histopathology and ACR-TIRADS, the system's malignancy risk increased progressively from R2 to R5: 0%, 9.2%, 62.8%, and 93.0%, respectively. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for distinguishing between benign and malignant nodules were 91.2%, 81%, 81.6%, 91.3%, and 86.2%.
The EU-TIRADS 2017 system proved to be extremely useful in assessing thyroid nodules, particularly in the TIRADS 5 classification.

Introduction

In the general population, nodular lesions in the thyroid gland are very common, with a frequency of up to 68% when performing incidental ultrasound in adults with high-resolution probes.[1] The majority of lesions are benign. Since more than 90% of thyroid cancers are well-differentiated, progress silently, have a low level of malignancy with a good prognosis and have a 5-year survival rate of 95-97%,[2,3] detecting early-stage thyroid nodules and malignant risk stratification (RSS) will help guide disease monitoring and treatment. Currently, the two main methods used to manage and monitor simple thyroid nodules are ultrasound and fine needle aspiration cytology, which can be repeated with cytology or surgical histopathological diagnosis in cases of intermediate-risk thyroid nodules.[4] In the world, there are many Thyroid Imaging Reporting and Data Systems (TIRADS) to classify thyroid nodules based on ultrasound characteristics of borders, shape, echogenicity, and echogenicity components, especially European (EU)-TIRADS 2017 and American College of Radiology (ACR)-TIRADS 2017. Updates recommend fine-needle aspiration, depending on the size of the thyroid nodule.[5] In particular, the EU-TIRADS classification table evaluates mainly the main malignant features but does not reduce their value, and it has been researched and applied in many countries and Vietnam. Therefore, to contribute to the assessment of the value of EU-TIRADS and to continue the research on ACR-TIRADS classification at Can Tho City Oncology Hospital, we performed an analysis with the goal of i) describing the imaging characteristics and evaluate thyroid nodular lesions on ultrasound according to the EU-TIRADS 2017 classification; and ii) surveying the value of the EU-TIRADS 2017 system through comparison with histopathological results and ACR-TIRADS.

Materials and Methods

Subjects

The study evaluated 347 patients with 435 cases of thyroid nodules and was conducted at Can Tho Oncology Hospital between June 2021 and April 2023. Patients were selected for the sample when they had an ultrasound assessment of characteristics according to the TIRADS system, were indicated for surgical removal of thyroid nodule lesions, and had histopathology results. The patients had surgery because of suspected malignant thyroid nodules or large-size damage affecting the quality of life.

Methods

This is a prospective, cross-sectional study with a convenient sample size. The sample size was calculated with Eq. 1:

$$TP + FN = \frac{{Z_\alpha}^2 x\, p_{sp} x\, (1-p_{sp})}{c^2}$$

$$n_{(sp)} = \frac{FP+TN}{p_{dis}} \qquad \text{[Eq. 1]}$$

Where: Z_α is the desired confidence level of 95% ($Z_\alpha = 1.96$); p_{sp} is the probability of specificity (84.3%) according to research by Castellana *et al.*;[6] C is the allowable error (6%); and p_{dis} is the prevalence of thyroid nodules (68%).[7]

Substituting into the formula, we get the minimum sample size needed for the study, which is 207.

This study was approved by the institutional review board of Can Tho Oncology Hospital (Ref: 789/QĐ-BVUB). All patients gave informed consent to participate in the study, and their personal information was kept confidential.

A Siemens Acuson Juniper ultrasound machine with a linear probe frequency of 6.7-10 MHz was used for patients admitted to the hospital for thyroid nodule surgery. According to the EU TIRADS classification on ultrasound, TIRADS 2,3 lesions were classified as benign, and TIRADS 4,5 lesions were classified as malignant. Record postoperative surgical reports and collect histopathological results; classify diseased tissue into benign and malignant groups according to the World Health

Organization 2017 data processing is performed using SPSS 20.0 software. The EU-TIRADS 2017 system is presented in a summary diagram (Figure 1).[8]

Results

General characteristics of research subjects

This study included 347 patients with 435 thyroid nodules. Among them, 262 patients had one nodule, and 85 patients had two or more nodules. The incidence of the disease in women is higher than in men, with a male/female ratio of 1/5. The average age when thyroid damage was detected was 44.5±12.196 years old, with the youngest being 13 and the oldest being 79. The average size of thyroid nodules is 25.4±16.62 mm, in which the smallest size is 3mm and the largest is 100 mm (Table 1).

Men have a higher risk of malignant thyroid nodule lesions than women ($p<0.05$). The average size between the two groups of lesions is also statistically significant; the average size of malignant lesions is 18.33±14.3 mm, while benign lesions are 31.64±16.06 mm. However, there were no statistically significant differences in average age, living area, and location of the lesion.

Ultrasound imaging characteristics of thyroid nodules with histopathological results

The highest proportion was recorded of lesions with both solid and cystic components, hypoechoic, well-defined, oval shape, and no internal echogenic nodules (Table 2).

High suspicion features of EU-TIRADS 5 all show high specificity (including markedly hypoechoic, irregular margins encroaching beyond the thyroid gland, and taller-than-wide, microcalcifications), while the sensitivity is not high. The reverb is poor, and the sensitivity is quite good (Figure 2).

Value of the European Thyroid Imaging Reporting and Data System 2017

Comparing the results of the EU-TIRADS system with histopathology, the corresponding malignancy rates of each EU-TIRADS group 2, 3, 4, and 5 are 0%, respectively; 9.2%; 62.8%; and 93% are consistent with world studies (Figure 3).

Analyzing the receiver-operating characteristic (ROC) curve, the area under the curve (AUC) of EU is 0.91 and the ACR is 0.90 (≥ 0.9). To achieve an optimal balance between sensitivity and specificity, we choose R4 (EU) and TR4 (ACR) as the cut-off points (Figure 4).

Comparing the EU-TIRADS and ACR-TIRADS systems, we see that ACR-TIRADS has high specificity and positive predictive value, while EU-TIRADS has sensitivity and a higher negative predictive value (Table 3).

Discussion

General characteristics of research subjects

Our study was performed on 347 patients. There was a clear difference in the proportion of patients with thyroid nodular lesions. According to gender, with a male/female ratio of 1/5, men have a higher risk of malignant thyroid nodules than women. In terms of size, the benign lesion group often has a larger average size than the malignant lesion group. Consistent with the research of author Fan Xiao *et al*., they studied a group of 434 pathologically confirmed thyroid nodules, including 259 malignant thyroid nodules: male/female ratio is 1/5; 61.4% of men had malignant lesions; the average age was 45±12 years old. The average size of benign lesions is 20±14 mm, and malignant lesions are 11.5±8 mm.[9]

Ultrasound imaging characteristics of thyroid nodular lesions compared with histopathological results

Compositions

100% cystic and sponge are benign; mixed components account for 74.9% of benign lesions. Besides, the predominant solid component is malignant, with a rate of 72.7%, consistent with the systematic

analysis of Molina-Vega *et al*., with 82-91% of malignant lesions being solid components.[10]

Echogenicity
Hypoechoic thyroid nodules have the highest rate and are predominantly malignant, while markedly hypoechoic thyroid nodules suggest high malignancy with a rate of 88.5%, similar to the study by Kovatcheva *et al.* in 942 thyroid nodules.[11]

Shape
Most lesions have an oval shape, and non-oval lesions often show histopathological results as malignant lesions. In 2018, Xu *et al.* studied 2465 thyroid nodules and showed that 81.5% of the taller-than-wide is malignant.[12] A growth pattern demonstrating a "taller-than-wide" appearance (defined as an anteroposterior diameter that exceeds the transverse diameter) when imaging the thyroid in the transverse plane) is predictive of malignancy).

Margins
Most lesions were well-defined, accounting for 75.2%, with 64.7% of them being benign. Groups of lesions suggestive of malignancy had irregular margins (including spiculated, lobulated, or multi-arcillary) and invasion beyond the thyroid gland, with malignant rates of 96.8% and 100%, respectively, consistent with research by Skowrońska *et al.*, with irregular margins accounting for a high rate of malignancy (75%) in 140 thyroid nodules.[13] Shen *et al.* had 2.6% of nodules that invaded outside the thyroid gland were malignant.[14]

Internal components
The majority of lesions have no internal echogenic nodules at a rate of 66.7%; 81.8% of lesions with comet tail artifacts are benign; coarse calcifications lesions are usually benign. The malignant rate of lesions with microcalcifications and rim calcifications is quite high, at 94.1% and 61.5%, respectively. Similar to the study by Kovatcheva *et al.*, 75% of lesions have no echogenic nodules inside, and the rate of malignancy in lesions with thick echo spots is 63.1%.[11]

Value of the European* Thyroid Imaging Reporting and Data System *2017
Comparing the results of EU-TIRADS classification with histopathology, the proportion of lesions distributed according to EU-TIRADS groups 2, 3, 4, and 5 is 2,5%, respectively; 45.1%; 19.8%; and 32.6%, with the corresponding malignancy rate of each group being 0%, respectively; 9.2%, 62.8%, and 93.0%. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in distinguishing benign and malignant lesions were 91.2%, 81%, and 81.6%, respectively, 91.3% and 86.2%. In the study by Hekimsoy *et al*., with 251 thyroid nodules, including 189 benign nodules (75.30%) and 62 malignant nodules (24.70%), based on histological assessment, sensitivity, and specificity rates were 73% and 80% for EU-TIRADS, with an area under the curve of 0.8.[15] A systematic analysis by Castellana *et al*. with databases searched and retrieved up to December 2019, including 7 studies, evaluated 5672 thyroid nodules. The incidence of malignancy in each group according to EU-TIRADS was R2=0.5%, TR3=5.9%, R4=21.4%, and R5=76.1%. The sensitivity, specificity, positive predictive value, and negative predictive value of R5 are 83.5%, 84.3%, 76.1%, and 85.4%, respectively.[6]

Conclusions
After studying 435 thyroid nodules in 347 patients, it was found that female patients predominated, and men had a higher risk of malignancy. The average size of malignant lesions is usually smaller than that of benign lesions. According to the 2017 EU-TIRADS system, signs suggestive of malignancy include a taller-than-wide, irregular margins, invasion beyond the thyroid gland, thick echo spots, and markedly hypoechoic, indicating a high risk of cancer.

When comparing EU-TIRADS system results with histopathology, group R5 had the highest malignancy rate. The ROC AUC of EU-TIRADS >0.9 showed a very good ability to discriminate between benign and malignant thyroid nodule lesions, with high sensitivity and negative predictive value.

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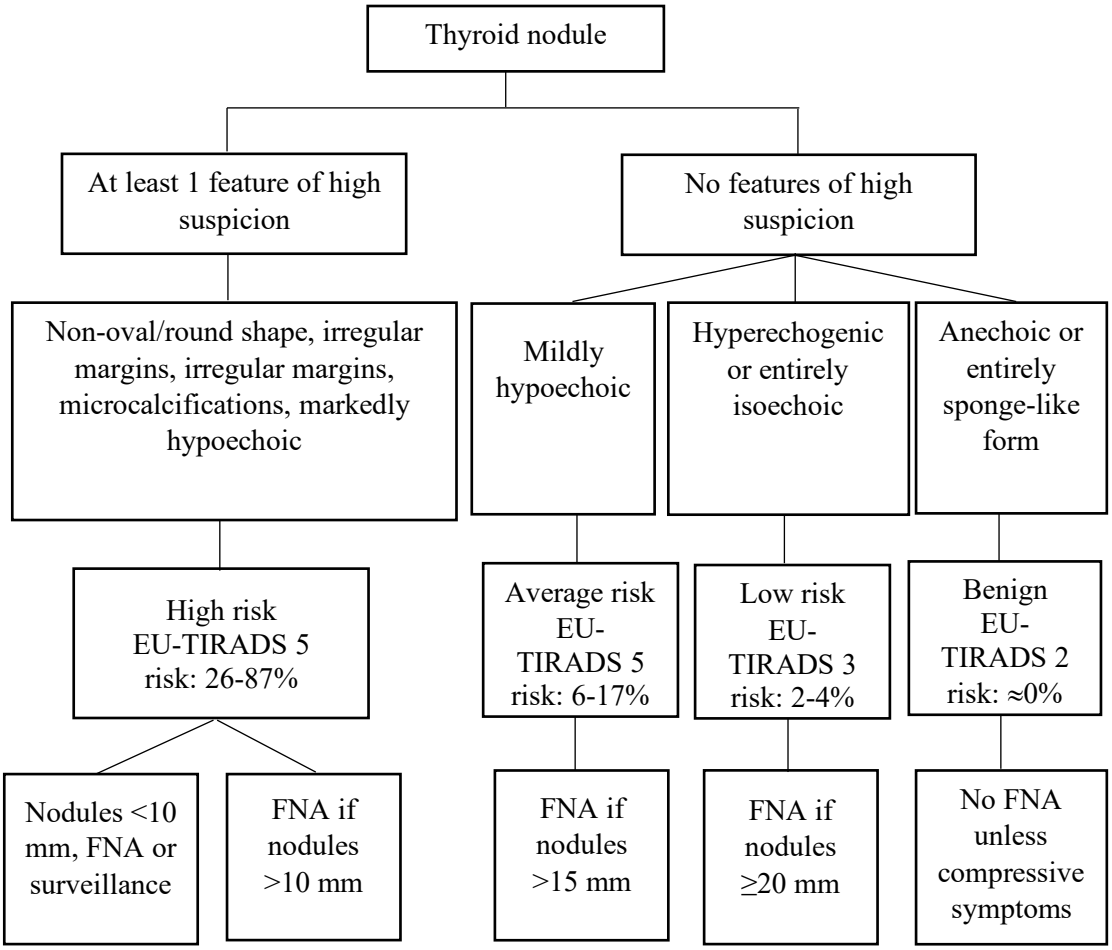


Figure 1. European Thyroid Imaging Reporting and Data System 2017 classification scheme.[8] Fine needle aspiration should be performed in case suspicious lymph nodes are found. FNA, fine needle aspiration; EU-TIRADS, European Thyroid Imaging Reporting and Data System.

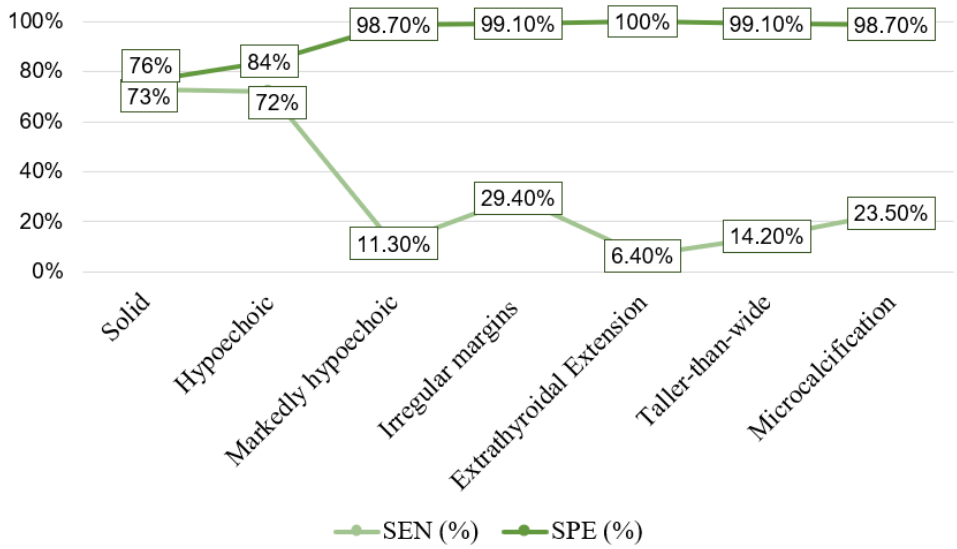
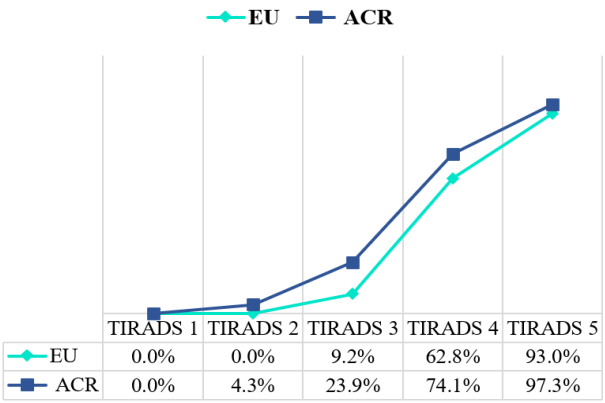


Figure 2. Sensitivity (SEN) and specificity (SPE) chart of some ultrasound characteristics suggestive of malignancy.



	TIRADS 1	TIRADS 2	TIRADS 3	TIRADS 4	TIRADS 5
EU	0.0%	0.0%	9.2%	62.8%	93.0%
ACR	0.0%	4.3%	23.9%	74.1%	97.3%

Figure 3. The p-charts stratify thyroid nodule lesions according to the European (EU) Thyroid Imaging Reporting and Data System (TIRADS) and the American College of Radiology (ACR) TIRADS.

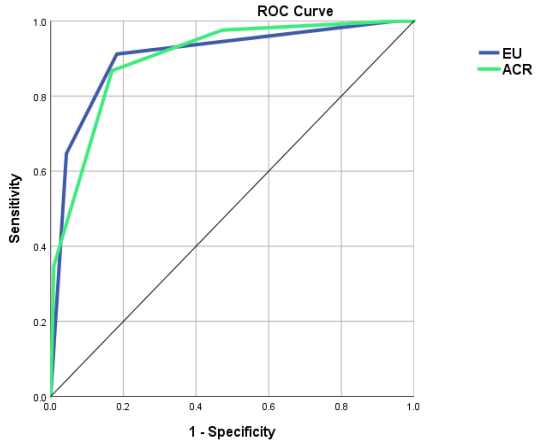


Figure 4. Receiver-operating characteristic curve graph of two Thyroid Imaging Reporting and Data Systems.

Table 1. Epidemiological characteristics of thyroid nodules.

General features	Histopathological results		Total	p
	Benign	Malignant		
Armor multiplier number, n (%)	231 (53.1)	204 (46.9)	435 (100)	
Sex, n (%)				
Male	17 (29.8)	40 (70.2)	57	<0.05
Female	136 (46.9)	154 (53.1)	290	
Average age	44.7±11	44.4±13.6	44±12.9	>0.05
Living area, n (%)				
City	47 (46.1)	55 (53.9)	102	>0.05
Countryside	106 (43.2)	139 (56.7)	245	
Location				
Right lobe	112	112	224	>0.05
Left lobe	113	86	199	
Isthymus	6	6	12	
Middle size	31.64±16.06	18.33±14.3	25.4±16.6	<0.05

Table 2. Ultrasound imaging characteristics of thyroid nodules according to the Thyroid Imaging Reporting and Data System.

Ultrasound image characteristics	Histopathological results, n (%)		Total	p
	Malignant	Benign		
Composition				<0.001
▪ Cystic	0	6 (100)	6	
▪ Spongiform	0	5 (100)	5	
▪ Mixed cystic and solid	55 (25.1)	164 (74.9)	219	
▪ Solid or almost completely solid	149 (72.7)	56 (27.3)	205	
Echogenicity				<0.001
▪ Anechoic	0	6 (100)	6	
▪ Spongiform	0	5 (100)	5	
▪ Hyperechoic or isoechoic	34 (15.9)	180 (84.1)	214	
▪ Hypoechoic	147 (79.9)	37 (20.1)	184	
▪ Markedly hypoechoic	23 (88.5)	3 (11.5)	26	
Margins				<0.001
▪ Well-defined	117 (35.3)	214 (64.7)	331	
▪ Irregular margins (spiculated/microlobulated)	60 (96.8)	2 (3.2)	62	
▪ Il-defined margin	14 (48.3)	15 (51.7)	29	
▪ Extrathyroidal extension	13 (100)		13	
Shape				<0.001
▪ Wider-than-tall (oval)	168 (42.4)	228 (57.6)	396	
▪ Round	7 (87.5)	1 (12.5)	8	
▪ Taller-than-wide	29 (93.5)	2 (6.5)	31	
Components inside the lesion				<0.001
▪ None	118 (40.7)	172 (59.3)	290	
▪ Comet tail	2 (18.2)	9 (81.8)	11	
▪ Macrocalcification	28 (40)	42 (60)	70	
▪ Peripheral calcification	8 (61.5)	5 (38.5)	13	
▪ Microcalcification	48 (94.1)	3 (5.9)	51	
Total	204	231	435	Fisher's exact test

Table 3. The value of the European Thyroid Imaging Reporting and Data System grading in diagnosing thyroid cancer.

TIRADS classification	Malignant	Benign	SEN (%)	SPE (%)	PPV (%)	NPV (%)	ACC (%)
EU 4-5	186	42	91.2	81	81.6	91.3	86.2
EU 2-3	18	189					
ACR 4-5	177	39	86.8	83.1	81.9	87.7	84.8
ACR 1-3	27	192					

EU, European; ACR, American College of Radiology; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy.