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THE IMPLEMENTATION OF ACR TI-RADS IN CLINICAL PRACTICE

KLİNİK PRATİKTE ACR-TIRADS'IN UYGULANMASI

Bengi BALCI[1], Mehmet USTUN[2], Mustafa BOZDAG[3], Ali ER[3], Dudu SOLAKOGLU[4], Cengiz AYDIN[2]

[1] Department of General Surgery, Akdeniz Saglik Vakfi Yasam Hospital, Antalya, TÜRKİYE
[2] Department of General Surgery, Izmir Tepecik Training and Research Hospital, İzmir, TÜRKİYE
[3] Department of Radiology, Izmir Tepecik Training and Research Hospital, İzmir, TÜRKİYE
[4] Department of Pathology, Izmir Tepecik Training and Research Hospital, İzmir, TÜRKİYE

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Öz

Amaç
Amerikan Radyoloji Koleji Tiroid Görüntüleme, Raporlama ve Veri Sistemi'nin tanısal doğruluğunu araştırmak

Gereç ve Yöntem
Ağustos 2017 ve Eylül 2018 arasında merkezimizde tiroid cerrahisi uygulanan 62 hastadan toplam 151 nodül toplanmıştır. Her bir nodülün ultrasonografik özellikleri iki radyolog tarafından kaydedilmiş ve Amerikan Radyoloji Koleji Tiroid Görüntüleme, Raporlama ve Veri Sistemi'ne göre sınıflanmış, ve histopatolojik olarak birebir karşılaştırılmıştır.

Bulgular
151 tiroid nodül verisi ortanca boyutu ultrason ve patolojik spesimenler üzerinde sırasıyla 19 (3-85) mm ve 17 (0-97) mm olarak ölçülmüştür. Papiller karsinom 28 hastada (%45), papiller mikrokarsinom 14 hastada (%22.5), ve Hurthle hücreli karsinom 1 (%1.6) hastada saptanmıştır. Bu nodül risk belirleme modeli için genel sensitivite, spesifite, pozitif prediktif değer ve negatif prediktif değer sırasıyla %82.5, %57, %64.58, ve %77.67 olarak analiz edilmiştir.

Sonuç
İnce iğne aspirasyon biyopsisi için kesin bir boyut eşiği belirlemek yanlış yönlendirici olabilir, bunun yerine ultrasonda malign özelliklerin belirlenerek cerrahi kararın kişi bazında verilmesi önerilmelidir.

Anahtar Kelimeler: Mikrokarsinoma, Sensitivite, Spesifite, TIRADS, Tiroid nodülü

Abstract

Objective
To investigate the diagnostic accuracy of the Thyroid Imaging, Reporting and Data System of the American College of Radiology in thyroid nodules.

Material and Method
A total of 151 nodules were collected from 62 patients undergoing thyroid surgery in our center between August 2017 and September 2018. Ultrasonographic features of each nodule were recorded and classified according to the Thyroid, Imaging Reporting and Data System of the American College of Radiology by two radiologists and compared with a one-to-one basis on histopathology.

Sorumlu yazar ve iletişim adresi / Corresponding author and contact address: B.B. / bengibalci@gmail.com
Müracaat tarihi/Application Date: 29.05.2023 • Kabul tarihi/Accepted Date: 06.09.2023
ORCID IDs of the authors:B.B: 0000-0002-0630-5097; M.U: 0000-0001-7778-5609;
M.B: 0000-0002-0741-587X; A.E: 0000-0003-3708-1214; D.S: 0000-0002-4126-5326;
C.A: 0000-0002-7254-298X

Results
The median size of 151 thyroid nodules measured on the ultrasound and in the pathology specimens were 19 (3-85) mm and 17 (0-97) mm, respectively. Papillary carcinoma was demonstrated in 28 patients (45%), papillary microcarcinoma in 14 patients (22.5%), and Hurthle cell carcinoma in 1 (1.6%) patient. Overall sensitivity, specificity, positive predictive value, and negative predictive value for this nodule risk stratification model were analyzed as 82.5%, 57%, 64.58%, and 77.67%, respectively.

Conclusion
Setting a definitive size threshold for fine needle aspiration might be misleading, instead signifying the malignant features on ultrasonography, and making a decision for surgery on an individual base should be recommended.

Keywords: Microcarcinoma, Sensitivity, Specificity, Thyroid nodule, TIRADS

Introduction

Thyroid nodules are detected between 20 to 70% of the population and the prevalence is increased with iodine deficiency (1, 2). Ultrasonography (US) is currently the most used diagnostic tool for evaluating thyroid nodules (3). The decision of follow-up and/or surgery is made according to the ultrasonographic features of thyroid nodules and fine needle aspiration (FNA) results. However, mandating FNA for each nodule is not a practical option, since only less than 15% of FNAs are found to be malignant. Moreover, there is a risk of inconclusive results and overdiagnosis.

In order to decrease unnecessary FNAs, thyroid nodule risk stratification systems were developed based on certain ultrasonographic features such as irregular margins, hypoechogenicity, microcalcifications, and taller than wide appearance which are all strongly associated with malignancy (4-6).

Current data regarding these thyroid nodule risk stratification systems are contradictory depending on the country, region, and thyroid nodule prevalence in the population where the study was conducted (7-9). Among those, the Thyroid Imaging, Reporting and Data System of the American College of Radiology (ACR TI-RADS) stand upfront by creating standardized terms for thyroid US reports, signifying nodules with high risk for malignancy, and ultimately decreasing the number of unnecessary FNAs (10, 11).

This prospective study aimed to evaluate the diagnostic accuracy of ACR TI-RADS and to determine difficulties in the application of nodule risk stratification systems in routine clinical practice.

Material And Method

Study Design and Inclusion Criteria

This study was designed as a prospective study and was conducted in a single-tertiary center. It was approved by the Ethical Committee of Izmir Education and Research Hospital (17.08.2017/9/6) and all patients' written consents were taken. The study was conducted in line with the principles of the Helsinki Declaration and was reported according to the STROBE guidelines (12). Patients were recruited among those who complained of any thyroid-related problems and underwent thyroid Doppler US in our institution between August 2017 and September 2018. The only exclusion criterion was the history of thyroid surgery.

Thyroid Doppler US was preoperatively performed in all patients by the same two radiologists. The sizes of each nodule were measured and ACR TI-RADS scores were calculated according to the five ultrasonographic features: composition, echogenicity, shape, margins, and echogenic foci as described by the original study (10). The maximum number of four nodules with the highest scores of ACR TI-RADS were chosen in patients with multinodular goiter.

Of 130 patients who met the eligibility criteria, 62 of them were offered surgical intervention which was given based on the ATA guidelines including suspicion or diagnosis of malignancy on FNA, cosmetic issues related to goiter, toxic solitary nodule, or multinodular goiter (4).

Study Variables

Demographic and clinical features including age, gender, preoperative diagnosis, the size, and number of nodules, ACR TI-RADS scores, FNA results, intraoperative and postoperative complications, and the length of hospital stay were noted.

Surgical specimens were investigated by a single pathologist who was blind to the preoperative ultrasonographic findings. Each nodule on the specimen was reported for its size, location, and

histopathological result. The one-to-one matching of each nodule's histopathological diagnoses with the corresponding nodule on the US was performed meticulously and evaluated for diagnostic accuracy by the principal investigator.

Statistical Analysis

The data was analyzed using SPSS 22.0. The median size of the thyroid nodules on the US and specimens were calculated and compared using non-parametric tests with Wilcoxon signed rank test. Overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for ACR TI-RADS were analyzed by using the indications of FNA given for each nodule preoperatively. Thyroid nodules were also categorized according to their scores as TR1, TR2, TR3, TR4, and TR5 subgroups. Sensitivity, specificity, PPV, and NPV for ACR TI-RADS were also calculated for each of these subgroups.

Results

62 patients were included in this study and 151 nodules were investigated. The median age was found to be 47(25-76) years. The median size of thyroid nodules measured on the US and in the pathology specimens were 19 (3-85) mm and 17 (0-97) mm, respectively (Table 1). There was found to be a statistically significant difference between the sizes of nodules measured on ultrasound and pathology specimens ($p<0.05$).

Total thyroidectomy and hemi-thyroidectomy were performed in 54 and 8 patients, respectively. Papillary carcinoma was demonstrated in 28 patients (45%), papillary microcarcinoma in 14 patients (22.5%), and Hurthle cell carcinoma in 1 (1.6%) patient. Single-focus of carcinoma was detected in 25 patients, whereas multifocal localization of carcinoma was detected in 18 patients.

Table 1 Clinical features of the study population

Variables	N of patients (%) or median
Gender	
Male	14
Female	48
Age (year)	47 (25-76)
Indications for surgery	
Multinodular goiter	38
Toxic nodular goiter	3
Graves disease	2
AUS	4
Follicular neoplasia	5
Suspicious for malignancy	4
Malignant cytology	6
Size of nodules on thyroid US	19 (3-85) mm
Total thyroidectomy	54
Hemi-thyroidectomy	8
Size of nodules on pathology specimens	17 (0-97) mm
Pathology results	
Papillary carcinoma	28 (45%)
Papillary microcarcinoma	14 (22.5%)
Hurthle cell carcinoma	1 (1.6%)

Abbreviations: N, number; AUS, Atypia of undetermined significance; US, ultrasound.

Table 2 Median size of nodules on US and pathology specimens, malignancy rates, sensitivity, specificity, PPV and NPV for ACR TI-RADS in TR subgroups.

Variables	TR1 (N ofnodules:21)	TR2 (N ofnodules:34)	TR3 (N of nodules:46)	TR4 (N ofnodules:30)	TR5 (N ofnodules:20)
Median size of nodules on US	12 mm (4-50)	24.5 mm (5-75)	23 mm (6-62)	15 mm (3-85)	10.25 mm (5-46)
Median size of nodules on specimens	10 mm (0-40)	20 mm (3-65)	20 mm (0-97)	17 mm (0-90)	10 mm (4-60)
The number of malignant nodules	1(4.76%)	8(23.5%)	15(32.6%)	12(40%)	18(90%)
Sensitivity	0	0	73%	50%	66%
Specificity	1	1	67%	50%	50%
Positive Predictive Value (PPV)	N/a	N/a	52%	40%	92%
Negative Predictive Value (NPV)	95%	76%	84%	60%	14%

Abbreviations: TR, Tirads; N, number; US, ultrasound; PPV, positive predictive value; NPV, negative predictive value.

Among 151 nodules, 21 nodules (13%) were categorized as TR1, 34 nodules (22.5%) as TR2, 46 nodules (30%) as TR3, 30 nodules (19%) as TR4, and 20 nodules (13%) as TR5. The median size of thyroid nodules was measured as 12 mm (4-50), 24.5 mm (5-75), 23 mm (6-62), 15 mm (3-85), 10.25 mm (5-46) in TR1, TR2, TR3, TR4, and TR5 respectively (Table 2).

Malignancy rates were calculated for each subgroup as 4.76% in TR1 (1/21), 23.5% in TR2 (8/34), 32.6% in TR3 (15/46), 40% in TR4 (12/30), 90% in TR5 (18/20). Overall sensitivity, specificity, PPV, and NPV were analyzed as 82.5%, 57%, 64.58%, and 77.67%, respectively.

Discussion

Thyroid US has been widely used in diagnosing thyroid pathologies in clinical practice. Although ultrasonographic features such as macrocalcifications, irregular margins, punctate echogenicity, and taller than wide shape suggest strong suspicion for malignancy, indications for FNA under US guidance are different based on the nodule risk stratification systems (6). The ACR TI-RADS was investigated in the present study regarding diagnostic performance to guide the clinical implementation of this risk model.

The ACR TI-RADS has a high size threshold for FNA: >2.5 cm in mildly suspicious nodules (TR3), >1.5 cm in moderately suspicious nodules (TR4), and >1 cm in highly suspicious nodules (TR5) which results in decreasing the number of unnecessary FNAs. This fact increases the importance of whether the nodules are designated to the right subgroup of TIRADS, especially considering the interobserver variability among radiologists performing US (13,14). Moreover, ACR-TIRADS is a score-based system that is not simple and easy to apply clinically (15). It requires the initial assignment of a varying number of points in multiple distinct categories and then calculating the sum of these points across categories (16).

Furthermore, as we demonstrated in our study, the sizes of nodules measured on the US and actual pathology specimens can be quite different resulting in misleading the indication of the FNA threshold. The number of nodules that ACR TI-RADS recommended to follow without FNA was 103 out of 151 nodules, and 23 of those were found to be malignant on

histopathology. Nevertheless, 17 of those nodules were found to be papillary microcarcinomas.

Several studies regarding nodule risk stratification modules have been conducted in terms of demonstrating their specificity and sensitivity (17-20). In a multicenter study comparing ACR TI-RADS, European Thyroid Imaging and Reporting Data System (EU-TIRADS) and Korean Society of Thyroid Radiology (KSThR); the malignancy rates were found to be 7.5% in TR3, 40.1% in TR4, and 81.4% in TR5 for ACR TI-RADS. The ACR TI-RADS showed the best sensitivity (96.6%) but the lowest specificity (52.9%), while the KSThR had the highest specificity with 87.4% (19). On the other hand, Koc et al. reported that ACR TI-RADS had 48.89% sensitivity and 60.63% specificity, with the highest accuracy rate compared to EU-TIRADS and ATA guidelines (21).

Contrary to their findings, in the present study, we demonstrated that ACR-TIRADS had an overall 82.5% specificity and 57% sensitivity. This might be explained by the high number of microcarcinomas in a relatively small study population which is also the major limitation of our study. Moreover, it is known that nodules measuring under 10 mm are the major pitfalls for ACR TI-RADS and other nodule risk stratification systems, even though the necessity of operating on patients with microcarcinoma is still debated (22,23).

Another drawback of present study was the higher malignancy rates for TR3 and TR4 than the recommended range of ACR-TIRADS guidelines, that might be attributed to the deviation caused by sub-centimeter nodules and different observers. This had a significant effect on overall PPV(64.58%) and NPV(77.67%).

The use of thyroid nodule risk stratification systems should carefully be practiced and assessed in developing countries with endemic multinodular goiter. Even with experienced radiologists, the difficulties in assessing the nodules in patients with multinodular goiter cannot be overseen. The presence of significant differences in the size of the nodules on US and pathology specimens should always be considered. Therefore, instead of setting a size threshold for FNA, signifying the malignant features on ultrasonography and making a decision for surgery on an individual base should be recommended.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
This study has been approved by the Ethical Committee of Izmir Education and Research Hospital (17.08.2017/9/6). It was conducted in line with the principles of the Helsinki Declaration. Written informed consent to participate and publish was obtained from all individual participants included in the study.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
BB: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

MU: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology.

MB: Investigation; Visualization; Writing-original draft.
AE: Investigation; Validation; Writing-original draft.

DS: Investigation Resources; Visualization.

CA: Project administration; Resources; Supervision; Validation; Writing-review & editing.

References

1. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P, AACE/ACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines For Clinical Practice for The Diagnosis and Management of Thyroid Nodules-2016 Update. Endocr Pract. 2016 May;22(5):622-39. doi: 10.4158/EP161208.GL.
2. Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. Lancet. 2008 Oct 4;372(9645):1251-62. doi: 10.1016/S0140-6736(08)61005-3.
3. Grani G, Lamartina L, Biffoni M, Giacomelli L, Maranghi M, Falcone R, Ramundo V, Cantisani V, Filetti S, Durante C. Sonographically Estimated Risks of Malignancy for Thyroid Nodules Computed with Five Standard Classification Systems: Changes over Time and Their Relation to Malignancy. Thyroid. 2018 Sep;28(9):1190-1197. doi: 10.1089/thy.2018.0178.
4. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumber-

ger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan;26(1):1-133. doi: 10.1089/thy.2015.0020.
5. Horvath E, Silva CF, Majlis S, Rodriguez I, Skoknic V, Castro A, Rojas H, Niedmann JP, Madrid A, Capdeville F, Whittle C, Rossi R, Domínguez M, Tala H. Prospective validation of the ultrasound based TIRADS (Thyroid Imaging Reporting and Data System) classification: results in surgically resected thyroid nodules. Eur Radiol. 2017 Jun;27(6):2619-2628. doi: 10.1007/s00330-016-4605-y.
6. Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, Jung HK, Choi JS, Kim BM, Kim EK. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology. 2011 Sep;260(3):892-9. doi: 10.1148/radiol.11110206.
7. Moon WJ, Baek JH, Jung SL, Kim DW, Kim EK, Kim JY, Kwak JY, Lee JH, Lee JH, Lee YH, Na DG, Park JS, Park SW; Korean Society of Thyroid Radiology (KSThR); Korean Society of Radiology. Ultrasonography and the ultrasound-based management of thyroid nodules: consensus statement and recommendations. Korean J Radiol. 2011 Jan-Feb;12(1):1-14. doi: 10.3348/kjr.2011.12.1.1.
8. Qi Q, Zhou A, Guo S, Huang X, Chen S, Li Y, Xu P. Explore the Diagnostic Efficiency of Chinese Thyroid Imaging Reporting and Data Systems by Comparing with the Other Four Systems (ACR TI-RADS, Kwak-TIRADS, KSThR-TIRADS, and EU-TI-RADS): A Single-Center Study. Front Endocrinol (Lausanne). 2021 Oct 27;12:763897. doi: 10.3389/fendo.2021.763897.
9. Gao L, Xi X, Jiang Y, Yang X, Wang Y, Zhu S, Lai X, Zhang X, Zhao R, Zhang B. Comparison among TIRADS (ACR TI-RADS and KWAK- TI-RADS) and 2015 ATA Guidelines in the diagnostic efficiency of thyroid nodules. Endocrine. 2019 Apr;64(1):90-96. doi: 10.1007/s12020-019-01843-x.
10. Grant EG, Tessler FN, Hoang JK, Langer JE, Beland MD, Berland LL, Cronan JJ, Desser TS, Frates MC, Hamper UM, Middleton WD, Reading CC, Scoutt LM, Stavros AT, Teefey SA. Thyroid Ultrasound Reporting Lexicon: White Paper of the ACR Thyroid Imaging, Reporting and Data System (TIRADS) Committee. J Am Coll Radiol. 2015 Dec;12(12 Pt A):1272-9. doi: 10.1016/j.jacr.2015.07.011.
11. Grani G, Lamartina L, Ascoli V, Bosco D, Biffoni M, Giacomelli L, Maranghi M, Falcone R, Ramundo V, Cantisani V, Filetti S, Durante C. Reducing the Number of Unnecessary Thyroid Biopsies While Improving Diagnostic Accuracy: Toward the "Right" TIRADS. J Clin Endocrinol Metab. 2019 Jan 1;104(1):95-102. doi: 10.1210/jc.2018-01674.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014 Dec;12(12):1495-9. doi: 10.1016/j.ijsu.2014.07.013.
13. Park SJ, Park SH, Choi YJ, Kim DW, Son EJ, Lee HS, Yoon JH, Kim EK, Moon HJ, Kwak JY. Interobserver variability and diagnostic performance in US assessment of thyroid nodule according to size. Ultraschall Med. 2012 Dec;33(7):E186-E190. doi: 10.1055/s-0032-1325404.
14. Grani G, Lamartina L, Cantisani V, Maranghi M, Lucia P, Durante C. Interobserver agreement of various thyroid imaging reporting and data systems. Endocr Connect. 2018 Jan;7(1):1-7. doi: 10.1530/EC-17-0336.
15. Yoon SJ, Na DG, Gwon HY, Paik W, Kim WJ, Song JS, Shim MS. Similarities and Differences Between Thyroid Imaging Reporting and Data Systems. AJR Am J Roentgenol. 2019 Aug;213(2):W76-W84. doi: 10.2214/AJR.18.20510.
16. Kim DH, Kim SW, Basurrah MA, Lee J, Hwang SH. Diagnostic Performance of Six Ultrasound Risk Stratification Systems for Thyroid Nodules: A Systematic Review and Network Meta-Analysis. AJR Am J Roentgenol. 2023 Jun;220(6):791-803. doi: 10.2214/AJR.22.28556.
17. Yang W, Fananapazir G, LaRoy J, Wilson M, Campbell MJ. Can the American Thyroid Association, K-Tirads, and Acr-Tirads Ultrasound Classification Systems Be Used to Predict Malignancy in Bethesda Category IV Nodules? Endocr Pract. 2020 Sep;26(9):945-952. doi: 10.4158/EP-2020-0024.
18. Hekimsoy İ, Öztürk E, Ertan Y, Orman MN, Kavukçu G, Özgen AG, Özdemir M, Özbek SS. Diagnostic performance rates of the ACR-TIRADS and EU-TIRADS based on histopathological evidence. Diagn Interv Radiol. 2021 Jul;27(4):511-518. doi: 10.5152/dir.2021.20813.
19. Xu T, Wu Y, Wu RX, Zhang YZ, Gu JY, Ye XH, Tang W, Xu SH, Liu C, Wu XH. Validation and comparison of three newly-released Thyroid Imaging Reporting and Data Systems for cancer risk determination. Endocrine. 2019 May;64(2):299-307. doi: 10.1007/s12020-018-1817-8.
20. Ha EJ, Na DG, Moon WJ, Lee YH, Choi N. Diagnostic Performance of Ultrasound-Based Risk-Stratification Systems for Thyroid Nodules: Comparison of the 2015 American Thyroid Association Guidelines with the 2016 Korean Thyroid Association/Korean Society of Thyroid Radiology and 2017 American College of Radiology Guidelines. Thyroid. 2018 Nov;28(11):1532-1537. doi: 10.1089/thy.2018.0094.
21. Koc AM, Adıbelli ZH, Erkul Z, Sahin Y, Dilek I. Comparison of diagnostic accuracy of ACR-TIRADS, American Thyroid Association (ATA), and EU-TIRADS guidelines in detecting thyroid malignancy. Eur J Radiol. 2020 Dec;133:109390. doi: 10.1016/j.ejrad.2020.109390.
22. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg. 2010 Jun;34(6):1222-31. doi: 10.1007/s00268-009-0359-x.
23. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014 Jan;24(1):27-34. doi: 10.1089/thy.2013.0367.