

European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS

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Supplementary Material

Working methods and grading of recommendations

Working methods

A chairperson was selected to lead the task force (LL) and five other members were chosen based on clinical expertise, academic record, and representation of endocrinology and radiology (SB, CD, MFE, RN, GR). The task force members were subsequently endorsed by the ETA Guidelines Board and the Executive Committee. Each panel member declared no conflict of interest. Relevant articles were identified by searching Medline at PubMed (US National Library of Medicine), using the following MESH terms «ultrasound AND thyroid nodule AND risk stratification», «ultrasound AND thyroid nodule AND TI-RADS», «ultrasound AND thyroid nodule AND TIRADS», from 1990 to August 2016. Additional reports judged relevant were added.

Recommendations were developed based on the literature, including published guidelines and expert opinion where appropriate. A preliminary document was generated by the chairperson and critically reviewed by the task force members. Deliberations within the panel took place via electronic communication and during a meeting in Copenhagen on September 4-5th, 2016. The drafts were revised repeatedly by the panel until consensus was reached, then by two independent reviewers, and finally by the ETA Guidelines Board. The proposal was then posted on the ETA website for all members to review. Suggestions and comments were considered for the final version, which was approved by the ETA in March 2017.

Grading of recommendations

The ETA Executive Committee elected to rate the recommendations according to the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Group (GRADE). Definitions of the strength of the recommendation and the quality of the evidence of the grading are reported in online supplementary Table 3 [1, 2].

References

1. Norris SL, Bero L: GRADE Methods for Guideline Development: Time to Evolve? *Ann Intern Med* 2016;[Epub ahead of print].

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Supplementary Table 1. Diagnostic values of the existing US scoring systems for risk-based guidance in planning FNA of thyroid nodules. All values are in percentage (%).

	FRENCH TIRADS [3]	Korean TIRADS [4]	ATA [5]	Range
Sensitivity	95	81	95	81 – 95
Specificity	45	71	37	37 - 71
Negative predictive value	99	93	97	93 - 99
Positive predictive value	48	45	25	25 – 48
Accuracy	48	48	73	48 - 73

Supplementary Table 2. An overview of the standardized US scoring systems proposed or endorsed by international practice guidelines for risk-based guidance in planning FNA of thyroid nodules

Risk score	French TIRADS (2013)	Korean TIRADS (2016)	ATA (2016)	AACE/ACE-AME (2016)
Suspicious US features	<ul style="list-style-type: none"> Taller-than-wide/taller-than-long Spiculated or lobulated borders Marked hypoechogenicity Microcalcifications High stiffness on elastography 	<ul style="list-style-type: none"> Microcalcification Taller-than-wide shape Spiculated/microlobulated margins 	<ul style="list-style-type: none"> Irregular margins (infiltrative, microlobulated) Microcalcifications Taller-than-wide shape Rim calcifications with small extrusive soft-tissue component Evidence of extrathyroidal extension 	<ul style="list-style-type: none"> Marked hypoechogenicity Spiculated or lobulated margins Microcalcifications Taller-than-wide shape Extrathyroidal growth Pathologic adenopathy
Category	<p>TIRADS 2: benign (0%)</p> <ul style="list-style-type: none"> Simple cyst Septated cyst Spongiform nodule Isolated macrocalcification 	<p>TIRADS 2: benign (<3%)</p> <ul style="list-style-type: none"> Purely or partially cystic nodule with comet-tail artefacts Spongiform 	<p>Benign (<1%)</p> <ul style="list-style-type: none"> Purely cystic nodules (no solid component) 	<p>Low-risk thyroid lesion (1%)</p> <ul style="list-style-type: none"> Cysts (fluid component >80%) Mostly cystic nodules with reverberating artefacts and not associated with suspicious US signs Isoechoic spongiform nodules, either confluent or with regular halo
	<p>TIRADS 3: probably benign (0.25%)</p> <ul style="list-style-type: none"> Iso- and hyperechoic Oval-shape Regular borders 	<p>TIRADS 3: low suspicion (3-15%)</p> <ul style="list-style-type: none"> Partially cystic or iso- and hyperechoic nodule without any of the 3 suspicious US features 	<p>Very low suspicion (<3%)</p> <ul style="list-style-type: none"> Spongiform or partially cystic nodules without any of the sonographic features described in low-, intermediate-, or high-suspicion patterns <p>Low suspicion (5-10%)</p> <ul style="list-style-type: none"> Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or extrathyroidal extension, or taller-than-wide shape 	<p>Intermediate-risk thyroid lesion (5-15%)</p> <ul style="list-style-type: none"> Slightly hypoechoic or isoechoic nodules, with ovoid-to-round shape, smooth or ill-defined margins. May be present: <ul style="list-style-type: none"> Intranodular vascularization Elevated stiffness at elastography Macro- or continuous rim calcifications Indeterminate hyperechoic spots

	<p>TIRADS 4A: suspicious nodules; low risk of malignancy (6%)</p> <ul style="list-style-type: none"> ▪ Mildly hypoechoic ▪ Oval-shape ▪ Regular borders 	<p>TIRADS 4: intermediate suspicion (15-50%)</p> <ul style="list-style-type: none"> ▪ Solid hypoechoic nodule without any of the 3 suspicious US features ▪ Partially cystic or iso- and hyperechoic nodule with any of the 3 suspicious US features 	<p>Intermediate suspicion (10-20%)</p> <ul style="list-style-type: none"> ▪ Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension or taller-than-wide shape 	
	<p>TIRADS 4B: suspicious nodules; high risk of malignancy (69%)</p> <ul style="list-style-type: none"> ▪ One or two features of high suspicion <p>Tirads 5: malignant nodules (~100%)</p> <ul style="list-style-type: none"> ▪ Three to five features of high suspicion and/or presence of a lymph node suspected to contain metastasis of thyroid origin 	<p>TIRADS 5: high suspicion (>60%)</p> <ul style="list-style-type: none"> ▪ Solid hypoechoic nodule with any of the 3 suspicious US features 	<p>High suspicion (>70-90%)</p> <ul style="list-style-type: none"> ▪ 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 	<p>High-risk thyroid lesion (50-90%) Nodule with any of six suspicious US features</p>

Supplementary Table 3. Terms and definitions according to ‘GRADE’

Grading type	Definition
Strength of the recommendation (SOR)	
Grade 1	<p>Strong recommendation (for or against)</p> <p>Applies to most patients in most circumstances</p> <p>Benefits clearly outweigh the risk (or vice versa)</p>
Grade 2	<p>Weak recommendation (for or against)</p> <p>Best action may differ depending on circumstances or patient values</p> <p>Benefits and risks or burdens are closely balanced, or uncertain</p>
Quality of the evidence (QOE)	
+++	<p>High quality; evidence at low risk of bias, such as randomized trials showing consistent results directly applicable to the recommendation</p>
++	<p>Moderate quality; studies with methodological flaws, showing inconsistent or indirect evidence</p>
+	<p>Low quality; case series or unsystematic clinical observations</p>

Supplementary Figure Legends

Figure 1. Protrusion into adjacent structure and disruption of capsular margin is seen, meaning very likely extrathyroidal extension. Seen in transverse plane.

Figure 2. Capsular abutment and continuous capsule: lack of normal tissue between the thyroid nodule and the thyroid capsule in longitudinal (left picture) and transverse (right picture) planes.

Figure 3. Presence of more than 2mm normal thyroid parenchyma between the nodule and a continuous capsule in longitudinal (left picture) and transverse (right picture) planes.

Figure 4. Central intranodular macro calcifications alone is not consistently associated with malignancy. Longitudinal (left) and transverse planes (right).

Figure 5. Isolated macrocalcification, occupying an entirely calcified nodule: low risk. Longitudinal plane.

Figure 6. Disrupted peripheral rim macrocalcifications. Increases risk of malignancy. Longitudinal (left) and transverse planes (right).

Figure 7. Hyperechoic spots. Colloid crystals, fibrin debris which generate comet-tail artefacts/reverberations and are almost always suggestive of benignity. Seen here in transverse plane.

Figure 8. Hyperechoic spots. Posterior acoustic enhancement of the back wall of a microcystic cavities. This is mostly seen with high frequency probes and may be better analysed by magnifying the image. They are suggestive of benignity. Transverse plane (left) and longitudinal plane (right).

Figure 9. True microcalcifications correspond to psammoma bodies and are multiple round echogenic foci around 1 mm in size, without posterior shadowing, located in the solid component of a nodule. Microcalcifications are highly suggestive of malignancy, in particular when associated with macrocalcifications.

Figure 10. Hyperechoic spots of uncertain significance rather linear than round and with no microcystic cavities or comet-tail artefacts. Transverse (left) and longitudinal planes (right).

Figure 11. Thin halo in longitudinal (left picture) and transverse (right picture) planes

Figure 12. Thick halo.

Figure 13. Type I vascularity, absent or scanty.

Figure 14. Type II vascularity, perinodular and/or slight intranodular. Transverse and longitudinal planes.

Figure 15. Type III vascularity, marked intranodular and slight perinodular. Transverse plane.

Figure 16. Normal strain elastography in comparison to normal thyroid tissue (left). US shows a hypoechoic nodule which has an oval shape and smooth margins with no high risk features. Transverse plane.

Figure 17. High stiffness on strain elastography (left). US shows a high risk nodule with an irregular, ill defined, marked hypo echoic nodule (right). Transverse plane.

Figure 18. Normal SWE elastography. Stiffness value: 6,6kPa. Transverse plane.

Figure 19. High stiffness (90kPa) on SWE. Transverse plane.