Open Access Surgery

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Diagnostic Values of Solid Features in Different Sizes Thyroid Nodules Based on C-TIRADS

Hu Huang[1,*], Hong-Jian Li[2,*], Qi Gao[3], Ming-Jie Zhu[1], Wei-Min Li[4]

[1]Department of Thyroid and Breast Surgery, Affiliated Hospital of Jiangnan University, Wuxi, People's Republic of China; [2]Department of Ultrasonography, Huai'an Cancer Hospital, Huai'an, People's Republic of China; [3]Department of Ultrasonography, Zhongda Hospital Southeast University, Nanjing, People's Republic of China; [4]Department of Ultrasonography, Affiliated Hospital of Jiangnan University, Wuxi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wei-Min Li, Department of Ultrasonography, Affiliated Hospital of Jiangnan University, No. 1000 Hefeng Road, Wuxi, 214000, People's Republic of China, Email 1005342597@qq.com

Objective: As a positive features in C-TIRADS (Chinese Thyroid Imaging Reporting and Data System) guidelines, solid features represent the latest positive indicator, which differs from those in other guidelines. This study was to explore the diagnostic value of the solid features for thyroid nodules of different sizes.

Methods: Between January 2022 and October 2023, a total of 1561 patients with 1790 thyroid nodules confirmed by surgical pathology were prospectively included in this study. These nodules were divided into three groups based on their maximum diameter: Group A_1 (≤10mm), Group A_2 (>10mm, <20mm), and Group A_3 (≥20mm). The component characteristics of thyroid nodules in each group were analyzed. Based on the surgical pathology results, Receiver Operating Characteristic (ROC) curves were constructed to evaluate the diagnostic efficiency of C-TIRADS solid features for thyroid nodules of different sizes.

Results: As the size of thyroid nodules increased, the incidence of cystic changes in both benign and malignant nodules showed a linear increasing trend (Z-values of 46.251 and 156.586, respectively; P values <0.001 for both). The occurrence rate of solid malignant nodules was higher than that of benign nodules in all groups, with Area Under Curve (AUC) values of 0.620, 0.723, and 0.767, respectively.

Conclusion: With the increase in the size of thyroid nodules, the diagnostic value of solid features for thyroid cancer progressively increases. The specificity of thyroid nodule diagnosis also increases progressively. Which may have certain value in the evaluation process using C-TIRADS, particularly in the management of thyroid nodules in clinical settings.

Keywords: C-TIRADS, ultrasound, thyroid nodule

Introduction

The increased use of ultrasound technology in examining the thyroid has led to a higher detection rate of thyroid nodules. Studies indicate that approximately 70% of the global population has thyroid nodules, with the majority being benign and only about 10–15% being malignant.[1–3] The Chinese Thyroid Imaging Reporting and Data System (C-TIRADS), tailored to the specifics of China, serves as one of the guidelines for stratifying the malignancy risk of thyroid nodules and has been extensively applied.[4] Compared to other classification systems, the C-TIRADS-based solid features represent the latest positive feature, which means the thyroid nodule is entirely composed of solid tissue and does not contain any cystic components. Compared with other guidelines, solid feature was taken as an independent suspicious indicator for thyroid nodules, such as ACR-TIRADS, solid or almost solid is an feature scoring 2, while 2021 K-TIRADS uses a pattern-based system that stratifies the malignancy risk of a nodule using a combination of composition, echogenicity, and suspicious US features, punctate echogenic foci (microcalcifications), nonparallel orientation (taller than wide shape), and irregular margins are malignant features, solid hypoechoic is just as a basic features.[5–7] Given that the incidence of cystic changes in thyroid nodules tends to increase with nodule size, this study hypothesizes that the

Received: 23 May 2024
Accepted: 15 August 2024
Published: 19 August 2024

diagnostic value of solid features may vary with the size of the thyroid nodule. The study conducted an analysis of the structural properties in thyroid nodules of varied sizes to evaluate the diagnostic relevance of their solid features across different dimensions.

Methods

Study Subjects

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Affiliated Hospital of Jiangnan University, Huai'an Cancer Hospital, and Zhongda Hospital Southeast University (No. 2021092). Written informed consent was given by all participants before study inclusion. A total of 1561 patients with 1790 thyroid nodules who were diagnosed and underwent surgical pathology at Affiliated Hospital of Jiangnan University, Huai'an Cancer Hospital, and Zhongda Hospital Southeast University from January 2022 to February 2024 were enrolled in this study. Inclusion criteria for the patients were: (i) newly discovered thyroid nodules; (ii) underwent surgical pathology examination; (iii) complete and reliable ultrasound and clinical data. Exclusion criteria included: (i) thyroid nodules affected by puncture or treatment; (ii) nodules not examined by pathology or fine-needle aspiration biopsy; (iii) diffuse diseases with no obvious nodules observed on ultrasound.

Research Methods

Color Doppler ultrasound imaging instruments such as SonoScape S60 (SonoScape Medical Corp.), Logiq E9 (General Electric Co.), and Resona R7 (Mindray Medical Inc.) were utilized in our study. Patients were positioned supine for comprehensive neck exposure during the scans. The thyroid was examined using a combination of transverse and longitudinal scanning, with multi-sectional and multi-angle observations of the thyroid nodules. The evaluation of nodules was performed by two experienced attending physicians, each with a decade of practice. Discrepancies were resolved by a senior chief physician's review. The nodules were categorized into three size-based groups: Group A_1 (up to 10mm), Group A_2 (over 10mm and under 20mm), and Group A_3 (20mm and above). The assessment of thyroid nodule structural features was based on the C-TIRADS classification system,[4] including solid, predominantly solid, predominantly cystic, cystic, and spongiform. Solid nodules were identified as entirely solid structures, devoid of any cystic elements.

Statistical Analysis

Statistical analysis was executed using SPSS 26.0 and MedCalc 19.3.1. Continuous variables conforming to the normal distribution were presented as mean ± standard deviation and analyzed by independent sample *t*-test; those not conforming to the normal distribution were presented as median and quartiles and analyzed by Man-Whitney *U*-test. The independent samples *t*-test was applied for two-group comparisons. Count data were shown as frequency and percentage, analyzed using the Chi-square test and Fisher's exact test, while multi-group comparisons utilized the Chi-square test. The linear trend Chi-square test was used for incidence rate trend analysis. Receiver operating characteristic curves (ROC) were plotted to assess the prediction efficacy of the solid feature based on surgical pathology outcomes, AUC and Youden index for each group were calculated further. Diagnostic efficiency was categorized based on AUC values: 0.85–0.95 as good, 0.70–0.85 as moderate, and 0.50–0.70 as low. Statistical significance was set at $P<0.05$.

Results

Clinical Baseline Data

In our study, there were 623 male and 938 female patients, aged between 16–81 years, with an average age of 49.07±12.31 years. The maximum diameter of the nodules ranged from 2 to 86mm, with an average of 14.65 ±13.56mm. In Group A_1, there were 806 patients with 1170 nodules, consisting of 353 males and 553 females aged between 17 and 75 years, averaging 49.57±12.39 years. Nodules in this group had diameters from 2 to 10mm, with an average of 5.43±2.21mm, and were distributed as follows: 545 in the left lobe, 596 in the right lobe, and 29 in the isthmus. Group A_2 comprised 294 patients with 344 nodules, including 139 males and 227 females, aged 16–79 years, with a mean age of 51.41±12.73 years. In Group A_2, nodules ranged from 11 to 19mm in diameter, averaging 14.42±2.76mm, with 173 in the left lobe, 167 in the right, 3 in the isthmus, and 1 in the pyramidal lobe. Group A_3 consisted of 261 patients with 276 nodules, including 131 males and 178 females, aged 19–81 years, with an average age of 51.53±13.55 years. The nodules in A_3 varied from 20 to 86mm in diameter, averaging 35.13±12.03mm, located as 181 in the left lobe, 93 in the right, and 2 in the isthmus.

Pathological Results

Pathological classifications for thyroid nodules in each group adhered to the 2022 Fifth Edition of the WHO Classification of Endocrine Organ Tumors, specific to Thyroid.[8,9] A detailed distribution of these classifications is presented in Table 1.

Trends in the Incidence of Cystic Changes in Thyroid Cancer of Different Sizes

In this study, low-risk thyroid nodules were categorized as malignant. In Group A_1, out of 965 malignant nodules, the incidence of cystic changes was 0.31% (3/965). In Group A_2, among 179 malignant nodules, the incidence of cystic changes was 3.91% (7/179). In Group A_3, of the 79 malignant nodules, the incidence of cystic changes was 25.31% (20/79). A linear increasing trend in the incidence of cystic changes was observed across all malignant nodules (Z=156.586, P<0.001). In Group A_1, among 205 benign nodules, the incidence of cystic changes was 24.39% (50/205). In Group A_2, out of 165 malignant nodules, the incidence of cystic changes was 48.48% (80/165). In Group A3, among 197 malignant nodules, the incidence of cystic changes was 78.68% (155/197). A linear increasing trend in the incidence of cystic changes was also observed in all benign nodules (Z=46.251, P<0.001). With the increase in the maximum diameter of the nodules, the incidence of cystic changes also gradually increased (Figure 1). Representative ultrasound images showcasing malignant thyroid nodules from each group are depicted in Figures 2–4.

ROC Curves and Diagnostic Efficiency of Solid Features for Thyroid Nodules in Each Group

ROC curves were drawn based on pathological results (Figure 5). The results indicated that the AUC values for Groups total sample, A_2, and A_3 were 0.739 (95% CI:0.718–0.759), 0.723 (95% CI:0.672–0.770), and 0.767 (95%

Table 1 Pathological Results in Each Group n (%)

Pathological Results	Total Samples	Group A_1	Group A_2	Group A_3
Benign	567 (31.68)	205 (11.45)	165 (9.22)	197 (11.01)
Nodular goiter	442 (24.69)	152 (8.49)	133 (7.43)	156 (8.72)
Follicular adenoma	77 (4.30)	23 (1.28)	17 (0.95)	37 (2.07)
Oncocytoma	6 (0.33)	3 (0.17)	3 (0.17)	0 (0)
Lymphocytic thyroiditis	33 (0.17)	21 (0.06)	9 (0.50)	3 (0.17)
Granulomatous thyroiditis	9 (0.50)	6 (0.33)	3 (0.17)	0 (0)
Low-risk	15 (0.84)	1 (0.06)	6 (0.33)	8 (0.45)
Non-invasive follicular thyroid tumor with papillary-like nuclear features	5 (0.28)	0 (0)	4 (0.22)	1 (0.06)
Thyroid tumor with undetermined malignant potential	10 (0.56)	1 (0.06)	2 (0.11)	7 (0.39)
Malignant	1208 (71.51)	964 (53.85)	173 (9.66)	71 (3.97)
Papillary carcinoma	1171 (65.42)	959 (53.58)	166 (9.27)	46 (2.57)
Follicular thyroid cancer	20 (0)	4 (0.22)	5 ()	11 (0.61)
Lymphoma	6 (0.33)	0 (0)	0 (0)	6 (0.33)
Anaplastic carcinoma	4 (0.22)	0 (0)	0 (0)	4 (0.22)
Medullary carcinoma	6 (0.33)	1 (0.06)	2 (0.11)	3 (0.17)
Metastatic carcinoma	1 (0.06)	0 (0)	0 (0)	1 (0.06)

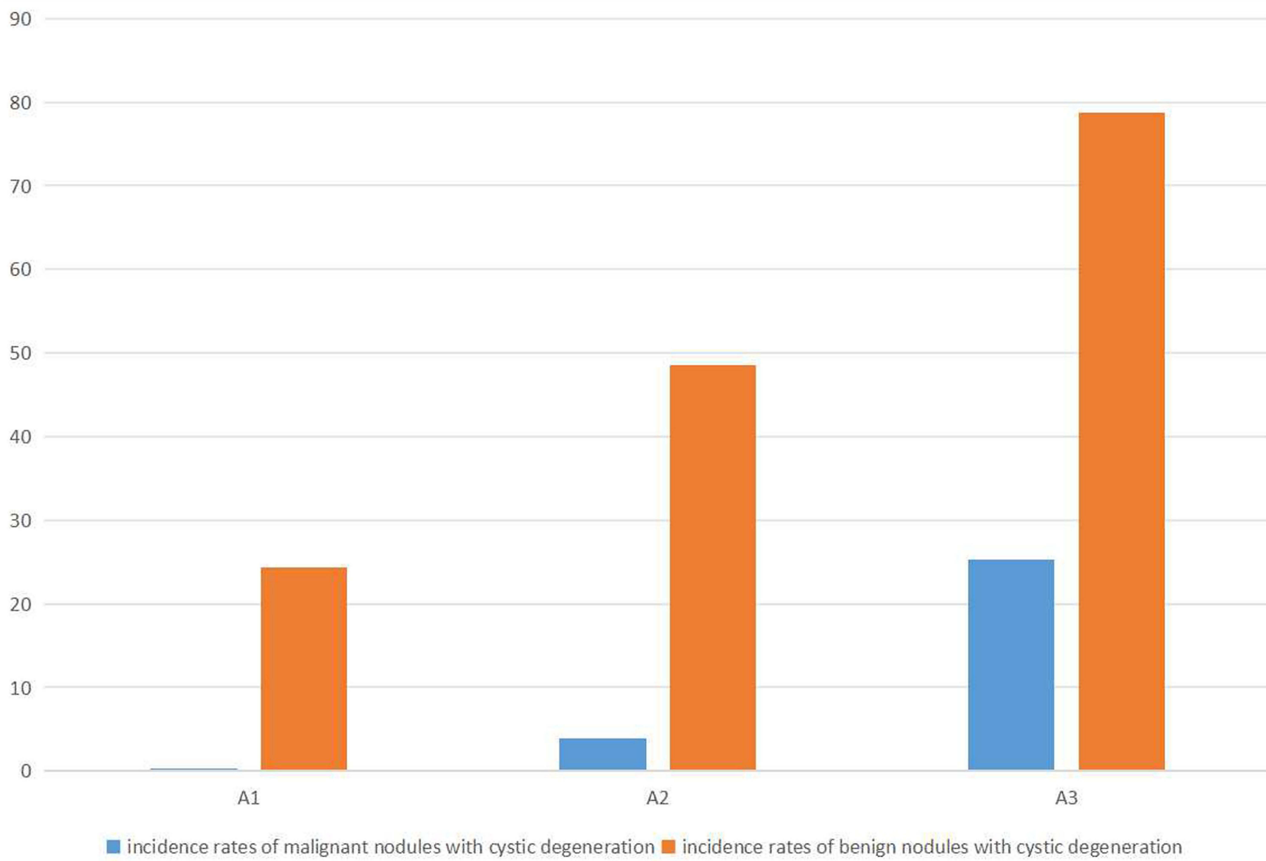

Figure 1 Incidence rates of cystic degeneration in benign versus malignant thyroid nodules with different size.

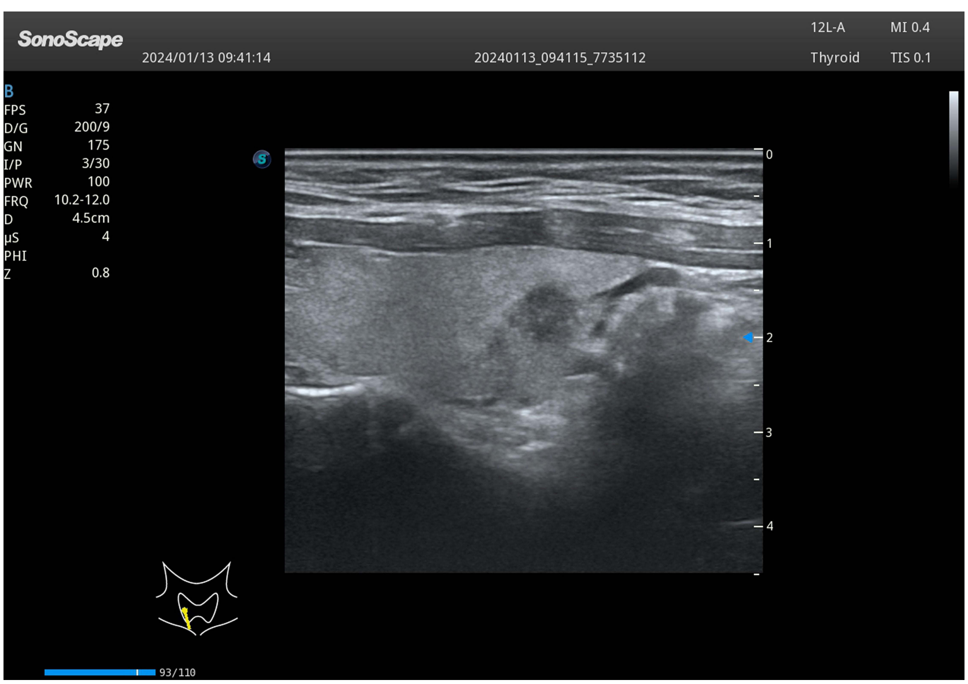

Figure 2 Ultrasound of a thyroid nodule in a 53-year-old female. A 6mm solid nodule in the right thyroid lobe, which was identified as papillary thyroid cancer after a surgical examination.

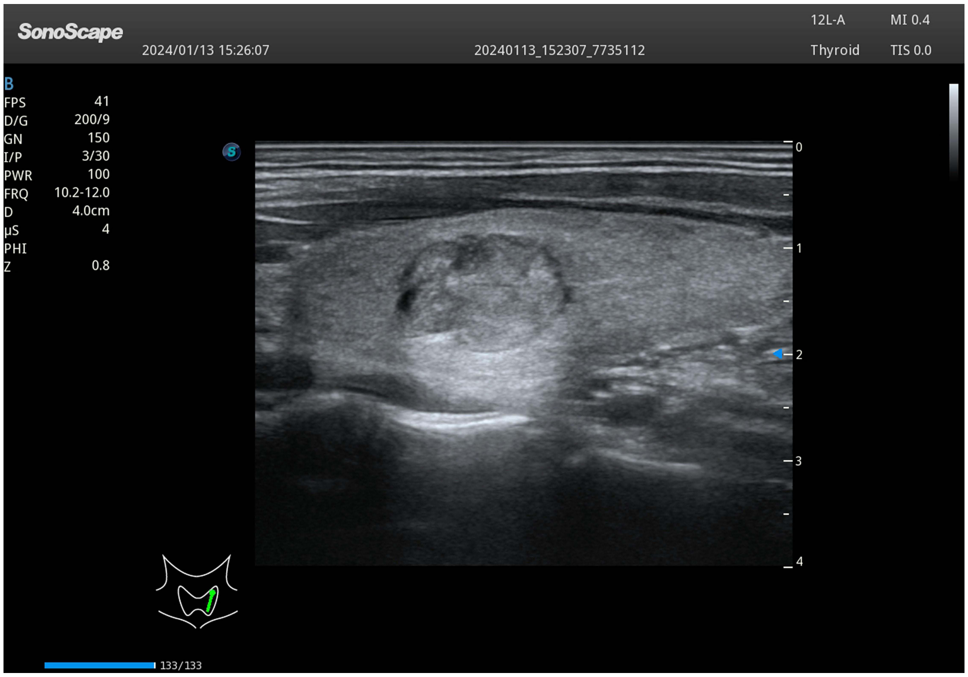

Figure 3 Ultrasound of a thyroid nodule in a 41-year-old female. A almost solid nodule in the left lobe of the thyroid, measuring 16mm in maximum diameter, which was also diagnosed as medullary carcinoma through surgical pathology.

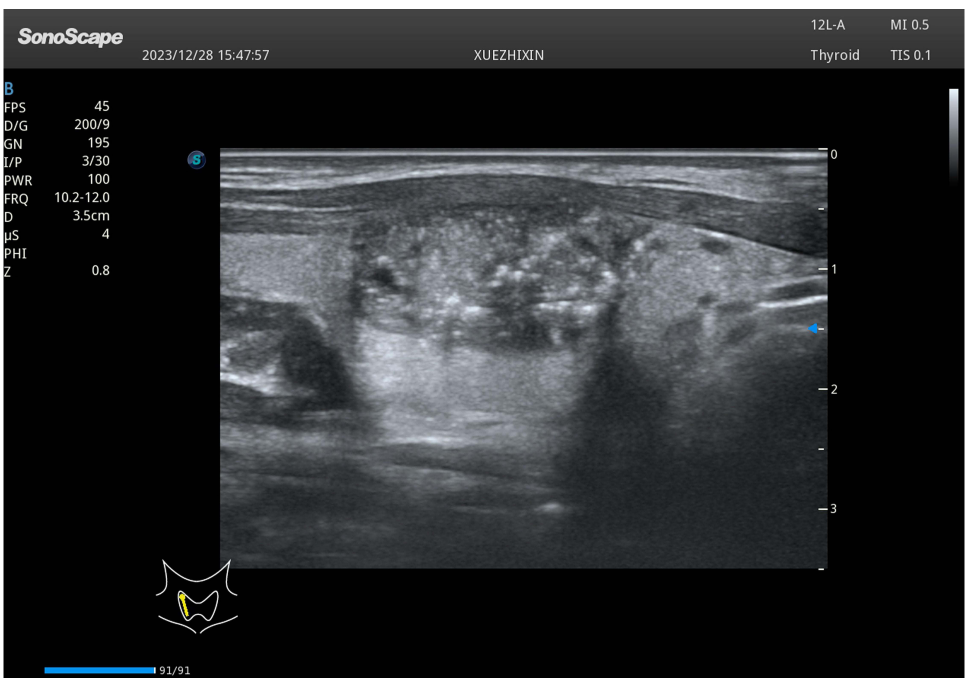

Figure 4 Ultrasound image of a thyroid nodule in a 51-year-old male. A 36mm cystic-solid nodule in the right lobe, which was diagnosed as papillary thyroid cancer after surgical examination.

CI:0.712–0.815), respectively, suggesting moderate diagnostic efficiency (>0.70). The AUC for Group A_1 was 0.620, indicating lower diagnostic efficiency (0.50–0.70). The sensitivity and specificity for each group are presented in Table 2.

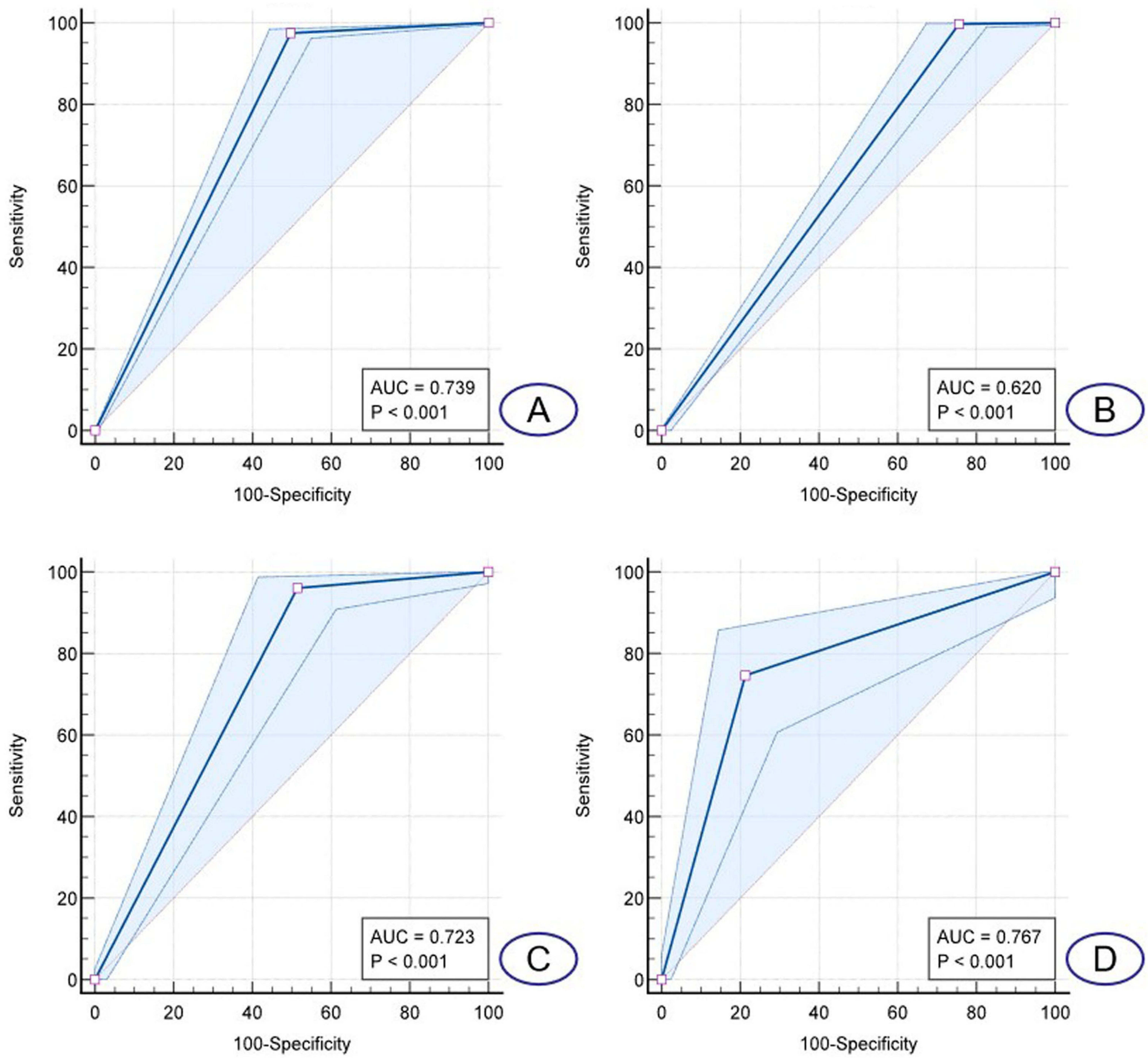

Figure 5 ROC curves for each group (**A**) ROC curve for all sample (**B**) ROC curve for Group A_1 (**C**) ROC curve for Group A_2 (**D**) ROC curve for Group A3.

Discussion

C-TIRADS is a thyroid classification system proposed by Professor Jian-qiao Zhou and others, taking into account the specific national conditions of China. This system defines positive features such as vertical orientation, solid, extremely hypoechoic, and ill-defined/irregular margins/extrathyroidal extension. Each of these features is assigned a score of 1

Table 2 The Diagnostic Efficacy of Solid Feature for Thyroid Nodules with Different Sizes

Groups	AUC	95% CI	Youden Index	Sensitivity	Specificity
Total samples	0.739	0.718–0.759	0.4781	97.55% (1193/1223)	50.26% (285/567)
A_1	0.620	0.592–0.648	0.2408	99.69% (962/965)	24.39% (50/205)
A_2	0.723	0.672–0.770	0.4457	96.09% (172/179)	48.48% (80/165)
A_3	0.767	0.712–0.815	0.5336	74.68% (59/79)	78.68% (155/197)

point.[4] Due to its simplicity and convenience, C-TIRADS has been extensively adopted in China. Various TI-RADS (Thyroid Imaging Reporting and Data System) classification systems exist worldwide. Compared to other TI-RADS systems, the solid features of C-TIRADS are new positive features, which means the thyroid nodule is entirely composed of solid tissue and does not contain any cystic components and this feature have sparked some controversy. As thyroid nodules increase in size, the probability of cystic degeneration increases, which may lead to missed diagnosis of some malignant nodules. Some scholars believe that this may cause some overdiagnosis for thyroid microcarcinoma as well. For ACR-TIRADS, solid or almost solid is an positive feature scoring 2 point while C-TIRADS treat solid as a main positive feature. Zhou believe that the malignant risk for solid is only 2–10%, which would not some overdiagnosis.[4] The diagnostic value of this system for thyroid nodules of different sizes warrants further exploration. In this study, using surgical pathology as the gold standard and analyzing 1790 thyroid nodules of varying sizes, it was found that as the volume of thyroid nodules increases, the diagnostic efficiency of the solid features for thyroid nodules gradually improves. This results may provide a basis for sonographers to upgrade or downgrade thyroid nodules based on their own experience.

This study demonstrates that for tiny thyroid nodules, the solid features exhibit relatively low diagnostic efficiency for diagnosing thyroid microcarcinoma, with an AUC of 0.620. Of the 1790 thyroid nodules included in this study, 1170 were minute nodules, comprising 1117 solid nodules and 53 cystic nodules. The pathological types were primarily minute papillary thyroid carcinomas. Current research suggests that the ultrasonic features of minute papillary thyroid carcinomas are quite typical, including solid hypoechogenicity, vertical position, microcalcifications, and blurred margins,[10–12] and with ongoing research, the diagnostic accuracy of ultrasound for these features is gradually improving. In cases of small benign thyroid nodules, the pathological classifications are varied, encompassing conditions like nodular goiter, chronic lymphocytic thyroiditis, follicular adenoma, and granulomatous thyroiditis. Current studies have shown that the ultrasonic features of chronic lymphocytic thyroiditis and granulomatous thyroiditis overlap to some extent with those of papillary thyroid carcinoma,[13,14] which can affect the ultrasound assessment of thyroid nodules. Follicular adenomas primarily appear as solid hypoechoic nodules, often accompanied by a halo, making them challenging to distinguish from follicular thyroid carcinoma,[15,16] thus reducing the diagnostic efficiency for thyroid microcarcinoma. Additionally, this study included a significant number of nodular goiters. Current research indicates that nodular goiters on ultrasound often appear as cystic-solid nodules. However, smaller nodular goiters with stromal collagenization, hemorrhage, calcification, multinucleated giant cell aggregation, and cholesterol crystal formation can also present as highly suspicious solid nodules.[17–19] Therefore, it is believed that when the nodule size is smaller, the probability of cystic changes decreases, which in turn increases the difficulty in differentiating them from minute thyroid cancers. This could be why the solid features have high sensitivity but low specificity for diagnosing minute thyroid cancers.

Compared to thyroid microcarcinoma, larger thyroid nodules have an increasing probability of cystic changes,[20,21] commonly associated with diseases like nodular goiter, follicular tumors, and papillary thyroid carcinoma. The results of this study indicate that with the increase in thyroid nodule volume, the incidence of cystic changes in both benign and malignant nodules shows a linear upward trend. However, this does not hinder the improvement in the diagnostic efficiency of solid features for thyroid cancer. In this study, the AUCs for Groups A_2 and A_3 were 0.723 and 0.769, respectively, lying between 0.70 and 0.85, which is a significant improvement in diagnostic efficiency compared to thyroid microcarcinoma. I believe that although the probability of cystic changes in thyroid nodules increases with size, benign nodules confirmed by surgical pathology are more likely to undergo cystic changes compared to thyroid cancer. This is why the diagnostic efficiency for thyroid cancer also gradually increases in this study. Additionally, as the thyroid nodule size increases, the specificity of the solid features for diagnosing thyroid cancer also gradually increases. This is related to the increased likelihood of cystic changes in benign thyroid nodules, especially in nodular goiter, where larger nodules often have more typical structural features, including predominantly cystic, spongiform, or cystic-solid characteristics,[22,23] with relatively lower incidence of solid parts. On the other hand, the sensitivity of the solid features for diagnosing larger thyroid nodules gradually decreases. Although the likelihood of cystic changes in thyroid cancer increases, it does not significantly affect the assessment of larger thyroid nodules. Our present study focuses solely on the diagnostic value of solid features for thyroid cancer. In clinical practice, when using C-TIRADS to assess thyroid nodules, it is essential to combine information about the morphology of nodules and edges and punctate echogenic foci for a comprehensive evaluation. Therefore, the author believes that for solid thyroid nodule>10mm, ultrasound-guided fine needle aspirate (FNA)is recommended. The Bethesda classification system for reporting thyroid cytopathology is the standard for interpreting FNA. However, Mulita F et al suggested that incidental malignancy was found in 1.53% and 19.19% in Bethesda II and III thyroid nodules, so they hold the opinion that FNA categorized as Bethesda category II and III may have a higher risk of malignancy than traditionally believed.[24,25] For solid thyroid nodules≤10mm, as they still contain a considerable number of benign nodules, further evaluation can be made based on their location with the thyroid capsule, trachea, or recurrent laryngeal nerve. If the nodule is adjacent to the capsule, trachea, or recurrent laryngeal nerve and nodule is malignant, the risk of neck metastasis may increases, ultrasound-guided FNA can be considered. If the nodule is not adjacent to the capsule, trachea, or recurrent laryngeal nerve, although it is malignant, the risk of neck lymph node metastasis is also reduced, follow up observation can be chosen, which is almost consistent with the management recommendations in the C-TIRADS guidelines.

Limitations

The different size of the groups will greatly affect the validity of the results, especially for thyroid nodules >10mm, <20mm and ≥20mm, the sample size are small. This study only analyzed thyroid nodules confirmed by surgical pathology. In clinical practice, thyroid malignancies are more likely to undergo further treatment, while smaller benign thyroid nodules are primarily observed through follow-up without intervention. Therefore, the data on the incidence of cystic changes in nodules, especially in benign nodules, may differ from actual clinical situations.

Conclusion

As the size of thyroid nodules increases, the diagnostic efficiency of C-TIRADS solid features for thyroid nodules gradually improves. The specificity of thyroid nodule diagnosis also increases progressively. Our findings highlights the importance of considering nodule size in the evaluation process using C-TIRADS, particularly in the management of thyroid nodules in clinical settings.

Ethical Statement

The study was approved by the Ethics Committee of Affiliated Hospital of Jiangnan University, Huai'an Cancer Hospital, and Zhongda Hospital Southeast University (No. 2021092). Written informed consent was given by all participants before study inclusion. For the patient's information provided by Affiliated Hospital of Jiangnan University, Huai'an Cancer Hospital, and Zhongda Hospital Southeast University during the treatment period due to illness, such as name, age, gender, occupation, address, ID card, related diseases and treatment plan. Due to the privacy of patients, the Affiliated Hospital of Jiangnan University, Huai'an Cancer Hospital, and Zhongda Hospital Southeast University keeps the above information confidential.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Alexander EK, Cibas ES. Diagnosis of thyroid nodules. *Lancet Diabetes Endocrinol*. 2022;10(7):533–539. doi:10.1016/S2213-8587(22)00101-2
2. Kobaly K, Kim CS, Mandel SJ. Contemporary Management of Thyroid Nodules. *Annu Rev Med*. 2022;27(3):517–528. doi:10.1146/annurev-med-042220-015032
3. Lam AK. Papillary thyroid carcinoma: current position in epidemiology, genomics, and classification. *Methods Mol Biol*. 2022;2534:1–15. doi:10.1007/978-1-0716-2505-7_1
4. Zhou J, Yin L, Wei X, et al. Chinese guidelines for ultrasound malignancy risk stratification of thyroid nodules: the C-TIRADS. *Endocrine*. 2020;70(2):256–279. doi:10.1007/s12020-020-02441-y
5. Tessler FN, Middleton WD, Grant EG, et al. ACR thyroid imaging reporting and data system (TI-RADS): white paper of the ACR TI-RADS committee. *J Am Coll Radiol*. 2017;14(5):587–595. doi:10.1016/j.jacr.2017.01.046

6. Shin JH, Baek JH, Chung J, et al. The Korean society of thyroid radiology (KSThR) and the Korean society of radiology. ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean Society of thyroid radiology consensus statement and recommendations. *Korean J Radiol*. 2016;17(3):370–395. doi:10.3348/kjr.2016.17.3.370
7. Russ G, Bonnema SJ, Erdogan MF, et al. European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: EU-TI-RADS. *Eur Thyroid J*. 2017;6(5):225–237. doi:10.1159/000478927
8. Mete O, Wenig BM. Update from the 5th edition of the world health organization classification of head and neck tumors: overview of the 2022 WHO classification of head and neck neuroendocrine neoplasms. *Head Neck Pathol*. 2022;16(1):123–142. doi:10.1007/s12105-022-01435-8
9. Baloch ZW, Asa SL, Barletta JA, et al. Overview of the 2022 WHO classification of thyroid neoplasms. *Endocr Pathol*. 2022;33(1):27–63. doi:10.1007/s12022-022-09707-3
10. Abe I, Lam AK. Assessment of papillary thyroid carcinoma with ultrasound examination. *Methods Mol Biol*. 2022;2534:17–28. doi:10.1007/978-1-0716-2505-7_2
11. Li QL, Ma T, Wang ZJ, et al. The value of contrast-enhanced ultrasound for the diagnosis of metastatic cervical lymph nodes of papillary thyroid carcinoma: a systematic review and meta-analysis. *J Clin Ultrasound*. 2022;50(1):60–69. doi:10.1002/jcu.23073
12. Gao X, Yang Y, Wang Y, et al. Efficacy and safety of ultrasound-guided radiofrequency, microwave and laser ablation for the treatment of T1N0M0 papillary thyroid carcinoma on a large scale: a systematic review and meta-analysis. *Int J Hyperthermia*. 2023;40(1):2244713. doi:10.1080/02656736.2023.2244713
13. Zhang Q, Zhang S, Pan Y, et al. Deep learning to diagnose hashimoto's thyroiditis from sonographic images. *Nat Commun*. 2022;13(1):3759. doi:10.1038/s41467-022-31449-3
14. Zhang Q, Liao L, Peng Q, et al. Value of contrast-enhanced ultrasound in differentiating clinically atypical subacute thyroiditis from papillary thyroid carcinomas. *Ultrasound Med Biol*. 2021;47(12):3384–3392. doi:10.1016/j.ultrasmedbio.2021.09.001
15. Lin Y, Lai S, Wang P, et al. Performance of current ultrasound-based malignancy risk stratification systems for thyroid nodules in patients with follicular neoplasms. *Eur Radiol*. 2022;32(6):3617–3630. doi:10.1007/s00330-021-08450-3
16. Yu B, Li Y, Yu X, et al. Differentiate thyroid follicular adenoma from carcinoma with combined ultrasound radiomics features and clinical ultrasound features. *J Digit Imaging*. 2022;35(5):1362–1372. doi:10.1007/s10278-022-00639-2
17. Hristu R, Eftimie LG, Paun B, et al. Pixel-level angular quantification of capsular collagen in second harmonic generation microscopy images of encapsulated thyroid nodules. *J Biophotonics*. 2020;13(12):e202000262. doi:10.1002/jbio.202000262
18. Guerlain J, Perie S, Lefevre M, et al. Localization and characterization of thyroid microcalcifications: a histopathological study. *PLoS One*. 2019;14(10):e0224138. doi:10.1371/journal.pone.0224138
19. Pang T, Huang L, Deng Y, et al. Logistic regression analysis of conventional ultrasonography, strain elastosonography, and contrast-enhanced ultrasound characteristics for the differentiation of benign and malignant thyroid nodules. *PLoS One*. 2017;12(12):e0188987. doi:10.1371/journal.pone.0188987
20. Peng Y, Zhou W, Zhan WW, et al. Ultrasonographic assessment of differential diagnosis between degenerating cystic thyroid nodules and papillary thyroid microcarcinomas. *World J Surg*. 2017;41(10):2538–2544. doi:10.1007/s00268-017-4060-1
21. Zhang Y, Chu X, Liu Y, et al. The influence of nodule size on clinical efficacy of ethanol ablation and microwave ablation on cystic or predominantly cystic thyroid nodules. *Endocr Connect*. 2022;11(11):e220248. doi:10.1530/EC-22-0248
22. Kelly BS, Govender P, Jeffers M, et al. Risk stratification in multinodular goiter: a retrospective review of sonographic features, histopathological results, and cancer risk. *Can Assoc Radiol J*. 2017;68(4):425–430. doi:10.1016/j.carj.2017.03.002
23. Niedziela M, Muchantef K, Foulkes WD. Ultrasound features of multinodular goiter in DICER1 syndrome. *Sci Rep*. 2022;12(1):15888. doi:10.1038/s41598-022-19709-0
24. Mulita F, Iliopoulos F, Tsilivigkos C, et al. Cancer rate of Bethesda category II thyroid nodules. *Med Glas*. 2022;19:53–61. doi:10.17392/1413-21
25. Mulita F, Plachouri MK, Liolis E, et al. Patient outcomes following surgical management of thyroid nodules classified as Bethesda category III (AUS/FLUS). *Endokrynol Pol*. 2021;72(2):143–144. doi:10.5603/EP.a2021.0018