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● *Original Contribution*

RELATIONSHIP BETWEEN MORPHOLOGIC CHARACTERISTICS OF ULTRASONIC CALCIFICATION IN THYROID NODULES AND THYROID CARCINOMA

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Abstract—The aim of this study was to investigate the relationship between morphologic characteristics of the calcifications detected by ultrasound in thyroid nodules and thyroid carcinoma. Morphologic characteristics of the calcifications on pre-operative ultrasound examinations of thyroids were compared with post-operative pathologic diagnoses in 543 patients undergoing thyroid surgery. Calcifications were divided into microcalcifications (≤2 mm) and macrocalcifications (>2 mm), and the latter were divided into eggshell calcifications in a row, eggshell discontinuous calcifications, irregular calcifications and multilayer-like calcifications, labeled types I−V. We found that thyroid microcalcifications and partial macrocalcifications, such as eggshell discontinuous calcifications, and multilayer-like calcifications were associated with thyroid carcinoma. In conclusion, microcalcifications were more commonly found in malignant thyroid nodules, particularly in papillary thyroid carcinoma. Eggshell discontinuous macrocalcifications and multilayer-like macrocalcifications also occurred mainly in malignant nodules. (E-mail addresses: doctor505@hotmail.com, ttyyus@sina.com) © 2019 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology.

Key Words: **Thyroid carcinoma, Microcalcification, Macrocalcification, Ultrasonography.**

INTRODUCTION

Calcifications are commonly seen in thyroid ultrasonic images in both benign and malignant nodules (Chen et al. 2009). The worldwide incidence of thyroid carcinoma is rising. It accounts for roughly 1% of all new malignant diseases (Golbert et al. 2005; Vigneri et al. 2015; Kitahara and Sosa 2016; Roman et al. 2017). Microcalcifications (≤2 mm) are known to be associated with thyroid malignant nodules (Lee et al. 2008; Shi et al. 2012). Several studies have refocused attention on macrocalcifications (>2 mm) in thyroid nodules. Eggshell or rim-like peripheral calcifications formerly were thought to be an indicator of benignancy; however, cases of papillary thyroid carcinoma and anaplastic carcinoma associated with this type of calcification have been reported (Yoon et al. 2007; Kim et al. 2008).

Besides the high-resolution, real-time and dynamic examination, the recognition of the correlation between pathologic characteristics of thyroid malignant lesions and the calcifications detected by ultrasound is one of the reasons why ultrasound examination has become an indispensable method in thyroid nodule screening (Füessl 2011). Previous studies have focused mainly on microcalcifications. The present study investigated the detection of different types of calcifications by ultrasound and their relationship with thyroid carcinoma.

METHODS

Patients

This retrospective study was approved by the institutional review boards (IRBs) of Beijing Tiantan Hospital and Shanghai Jiao Tong University Affiliated 6th People's Hospital. Data for patients in this study were obtained using a standard-of-care clinical protocol, and IRBs waived the requirement for informed consent from

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all patients. This study was conducted in accordance with the Declaration of Helsinki.

We retrospectively selected 543 patients with 543 nodules in which calcifications were detected with pre-operative ultrasound and had post-operative pathology results, in both Beijing Tiantan Hospital and Shanghai Jiao Tong University Affiliated 6th People's Hospital. All patients were diagnosed by histopathologic analysis of resected hemithyroidectomy or total thyroidectomy specimens from the pathology report databases between January 1, 2014 and November 1, 2018.

Ultrasound examination

Sonographic examinations of the thyroid gland were performed with the Hi Vision 900 system with a EUP-L74 M linear array probe (Hitachi Medical Corp. Inc, Tokyo, Japan; transducer frequency: 5−13 MHz), HD15 system with L12-5 linear array probe (Philips Healthcare, Bothell, WA, USA; transducer frequency: 5−12 MHz),or Mylab90 system with a LA523 linear array probe (Esaote, Genoa, Italy; transducer frequency: 4−13 MHz).

In addition to age and sex, the morphology and distribution of any calcification were also recorded (Fig. 1). two sonographers with more than 3 y of specialization in thyroid ultrasound were chosen to determine the category of calcifications. When they had diverse opinions, another seasoned sonographer joined in to categorize the calcifications. Microcalcifications (type I) detected by ultrasound were arranged in scattered or clustered hyper-echogenic spots and were <2 mm in diameter, with or without acoustic shadowing. Macrocalcifications were defined in our study as calcifications having a maximum diameter >2 mm. Among them, eggshell calcifications in a row (type II) appeared in an arc or circular shape with a continuous hyper-echogenic line and obvious acoustic shadowing in nodules or at the edge of nodules. Eggshell discontinuous calcifications (type III) were similar to eggshell calcifications in a row, but the hyper-echogenic line was discontinuous and had one or more interruptions. Irregular calcifications (type IV) in nodules were characterized by an irregular shape and disorganized distribution and had acoustic shadowing. Multilayer-like calcifications (type V) had multiple layers or imbricate arrangements of hyper-echogenic calcifications within the nodules, accompanied by acoustic shadowing (Fig. 1).

Pathologic assessment

Thyroid samples obtained during surgeries were embedded in paraffin for pathologic examination. A 4-μm section was cut from the block and stained with hematoxylin and eosin. The slides were examined by three pathologists.

Statistical analyses

We analyzed the data in terms of counts and frequency. A χ^2-test or Fisher's test was used for statistical comparison. Ninety-five percent confidence intervals (CIs) of the incidence rate and p values were calculated. A p value <0.05 was considered to indicate statistical significance. Statistical analysis was performed with commercially available software (SPSS Version 13.0, IBM, Armonk, NY, USA).

RESULTS

A total of 543 patients aged between 21 and 80 y (mean ± standard deviation: 49.3 ± 13.2 y) admitted for thyroid surgery were included in the study. Positive calcification signs were seen during the pre-operative ultrasound examination in all patients.

Among 543 patients, 339 patients (62.4%) had microcalcifications and 204 patients (37.6%) had macrocalcifications. The incidence of microcalcifications (type I) was higher in malignant nodules than in benign nodules (225 cases vs. 114 cases, 95% CI: 0.373−0.456, $p < 0.01$). Among macrocalcifications, types III and V were more often seen in malignant nodules (12 cases vs. 3 cases, 95% CI: 0.010−0.035/18 cases vs. 9 cases, 95% CI: 0.018−0.048, respectively, p <0.01) (Table 1). Among 225 patients with microcalcifications, 210 were confirmed to have papillary carcinoma (Table 2). Furthermore, type II was detected more often in benign nodules (9 cases vs. 3 cases, 95% CI: 0.006−0.027, $p <$ 0.01) (Table 1). All the benign lesions with type II were adenomas (Table 3).

In our study, 210 cases were confirmed to have benign lesions. There were 117 cases of adenoma, 66 cases of nodular goiter, 12 cases of Hashimoto's thyroiditis and 15 cases of hyperplasia (Table 3). Among benign nodules, microcalcifications (type I) were found mainly in adenoma and nodular goiter (60 cases and 39 cases, respectively). Type II and type III were found in adenomas only (9 and 3 cases, respectively). Similar to type I, type IV was detected mainly in adenomas and nodular goiters (42 cases and 21 cases, respectively). Nine cases of type V included 3 cases of adenoma and 6 cases of nodular goiter.

Three hundred thirty-three cases of malignant lesions included 312 cases of papillary carcinoma, 15 cases of follicular carcinoma, 3 cases of undifferentiated cancer and 3 cases of medullary carcinoma (Table 2). Papillary carcinoma was the main form of cancer in malignant nodules. Types I (microcalcifications), III, IV and V were found mainly in papillary carcinoma (210, 12, 75 and 15 cases, respectively). All cases of follicular carcinoma (15 cases) were associated with microcalcifications (type I), and all the cases of

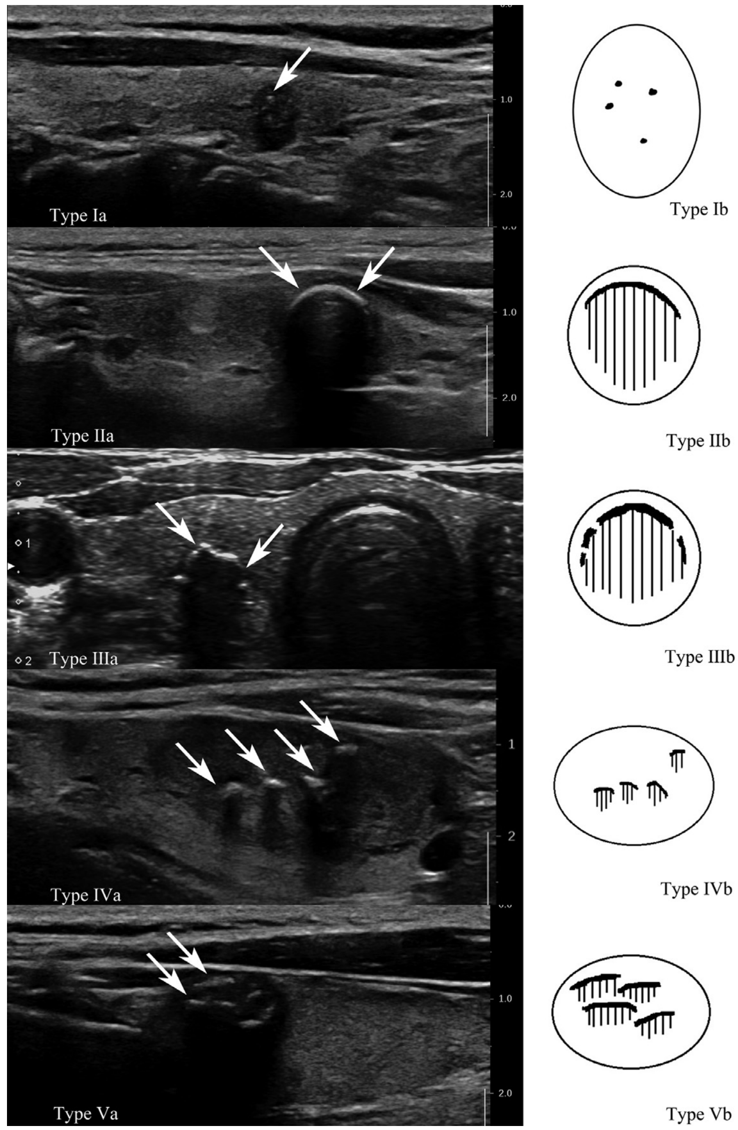

Fig. 1. Ultrasound images (a) and schematics (b) of the morphologic characteristics of calcifications. Type I microcalcifications appear as scattered hyper-echogenic spots ≤2 mm in diameter; the *white arrow* indicates a microcalcifications. Type II calcifications are arc-shaped macrocalcifications with a continuous hyper-echogenic line and obvious acoustic shadowing at the edge of nodules; *white arrows* indicate smooth calcifications. Type III calcifications are arc-shaped macrocalcifications with a discontinuous hyper-echogenic line and obvious acoustic shadowing; *white arrows* indicate the interruption. Type IV calcifications are macrocalcifications with an irregular shape, disorganized distribution and acoustic shadowing; *white arrows* indicate the irregular calcification. Type V calcifications are macrocalcifications appearing as multiple layers or imbricate arrangements with acoustic shadowing; *white arrows* indicate multilayer-like calcifications. In the schematics (b) of type I−V calcifications, *vertical lines* represent acoustic shadowing.

Table 1. Distribution of various calcifications in benign and malignant thyroid lesions.

Lesions	No. (%) of calcifications					
	Type I	Type II	Type III	Type IV	Type V	Total
Benign	114 (21.0)	9 (1.7)	3 (0.6)	75 (13.8)	9 (1.7)	210 (38.7)
Malignant	225 (41.4)*	3 (0.6)*	12 (2.2)*	75 (13.8)	18 (3.3)*	333 (61.3)
Total	339 (62.4)	12 (2.2)	15 (2.8)	150 (27.6)	27 (5.0)	543

* $p < 0.01$, compared with calcifications in benign lesions.

Table 2. Distribution of various calcifications in malignant thyroid lesions

Pathologic diagnosis	No. (%) of calcifications					
	Type I	Type II	Type III	Type IV	Type V	Total
Papillary carcinoma	210 (63.1)	0 (0)	12 (3.6)	75 (22.5)	15 (4.5)	312 (93.7)
Follicular carcinoma	15 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)	15 (4.5)
Undifferentiated cancer	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.9)	3 (0.9)
Medullary carcinoma	0 (0)	3 (0.9)	0 (0)	0 (0)	0 (0)	3 (0.9)
Total	225 (67.6)	3 (0.9)	12 (3.6)	75 (22.5)	18 (5.4)	333 (100)

Table 3. Distribution of various calcifications in benign thyroid lesions

Pathologic diagnosis	No. (%) of calcifications					
	Type I	Type II	Type III	Type IV	Type V	Total
Adenoma	60 (28.6)	9 (4.3)	3 (1.4)	42 (20)	3 (1.4)	117 (55.7)
Nodular goiter	39 (18.6)	0 (0)	0 (0)	21 (10)	6 (2.9)	66 (31.4)
Hashimoto's thyroiditis	12 (5.7)	0 (0)	0 (0)	0 (0)	0 (0)	12 (5.7)
Hyperplasia of thyroid tissue	3 (1.4)	0 (0)	0 (0)	12 (5.7)	0 (0)	15 (7.1)
Total	114 (54.3)	9 (4.3)	3 (1.4)	75 (35.7)	9 (4.3)	210 (100)

undifferentiated cancer (3 cases) were associated only with multilayer-like calcifications (type V). Eggshell calcifications in a row (type II) were found in medullary carcinoma only (3 cases).

In Table 4, we outline calcification type by sex and age for all patients. Males and females did not differ with respect to type of calcification ($p > 0.05$). Microcalcifications (type I) were more often seen in patients <45 y old (244 cases vs. 95 cases, 95% CI: 0.407−0.491, $p < 0.01$). All types of macrocalcifications were more often found in patients >45 y old (8 case vs. 4 cases in type II, 95% CI: 0.005−0.025; 10 cases vs. 5 cases in type III, 95% CI:0.007−0.030; 105 cases vs. 45 cases in type IV, 95% CI: 0.160−0.227, 19 cases vs. 8 cases in type V, 95% CI: 0.019−0.050. $p < 0.01$).

DISCUSSION

As reported in a previous study, ultrasound had a sensitivity and specificity in detecting thyroid nodule calcifications of 78.8% and 61.3%, respectively (Seiberling et al. 2004). The ultrasound image can be used as the first step in thyroid nodule calcification screening. However, some previous studies did not include the associations of different types of calcifications with malignant disease or simply divided calcifications into only microcalcifications and macrocalcification (Seiberling et al. 2004; Shi et al. 2012). In this study we not only divided calcification into microcalcifications and macrocalcifications, but we also divided macrocalcifications into four types with respect to their shapes and study their relationships with thyroid carcinoma.

In the present study, the incidence of malignancy was higher in patients with calcifications (61.3%) compared with the incidence of benignity in patients with calcifications (38.7%), suggesting that the occurrence of calcification may be a sign of thyroid carcinoma and, thus, can be used to predict thyroid carcinoma. Why calcifications form in thyroid nodules has been reported in previous studies. Calcifications in malignant thyroid lesions usually form because of the proliferation of blood vessels and dense fibrous tissue and the deposition of calcium salts (Kakkos et al. 2000; Das et al. 2008). These

Table 4. Distribution of various calcifications in patients with respect to age and sex

Lesion status	No. (%) of calcifications					
	Type I	Type II	Type III	Type IV	Type V	Total
Sex						
Male	145 (26.7)	2 (0.4)	3 (0.6)	65 (12.0)	3 (0.6)	218
Female	194 (35.7)	10 (1.8)	12 (2.2)	85 (15.7)	24 (4.4)	325
Age						
≥45 y	95 (17.5)	8 (1.5)	10 (1.8)	105 (19.3)	19 (3.5)	237
<45 y	244 (44.9)*	4 (0.7)*	5 (0.9)*	45 (8.3)*	8 (1.5)*	306

* $p < 0.01$, compared with calcifications in those aged ≥45 y.

calcifications are usually small. Research has revealed that microcalcifications detected by ultrasound may be pathologically related to psammoma bodies in follicular carcinoma (Kim et al. 2018). On the other hand, calcifications in both malignant and benign thyroid lesions may form on the walls of nodules or fibrosis spacing after inflammation and hematoma absorption (Wang et al. 2006). These are usually large and appear as surrounding enveloped calcification or cystic pseudo-calcification. Macrocalcifications are not only found in benign thyroid nodules. Microcalcifications were considered to be the most specific sonographic indicator in the diagnosis of papillary thyroid carcinoma (Khoo et al. 2002). In the present study, microcalcifications were seen more often in malignant nodules (41.4% vs. 21.0%), and among all malignant nodules, microcalcifications were more often seen in papillary carcinoma (63.1%). We also found that microcalcification is a specific sign of papillary thyroid carcinoma.

In a previous study, other types of calcifications, including macrocalcifications and eggshell or rim calcifications, were thought to be more common in benign lesions than in malignant lesions (Oh et al. 2014). But macrocalcifications also could be seen in patients with malignancies (Yaturu and Rainer 2010). In our study, we divided macrocalcifications into eggshell calcifications in a row (type II), eggshell discontinuous calcifications (type III), irregular calcifications (type IV) and multilayer-like calcifications (type V). As indicated by our results, eggshell calcifications in a row (type II) were more often seen in benign nodules, eggshell discontinuous calcifications (type III) and multilayer-like calcifications (type V) were more often seen in malignant nodules and irregular calcifications (type IV) had the same incidence in all nodules. Type IV calcifications in malignant nodules were found only in papillary carcinoma. In this study, we divided macrocalcifications into four types and studied the relationship between calcification and thyroid carcinoma in more detail than done in previous studies. Type III and type V macrocalcifications were more often seen in malignant nodules.

Previous studies reported that the risk of thyroid carcinoma in patients <40 y of age with calcification was 1.52-fold higher than that in patients ≥40 y of age (Shi et al. 2012), and the specificities of calcification for a malignant tumor diagnosis in the two age groups were 87% and 57%, respectively (Kakkos et al. 2000). In our study, microcalcifications were more often found in younger people (<45 y), and all types of macrocalcifications were more often found in older people (≥45 y). There was no difference in the incidence of calcifications between males and females, suggesting that calcification is not related to sex.

Our study also had limitations. The study population could potentially be unrepresentative, because this study was retrospective and included only patients who underwent surgery. The rates of occurrence of some types of calcifications in some diseases were zero. It is recommended that a similar study be performed with a larger sample size to the incidence of each type of calcification in malignant thyroid nodules.

CONCLUSIONS

Microcalcifications detected by ultrasound were more often found in thyroid carcinoma, particularly papillary thyroid carcinoma. In addition, eggshell discontinuous calcifications and multilayer-like calcifications in macrocalcifications occurred mainly in malignant nodules, but studies with larger samples are needed.

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Conflict of interest disclosure—All authors declare that they have no competing interests.

REFERENCES

Chen G, Zhu XQ, Zou X, Yao J, Liang JX, Huang HB, Li LT, Lin LX. Retrospective analysis of thyroid nodules by clinical and pathological characteristics, and ultrasonographically detected calcification correlated to thyroid carcinoma in South China. Eur Surg Res 2009;42:137–142.

Das DK, Sheikh ZA, George SS, Al-Baquer T, Francis IM. Papillary thyroid carcinoma: Evidence for intracytoplasmic formation of precursor substance for calcification and its release from well-preserved neoplastic cells. Diagn Cytopathol 2008;36:809–812.

Füessl HS. Management of nodular goiter: A solution for thyroid nodules. MMW Fortschr Med 2011;153:14–17.

Golbert L, Wajner SM, Rocha AP, Maia AL, Gross JL. Differentiated thyroid carcinoma: initial evaluation and follow-up. Arq Bras Endocrinol Metabol 2005;49:701–710. [In Portuguese.].

Kakkos SK, Scopa CD, Chalmoukis AK, Karachalios DA, Spiliotis JD, Harkoftakis JG, Karavias DD, Androulakis JA, Vagenakis AG. Relative risk of cancer in sonographically detected thyroid nodules with calcifications. J Clin Ultrasound 2000;28:347–352.

Khoo ML, Asa SL, Witterick IJ, Freeman JL. Thyroid calcification and its association with thyroid carcinoma. Head Neck 2002;24:651–655.

Kim BM, Kim MJ, Kim EK, Kwak JY, Hong SW, Son EJ, Kim KH. Sonographic differentiation of thyroid nodules with eggshell calcifications. J Ultrasound Med 2008;27:1425–1430.

Kim BK, Lee EM, Kim JH, Oak SY, Kwon SK, Choi YS, Kim YO. Relationship between ultrasonographic and pathologic calcification patterns in papillary thyroid cancer. Medicine (Baltimore) 2018;97:E12675.

Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. Nat Rev Endocrinol 2016;12:646–653.

Lee JW, Yoon DY, Choi CS, Chang SK, Yun EJ, Seo YL, Rho YS, Cho SJ, Kim KH. Anaplastic thyroid carcinoma: Computed tomographic differentiation from other thyroid masses. Acta Radiol 2008;49:321–327.

Oh EM, Chung YS, Song WJ, Lee YD. The pattern and significance of the calcifications of papillary thyroid microcarcinoma presented in preoperative neck ultrasonography. Ann Surg Treat Res 2014;86:115–121.

Roman BR, Morris LG, Davies L. The thyroid cancer epidemic, 2017 perspective. Curr Opin Endocrinol Diabetes Obes 2017; 24:332–336.

Seiberling KA, Dutra JC, Grant T, Bajramovic S. Role of intrathyroidal calcifications detected on ultrasound as a marker of malignancy. Laryngoscope 2004;114:1753–1757.

Shi C, Li S, Shi T, Liu B, Ding C, Qin H. Correlation between thyroid nodule calcification morphology on ultrasound and thyroid carcinoma. J Int Med Res 2012;40:350–357.

Vigneri R, Malandrino P, Vigneri P. The changing epidemiology of thyroid cancer: Why is incidence increasing? Curr Opin Oncol 2015;27:1–7.

Wang N, Xu Y, Ge C, Guo R, Guo K. Association of sonographically detected calcification with thyroid carcinoma. Head Neck 2006;28:1077–1083.

Yaturu S, Rainer L. Thyroid nodule with eggshell calcification and oncocytic thyroid cancer. Med Sci Monit 2010;16:CS25–CS28.

Yoon DY, Lee JW, Chang SK, Choi CS, Yun EJ, Seo YL, Kim KH, Hwang HS. Peripheral calcification in thyroid nodules: Ultrasonographic features and prediction of malignancy. J Ultrasound Med 2007;26:1349–1355.