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Histopathological Analysis of Thyroid Nodules with Taller-Than-Wide Shape in Adults

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Background: The ultrasound examination (USE) feature of taller-than-wide (TTW) shape is highly specific but low sensitive in diagnosis of thyroid carcinoma. Relationships between other USE malignant features (such as irregular margin, ill-defined, markedly hypoechoic, and microcalcification) with histopathological features have been well investigated, while studies about the histopathologic features of TTW shape are rare.
Aim: The present study aimed to investigate the histopathological features of thyroid nodules with TTW shapes.
Methods: A total of 85 thyroid nodules with TTW were selected from 1680 consecutive patients who underwent thyroid resection. USE features of the nodules, including size, location, boundary, margin, composition, echogenicity, and calcification, were recorded according to the China Thyroid Imaging Reporting and Data System (C-TIRADS). Hypoechoic lesions were further categorized as mild, moderate or markedly hypoechoic lesions. The histological features of the specimens were evaluated according to the arrangement of follicular cells, presence of papillary structures or psammoma bodies, degree of fibrosis, and amount of lymphoid infiltration. Differences in the USE and histological features between benign and malignant nodules were compared.
Results: Among the 85 nodules, 72 (84.71%) were malignant, and 13 (15.29%) were benign. Only echogenicity showed a statistically significant difference between benign and malignant nodules (P=0.003). Apart from microfoci, papillary structures, and psammoma bodies, the degree of fibrosis was also significantly different between benign and malignant tumors (all P<0.05). Regression analysis showed a trend of decreasing nodule echogenicity with increasing fibrosis frequency (odds ratio [OR] = 4.500).
Conclusion: Extensive fibrosis is the most common histopathological feature of thyroid cancer and corresponds to hypoechogenicity in USE. TTW-shaped thyroid nodules are highly suggestive of malignancy, especially those with moderate or markedly hypoechogenicity.
Keywords: ultrasound, taller-than-wide shape, thyroid nodules, histopathological features

Introduction

The presence of a taller-than-wide (TTW) shape on ultrasound examination (USE) is closely associated with malignancy, exhibiting a higher diagnostic odds ratio than other malignant features such as irregular margin, ill-defined, markedly hypoechoic, and microcalcification.[1,2] This feature was first recognized in 2002 because of the observed growth of benign nodules in normal tissue planes, while malignant nodules expand across tissue planes.[3] Previous studies showed that the diagnostic specificity of TTW in the diagnosis of thyroid carcinoma was as high as 85.2%–96.85%, but the sensitivity varied from 0% to 81.4%,[4,5] more investigation is needed to deeper understanding this special USE feature.

USE is the preferred imaging modality for screening thyroid nodules, while pathological testing is the gold standard for definitive diagnosis. Both of them analyze structures of thyroid from different angles with different principles. Most popular guidelines list microcalcification, irregular margin, ill-defined, markedly hypoechoic and TTW shape as malignancy USE features.[6–11] Investigations have verified the relations between some of these features and pathological findings. For instance, ill-defined boundaries on USE exhibit infiltration into the surrounding tissue or irregular margins by histology.[12] Microcalcifications in thyroid nodules often reflect the presence of psammoma bodies, a specific

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histopathological structure diagnosing papillary thyroid carcinoma (PTC).[13,14] However, well-defined boundary was also found in PTC, and microcalcifications of USE might often detect in benign nodules, for some of them might be dystrophic calcifications or inspissated colloid.[12,13] The relationship between USE features and histopathological structures is still ambiguous.[15,16]

PTC is the most common malignancy of the thyroid and the most studied of USE. The diagnosis of PTC is mainly based on the characteristic changes of the cell nucleus such as "ground-glass" nuclei, nuclear overlap, nuclear sulcus and nuclear inclusions.[17] In addition, neoplastic papillae and psammoma bodies are also specific diagnostic indicators of PTC.[17] Recently, pathological studies showed that dense fibrosis in stromal may be another vital indicator of PTC.[18,19] A few studies focused on the relationship between fibrosis content and USE features found that the amount of fiber in a nodule correlated well with the degree of echogenicity.[14,20] The more fiber in a nodule, the lower was the echogenicity, and the likelihood of malignancy improved.[21,22] As for the TTW shape, most studies mainly focused on analyzing its correlation with malignancy, few on its histopathological structures.[15,16] We hypothesized that there would be a significant histopathological difference between benign and malignant thyroid nodules with a TTW shape. Therefore, we retrospectively analyzed the histopathologic structures of 85 nodules with TTW shapes to further understand this specific US feature.

Methods

Study Population

The study complied with the Declaration of Helsinki and was approved by the ethic committee of Guigang People's Hospital (GYYXLL-20211229-41). A retrospective analysis was conducted on 1680 individuals who underwent partial or complete thyroidectomies at our facility between September 2019 and July 2023. These were the conditions for inclusion: (1) patients had thyroid ultrasound scans three months prior to surgery in our hospital, and the archived USE images (in both transverse and longitudinal plains) were clearly reviewed by sonologists (including the location, shape, size, boundary, echotexture, echogenicity of the nodule and the anterior neck muscles were clearly identified); (2) patients had thyroidectomies and received a definitive histopathological diagnosis; (3) nodules with TTW shape, which was defined as a greater anteroposterior diameter than the transverse diameter or longitudinal diameter on US image;[5] and (4) the number and location of nodules found on ultrasound were consistent with the postoperative section information. All data were collected from the hospital electronic archive system and de-identified in the study. The institutional review board of Guigang People's Hospital approved this retrospective study and waived the requirement for informed consent from the patients (NO. GYYXLL-20210601-15) for no intervention was done. The study was done in accordance with the principles of the Declaration of Helsinki. A flowchart illustrating the patient selection process is shown in Figure 1.

Ultrasound Examination and Ultrasound Image Analysis

Ultrasound scans of the thyroid and neck were performed using a 5–12-MHz linear array transducer (LOGIQ S8 or LOGIQ E9, GE Healthcare Wauwatosa, WI, USA). At least two sonograms of each nodule were preserved in both transverse and longitudinal plains and stored numerically in the archived USE. An experienced sonologist with 15 years of experience in thyroid ultrasound retrospectively viewed the sonograms. The reviewer, who had no previous knowledge of the pathologic diagnosis, determined the presence of TTW shape in the nodules and recorded the ultrasound features of the nodules according to the China Thyroid Imaging Reporting and Data System (C-TIRADS).[11] The recording ultrasound features included location (upper, middle, and lower), size (maximum longitudinal, anteroposterior, and transverse diameters), boundary (defined or ill-defined), margin (regular or irregular), composition (solid, predominantly solid, predominantly cystic, cystic, or spongiform), calcification (microcalcification or non-microcalcification), and echogenicity (hyperechoic, isoechoic, hypoechoic, or anechoic). The degree of hypoechogenicity was further categorized into mild (hypoechoic relative to the thyroid parenchyma but hyperechoic relative to the anterior neck muscles), moderate (similar echogenicity to the anterior neck muscles), and markedly hypoechogenicity (hypoechoic relative to the anterior neck muscles), with the reference standard of adjacent thyroid tissue and

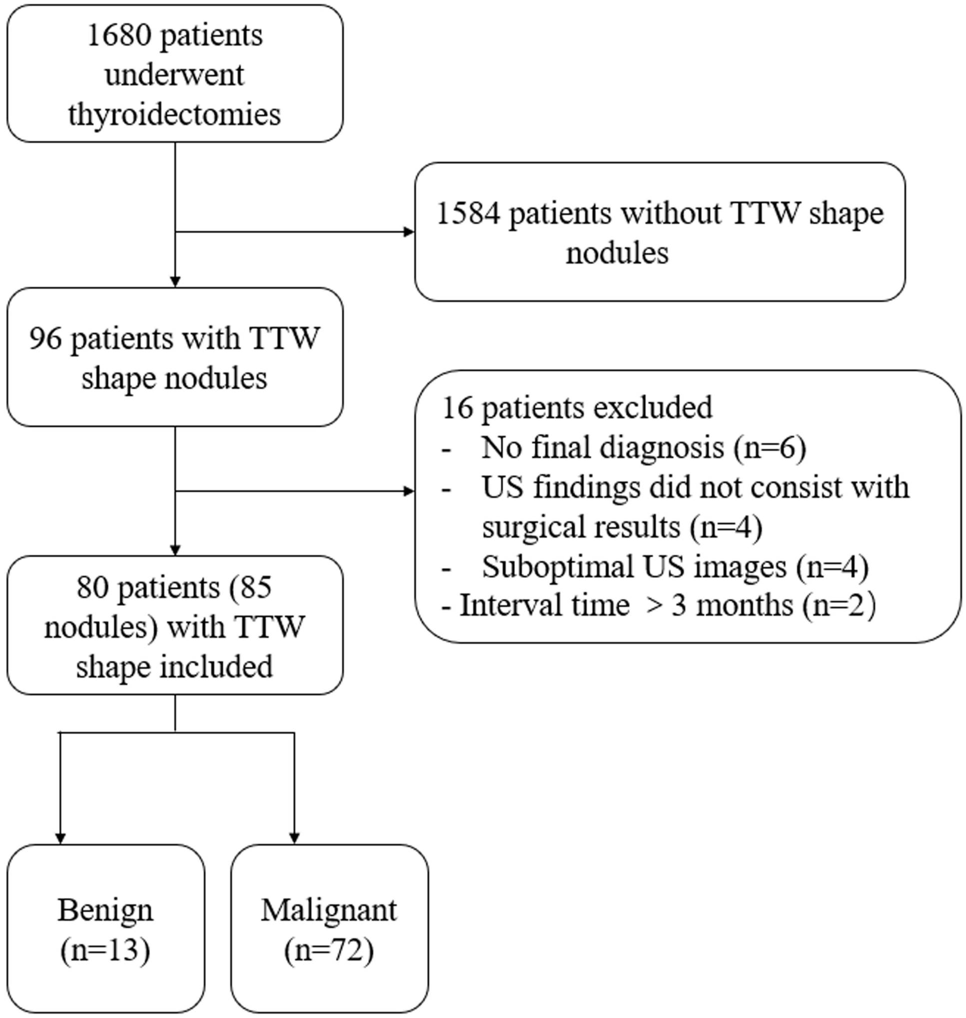

Figure 1 Flowchart of criteria for patient selection.

anterior neck muscles (Figure 2A–D).[23] When the echotexture of a nodule was inhomogeneous, main echogenicity was considered.

Nodule Histology Analysis

The pathological structural analysis of the selected nodules was conducted by an experienced pathologist via light microscopy. The pathologist was unaware of the pathologic diagnosis and the USE features of the nodules. The interpreter evaluated the histological features of the nodule in five categories: arrangement of follicular cells (normal follicle or microfollicle), presence of papillary structures or psammoma bodies, degree of fibrosis in tumor stroma (focal or widespread), and the amount of lymphoid infiltration in tumor stroma. Widespread fibrosis and lymphoid infiltration were defined as proportions of fibrosis or lymphoid infiltration >30%.[14]

Data Analysis and Statistics

Statistical analyses were performed using SPSS version 27.0. Data normality was assessed via Kolmogorov–Smirnov (K-S) test. Normally distributed measurement data were presented as $\overline{mean} \pm SD$, non-normally distributed data were presented as median (interquartile range), and categorical data were expressed as counts (percentages). The comparison of normally distributed data between the two groups was performed using an independent sample *t*-test, and the Mann–Whitney *U*-test was used to compare two non-normally distributed data. The composition ratios for the counted data

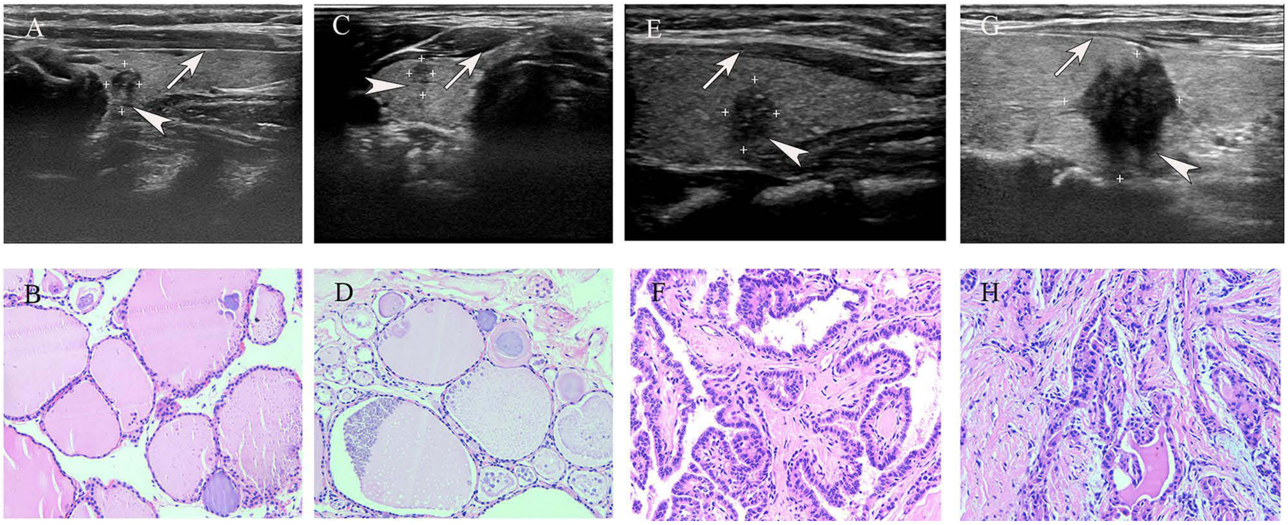

Figure 2 Nodules with different echogenicity and histopathological specimens (hematoxylin-eosin stain, ×20) illustrations. The nodule echogenicity was compared to that of anterior strap muscle (white arrows). (**A**) An isoechoic nodule (indicated by arrowhead and identified between the calipers "+") with the dominant echoic closed to the anterior strap muscle, histopathological specimen shows a benign nodular goiter (**B**). (**C**) A mild hypoechoic nodule (indicated by arrowhead and identified between the calipers "+") and histopathological slice also shows a benign nodular goiter (**D**). (**E**) A moderate hypoechoic nodule (indicated by arrowhead and identified between the calipers "+") with histopathological slice showing a papillary carcinoma (**F**). (**G**) A markedly hypoechoic nodule (indicated by arrowhead and identified between the calipers "+") with histopathological slice also showing a papillary carcinoma (**H**).

were compared using the chi-square test or Fisher's exact test. Multivariable ordinal logistic regression analysis was performed with nodule echogenicity as dependent variable and histological features as independent variables. The results were presented as odds ratio (OR) with 95% confidence interval (CI). Statistical significance was set at $P < 0.05$.

Results

85 TTW nodules from 80 patients (25 men and 55 women) were included in this study. The average age was 47.45 ± 13.18y(range 14 ~ 76y). The mean maximum diameter was 6.9[5.1, 10.3]mm, and the TTW ratio was 1.20[1.10, 1.33]. Among the 85 nodules, 72 (84.71%) were malignant, and 13 (15.29%) were benign. Histopathological diagnoses of the nodules are presented in Table 1. No statistical differences in sex, age, tumor size, or TTW ratio were observed between the benign and malignant groups (Table 2).

All nodules were classified as 4B or higher according to the C-TIRADS classification and all were solid components. Except for echogenicity, neither US characteristics nor C-TIRADS classification differed significantly between the benign and malignant nodules. Most nodules were mild or moderately hypoechogenic (83.6%), and only a small portion were iso/hyperechogenic or markedly hypoechogenic (16.4%). A comparison of the results is presented in Table 3.

Table 1 Histopathologic Findings of the Nodules

Finding	Number (%) of Nodules
Malignant (n=72)	
Papillary carcinoma	71 (98.61)
Follicular carcinoma	1 (1.39)
Benign (n=13)	
Nodular goiter	9 (69.23)
Surgical scars	1 (7.69)
Hashimoto's thyroiditis	1 (7.69)
Subacute thyroiditis	1 (7.69)
Eosinophilic follicular tumor	1 (7.69)

Table 2 Distribution of Nodules Between Malignant and Benign, Regarding Age, Sex, Maximum Diameter and TTW Ratio

Demographics	Total[n(%)] n=85	Benign[n(%)] n=13	Malignant[n(%)] n=72	*P*
Women	55(68.8)	11(84.6)	44(65.7)	0.177[a]
Age, average (SD)	47.5(13.2)	48.8(12.5)	47.2(13.4)	0.696[b]
Maximum diameter, median	6.9mm(5.1,10.3)	8.4mm(4.8,15.0)	7.1mm(5.4,10.0)	0.424[c]
TTW ratio, median	1.2(1.1,1.3)	1.24(1.12,1.31)	1.20(1.10,1.33)	0.396[c]

Notes: [a]chi-square test; [b]independent sample *t*-test; [c]Mann–Whitney *U*-test.

Table 3 Ultrasound Characteristics of the Nodules

Ultrasound Characteristic	Total[n(%)] n=85	Benign[n(%)] n=13	Malignant[n(%)] n=72	*P*
Location				
Upper	18(21.2)	1(7.7)	17(23.6)	0.243[b]
Middle	32(37.6)	4(30.8)	28(38.9)	
Lower	35(41.2)	8(61.5)	27(37.5)	
Margin				
Regular	29(34.1)	7(53.8)	22(30.6)	0.189[a]
Irregular	56(65.9)	6(46.2)	50(69.4)	
Boundary				
Clear	70(82.4)	11(84.6)	59(81.9)	1.000[a]
Ill-defined	15(17.6)	2(15.4)	13(18.1)	
Calcification				
Non-microcalcification	46(54.1)	7(53.8)	39(54.1)	0.983[a]
Microcalcification	39(45.9)	6(46.2)	33(45.9)	
Echogenicity				
Iso/Hyper echogenic	3(3.5)	2(15.4)	1(1.4)	0.003[b]
Mild hypoechogenic	34(40.0)	9(69.2)	25(34.7)	
Moderate hypoechogenic	37(43.6)	1(7.7)	36(50.0)	
Markedly hypoechogenic	11(12.9)	1(7.7)	10(13.9)	
C-TIRADS classification				
4B	20(23.5)	5(38.5)	15(20.8)	0.453[b]
4C	53(62.4)	7(53.8)	46(63.9)	
5C	12(14.1)	1(7.7)	11(15.3)	

Notes: [a]chi-square test; [b] Fisher's exact test.
Abbreviation: C-TIRADS, China Thyroid Imaging Reporting and Data System.

Nodular goiters accounted for a large part of benign lesions in this cohort. The typical histopathologic features of nodular goiter were thyroid tissue segmented by proliferating fibrous tissue into lots of follicles of various sizes. The follicles were covered by flattened epithelium and filled in with goiter (Figure 2E and F). Otherwise, PTC accounted for the vast majority of malignancies, which characterized by the presence of micro-papillae, composed of a central axis of fibro-vascular, branched, and coated by axes rich in collagen fibers. Psammoma bodies were also common in PTC (Figure 2G and H). Apart from micro-papillae, axis of fibro-vascular and psammoma bodies, the rate of fibrosis >30% was also higher in malignant nodules than in benign nodules. There was no difference in lymphoid infiltration between the two groups. Histological feature comparisons are presented in Table 4.

Further logistic regression analysis showed a trend of decreasing nodule echogenicity with increasing fibrosis frequency (>30%) (P = 0.018, OR = 4.500, 95% CI (1.299–15.580). There was no trend for other histological features with changes in nodule echogenicity (all $P > 0.05$) (Table 5).

Table 4 Histological Features of the Nodules

Histological Features	Benign Nodules (n=13)	Malignant Nodules (n=72)	*P*
Fibrosis(>30%)	5(38.46)	64(88.89)	<0.001[a]
Microfollicular	0(0)	18(25.0)	0.042[b]
Papilla with fibrovascular axis	0(0)	69(95.83)	<0.001[b]
Lymphoid infiltration (>30%)	6(46.15)	30(41.67)	0.763[a]
Psammoma body	0(0)	27(37.50)	0.007[b]

Notes: [a]chi-square test; [b]Fisher's exact test.

Table 5 Multivariable Logistic Regression Analysis of Nodule Echogenicity and Histological Features

Histological Features	OR	95% CI	P
Fibrosis (>30%)	4.500	1.299~15.580	0.018
Microfollicular	1.314	0.426~4.055	0.634
Papilla with fibrovascular axis	0.457	0.140~1.487	0.194
Lymphoid infiltration (>30%)	1.388	0.603~3.193	0.441
Psammoma body	2.117	0.819~5.474	0.122

Discussion

The mechanism by which malignant thyroid nodules grow across normal tissue plains has not been verified. One of the convincing mechanisms was that malignant nodules were often stiff and infiltrated into the surrounding tissues, thus not easily compressed by the probe during US examination.[24] Contrarily, benign nodules were often much softer and more easily compressed than malignant ones, thus TTW shape were not common in them. Otherwise, dense or diffuse fibrosis was often observed in thyroid carcinomas, which would also make malignant nodules less compressible and result in a TTW shape.[25] In the present study, the rate of extensive fibrosis in malignant nodules was most higher than benign ones (88.89% vs 38.46%), consisted with results of Wang et al.[26] Infiltration growth and diffuse fibrosis accounted for most of the TTW shape.

Several studies have shown that the TTW shape is a strong predictive sign of malignancy, either as a sole criterion or in combination with other malignant features.[27,28] The rate of benign TTW shape in the present study was 15.29%, which indicated a false-positive rate for this US character. In the present study, the difference in the US characteristics between benign and malignant nodules was not significant, except for the degree of echogenicity. The echogenic degree of malignant nodules was lower than that of the benign nodules. In the benign group, most nodules (69.2%) were mildly hypoechogenic, whereas in the malignant group, most nodules (50%) were moderately hypoechogenic and markedly hypoechogenic (13.9%), as previously reported by Lee et al and Delfim et al.[22,23]

Previous studies showed that the malignancy risk of hypoechoic nodules was higher than that of isoechoic or hyperechoic ones.[2,6,29] However, this USE feature is less specific for malignancy. Investigators proposed that subdivision of hypoechoic be great help in differentia malignant from benign.[22,23] In their study, hypoechoic was divided into three degrees: mild, moderate, and markedly, and results showed that no significant difference was seen between the malignancy risk of mildly hypoechoic and iso-hyperechoic nodules, between moderate and markedly hypoechoic nodules. However, malignancy risk of moderate and markedly hypoechoic nodules was significantly higher than the mild and iso-hyperechoic ones. The result of this present study was consisted with their results. C-TIRADS uses only markedly hypoechoic as a malignant feature for higher specificity, which might result in lower sensitivity.[11] We proposed that both moderate and markedly hypoechogenicity be grouped as malignant risk factors for better diagnostic accuracy.

In the present study, there was a trend of decreasing nodule echogenicity with increasing frequency of fibrosis, which is consistent with the studies of Chen et al and Kim et al[14,20] Chen et al first evaluated the relationship between sonographic textural features and histopathologic components.[20] They confirmed the echogenicity of fibrosis, papillary cancer cells, follicular cells, and follicles was from low to high. These components are often mixed in different

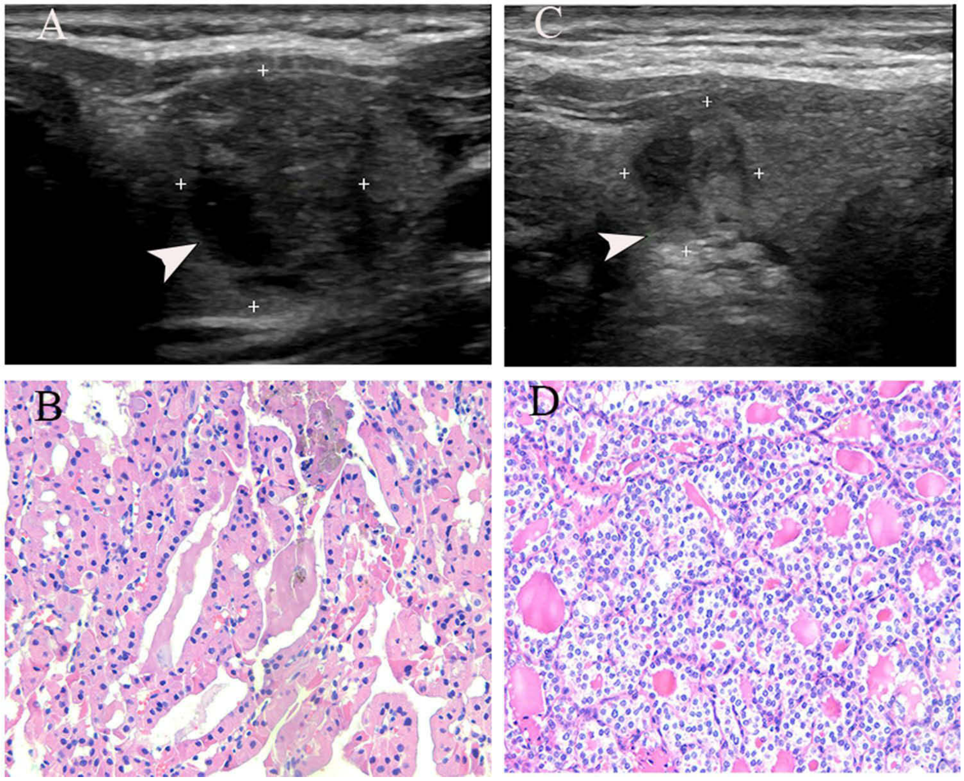

Figure 3 Two follicular nodules with isoechoic and histopathological specimens (hematoxylin-eosin stain, ×20) illustrations. (**A**) An isoechoic nodule (indicated by arrowhead and identified between the calipers "+") with histopathological slice showing an eosinophilic follicular adenoma (**B**). (**C**) An isoechoic nodule (indicated by arrowhead and identified between the calipers "+") with histopathological slice showing a follicular carcinoma (**D**).

proportions, leading to varied echo patterns in thyroid nodules. Kim et al also found that nodule echogenicity decreased when the percentage of fibrosis increased.[14] They advocated that FNA or CNB should be performed at different sites in nodules with heterogeneous echogenicity, as different echogenicity might represent different histologic features.

Although our results showed that mild hypoechoic or isoechoic thyroid nodules with a TTW shape may often be found in benign nodules, special attention should be paid to follicular neoplasms. Two follicular neoplasms were observed in this study, both of which were isoechoic (Figure 3). This is consistent with the results of previous studies,[30,31] which showed that follicular neoplasms are often isoechoic or mildly hypoechoic. Although follicular nodules were rich with micro-papillae or solid components which are also seen in PTC, extensive fibrosis was rarely in follicular nodules. This could explain why the echogenicity of PTC lower than the follicular nodules. The same goes for the follicular subtype thyroid carcinoma and classic ones. We also proposed that when there is an isoechoic or mild hypoechoic nodule with a TTW shape, follicular neoplasm should not be neglected, and the biopsy specimen should contain the nodule boundary to determine the existence of a capsule.[14]

Limitations of the Study

Our study has several limitations. First, selection bias existed only for patients who underwent surgery, and the pathological results were confirmed. Second, this retrospective study had some limitations in interpreting the TTW shape. Third, only a few cases of follicular and inflammatory nodules were included in this study.

Conclusion

In conclusion, extensive fibrosis was the most common histopathological feature of thyroid cancers, which appeared in the form of hypoechogenicity on US. TTW-shaped thyroid nodules are highly suggestive of malignancy, especially those with moderate or marked hypoechogenicity. However, isoechoic or mild hypoechoic nodules with TTW shapes often indicate benign or follicular neoplasms.

Abbreviation

TTW, taller than wide; C-TIRADS, China Thyroid Imaging Reporting and Data System; US, ultrasound; FNA, fine-needle aspiration; CNB, core-needle biopsy.

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Disclosure

The authors declare no conflicts of interest.

References

1. Papapostolou KD, Evangelopoulou CC, Ioannidis IA, et al. Taller-than-wide thyroid nodules with microcalcifications are at high risk of malignancy. *In Vivo*. 2020;34(4):2101–2105. doi:10.21873/invivo.12014
2. Rago T, Vitti P. Risk stratification of thyroid nodules: from ultrasound features to TIRADS. *Cancers*. 2022;14(3):717. doi:10.3390/cancers14030717
3. Kim EK, Park CS, Chung WY, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. *Am J Roentgenol*. 2002;178(3):687–691. doi:10.2214/ajr.178.3.1780687
4. Grani G, Lamartina L, Ramundo V, et al. Taller-than-wide shape: a new definition improves the specificity of TIRADS systems. *Eur Thyroid J*. 2020;9(2):85–91. doi:10.1159/000504219
5. Kim SY, Na DG, Paik W. Which ultrasound image plane is appropriate for evaluating the taller-than-wide sign in the risk stratification of thyroid nodules? *Eur Radiol*. 2021;31(10):7605–7613. doi:10.1007/s00330-021-07936-4
6. Haugen BR, Alexander EK, Bible KC, et al. 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;26(1):1–133. doi:10.1089/thy.2015.0020
7. Gharib H, Papini E, Garber JR, et al. 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 appendix. *Endocr Pract*. 2016;22:1–60. doi:10.4158/ep161208.Gl
8. Russ G, Bonnema Steen J, Erdogan Murat F, Durante C, Ngu R, Leenhardt L. European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. *European Thyroid J*. 2017;6(5):225–237. doi:10.1159/000478927
9. Shin JH, Baek JH, Chung J, et al. 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. doi:10.3348/kjr.2016.17.3.370
10. Tessler FN, Middleton WD, Grant EG. Thyroid imaging reporting and data system (TI-RADS): a user's guide. *Radiology*. 2018;287(1):29–36. doi:10.1148/radiol.2017171240
11. Zhou J, Yin L, Wei X, et al. 2020 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
12. Wang Y, Li L, Wang Y-XJ, et al. Ultrasound findings of papillary thyroid microcarcinoma: a review of 113 consecutive cases with histopathologic correlation. *Ultrasound Med Biol*. 2012;38(10):1681–1688. doi:10.1016/j.ultrasmedbio.2012.05.019
13. Tahvildari AM, Pan L, Kong CS, Desser T. Sonographic-pathologic correlation for punctate echogenic reflectors in papillary thyroid carcinoma: what are they? *J Ultrasound Med*. 2016;35(8):1645–1652. doi:10.7863/ultra.15.09048
14. Kim JH, Na DG, Lee H. Ultrasonographic echogenicity and histopathologic correlation of thyroid nodules in core needle biopsy specimens. *Korean J Radiol*. 2018;19(4):673–681. doi:10.3348/kjr.2018.19.4.673
15. Mattingly AS, Noel JE, Orloff LA. A closer look at "taller-than-wide" thyroid nodules: examining dimension ratio to predict malignancy. *Otolaryngol Head Neck Surg*. 2022;167(2):236–241. doi:10.1177/01945998211051310
16. Guo Q, Li J, Xin J, Chen X. Analysis of anteroposterior-to-transverse ratio in predicting thyroid malignancy on ultrasonography. *J Laryngol Otol*. 2023;137(5):546–550. doi:10.1017/s0022215122000482
17. Jung CK, Bychkov A, Kakudo K. Update from the 2022 World Health Organization classification of thyroid tumors: a standardized diagnostic approach. *Endocrinol Metab*. 2022;37(5):703–718. doi:10.3803/EnM.2022.1553
18. Rago T, Scutari M, Loiacono V, et al. Low elasticity of thyroid nodules on ultrasound elastography is correlated with malignancy, degree of fibrosis, and high expression of Galectin-3 and Fibronectin-1. *Thyroid*. 2017;27(1):103–110. doi:10.1089/thy.2016.0341
19. Liu X, Zhang S, Gang Q, et al. Interstitial fibrosis in papillary thyroid microcarcinoma and its association with biological behavior. *Oncol Lett*. 2018. doi:10.3892/ol.2018.7928
20. Chen SJ, Yu SN, Tzeng JE, et al. Characterization of the major histopathological components of thyroid nodules using sonographic textural features for clinical diagnosis and management. *Ultrasound Med Biol*. 2009;35(2):201–208. doi:10.1016/j.ultrasmedbio.2008.08.017
21. Chen SJ, Chang CY, Chang KY, et al. Classification of the thyroid nodules based on characteristic sonographic textural feature and correlated histopathology using hierarchical support vector machines. *Ultrasound Med Biol*. 2010;36(12):2018–2026. doi:10.1016/j.ultrasmedbio.2010.08.019
22. Delfim RLC, Assumpção LR, Lopes F, de Fátima Dos Santos Teixeira P. Does a three-degree hypoechogenicity grading improve ultrasound thyroid nodule risk stratification and affect the TI-RADS 4 category? A retrospective observational study. *Arch Endocrinol Metab*. 2023;67(4):e000608. doi:10.20945/2359-3997000000608
23. Lee JY, Na DG, Yoon SJ, et al. Ultrasound malignancy risk stratification of thyroid nodules based on the degree of hypoechogenicity and echotexture. *Eur Radiol*. 2020;30(3):1653–1663. doi:10.1007/s00330-019-06527-8

24. Yoo MH, Kim HJ, Choi IH, et al. Efficacy of differential diagnosis of thyroid nodules by shear wave elastography—the stiffness map. *J Clin Endocrinol Metab*. 2021;5(11). doi:10.1210/jendso/bvab154
25. Fukuhara T, Matsuda E, Endo Y, et al. Correlation between quantitative shear wave elastography and pathologic structures of thyroid lesions. *Ultrasound Med Biol*. 2015;41(9):2326–2332. doi:10.1016/j.ultrasmedbio.2015.05.001
26. Wang H-Q, Li Y, Song X, et al. Significance of interstitial fibrosis and p16 in papillary thyroid carcinoma. *Endocr J*. 2022;69(10):1253–1259. doi:10.1507/endocrj.EJ22-0010
27. Chen SP, Hu YP, Chen B. Taller-than-wide sign for predicting thyroid microcarcinoma: comparison and combination of two ultrasonographic planes. *Ultrasound Med Biol*. 2014;40(9):2004–2011. doi:10.1016/j.ultrasmedbio.2014.03.023
28. Ren J, Liu B, Zhang LL, et al. A taller-than-wide shape is a good predictor of papillary thyroid carcinoma in small solid nodules. *J Ultrasound Med*. 2015;34(1):19–26. doi:10.7863/ultra.34.1.19
29. Pant Arpana, O, Gurung G, Pradhan S. Ultrasound findings in thyroid nodules: a radio–cytopathologic correlation. *J Med Ultrasound*. 2018;26(2). doi:10.4103/jmu.Jmu_7_17
30. Castellana M, Piccardo A, Virili C, et al. Can ultrasound systems for risk stratification of thyroid nodules identify follicular carcinoma? *Cancer Cytopathol Apr*. 2020;128(4):250–259. doi:10.1002/cncy.22235
31. Park KW, Shin JH, Hahn SY, et al. Ultrasound-guided fine-needle aspiration or core needle biopsy for diagnosing follicular thyroid carcinoma? *Clin Endocrinol*. 2020;92(5):468–474. doi:10.1111/cen.14167