Malignancy risk assessment of thyroid nodules: Evaluation of EU-TIRADS classification

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ABSTRACT

Objective: the management of thyroid nodules is highly dependent on risk assessment based on sonographic findings. The objective of this study is to evaluate the EU-TIRADS classification in the diagnosis of malignancy of a thyroid nodule.

Materials and methods: In 5 years (from 2013 to 2017), patients assessed with pre-operative ultrasound (US) were retrospectively enrolled in this study. Nodules were categorised according to EU-TIRADS classification. Final Histopathological diagnosis was obtained from the thyroidectomy specimen. Sensitivity, specificity, positive and negative predictive values and likelihood ratios were calculated.

Results: The study included 222 patients with 349 nodules. Overall malignancy was 14.89 %. An increased aggregate risk of nodule malignancy was noted if the final EU-TIRADS level increased from EU-TIRADS I to EU-TIRADS V. It was 2.27 % (1/44) in EU-TIRADS II, 7.18 % (11/153) in EU-TIRADS III, 7.4 % (2/27) in EU-TIRADS IV and 30,4 % (38/125) in EU-TIRADS V.

The risk of malignancy was significantly associated with the strongly hypoechogenic character of the nodule, irregular margins, microcalcifications, ultrasonographic suspicious lymph nodes ($p < 0.01$, in all cases) and non-oval shape ($p = 0,046$). The overall sensitivity and specificity of this classification was respectively 76% and 62%. The positive predictive value (PPV) and the negative predictive value (NPV) were 26% and 93%, respectively.

Conclusion: EU-TIRADS classification allows thyroid nodules staging and allows selection of nodules requiring fine needle aspiration biopsy (FNAB). It is a simple and easy tool, but remains an operator dependent examination. This explains the number of false positives and false negatives.

INTRODUCTION

Thyroid nodules are a common pathology in the general population. The prevalence is continuously increasing. A large part of these nodules are currently diagnosed at an asymptomatic stage, during an imaging performed for another symptom. Their prevalence increases from 5 to 10% at the clinical examination to 50% on ultrasound. The majority of thyroid nodules is benign. The percentage of malignancy does not exceed 5% (1,2).

The stake of the practitioner, in front of a thyroid nodule, is to eliminate a cancer while limiting a surgery not without functional risks sometimes vital.

The system EU-TIRADS is an acronym for European Thyroid Imaging Reporting and Data System. It is a standardized system of thyroid ultrasound analysis and reporting designed to make uniform the descriptions and procedures for dealing with a thyroid nodule(3).

The objective of this study is to evaluate the contribution and limits of the classification Ultrasound EU-TIRADS in the diagnosis of malignancy of a thyroid nodule.

METHODS:

This is a single-center, retrospective analytical study that collected the observations of patients with thyroid nodule surgery over a period of 5 years between January 2013 and December 2017 at the ENT and head and neck surgery department of the Taher Sfar Hospital Mahdia.

The study included patients operated for thyroid nodules (single nodule or multi nodular goiter) in the ENT department of Mahdia and for whom we have standardized cervical ultrasound report according to the EU-TIRADS classification and an anatomo-pathological study corresponding to the same nodule.

Were excluded from the study all the nodules which preoperative ultrasound didn't mention the stage EU-TIRADS and didn't describe the totality of criteria allowing to classify them according to EU-TIRADS classification.The nodules which the final anatomo-pathological report is not available were also excluded.

During the study period, 222 patients were operated on for nodular thyroid pathology. The number of nodules analyzed during the study was 367. Eighteen nodules were excluded from the analysis because of the absence either of EU-TIRADS staging of the nodule, the histological nature on the final reports of the operative specimens or both. The final number of thyroid nodules included in this study was 349.

All nodules that satisfy the inclusion criteria were classified from stage 1 to stage 5 according to the EU-TIRADS classification [Table I].

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A histological description of each nodule was provided in the definitive anatomo-pathological reports defining its size and localization in the gland.
The predictive ultrasound data was compared to the final histological results in order to determine the Cut-off stage of ultrasound malignancy and the degree of association by Cohen's Kappa test.

The collected data were captured and analyzed by the SPSS Statistics software. Normality was determined by the Kolmogorov-Smirnov test.
In the absence of normality, the quantitative variables were expressed by their medians and the 25-75th interquartiles and the qualitative variables by their numbers and percentages.
We performed the precision of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of the EU-TIRADS classification.

Table I: European Thyroid Imaging Reporting and Data System (EU-TIRADS)

Category	US features	Malignancy risk, %
EU-TIRADS 1: normal	No nodules	None
EU-TIRADS 2: benign	Pure cyst Entirely spongiform	≈ 0
EU-TIRADS 3: low risk	Ovoid, smooth isoechoic/ hyperechoic No features of high suspicion	2 - 4
EU-TIRADS 4: intermediate risk	Ovoid, smooth, mildly hypoechoic No features of high suspicion	16 - 17
EU-TIRADS 5: high risk	At least 1 of the following feature of high suspicion: -Irregular shape -Irregular margins -Microcalcifications -Marked hypoechogenicity	26 - 87

RESULTS:

The average age was 47 years (ranging from 15 to 87 years) with a female predominance (sex ratio = 0.094). Anterior cervical basal swelling was the most frequent reason of consultation. The accidental ultrasound discovery of the nodule was noted only in 0.9% of patients [Table II].
The thyroid nodules were divided according to the EU-TIRADS classification into four stages (II, III, IV and V) which prevalences were respectively 12%, 44%, 38% and 6%.

Table II: Distribution of patients by age, gender, history and reason for consultation.

Age	Mean 47 years Extremes 15 to 87 years
Gender	Female 192 (86.5 %) Male 30 (13.5 %)
Family history	Dysthyroidism 37 (17, 4%) Thyroid neoplasia 2 (0.94%) Dysthyroidism + thyroid neoplasia 2 (0.94%)
Personal history	Dysthyroidism 14 (6.6%) Previous lobo-isthmectomy 2 (0.94%) Irradiation 0 Taking drugs rich in iodine 0
Reasons for consultation	Cervical swelling 198 (93.9%) Dysthyroidism 8 (3.7%) Compression signs 63 (29.6%) Cervical lymphadenopathy 7 (3.3%) Ultrasound finding 2 (0.9%)

The 349 nodules collected were divided into 2 groups. The first group contained 196 nodules (56.16%) classified ultrasonographically as low risk of malignancy (EU-TIRADS II and III) and the second group included 153 nodules (43.84%) classified ultrasonographically as high risk of malignancy (EU-TIRADS IV and V).
This distribution was based on the results found in the literature to determine the potential risk of malignancy. The overall percentage of malignancy in the definitive histologic examination was 14.89%. The percentage of malignancy corresponding to each group was 6.09 % for group 1 and 26.31 % for group 2 [Table III].

Table III: Distribution of benign and malignant nodules according to the EU-TIRADS classification.

Group Histology	Groupe 1 (EU-TIRADS II/ III)	Groupe 2 (EU-TIRADS IV/V)	Total
Benign	185	112	297
Malignant	12	40	52
Total	197	152	349

We evaluated the association between malignancy and ultrasound findings.
The average size of the nodules was 2.6 cm with extremes ranging from 0.3 cm to 9 cm. The threshold value of the nodule size corresponding to the best specificity (Sp = 90%) in the prediction of benignity was ≥ 3.7 cm. (p=0,002)
In our series, 334 nodules (95,7%) had an oval shape against 15 nodules (4,3%) with a non-oval shape thicker than wide. According to our results, there was a significant statistical difference between the two groups (p=0,046).
Within the histologically malignant nodules, 50% had micro calcifications on ultrasound versus 24.5% for benign nodules. This aspect was significantly associated with malignancy ($p < 0.01$). The strongly hypoechogenic character of the nodule was significantly associated with malignancy ($p < 0.01$). Irregular margins are significantly associated to malignancy in 38.5% ($p < 0.01$). The presence of suspicious lymphadenopathy on ultrasound is associated to 23.5% of malignant nodules. This association is statistically significant ($p < 0.01$) [Table IV].

Table IV: Distribution of the major signs of the EU-TIRADS classification between the two groups of nodules.

Ultrasound characters	Benign nodules (%)	malignant nodules (%)	P value	K
Non-oval shape	2,34 %	15,38 %	0,046	0.029
Strongly hypoechogenic	5,36 %	38,46 %	< 0.01	0.74
Irregular margins	4,03 %	38.5 %	< 0.01	0.41
Microcalcifications	24,49 %	50 %	< 0.01	0.52

The percentage of malignancy corresponding to each ultrasound stage was 2.27% for stage II, 7.18% for stage III, 7.4% for Stage IV, 30,4% for Stage V.
The overall performance of the EU-TIRADS classification was calculated according to its "intrinsic" characteristics: information capacity specific to the test (Sensitivity, specificity) and "extrinsic" ratios that vary with prevalence (positive predictive value, negative predictive value) in the comparing to the reference examination; definitive histology in our case.
The overall sensitivity and specificity of this classification was respectively 76% and 62%. The positive predictive value (PPV) and the negative predictive value (NPV) were 26% and 93%, respectively.

DISCUSSION:

Ultrasonography is the first morphological examination to be performed when TSH is normal or elevated and a thyroid nodule is suspected or sought [4]. The widespread use of this technique has resulted in the detection of nodules in large numbers of the population. It has become essential to define reliable and reproducible ultrasound selection criteria to decide the therapeutic approach.
The first TIRADS classification was established by Horvath et al in 2009. It was based essentially on the existence of microcalcifications, a capsule, echogenicity and vascularization [5,6]. It was in 2011 that Russ and collaborators proceeded to elaborate a well coded score modeled on the BI-RADS and created an atlas. They proposed a simple diagnostic tree that allows an unambiguous and rapid scoring of thyroid nodules with a sensitivity greater than 95% [7].
In 2017 there was a transition from the TIRADS system to the EU-TIRADS, which stands for the European Thyroid Imaging Reporting and Data System. EU-TIRADS classification has 5 scores based on the analysis of the nodule echogenicity, shape, contours and microcalcifications [8].
Despite these modifications, considerable number of false-positives and false-negatives were noticed and proved to be anxiety-generators.
According to the literature, the nodules with a non-oval shape are suspect of malignancy [9,10,11]. In our series, 15 nodules had a non-oval shapes of which 8 were malignant, which represents only 15.38% of malignant nodules diagnosed. The relationship between shape and malignancy was statistically significant (p = 0,046).
According to the majority of authors, the hypoechogenic appearance is a sign of malignancy [13,15,16]. A solid hypoechogenic nodule is a cancer in 63% of cases for Solbiati, in 61.9% of cases for Leenhardt, in 58.2% of cases in the Naoun series [4,17,18]. This characteristic was associated with malignancy in 55.5% of the cases in our series.
The irregularity of the contours favors malignancy according to several studies, as well as our study. The majority of authors found that microcalcifications were significantly related to malignancy [8,15,19,20]. In our series, microcalcifications were found in 50% of malignant nodules and in only 24.49% of benign nodules.
The evaluation of the EU-TIRADS classification and its reliability in the diagnosis of malignancy of a thyroid nodule through this study showed acceptable sensitivity and NPV and poor specificity and PPV (Sp = 62%; Se = 76%; VPN = 93%; VPP = 26%). These results joined some studies. In the Horvath and al series [5], the sensitivity and specificity of this classification were 99.6% and 74.35%, respectively. They were 86.53% and 41.6% in the series of Russ and al [8] and 93,6% and 94% in the series of Ito and al [21].
Several studies have shown that this classification has a high sensitivity in detecting malignancy with low specificity due to a considerable number of false negatives [22].
The echogenicity aspects analysis remains subjective and operator dependent. The differentiation between a weakly hypoechogenic nodule (criterion which classifies the nodule in EU-TIRADS IV) and isoechogenic one (criterion which classifies the nodule in EU-TIRADS III) is not obvious. It needs a well-trained radiologist. This could explain the percentage of malignancy close to these 2 classes, found in our series.
Some locoregional conditions may limit the accuracy of the examination such as surgical sequelae or radiotherapy and obesity. Another problem with using US as diagnosis method is that the morphological changes of malignant nodules < 1cm in diameter are usually lacking.
This examination needs better reliability to help on clinical decisions and predict patients' fate.
This classification offers a better reproducibility but have some limits. Extreme scores are often unambiguously established. However intermediary scores are more controversial. In these cases, the search for additional signs seems necessary and close monitoring for nodular growth or changes must be proposed to avoid unnecessary FNAB or false negatives [8,23].

CONCLUSION:

The EU-TIRADS classification allows the analysis, classification and monitoring of thyroid nodules in a robust and reproducible manner. It allows a quantitative stratification of the risk of malignancy. It is easy to apply even if some criteria remain operator-dependent. It aims to rationalize the indications of punctures and thyroid surgery. All the advances made in this regard aimed to improve the relevance of this test in the diagnosis of malignancy of the thyroid nodule.

Compliance with ethical standards

Conflict of interest: The authors stated that there is no conflict of interest.

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