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ORIGINAL RESEARCH

Comparing Diagnostic Efficacy of C-TIRADS Positive Features on Different Sizes of Thyroid Nodules

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Purpose: To explore the diagnostic value of positive features in the Chinese Thyroid Imaging Reporting and Data System (C-TIRADS) for thyroid nodules of different sizes.

Patients and Methods: A total of 1864 patients with 2347 thyroid nodules were selected from January 2021 to December 2022 and assessed according to C-TIRADS. According to the maximum diameter, nodules were divided into the A1 group (≤10 mm), A2 group (>10 mm,<20 mm), and A3 group (≥20 mm). With surgical pathology as the golden standard, the receiver operating characteristic curves (ROC) were constructed, and each group's area under the curve (AUC) was calculated. The diagnostic value of positive features in C-TIRADS for different sizes of thyroid nodules was analyzed.

Results: In all groups, malignant thyroid nodules had a higher incidence of positive features than benign nodules ($P < 0.05$). In A1 group, the diagnostic efficiency of C-TIRADS positive features for thyroid nodules was vertical orientation> ill-defined/irregular margin or extrathyroidal extension> solid composition> markedly hypoechoic> microcalcifications. The AUCs were 0.718, 0.675, 0.609, 0.558, and 0.581, respectively. In A2 group, the diagnostic efficacy of each positive features for thyroid nodules was ill-defined/irregular margins or extra-thyroid invasion> solid composition> microcalcifications> markedly hypoechoic> vertical orientation. The AUCs were 0.854, 0.730, 0.719, 0.670, and 0.609, respectively. In A3 group, the diagnostic efficacy of each positive features for thyroid nodules was ill-defined/irregular margin or extrathyroidal extension> microcalcifications> solid composition> vertical orientation> markedly hypoechoic. The AUCs were 0.847, 0.778, 0.767, 0.584, and 0.560, respectively.

Conclusion: C-TIRADS positive features exhibited different diagnostic efficacy for thyroid nodules of various sizes, especially for thyroid nodules ≤10 mm, for which all positive features had low diagnostic efficacy.

Keywords: ultrasound, C-TIRADS, sizes, thyroid nodule

Thyroid nodules are one of the most prevalent endocrine system diseases. Studies have shown that about 70% of the population worldwide have thyroid nodules, most benign and malignant nodules account for approximately 10%-15%.[1–3] Ultrasound imaging is simple and rapid with high resolution. Its value in detecting and evaluating thyroid nodules has gradually been recognized in clinical practice and has become the preferred examination method. However, varied sizes of thyroid nodules have distinct ultrasound assessment outcomes, which affects the diagnostic efficacy in some way.[4,5]

Our study analyzed ultrasonic features of thyroid nodules according to the Chinese Thyroid Imaging Reporting and Data System (C-TIRADS) and investigated the diagnostic efficacy of each positive index for different sizes of thyroid nodules.

Materials and Methods

General Information

A total of 1864 patients with 2347 nodules were prospectively selected. The patients were treated in the Affiliated Hospital of Jiangnan University, Eastern Theater General Hospital (formerly Bayi Hospital), and Zhongda Hospital

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Affiliated to Southeast University, from January 2021 to December 2022, confirmed by surgical pathology. There were 567 males and 1297 females, aged 15–83 years, with an average of 51.07±13.20 years. The maximum nodule diameter was 4–83 mm, averaging 12.65 ± 12.14 mm. The primary surgical indications are as follows: 1) Confirmed or suspected thyroid malignancy based on FNAB; 2) No definite FANB results but highly suspicious nodules on ultrasound for thyroid nodules >1 cm; 3) Nodules ≤10 mm with undefined fine-needle aspiration results but nodule C-TIRADS category ≥4 and the patient was very anxious and demanded surgical treatment, difficult to follow up; 4) Large-size nodule compressing surrounding tissues.

Apparatus and Methods

SonoScape S60 color Doppler ultrasound imaging system was used, and a linear array probe was selected, with a probe frequency of 7.8–15 MHz. During the examination, the patient was supine, with the bilateral neck fully exposed. The thyroid gland was scanned by combining transverse and longitudinal sections and observed from multiple sections and angles. The nodules were evaluated according to the C-TIRADS grading guidelines, including location, orientation, margin, acoustic halo, structure, echo, focal hyperechogenicity, posterior echo, size, etc. Two attending sonographers with more than 10 years of working experience and above qualifications evaluated all cases jointly. One chief physician reviewed inconsistent results. According to the maximum diameter of thyroid nodules, patients were classified into the A1 (≤10 mm), A2 (>10 mm, <20 mm), and A3 groups (≥20 mm). Ultrasound imaging features of thyroid nodules in different groups were evaluated with C-TIRADS, scored, and categorized.

Evaluation of C-TIRADS Positive Features

According to the C-TIRADS classification system, vertical orientation, solid composition, markedly hypoechoic, microcalcifications, and ill-defined/irregular margin or extrathyroidal extension were regarded as positive features.[6] Vertical orientation denotes that the long axis of the nodule and the skin tend to be perpendicular when evaluating the transverse or longitudinal section, and the anterior-posterior diameter of the nodule is greater than the left-right or upper-inferior diameter. A solid nodule is composed entirely of solid tissue and contains no cystic components. Markedly hypoechoic represents that nodules have lower echogenicity than strap neck muscles. Microcalcification refers to the presence of < 1 mm punctate strong echo in the nodule, and acoustic shadow may or may not appear in the rear. Nodule margin assessment depends on clarity and regularity. Irregular margins are spiculated, angular, or micro-lobulated; ill-defined margins denote that the border of the nodule is difficult to distinguish from the surrounding thyroid parenchyma; extrathyroidal invasion represents nodules invading the thyroid capsule, damaging the capsule. Adjacent soft tissue and/or vessels are invaded in severe cases.

Statistical Analysis

SPSS27.0 and MedCalc19.3.1 were used. Measurement data were expressed as mean ± SD. An independent sample *t*-test was used for comparison between two groups. Count data were expressed as frequency and percentage, and groups were analyzed using the χ^2 test and Fisher's exact probability method. Linear trends of groups were compared using the χ^2 test for trend. According to surgical pathology, a receiver operating characteristic curve (ROC) was plotted. The area under the curve (AUC) and the Youden index were calculated. An AUC of 0.85–0.95 indicates good diagnostic efficacy; an AUC of 0.70–0.85 indicates moderate diagnostic efficacy; an AUC of 0.50–0.70 denotes low diagnostic efficacy. The highest Youden index represents the best cutoff scores in each group, and P<0.05 refers to statistical significance.

Results

Pathological results

According to the 2020 fifth edition of WHO Classification of Endocrine Neoplasms (Thyroid Neoplasms).[7,8] A total of 2347 thyroid nodules were included in this study, including 731 benign cases (31.15%), 13 low-risk cases (0.56%), and 1603 malignant cases (68.30%). The pathological outcomes of thyroid nodules of different groups are as follows (Table 1).

Table 1 Pathological Results of Thyroid Nodules of Each Group

Pathological Results	A_1 Group	A_2 Group	A_3 Group
1. Benign	253	225	253
2. Nodular goiter	189	181	218
3. Follicular adenoma (FA)	25	35	31
4. Eosinophilic adenoma	2	5	3
5. Lymphocytic thyroiditis	24	3	1
6. Granulomatous thyroiditis	13	1	0
7. Low risk	0	7	6
8. Non-infiltrative follicular neoplasm (FN) with papillary nuclear features	0	4	2
9. Thyroid cancer with undetermined malignant potential	0	3	4
10. Malignant	1272	230	101
11. Papillary carcinoma	1264	221	78
12. Follicular carcinoma	6	7	9
13. Lymphoma	0	0	5
14. Undifferentiated carcinoma	0	0	5
15. Medullary carcinoma	2	2	3
16. Metastatic carcinoma	0	0	1

Ultrasound Feature Analysis

For statistical analysis, this study classified low-risk thyroid nodules as malignant. The sonographic features of thyroid nodules of different groups are as follows (Table 2). Significant differences were observed between groups ($P < 0.0001$). The representative images of thyroid nodules of each group are showed in Figure 1A–I.

Diagnostic Efficacy of C-TIRADS Positive Features for Thyroid Nodules

The diagnostic efficacy of positive features is shown in Table 3. Except for the PPV of vertical orientation and NPV of solid composition, significant differences were seen in other features between groups (all P values< 0.05). Meanwhile, the sensitivity and PPV of ill-defined/irregular margin or extrathyroidal extension, markedly hypoechoic, and solid

Table 2 C-TIRADS Positive Features in Benign and Malignant Thyroid Nodules of Each Group

Groups	Vertical Orientation	Solid Composition	Markedly Hypoechoic	Microcalcifications	Ill-Defined/ Irregular Margin or Extrathyroidal Extension
1. A_1					
2. Benign (n =35)	81	197	34	57	157
3. Malignant (n = 1272)	962	1268	377	435	1234
4. $\chi2$ value	185.687	265.824	28.129	13.147	321.751
5. P value	<0.001	<0.001	<0.001	<0.001	<0.001
6. A_2					
7. Benign (n = 225)	12	115	12	38	42
8. Malignant (n = 237)	94	230	64	143	212
9. $\chi2$ value	76.938	128.784	39.439	91.441	233.645
10. P value	<0.001	<0.001	<0.001	<0.001	<0.001
11. A_3					
12. Benign (n =35)	0	82	5	6	16
13. Malignant (n = 107)	18	59	15	62	81
14. $\chi2$ value		16.305	20.784	151.577	183.869
15. P value	<0.001	<0.001	<0.001	<0.01	<0.001

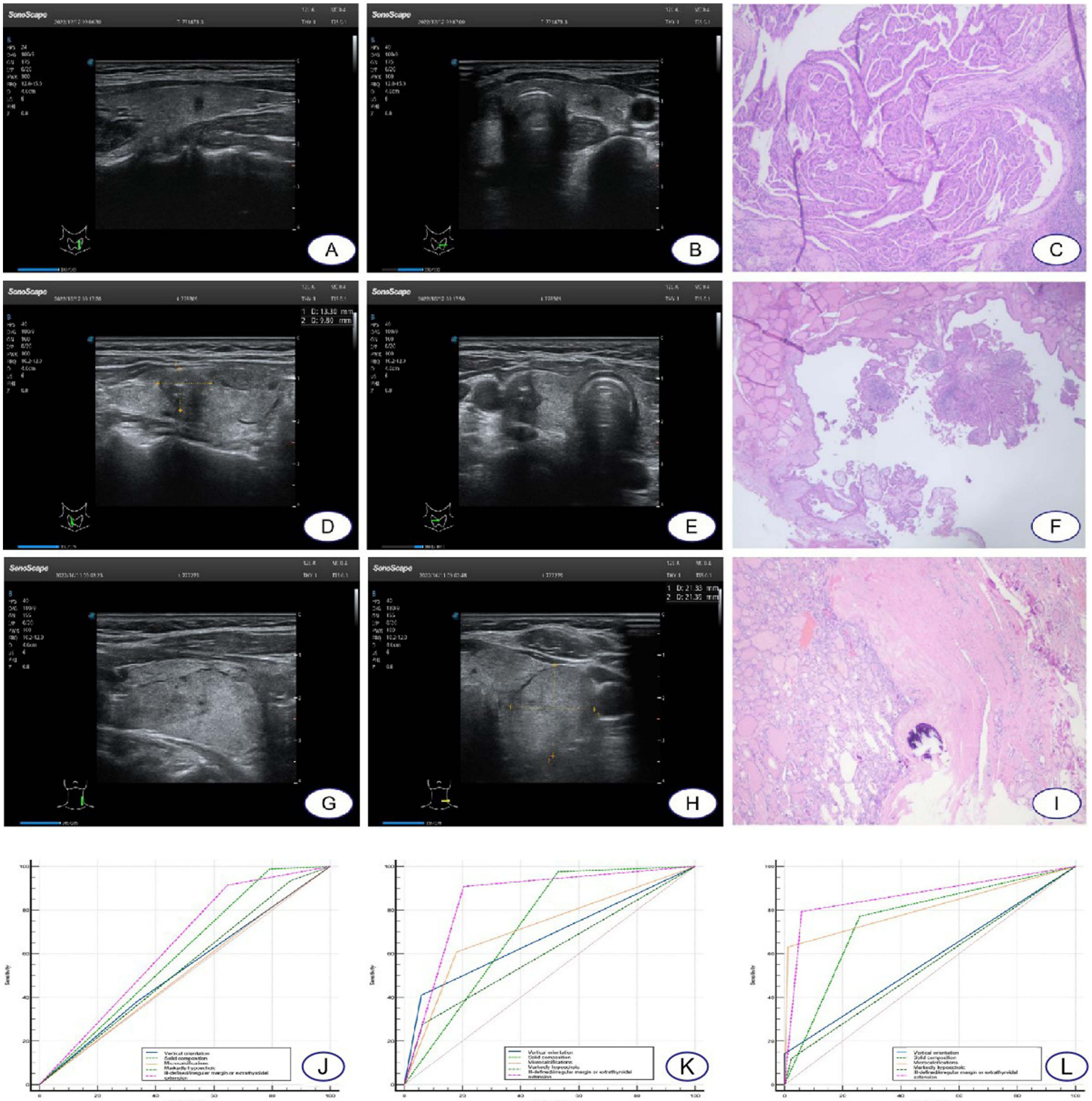

Figure 1 Typical ultrasonic imaging of thyroid nodules in each groups and ROC curves of each group. Longitudinal section (**A**) and transverse section (**B**) showed a left thyroid nodule ≤10 mm, postoperative pathology showing papillary thyroid microcarcinoma (**C**). Longitudinal section (**D**) and transverse section (**E**) showed a right thyroid nodule >10 mm, <20 mm, postoperative pathology showing papillary thyroid microcarcinoma (**F**). Longitudinal section (**G**) and transverse section (**H**) showed a left thyroid nodule ≥20 mm, postoperative pathology showing follicular adenoma (**I**). ROC curve of A_1 group (**J**). ROC curve of A_2 group (**K**). ROC curve of A_3 group (**L**).

composition for thyroid cancer decreased linearly with the increase of nodule size (all P values <0.05). The specificity and NPV of vertical orientations, ill-defined/irregular margin or extrathyroidal extension, and markedly hypoechoic increased linearly (all P values <0.05). Microcalcifications showed linearly increased sensitivity, specificity, and NPV for thyroid carcinoma with increasing nodule size (all P values <0.05).

ROC Curves of Thyroid Nodule Score of Each Group

The ROC curve (Figure 1J–L) was drawn according to the benign and malignant nature of nodules and their scores. The results showed that the diagnostic efficacy of each positive index in the A_1 group for thyroid nodules was vertical

Table 3 The Diagnostic Efficacy of Different Positive Features in Each Groups

Positive Features	Groups	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
1. Ill-defined/irregular margin or extrathyroidal extension	A_1	97.01% (1234/1272)	37.94% (96/253)	88.71% (1234/1391)	71.64% (96/134)
	A_2	89.45% (212/237)	81.33% (183/225)	83.46% (212/254)	87.98% (183/208)
	A_3	75.70% (81/107)	93.68% (237/253)	83.51% (81/97)	90.11% (237/263)
2. $\chi2$ values		99.700	207.326	7.106	25.973
3. P values		<0.001	<0.001	0.029	<0.001
4. Z values		96.915	188.990	6.137	20.664
5. P values		<0.001	<0.001	0.013	<0.001
6. Vertical orientation	A_1	75.63% (962/1272)	67.98% (172/253)	92.23% (962/1043)	35.68% (172/482)
	A_2	39.66% (94/237)	94.67% (213/225)	88.68% (94/106)	59.83% (213/356)
	A_3	16.82% (18/107)	100% (253/253)	100% (18/18)	73.98% (253/342)
7. $\chi2$ values		242.598	132.758	3.241	124.934
8. P values		<0.001	<0.001	0.198	<0.001
9. Z values		239.588	116.615	0.04	122.350
10. P values		<0.001	<0.001	0.842	<0.001
11. Microcalcifications	A_1	34.20% (435/1272)	77.47% (196/253)	88.41% (435/492)	18.97% (196/1033)
	A_2	60.34% (143/237)	83.11% (187/225)	79.01% (143/181)	66.55% (187/281)
	A_3	57.94% (62/107)	97.63% (247/253)	91.18% (62/68)	84.59% (247/292)
12. $\chi2$ values		73.181	45.745	11.420	517.763
13. P values		<0.001	<0.001	0.003	<0.001
14. Z values		60.542	43.109	1.233	497.812
15. P values		<0.001	<0.001	0.167	<0.001
16. Markedly hypoechoic	A_1	29.64% (377/1272)	86.56% (219/253)	91.73% (377/411)	19.66% (219/1114)
	A_2	27.0% (64/237)	94.67% (213/225)	84.21% (64/76)	55.18% (213/386)
	A_3	14.02% (15/107)	98.02% (248/253)	75% (15/20)	72.94% (248/340)
17. $\chi2$ values		12.090	26.962	9.143	387.056
18. P values		0.002	<0.001	0.010	<0.001
19. Z values		10.125	25.574	9.095	377.316
20. P values		0.001	<0.001	0.003	<0.001
21. Solid composition	A_1	99.69% (1268/1272)	22.13% (56/253)	99.69% (1268/1465)	93.33% (56/60)
	A_2	97.05% (230/237)	48.89% (110/225)	66.67% (230/345)	94.02% (110/117)
	A_3	76.64% (82/107)	76.68% (194/253)	58.16% (82/141)	88.58% (194/219)
22. $\chi2$ values		241.425	150.596	128.138	3.226
23. P values		<0.001	<0.001	<0.001	0.199
24. Z values		187.622	150.374	118.739	2.403
25. P values		<0.001	<0.001	<0.001	0.121

orientation> ill-defined/irregular margin or extrathyroidal extension> solid composition> markedly hypoechoic> microcalcifications. The AUCs were 0.718 (95% CI: 0.695–0.741), 0.675 (95% CI: 0.651–0.698), 0.609 (95% CI: 0.584–0.634), 0.581 (95% CI: 0.556–0.606), and 0.558 (95% CI: 0.533–0.583). Except for the difference between markedly hypoechoic and microcalcifications (Z = 1.690, P = 0.0910), the differences between other positive features were statistically significant (all $P < 0.05$). In the A_2 group, the diagnostic efficacy of each positive index for thyroid nodules was ill-defined/irregular margins or extra-thyroid invasion> solid composition> microcalcifications> markedly hypoechoic> vertical orientation. The AUCs were 0.854 (95% CI: 0.818–0.885), 0.730 (95% CI:0.687–0.770), 0.719 (95% CI: 0.675–0.759), 0.670 (95% CI: 0.625–0.713), 0.609 (95% CI: 0.563–0.654), respectively. Except for the difference between solid composition and microcalcifications (Z = 1.928, P = 0.0538), differences between other positive indicators were statistically significant (all $P < 0.05$). In the A3 group, the diagnostic efficacy of each positive index for thyroid nodules was: ill-defined/irregular margin or extrathyroidal extension> microcalcifications> solid composition> vertical orientation> markedly hypoechoic. The AUCs were 0.847 (95% CI: 0.805–0.882), 0.778 (95% CI: 0.731–0.820), 0.767

(95% CI: 0.719–0.809), 0.584 (95% CI: 0.531–0.636), and 0.560 (95% CI: 0.507–0.612), respectively. Except for the difference between solid composition and microcalcifications, markedly hypoechoic and vertical orientation were not significant (Z values were 1.207 and 0.351, and P values were 0.2274 and 0.7253), the differences between other positive features were statistically significant (all $P < 0.05$).

Discussion

TI-RADS is a thyroid classification system based on breast imaging reports and the management system. It established a standard imaging dictionary and performed standardized risk classification for thyroid nodule malignancy, which evades the influence of the sonographer's subjectivity. Currently, there are multiple TI-RADS classification systems worldwide. The TI-RADS system devised by the American College of Radiology (ACR) is the most influential. However, the ACR-TIRADS classification system aims to guide fine-needle aspiration, and categories 4 and 5 have relatively low malignancy rates, inconsistent with the current domestic clinical situation.[9] Thus, Professor Zhou Jianqiao et al developed a C-TIRDS classification system according to Chinese reality. Vertical orientation, solid composition, markedly hypoechoic, microcalcifications, and ill-defined/irregular margin or extrathyroidal extension are selected as positive features.[6] This system has been widely applied in China and is extensively acclaimed due to its convenient and rapid assessment of thyroid nodules. Because cytologic evaluation remains the diagnostic test of choice to distinguish benign from malignant thyroid nodules yet fails to discriminate as benign or malignant in up to one-third of cases. Although cytology is one of many clinical factors that inform decision making with regard to the management of thyroid nodules, additional risk factors to consider include: family history of thyroid malignancy, history of radiation exposure, nodule size, sonographic risk assessment, patient symptoms, and thyroid function. Diagnostic test accuracy must also be considered, with evaluation of test sensitivity, specificity, and the underlying disease prevalence in the population.[10] So in this study, surgical pathology were treated as the golden standard. The ultrasound features of 2347 thyroid nodules were analyzed, showing that positive features had distinct diagnostic efficacy on varying sizes of thyroid nodules. All positive features had relatively low diagnostic efficacy on thyroid nodules ≤10 mm.

For thyroid nodules ≤10 mm, the diagnostic efficacy of positive features in C-TIRADS from high to low was vertical orientation> ill-defined/irregular or extra-thyroidal invasion> solid composition> markedly hypoechoic> microcalcifications, among which vertical orientation had medium diagnostic efficacy, and the rest had relatively low efficacy. Via analysis, the pathology of malignant thyroid nodules ≤10 mm indicated PTMC as the dominant subtype. Research about PTMC has gradually matured. Its typical characteristics are all incorporated in the C-TIRADS classification system, including solid composition, ill-defined margins, vertical orientation, markedly hypoechoic, microcalcification, etc. Moreover, ultrasound has elevated diagnostic accuracy as exploration deepens. Nevertheless, for benign nodules in the A_1 group, chronic lymphocytic thyroiditis and granulomatous thyroiditis overlap considerably with thyroid microcarcinoma in sonographic features.[11–13] Additionally, it is tricky to differentiate follicular adenoma from follicular carcinoma using sonography.[14] Most nodular goiters have typical ultrasound features like cystic-solid, clear border, and transverse diameter greater than longitudinal diameter.[15] However, nodular goiters in this study were small, and their characteristics were found to be similar to PTMC for the first time. These nodules were mostly benign and degenerative, primarily caused by hemorrhage, degeneration, infarction, and fibrosis. During hematoma absorption, degenerated nodules gradually became irregular and exhibited malignant sonographic features as nodules gradually shrank.[16,17] When nodular goiters are accompanied by interstitial collagenization, calcification, and crystal formation, partial nodular goiters can display punctate strong echo with extended time. However, it is thorny to discriminate between solid thyroid micronodules and microcalcification using sonography, which affects sonographic evaluations of thyroid nodules. This may be why C-TIRADS positive features had low diagnostic efficacy on thyroid nodules ≤10 mm.

With increased nodule size, all positive features have changed diagnostic efficacy on thyroid nodules. In the A_2 group, the diagnostic efficacy of each positive index for thyroid nodules from high to low: ill-defined/irregular margins or extra-thyroid invasion> solid composition> microcalcifications> markedly hypoechoic> vertical orientation. The A_3 group: ill-defined/irregular margin or extrathyroidal extension> microcalcifications> solid composition> vertical orientation> markedly hypoechoic. Compared with thyroid nodules ≤10 mm, the diagnostic efficacy of all positive markers increased except for changed order and reduced diagnostic efficacy of vertical orientation. We consider the reason was that benign and malignant thyroid nodules have significant distinct sonographic features. Benign thyroid nodules of larger size are mainly nodular goiters. Nodular goiter and follicular adenoma are more common among benign thyroid nodules, and larger nodular goiter and follicular adenoma have a higher chance of developing cystic change.[18,19] This reduced the scores of benign thyroid nodules. Although partial papillary thyroid cancer cases could also be accompanied by cystic alterations, the incidence of other positive features was significantly higher than benign nodules, including ill-defined margins, microcalcification, etc. Meanwhile, follicular adenoma in benign nodules often coexists with the surrounding acoustic halo, which is conducive to ultrasound assessment.[18] Based on this, larger thyroid nodule size has a lower possibility of overlapping sonographic features between malignant and benign nodules, which facilitates further analysis of nodules with ultrasound imaging. This is why C-TIRADS positive features had higher diagnostic efficacy on thyroid nodules of larger sizes.

There are some limitations to this study. Although this study followed strict surgical standards, thyroid nodules ≤10 mm can choose to be followed up without biopsy. In this study, considerable thyroid nodules were ≤10 mm and underwent biopsy and surgery, which might lead to excessive treatment for thyroid microcarcinoma.

Conclusion

C-TIRADS positive features have varying diagnostic efficacy on thyroid nodules of different sizes. They had relatively low diagnostic efficacy for thyroid nodules ≤10 mm, which may increase the misdiagnosis rate of thyroid micronodules, thereby increasing overdiagnosis and overtreatment.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. 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. Individual consent for this retrospective analysis was waived. For the patient's information provided by the Affiliated Hospital of Jiangnan 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 keeps the above information confidential.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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