Original Article

Clinical utility of histogram analysis of grayscale sonograms in assessing sonographic suspicious malignant thyroid nodules

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Background: When sonographic suspicious malignant thyroid nodules initially proven to be inconsistent by aspiration, repeat fine-needle aspiration cytology (FNAC) is commonly recommended. Although FNAC is simple and reliable, it is also an invasive operation with inevitable false negative results. To determine which sonographic features and histogram parameters based on gray-scale ultrasonic images need repeat aspiration.

Methods: All of the nodules were suspicious for malignancy by preoperative ultrasound (US), and their initial FNAC findings indicated Bethesda category II, or III. Histogram analyses were performed for gray-scale ultrasonic images. Mean, variance, skewness, kurtosis, percentiles (1st, 10th, 50th, 90th, 99th), and sonographic features were compared between pathological benign nodules and malignant ones. Thereafter, receiver operator characteristic (ROC) curves were analyzed for the valuable indicators.

Results: One hundred and nineteen consecutive patients with 123 histopathologically diagnosed focal thyroid nodules were included in the cohort. The factors associated with malignancy were taller-than-wide shape [odds ratio (OR) =15.165; 95% confidence interval (CI): 3.157–72.854], irregular margins (OR =11.492; 95% CI: 1.747–75.573), microcalcifications (OR =5.107; 95% CI: 1.455–17.927) and skewness (OR =25.800; 95% CI: 1.034–76.422). The skewness of malignant thyroid nodules is higher than that of benign thyroid nodules and has an area under the curve (AUC) of 0.776 in the diagnosis.

Conclusions: For thyroid nodules suspicious on US but not on cytology, skewness, together with taller-than-wide shape, irregular margins and microcalcifications might be a promising marker for clinicians to perform repetitive FNACs.

Keywords: Ultrasound (US); thyroid; histogram analysis

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Introduction

Since the application of thyroid ultrasound (US), the incidence of thyroid malignant tumors has increased significantly (1). In total, 586,000 cases of thyroid cancer were reported worldwide in 2020 (2). Both US and fine-needle aspiration cytology (FNAC) play instrumental roles in the diagnosis and managements of thyroid nodules. High-resolution US is a morphological imaging technique that can facilitate the diagnosis of thyroid nodules (3,4) and is recommended as the first choice for detecting differentiated thyroid carcinoma (DTC) in the 2015 American Thyroid Association (ATA) guidelines (5). US-guided FNAC is the most accurate method in the management of thyroid nodules (6,7) and provides direct indications for surgery based on a worldwide consensus. However, in daily clinical work, discrepancies may be noted between the sonographic and cytological findings. In particular, the management of thyroid nodules considered suspicious of malignancy by US that have inconsistent cytological findings remains unclear. The 2015 ATA guidelines indicated that US-guided aspiration should be repeated if the cytology results indicate a Bethesda category of II (benign) with a highly suspicious US pattern, or III [atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)] (5). Although FNAC is simple and reliable, it is also an invasive operation with inevitable false negative results. Repeat FNAC will inevitably increase patients' economic burden and risk.

Histogram analysis based on US images has been demonstrated to be effective in previous studies to overcome the subjective bias between radiologists in ultrasonic diagnosis (8-10). This analysis can quantify the spatial change of the gray levels in the region of lesion that is not discernible to the naked eye. Moreover, this analysis is relatively easy for radiologists to perform using open-source software instead of highly specialized and complex computer processes. If histogram analysis can achieve the same accuracy as grayscale US, it will be of great benefit to identify benign and malignant thyroid nodules objectively and quantitatively.

In view of the indolent behavior and excellent prognosis of DTC and the concept of "less is more" emphasized by the 2015 ATA guidelines (11), the principle of current clinical management approaches is to minimize the adverse reactions caused by treatment and provide surveillance to ensure a curative effect. Our aim of this study was to analyze the traditional sonogram features and the objective histogram parameters of thyroid nodules suspicious on US but not on cytology and identify the independent predictive factors for malignancy to provide suggestions for the application of repeat FNAC. We present the following article in accordance with the STARD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-479/rc).

Methods

Patient identification

We reviewed 15,875 focal thyroid nodules in 7,658 consecutive patients who underwent cervical ultrasonography with discrete lesions in the thyroid in our institution from November 2018 to September 2020. Among them, 10,580 nodules in 4,583 patients underwent US-guided FNAC with suspected malignancy diagnosis by US. As shown in *Figure 1*, patients with sonographic findings suggestive of suspicious malignancy were recruited for the study. In addition, the patients needed to have cytology results indicating a classification of Bethesda category II or III. The exclusion criteria were as follows: (I) benign or probably benign nodules diagnosed for the first time and without malignant progression after 2 years of follow-up by US at this institution; (II) nodules rendered and reported as Bethesda categories I, IV, V or VI, and (III) previous thyroid resection at another institution with an uncertain diagnosis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences (No. NCC2020C-312). Informed consent of the patients was not required for reviewing the US images and clinical information.

US and FNAC procedures

The preoperative thyroid ultrasonography examinations were performed by board-certified radiologists who confirmed the clinical history of the patients. All US images were obtained with Philips AFFINITI 70 (Philips Medical Systems, Seattle, WA, USA), Philips EPIQ5 (Philips Medical Systems, Bothell, WA, USA), or GE logic E9 (General Electric Healthcare, Wauwatosa, WI, USA) ultrasonic diagnostic instruments with a 5- to 12-MHz or a 6- to 15-MHz linear array transducer. The patients were supine with the neck fully exposed. All thyroid glands and cervical lymph nodes were scanned. Finally, the US diagnosis for every thyroid nodule was classified into the following categories according to the ATA guidelines (5): (I) high suspicion, (II) intermediate suspicion, (III) low suspicion, (IV) very low suspicion, and (V) benign.

Typically, thyroid nodules that appear as pure cystic nodules with or without comet-tail artifacts were classified as "benign". "Probably benign" was used to classify thyroid nodules when benign US features, such as a circumscribed margin, isoechogenicity and parallel shape, were present. If a thyroid nodule had one or more malignant US features, such as solid appearance, marked hypoechogenicity, taller-than-wide shape, microcalcifications, irregular or microlobulated border and presence of internal vascularity (12,13), it was classified as "suspicious for malignancy".

All suspicious nodules were aspirated by senior

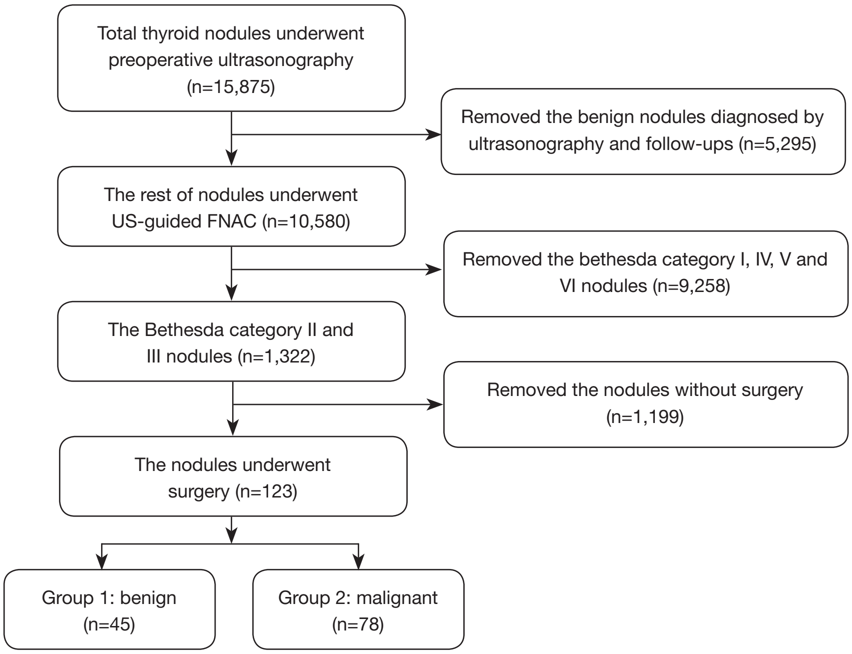

Figure 1 Diagram of study selection. US, ultrasound; FNAC, fine-needle aspiration cytology.

radiologists who had more than 10 years of experience in performing the FNAC procedure under the guidance of a real-time ultrasonography scan after local anesthesia was administered. FNAC was performed with a 22-gauge needle connected to a 5-mL syringe. All US-guided FNAC procedures were performed freehand without a syringe holder. For each nodule, aspiration was performed at least twice. All FNAC results were classified into one of six categories by senior cytopathologists from our institution based on the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC): I, non-diagnostic/unsatisfactory; II, benign; III, AUS/FLUS; IV, follicular cell neoplasm or suspicious for follicular cell neoplasm; V, suspicious malignant; VI, malignant. To control for bias, the radiologists were blinded to the US diagnosis of the nodule. Ultimately, surgery was recommended for Bethesda class IV, V, and VI nodules according to the 2015 ATA guidelines. The other nodules were treated with surgery or repeat FNAC or followed up according to personal preferences and the clinical situation of the patients.

Data collection

These nodules were divided into a benign group and malignant group based on the postoperative histopathology results. Patient demographic information, including age and sex, was collected. The following valuable ultrasonography features of the nodules were also obtained: nodule size (cm), multifocal/unifocal, echogenicity (hypoechogenicity, non-hypoechogenicity), calcifications (microcalcifications, non-microcalcifications), nodule margin (regular, irregular), nodule shape (taller-than-wide, parallel), sonography evidence of extrathyroidal extension (ETE) (absent, present) and combined with Hashimoto's thyroiditis (HT) (yes, no). All of the US images and FNAC cytology diagnoses were available in the Hospital Information System (HIS) and Picture Archiving and Communication System (PACS) of this hospital.

All of the valuable US variables were independently reviewed and analyzed by two board-certificated radiologists who had more than 5 years of experience in the diagnosis of thyroid nodules. The size of each nodule was evaluated at the longest aspect, and the shape (taller-than-wide/parallel) was assessed on transverse sections of the thyroid gland. However, coarse calcifications and microcalcifications often coexist in nodules. The risk for malignancy is associated with microcalcifications alone, so nodules with microcalcifications alone and nodules with both microcalcifications and coarse calcifications were included in this study. Microlobulated, spiculated or infiltrative borders are regarded as irregular margins (5). Combined HT was diagnosed when sonography showed typical hypoechogenicity with any one of the

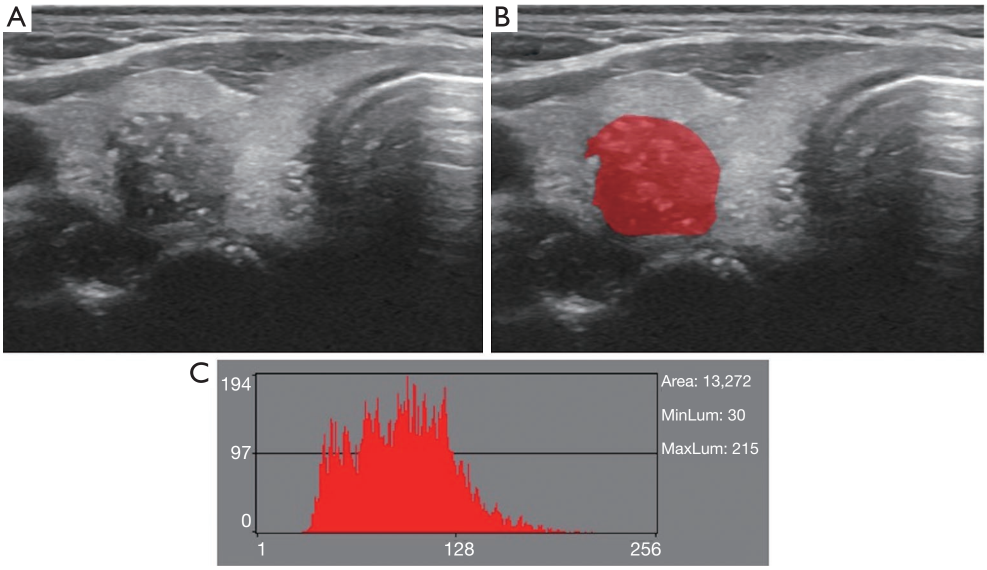

Figure 2 A 33-year-old woman with a 1.3-cm-diameter suspicious malignant thyroid nodule. (A) Transverse US image showed irregular margins, taller-than-wide shape and microcalcifications. (B) Regions of interest was manually circumscribed along the boundary of the nodule. (C) Graphs show the corresponding histogram analysis. Initial cytological finding was Bethesda category III. The final diagnosis after surgery was a papillary carcinoma. US, ultrasound.

following positive serological criteria: (I) antithyroid peroxidase antibody (TPOAb) or (II) antithyroglobulin antibody (TGAb). Any disagreements regarding US characteristics between the two radiologists were decided by a senior radiologist with at least 10 years of experience in the diagnosis of thyroid nodules.

Histogram analyses

The most representative and clearly visible longitudinal and transverse images of the nodule in BMP format were imported into the open-source software MaZda 4.6 (http://www.eletel.p.lodz.pl/mazda/) for histogram analysis (12). Two radiologists with more than 5 years of experience in the diagnosis of thyroid nodules who did not know the US diagnosis and histopathology results, drew the region of interest (ROI) separately as exactly as possible along the edge of the nodule (*Figure 2*). To reduce the influence of different ultrasonic diagnostic instruments and brightness changes, the normalization range of image gray intensity was limited to $\mu \pm 3\delta$ (μ, mean gray level value; δ, standard deviation) for ROIs in Mazda. Then, Mazda calculated the following voxel-based histogram parameters automatically for the ROIs: the mean, variance, skewness, kurtosis and cumulative frequency distributions of the 1st, 10th, 50th, 90th and 99th percentiles. Skewness refers to the degree of asymmetry based on the average. The skewness of symmetrically distributed data is zero. A negative skewness means that the data is tilted to the left, and a positive value means that the data is tilted to the right. Kurtosis indicates whether the histogram distribution is concentrated to the average value, positive kurtosis indicates steep distribution, and negative value indicates flat distribution (14,15).

We used the histogram parameters of the two radiologists to assess the interobserver consistency and used repeated measurements with an interval of one month by the younger radiologist to assess the intraobserver consistency.

Statistical analysis

All data were imported into SPSS 26.0 software for statistical analysis. Continuous variables were compared with independent sample *t*-test when normally distributed, Mann-Whitney U test when not normally distributed. Categorical data are expressed as a percentage and were compared by χ^2 analysis. The baseline characteristics, US features and histogram parameters of the thyroid nodules were compared between the benign and malignant pathological groups by using logistic regression analysis. If relevant, odds ratios (ORs) with 95% confidence intervals

(CIs) were calculated. Thereafter, receiver operator characteristic (ROC) analyses were analyzed for the significant parameters. Finally, the diagnostic efficacy of the selected independent risk factors was compared based on the following aspects: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC).

The repeatability of interobserver and intraobserver measurements was assessed by using intraclass correlation coefficients (ICCs) with 95% CIs. After performing the two-way random model, ICC scores were classified as follows: <0.40 indicates poor; 0.40–0.60 indicates moderate; 0.61–0.80 indicates good; and ≥0.81 indicates excellent. The predetermined threshold was $P<0.05$.

Results

Clinical and US parameters between the benign and malignant groups

During the whole research period, a total of 123 thyroid nodules were surgically treated, including 45 benign cases (36.6%) and 78 malignant cases (63.4%). The diagnosis of all thyroid nodules was confirmed by histology. The malignant lesions included 76 papillary thyroid cancers (PTCs), 1 medullary thyroid cancers (MTCs), and 1 follicular thyroid cancer (FTC). The benign lesions comprised nodular hyperplasia, adenomatous goiters, follicular proliferating lesions, and thyroiditis. Our cohort included 92 women (74.8%) and 31 men (25.2%). The mean interval between initial FNAC and surgery was 2.3 months with a range of 1–6 months. The relevant variables of the benign group differing significantly from those of the malignant group included nodule size, hypoechogenicity, calcifications, nodule margin, nodule shape and combined HT (*Table 1*).

Histogram parameters between the benign and malignant groups

The ICC for the repeatability of interobserver measurements of histogram parameters of grayscale ultrasonic images ranged from 0.713 to 0.890, and the ICC for the repeatability of intraobserver measurements of histogram parameters of grayscale ultrasonic images ranged from 0.985 to 0.997. Associations between the histogram parameters and malignancy are presented in *Table 2*. After multivariate logistic regression analysis, taller-than-wide shape (OR=15.165; 95% CI: 3.157–72.854), irregular margins (OR=11.492; 95% CI: 1.747–75.573), the presence of microcalcifications (OR =5.107; 95% CI: 1.455–17.927) and skewness (OR =25.800; 95% CI: 1.034–76.422) were independent indicators of malignant nodules (*Table 3*).

Comparison of diagnostic performance of traditional US features and histogram parameters

Figure 3 shows the AUCs of three US indexes and skewness significantly related to malignant nodules. Among the traditional US features, the taller-than-wide shape has the best diagnostic performance with an AUC of 0.750 followed by the irregular margins, which also has a good diagnostic performance, with an AUC of 0.676. Microcalcifications has the highest specificity of 0.911 (95% CI: 0.779–0.971), and PPV of 0.905 (95% CI: 0.765–0.969). Besides the AUC of the skewness significantly correlating with malignancy was 0.776. When the optimal cutoff value was set as 0.2006, the skewness has a sensitivity of 0.936 (95% CI: 0.850–0.976), a PPV of 0.760 (95% CI: 0.660–0.839) and an NPV of 0.815 (95% CI: 0.613–0.930) in the diagnosis (*Table 4*).

Discussion

Our study indicated the following findings. First, of the traditional US features, a taller-than-wide shape, irregular margins and the presence of microcalcifications were associated with an increased risk of thyroid cancer. Second, the skewness of malignant thyroid nodules is greater than that of benign thyroid nodules, which was identified as an independent predictor for discriminating between benign thyroid nodules and malignant thyroid nodules with an AUC of 0.776 in patients with suspicious US diagnoses but not cytology.

A taller-than-wide shape, irregular margins and the presence of microcalcifications are well-known indicators for malignancy in thyroid nodules that have been reported in various previous studies (5,13,16,17). A retrospective analysis showed that US microcalcifications in thyroid nodules had a high specificity of 93%, PPV of 75%, and NPV of 76.7% but a low sensitivity of 42.8% for malignancy (1). In another study, microcalcifications had a high specificity (90.8%) and a low sensitivity (44.2%) for predicting malignancy (17). Our investigations indicated similar results: presence of microcalcifications had a high specificity (91.1%) and high PPV (90.4%), but the sensitivity was low at 48.7%. This phenomenon can

Table 1 Comparison of clinical and ultrasonographic features among the benign and malignant groups

Variables	Total (n=123)	Postoperative histopathology		P value
		Benign (n=45)	Malignant (n=78)	
Age at diagnosis (years)				0.385
Range	22–75	24–45	22–75	
Median	46	48	45	
Sex				0.475
Female	92 (74.8)	32 (71.1)	60 (76.9)	
Male	31 (25.2)	13 (28.9)	18 (23.1)	
Nodule size (cm)				0.002
<2	86 (69.9)	24 (53.3)	62 (79.5)	
≥2	37 (30.1)	21 (46.7)	16 (20.5)	
Echogenicity				0.052
Hypoechogenicity	113 (91.9)	38 (84.4)	75 (96.2)	
Non-hypoechogenicity	10 (8.1)	7 (15.6)	3 (3.8)	
Margins				<0.001
Irregular	104 (84.6)	28 (62.2)	76 (97.4)	
Regular	19 (15.4)	17 (37.8)	2 (2.6)	
Shape				<0.001
Parallel	32 (26.0)	26 (57.8)	6 (7.7)	
Taller-than-wide	91 (74.0)	19 (42.2)	72 (92.3)	
Calcifications				<0.001
Microcalcifications	42 (34.1)	4 (8.9)	38 (48.7)	
Non-microcalcifications	81 (65.9)	41 (91.1)	40 (51.3)	
Focus				0.155
Unifocal	15 (12.2)	3 (6.7)	12 (15.4)	
Multifocal	108 (87.8)	42 (93.3)	66 (84.6)	
Sonography evidence of ETE				0.309
Yes	4 (3.3)	0	4 (5.1)	
No	119 (96.7)	45 (100.0)	74 (94.9)	
Combined with HT				0.045
Yes	32 (26.0)	7 (15.6)	25 (32.1)	
No	91 (74.0)	38 (84.4)	53 (67.9)	

Data in parentheses are percentages. ETE, extrathyroidal extension; HT, Hashimoto's thyroiditis.

Table 2 Comparison of histogram parameters among the benign and malignant groups

Variables	Benign (n=45)	Malignant (n=78)	P value
Mean	75.408 (62.038, 96.146)	51.788 (37.103, 59.307)	<0.001
Variance	358.020 (274.780, 455.335)	415.240 (275.908, 690.262)	0.171
Skewness	0.231±0.559	0.783±0.505	<0.001
Kurtosis	0.183 (−0.352, 1.108)	0.777 (0.058, 2.361)	0.011
Percentile 1%	37.000 (23.500, 48.000)	11.000 (1.000, 22.250)	<0.001
Percentile 10%	54.380±21.490	24.100±16.715	<0.001
Percentile 50%	76.000 (56.500, 97.000)	49.000 (35.750, 57.000)	<0.001
Percentile 90%	103.000 (87.500, 125.000)	77.000 (65.250, 91.500)	<0.001
Percentile 99%	128.310±31.284	114.33±35.585	0.030

Data in accordance with normal distribution are expressed by average ± standard deviation. Data that do not conform to the normal distribution are expressed by the median (25th percentile, 75th percentile).

Table 3 Multivariate logistic regression analysis of valuable features

Variables	OR (95% CI)	P value
Nodule size ≥2 cm	2.002 (0.423–9.482)	0.382
Hypoechogenicity	2.766 (0.398–19.248)	0.304
Irregular margins	11.492 (1.747–75.573)	0.011
Taller-than-wide shape	15.165 (3.157–72.854)	0.001
Microcalcifications	5.107 (1.455–17.927)	0.011
Combined with HT (yes)	1.590 (0.479–5.284)	0.449
Mean	0.662 (0.137–3.200)	0.608
Skewness	25.800 (1.034–76.422)	0.049
Kurtosis	0.542 (0.216–1.360)	0.192
Percentile 1%	0.996 (0.823–1.126)	0.637
Percentile 10%	0.868 (0.574–1.315)	0.505
Percentile 50%	1.593 (0.664–3.823)	0.297
Percentile 90%	0.980 (0.673–1.428)	0.917
Percentile 99%	1.047 (0.933–1.175)	0.431

OR, odds ratio; CI, confidence interval; HT, Hashimoto's thyroiditis.

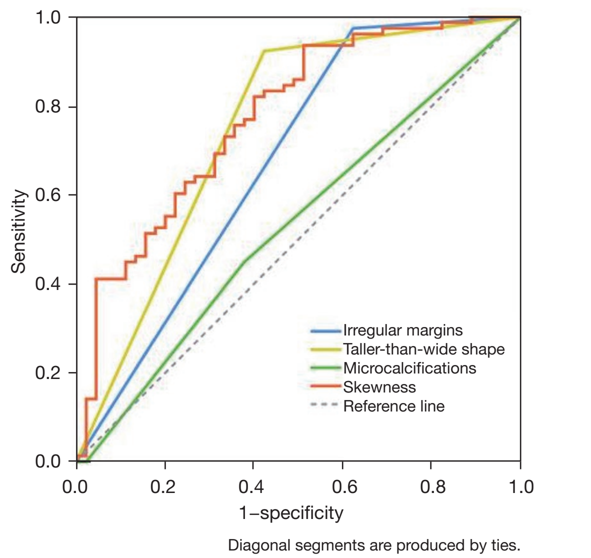

Figure 3 ROC curve and corresponding AUCs of three traditional US characteristics skewness and for prediction of malignance. ROC, receiver operator characteristic; AUCs, areas under the curve; US, ultrasound.

be caused by the different resolutions of the ultrasonic diagnostic instrument and the density and distribution of psammoma bodies.

Hypoechogenicity was not an effective predictor for thyroid cancer in our results. To date, the specificity of hypoechogenicity as a diagnostic criterion of malignancy has been uncertain. A study has confirmed that up to 55% of benign nodules are hypoechoic compared with the thyroid parenchyma, reducing the specificity of hypoechogenicity (17). These findings support our results. Additionally, we found that hypoechogenicity was a factor that led to false-positive US-based diagnoses. Of the 123 nodules, 45 benign nodules received false-positive diagnoses by US in the present study. Among them, the

Table 4 Diagnostic performance of the four risk indicators

Variables	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
Irregular margins	0.974 (0.902–0.995)	0.378 (0.242–0.535)	0.731 (0.633–0.811)	0.895 (0.655–0.982)	0.676 (0.570–0.782)
Taller-than-wide shape	0.923 (0.834–0.968)	0.578 (0.422–0.720)	0.791 (0.691–0.867)	0.813 (0.630–0.921)	0.750 (0.653–0.848)
Microcalcifications	0.487 (0.373–0.602)	0.911 (0.779–0.971)	0.905 (0.765–0.969)	0.506 (0.394–0.618)	0.530 (0.424–0.637)
Skewness	0.936 (0.850–0.976)	0.489 (0.339–0.640)	0.760 (0.660–0.839)	0.815 (0.613–0.930)	0.776 (0.689–0.862)

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

proportion of hypoechogenic/non-hypoechogenic nodules was 38/7. This finding may imply that hypoechogenicity can increase the probability of radiologists obtaining a false-positive diagnosis.

Histogram texture analysis applied to US images has been demonstrated to have high diagnostic performance on various organs (9-11). By calculating the histogram parameters, the distribution of imaging biomarkers on all voxels from different dimensions can be recognized (18). Our study showed that skewness of grayscale ultrasonic images enabled differentiation between benign and malignant thyroid nodules. Skewness is defined as an asymmetric scale based on the mean used to describe the symmetry of the histogram distribution. In histogram analysis extracted from grayscale US images, malignant thyroid nodules had higher skewness than benign nodules. These results indicate that gray levels inside the malignant nodules were more heterogeneous and diverse than those in the benign nodules possibly due to internal abnormal vascular deformation, necrosis and calcifications of malignant nodules.

The mean was calculated as the average value of pixel intensity on grayscale US images ranging from 0 (black) to 256 (white). In this study, the mean of histogram analysis is not an independent predictor of malignant nodules. The proportion of hypoechoic nodules in the benign nodule group was as high as 84%. Hypoechogenicity was not a valid predictor in distinguishing between benign and malignant groups. No significant difference in the mean pixel intensity in hypoechogenic nodules was noted between the benign and malignant groups, which may explain why the mean is not an independent predictor in our results.

This study has the following limitations. First, to ensure the accuracy of histogram analysis based on grayscale images, we selected the postoperative pathological results as diagnostic criteria and excluded a large number of patients who did not undergo surgery, resulting in a small sample size and inevitable selection bias. Second, the malignancy rate in this study was 63.4%. This rather high rate of malignant tumors may be because our institution is the largest tumor specialist hospital in the region, and we see patients with suspicious nodules that have been detected in local hospitals requiring further diagnosis and treatment. In summary, we propose performing further multicenter and large-scale studies to obtain more generalizable results.

In conclusion, for thyroid nodules suspicious on US but not on cytology, histogram analysis based on grayscale ultrasonic images can be a noninvasive, easy-to-achieve, effective auxiliary diagnostic tool of conventional ultrasonic features. Skewness together with taller-than-wide shape, irregular margins and microcalcifications might represent a promising marker for clinicians to perform repetitive FNACs.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-479/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-479/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-479/coif). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences (No. NCC2020C-312) and individual consent for this retrospective analysis was waived.

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