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Malignancy Risk Stratification of Thyroid Nodules with Macrocalcification and Rim Calcification Based on Ultrasound Patterns

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Objective: To determine the association of macrocalcification and rim calcification with malignancy and to stratify the malignancy risk of thyroid nodules with macrocalcification and rim calcification based on ultrasound (US) patterns.

Materials and Methods: The study included a total of 3603 consecutive nodules (≥ 1 cm) with final diagnoses. The associations of macrocalcification and rim calcification with malignancy and malignancy risk of the nodules were assessed overall and in subgroups based on the US patterns of the nodules. The malignancy risk of the thyroid nodules was categorized as high (> 50%), intermediate (upper-intermediate: > 30%, ≤ 50%; lower-intermediate: > 10%, ≤ 30%), and low (≤ 10%).

Results: Macrocalcification was independently associated with malignancy in all nodules and solid hypoechoic (SH) nodules ($p < 0.001$). Rim calcification was not associated with malignancy in all nodules ($p = 0.802$); however, it was independently associated with malignancy in partially cystic or isoechoic and hyperechoic (PCIH) nodules ($p = 0.010$). The malignancy risks of nodules with macrocalcification were classified as upper-intermediate and high in SH nodules, and as low and lower-intermediate in PCIH nodules based on suspicious US features. The malignancy risks of nodules with rim calcification were stratified as low and lower-intermediate based on suspicious US features.

Conclusion: Macrocalcification increased the malignancy risk in all and SH nodules with or without suspicious US features, with low to high malignancy risks depending on the US patterns. Rim calcification increased the malignancy risk in PCIH nodules, with low and lower-intermediate malignancy risks based on suspicious US features. However, the role of rim calcification in risk stratification of thyroid nodules remains uncertain.

Keywords: *Thyroid nodule; Calcification; Ultrasonography; Risk assessment; Data systems*

INTRODUCTION

Ultrasound (US) plays an essential role in assessing the risk of malignancy of thyroid nodules and in the decision to perform fine-needle aspiration (FNA) [1]. Most guidelines use US features including composition, echogenicity, microcalcification, spiculated/microlobulated (irregular) margin, and nonparallel orientation (taller than wide shape) to stratify the risk of thyroid nodule malignancy [2-6]. In contrast, the American College of Radiology (ACR) thyroid imaging reporting and data system (TI-RAD) use macrocalcification and rim calcification for risk stratification [6]. The American Thyroid Association (ATA) guidelines categorize hypoechoic nodules with rim calcifications

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accompanying small extrusive soft tissue components as high-suspicion nodules [2].

Many studies [7-12] have reported that macrocalcification is associated with malignancy and increases the malignancy risk of nodules. However, the ability of macrocalcification to independently predict malignancy remains controversial [8,10,11]. Several studies [7,12,13] have reported that rim calcification is associated with malignancy and may increase the malignancy risk of thyroid nodules. However, whether rim calcification can predict malignancy remains uncertain [8-10,14].

The malignancy risk of a thyroid nodule is determined by the US pattern, which is composed of many US features. The ability of a single US predictor for malignancy depends on the nodule composition and echogenicity [11]. Most previous studies on macrocalcification and rim calcification investigated the association of malignancy in all nodules but not according to US patterns. Thus, the present study assessed whether macrocalcification and rim calcification were associated with malignancy and to stratify the malignancy risks of nodules with macrocalcification or rim calcification based on their US patterns of the nodules.

MATERIALS AND METHODS

This retrospective study received Institutional Review Board approval (2019-05-004) and the requirement for informed consent was waived.

Study Population

A total of 4058 consecutive patients underwent US-guided FNA or core needle biopsy (CNB) for thyroid nodules between January 2011 and June 2019. Among 3649 patients with 4581 nodules measuring ≥ 1 cm, 970 nodules without final diagnoses were confirmed by surgical or biopsy examination (nondiagnostic FNA results [n = 481], atypical or follicular lesion of undetermined clinical significance [n = 411], follicular neoplasm or suspected follicular neoplasm [n = 47], and suspected malignancy [n = 31]) and eight nodules with suboptimal US image quality were excluded. The remaining 2862 patients with 3603 nodules were included in the final study population (2292 women and 570 men; mean age, 55.5 years) (Fig. 1). Malignant nodules (n = 493) were diagnosed based on histopathological examination after surgery (n = 369) or FNA or CNB examination (n = 124). Benign nodules (n = 3110) were diagnosed based on histopathological examination after surgery (n = 344), at least two benign FNA or CNB findings (n = 492), and one benign FNA or CNB finding (n = 2274). Fourteen simple cysts and 34 nodules with isolated macrocalcifications were excluded from the subgroup analysis because of an inability to assess nodule echogenicity.

US Examination and Image Analysis

All US examinations were performed using a 5 to 12-MHz linear probe and a real-time US system (IU22 or EPIQ7, Philips Healthcare). All US images of thyroid nodules obtained between January 2011 and February 2017 were retrospectively reviewed by one experienced radiologist with 22 years of experience in performing thyroid US. This radiologist had no prior knowledge of the FNA results or final diagnoses. US images of thyroid nodules obtained between March 2017 and June 2019 were prospectively evaluated by two radiologists with 22 years and 4 years of experience in performing thyroid US, respectively. The reviewers assessed the US features of the thyroid nodules for composition, echogenicity, margin, orientation, calcification (echogenic foci), spongiform appearance, and intracystic comet-tail artifact based on the Korean Society of Thyroid Radiology guidelines [3]. Microcalcification was defined as a punctate echogenic focus measuring 1 mm or less, with or without posterior acoustic shadowing within the solid portion. Macrocalcification was defined as an echogenic focus larger than 1 mm with posterior acoustic shadowing (Fig. 2). Rim (peripheral) calcification was defined as a peripheral curvilinear hyperechoic line with or without acoustic shadowing (complete or incomplete) (Figs. 3, 4). Isolated macrocalcification was defined as a calcified nodule with complete posterior acoustic shadowing, in which no soft tissue component was identified due to dense shadowing on the US image [15]. The US features of disrupted rim calcification and the presence of extrusive soft tissue components were assessed in nodules with rim calcification. Microcalcification, nonparallel orientation, and spiculated or microlobulated margins were categorized as suspicious US features [3]. The malignancy risks of the thyroid nodules were categorized as high (> 50%), intermediate (upper-intermediate: > 30%, ≤ 50%; lower-intermediate: > 10%, ≤ 30%), and low (≤ 10%).

Data Analysis and Statistical Analysis

The association of macrocalcification and rim calcification with malignancy and malignancy risk were assessed according to the US patterns of composition, echogenicity,

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Korean Journal of Radiology
KJR

and suspicious features. Fourteen simple cysts and 34 nodules with isolated macrocalcifications were excluded from the subgroup analysis because of an inability to assess nodule echogenicity. Chi-square or Fisher's exact tests were used to assess the significance of the relationships between macrocalcification or rim calcification and malignancy in all nodules and subgroups based on US patterns. Multivariable binary logistic regression analysis was performed to determine the independent predictors among US features. Chi-square or Fisher's exact tests were also used to determine whether macrocalcification and rim calcification increased the malignancy risk according to US patterns; to compare the malignancy risk of macrocalcification, rim calcification, and suspicious US features among the four subgroups categorized by composition and echogenicity; and to assess the associations of macrocalcification and rim calcification with the histopathological types of the malignant tumors. The statistical analyses were performed

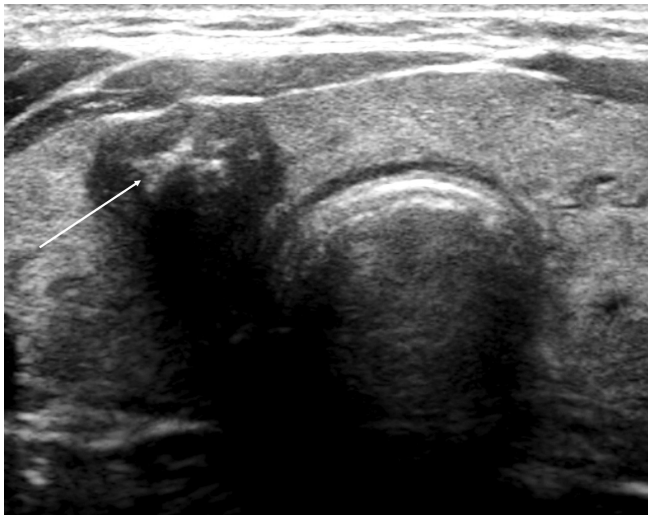

Fig. 2. A 55-year-old woman with a 1.2-cm right thyroid lobe nodule. The ultrasound image shows solid hypoechoic nodule with macrocalcification with posterior shadowing (arrow). A final diagnosis of conventional papillary carcinoma was established based on surgical pathology findings.

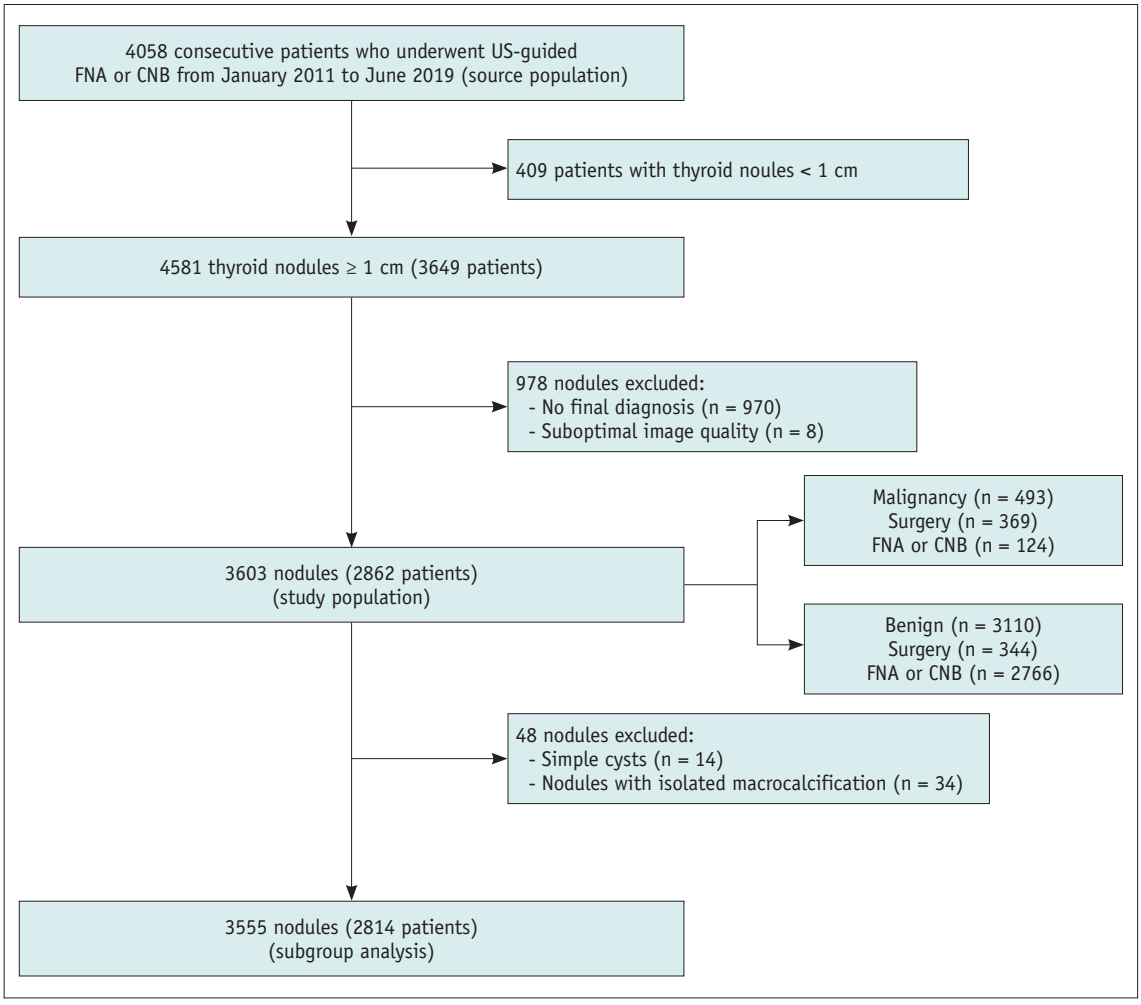

Fig. 1. Flow diagram of patient enrollment. CNB = core needle biopsy, FNA = fine-needle aspiration, US = ultrasound

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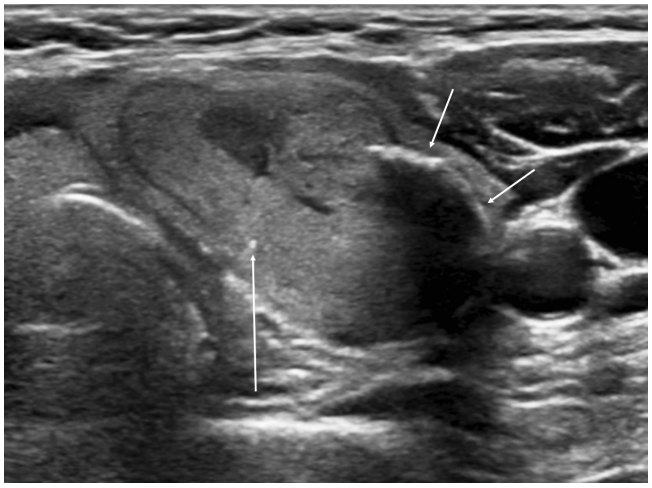

Fig. 3. A 48-year-old woman with a 2.7-cm left thyroid lobe nodule. The ultrasound image shows a solid, predominantly isoechoic nodule with incomplete rim calcification (short arrows) and a microcalcification (punctate echogenic foci) (long arrow). A final diagnosis of minimally invasive follicular thyroid carcinoma was established based on surgical pathology findings.

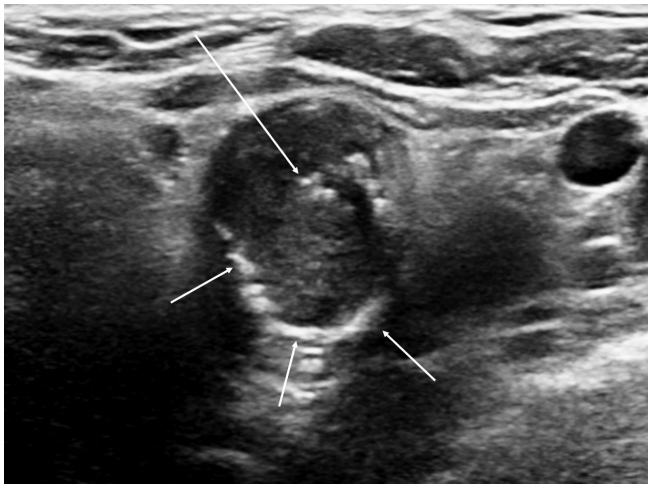

Fig. 4. A 63-year-old woman with a 2.0-cm left thyroid lobe nodule. The ultrasound image shows a solid hypoechoic nodule with incomplete rim calcification (short arrows) and suspicious ultrasound features of nonparallel orientation (taller than wide) and microcalcification (punctate echogenic foci) (long arrow), as well as multiple large echogenic foci. Findings from repeated ultrasound-guided fine-needle aspirations were nondiagnostic and core needle biopsy revealed benign follicular nodule with degeneration. A follow-up ultrasound performed 9 years after the initial fine-needle aspiration showed no change in the size of the nodule.

using IBM SPSS for Windows, version 24.0 (IBM Corp.). *P* values < 0.05 were considered statistically significant.

RESULTS

Demographic Data

The maximum size of the nodules ranged from 10 to 90 mm (median size, 17 mm; 25–75%, 13–25 mm). Of the 3603 nodules, 493 (13.7%) were malignant and 3110 (86.3%) were benign. The 493 malignant nodules included 444 (90.1%) papillary thyroid carcinomas (PTCs), 28 (5.7%) follicular thyroid carcinomas (FTCs), 8 (1.6%) anaplastic carcinomas, 6 (1.2%) metastasis, 4 (0.8%) lymphoma, and 3 (0.6%) medullary thyroid carcinomas. There were no significant differences in the malignancy risk of macrocalcification (32.9% vs. 35.1%, $p = 0.605$) and rim calcification (12.2% vs. 17.6%, $p = 0.532$) between the datasets of retrospective and prospective evaluations of the US features.

US Features associated with Thyroid Malignancy in Overall Nodules

Table 1 shows the US features associated with thyroid malignancy in all nodules. Solid composition, hypoechogenicity, microcalcification, nonparallel orientation, spiculated/microlobulated margins, and macrocalcification showed statistically significant associations with malignancy. Multivariable binary logistic regression analysis showed that solid composition, hypoechogenicity, three suspicious US features, and macrocalcification were independently associated with malignancy ($p < 0.001$). Rim calcification was not significantly associated with malignancy ($p = 0.802$). Moreover, nodules with disrupted rim calcification and hypoechoic nodules with small extrusive soft tissue components did not show a significantly higher malignancy risk than that for nodules with rim calcifications without these specific types (17.9% vs. 12.8%, $p = 0.737$ and 17.9% vs.10.7%, $p = 0.489$, respectively).

US Features associated with Thyroid Malignancy Based on Composition and Echogenicity US Patterns

Table 2 shows the associations of macrocalcification, rim calcification, and suspicious US features with malignancy according to the composition and echogenicity US patterns of the nodules. In solid hypoechoic (SH) nodules, macrocalcification and three suspicious US features were independently predictive of malignancy ($p < 0.001$). Rim calcification was more frequently found in benign nodules than in malignant nodules (5.5% vs. 1.1%, $p = 0.001$) and was not predictive of malignancy. In partially cystic or isoechoic and hyperechoic (PCIH) nodules, three suspicious US features and rim calcification were independently associated with malignancy ($p \leq 0.010$).

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Korean Journal of Radiology
KJR

Table 1. US Features associated with Thyroid Malignancy in Overall Nodules

US Features	Benign Nodules, n (%)	Malignant Nodules, n (%)	Malignancy Risk (%)	*P*	Multivariable Analysis†	
					Odds Ratio‡	*P*
All	3110	493	13.7			
Solid	1585 (50.9)	429 (87.0)	21.3	< 0.001	3.243 [2.359–4.459]	< 0.001
Hypoechoic	801 (26.1)	391 (80.6)	32.8	< 0.001	5.507 [4.206–7.210]	< 0.001
Microcalcification	666 (21.4)	294 (59.6)	30.6	< 0.001	3.825 [2.958–4.946]	< 0.001
Nonparallel	164 (5.3)	147 (29.8)	47.3	< 0.001	3.712 [2.662–5.177]	< 0.001
Spiculated/microlobulated margin	45 (1.4)	148 (30.0)	76.7	< 0.001	6.126 [4.090–9.175]	< 0.001
Macrocalcification	341 (11.0)	174 (35.3)	33.8	< 0.001	2.199 [1.642–2.946]	< 0.001
Rim calcification	64 (2.1)	11 (2.2)	14.7	0.802		
Presence of any suspicious feature*	816 (26.2)	367 (74.4)	31.0	< 0.001	NA	NA

*Microcalcification, nonparallel orientation (taller than wide), spiculated or microlobulated margin, †Binary logistic regression analysis, ‡Numbers in square brackets are confidence intervals. NA = not applicable, US = ultrasound

Comparisons of Malignancy Risks among Four Nodule Groups, Based on Composition and Echogenicity

Table 3 shows the malignancy risks of macrocalcification, rim calcification, and suspicious US features in the four groups of nodules categorized according to a combination of composition and echogenicity.

The malignancy risk differed significantly between the groups in the following decreasing order: SH, partially cystic hypoechoic, solid isoechoic and hyperechoic, and partially cystic isoechoic and hyperechoic nodules ($p < 0.001$) (Table 3). The malignancy risk of nodules with macrocalcification and nodules with any of the three suspicious US features were significantly higher in the SH group than those in the other groups (all, $p < 0.001$). No significant differences were observed in the malignancy risks of nodules with rim calcification among the four groups ($p = 0.457$).

Comparisons of Malignancy Risks between Thyroid Nodules with Macrocalcification and Rim Calcification

The calculated malignancy risk of macrocalcifications was higher than that of rim calcification (33.8% vs. 14.7%) in all nodules. The malignancy risk (35.0% [171/488]) of nodules with macrocalcification only was significantly higher than that of nodules with rim calcification only (16.7% [8/48]) or that of nodules with both macrocalcification and rim calcification (11.1% [3/27]) (all $p = 0.010$). No significant differences were observed between the malignancy risk of nodules with rim calcification only and that of nodules with both macrocalcification and rim calcification ($p = 0.736$).

Malignancy Risks of Thyroid Nodules with Macrocalcification and Rim Calcification according to Suspicious US Features

Macrocalcification significantly increased the malignancy risk in SH nodules irrespective of suspicious US features (all $p < 0.001$) and in PCIH nodules with suspicious US features ($p = 0.007$) (Supplementary Table 1). While rim calcification increased the malignancy risk in PCIH nodules with or without suspicious US features, the difference was no statistically significant ($p = 0.065$ and $p = 0.070$, respectively). In SH nodules without suspicious US features, the malignancy risk was stratified into lower- or upper-intermediate categories, depending on the macrocalcification. The malignancy risks of nodules with macrocalcification were stratified as upper-intermediate and high in SH nodules and low and lower-intermediate in PCIH nodules based on suspicious US features. The malignancy risks of nodules with rim calcification were stratified as low and lower-intermediate based on suspicious US features, irrespective of US patterns based on composition and echogenicity (Supplementary Table 1).

The Association of Macrocalcification and Rim Calcification with the Histopathology of the Malignancy

The frequency of macrocalcification was significantly higher in PTCs than that in FTCs (37.2% [165/444] vs. 7.1% [2/28], $p = 0.001$), while the frequency of rim calcification was significantly higher in FTCs than that in PTCs (14.3% [4/28] vs. 1.4% [6/444], $p = 0.002$). The proportion of PTCs was significantly higher in malignant tumors with SH US patterns than that in tumors with PCIH US patterns (92.0% [335/364] vs. 83.5% [101/121], $p = 0.007$) among 485 malignant tumors, except for eight tumors with

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Table 2. US Features associated with Thyroid Malignancy according to US Patterns Based on Composition and Echogenicity

Composition and Echogenicity	US Features	Benign Nodules, n (%)	Malignant Nodules, n (%)	Malignancy Risk (%)	*P*	Multivariable Analysis†	
						Odds Ratio‡	*P*
Solid hypoechoic	All	550	364	39.8	< 0.001		
	Microcalcification	109 (19.8)	221 (60.7)	66.9	< 0.001	3.854 [2.750–5.401]	< 0.001
	Nonparallel	48 (8.7)	123 (33.8)	71.9	< 0.001	3.621 [2.365–5.542]	< 0.001
	Spiculated/microlobulated margin	33 (6.0)	137 (37.6)	80.6	< 0.001	6.359 [4.040–10.010]	< 0.001
	Macrocalcification	68 (12.4)	139 (38.2)	67.1	< 0.001	3.049 [2.072–4.487]	< 0.001
	Rim calcification	30 (5.5)	4 (1.1)	11.8	0.001§		
	Presence of any suspicious feature*	162 (29.5)	288 (79.1)	64.0	< 0.001		
Partial cystic or iso- and hyperechoic nodules	All	2520	121	4.6	< 0.001		
	Hypoechogenicity	251 (10.0)	27 (22.3)	9.7	< 0.001	1.585 [0.955–2.629]	0.075
	Microcalcification	557 (22.1)	73 (60.3)	11.6	< 0.001	4.205 [2.793–6.330]	< 0.001
	Nonparallel	116 (4.6)	24 (19.8)	17.1	< 0.001	4.312 [2.515–7.392]	< 0.001
	Spiculated/microlobulated margin	12 (0.5)	11 (9.1)	47.8	< 0.001	6.709 [2.591–17.868]	< 0.001
	Macrocalcification	247 (9.8)	27 (22.3)	9.9	< 0.001	1.309 [0.784–2.185]	0.303
	Rim calcification	34 (1.3)	7 (5.8)	17.1	0.002	3.238 [1.321–7.940]	0.010
	Presence of any suspicious feature*	654 (26.0)	79 (65.3)	10.8	< 0.001		

14 simple cysts and 34 isolated macrocalcifications were excluded due to inability to assess nodule echogenicity in subgroups. *Microcalcification, nonparallel orientation (taller than wide), spiculated or microlobulated margin, †Binary logistic regression analysis, ‡Numbers in square brackets are confidence intervals, §Significantly associated with benign nodules. US = ultrasound

isolated macrocalcifications. Meanwhile, the proportion of FTCs was significantly higher in malignant tumors with PCIH US patterns than that in malignant tumors with SH US patterns (14.9% [18/121] vs. 2.7% [10/364], p < 0.001). The frequency of FTCs with rim calcification was higher in malignant tumors with PCIH US patterns than that in tumors with SH US patterns (2.5% [3/121] vs. 0.3% [1/364], p = 0.050). The presence of macrocalcification significantly increased the risk of PTC (32.0% [51/161] vs. 9.0% [279/3088], p < 0.001), while the presence of rim calcification significantly increased the risk of FTC (5.3% [4/75] vs. 0.7% [24/3528], p = 0.002) in all nodules. However, macrocalcification did not significantly increase the risk of FTC (p = 0.416) and rim calcification did not significantly increase the risk of PTC (p = 0.250).

DISCUSSION

The association of macrocalcification and rim calcification with malignancy and the malignancy risk of macrocalcification and rim calcification differed in all nodules and nodule subgroups according to the US patterns. Macrocalcification was independently associated with malignancy in all nodules and SH nodules and showed a higher malignancy risk in SH nodules than that in PCIH nodules. Our results suggested that the malignancy risk of nodules with macrocalcification depends on their composition and echogenicity. Meanwhile, rim calcification was independently associated with malignancy only in PCIH nodules and showed no significant differences in malignancy risk according to US patterns based on composition and echogenicity. Our results showed that macrocalcifications did not increase the malignancy risk of PCIH nodules without suspicious US features, which represented more than half of all nodules in US practice. Therefore, macrocalcifications do not increase the malignancy risk in most nodules encountered in clinical practice.

Our results also showed that the presence of macrocalcification significantly increased the malignancy risk of SH nodules irrespective of suspicious US features. The malignancy risk of SH nodules with macrocalcification and no concurrent suspicious US features was 39.2%, higher than the estimated malignancy risk range (10–20%) of intermediate suspicion nodules in the ATA guideline. This finding suggests that the inclusion of macrocalcification could further stratify the intermediate malignancy risk of SH nodules without suspicious US features to upper- and lower-

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Korean Journal of Radiology
KJR

Table 3. Malignancy Risk of Macrocalcification, Rim Calcification, and Suspicious US Feature in Four Nodule Categories Based on Composition and Echogenicity

US Features	Malignancy Risk, %				*P*
	Solid Hypoechoic	Solid Iso- and Hyperechoic	Partially Cystic Hypoechoic	Partially Cystic Iso- and Hyperechoic	
All	39.8	5.3	9.7	2.9	< 0.001
Macrocalcification	67.1	9.0	27.3	5.6	< 0.001
Rim calcification	11.8	17.4	33.3	8.3	0.457
Any suspicious feature*	64.0	13.2	17.1	6.5	< 0.001

14 simple cysts and 34 isolated macrocalcifications were excluded due to inability to assess nodule echogenicity in subgroups.
*Microcalcification, nonparallel orientation (taller than wide), spiculated or microlobulated margin. US = ultrasound

intermediate risk categories, which may, in turn, alter the treatment plan, such as a different biopsy size threshold.

The difference in the association of macrocalcification and rim calcification with malignancy may be related to the difference in the relationships of macrocalcification and rim calcification with the histopathology of malignant tumors. Our data showed that macrocalcification occurred more frequently in PTC than in FTC, while rim calcification occurred more frequently in FTC than in PTC. The proportion of FTCs was relatively higher in malignant tumors with a PCIH US pattern than that in malignant tumors with an SH US pattern. Previous studies [16-18] have also reported a close association between rim calcification and FTC.

Several studies [2, 19, 20] have suggested that the discontinuity of rim calcifications and a peripheral halo or thickening of the peripheral calcification are associated with a high risk of malignancy. However, the high predictive value of these specific rim calcification features was not supported by the results of the present study or those of another study that included a large sample of nodules with rim calcifications [21]. This discrepancy may be partly due to a slightly ambiguous definition of this feature of rim calcification as well as low interobserver agreement regarding extranodular soft tissue extrusion [21] and rim calcification [22].

The ACR guidelines [6] assign a higher malignancy risk to peripheral calcification than for macrocalcification. However, our study showed that nodules with rim calcification showed a lower malignancy risk than that in nodules with macrocalcification in the analysis of all nodules. Previous studies reported conflicting findings and variable results regarding the malignancy risk of nodules with rim calcification, including a higher malignancy risk [23,24], similar malignancy risk [7,10], and lower malignancy risk [8,25] than those of nodules with macrocalcifications. A recent study [23] reported that peripheral calcifications were highly associated with malignancy; however, the association with malignancy was not statistically proven. These conflicting results may be attributed to the possible differences in the definitions of rim calcification and the characteristics of the study population as the malignancy risks of the macrocalcification differed substantially according to the composition and echogenicity on US.

Meanwhile, although the presence of rim calcification slightly increased the malignancy risk in PCIH nodules, the diagnostic value of rim calcification is uncertain in the risk stratification of thyroid nodules. First, the presence of rim calcification did not significantly increase the malignancy risk of nodules with or without any suspicious US features and it did not result in higher risk categorization of nodules stratified according to suspicious US features. Second, the malignancy risk of nodules with rim calcification was lower than that of nodules with macrocalcification. Moreover, rim calcification did not increase the malignancy risk of nodules with macrocalcification since the malignancy risk of nodules with both macrocalcification and rim calcification was lower than that of nodules with macrocalcification only. Therefore, our study results do not support the strategy provided ACR TI-RAD, which allocated higher points to rim calcification than that for macrocalcification as a predictor of increased malignancy risk in thyroid nodules. Our findings showed that macrocalcification increased the risk of PTC, while rim calcification increased the risk of FTC. Although the diagnostic value of rim calcification is uncertain in the risk stratification of thyroid nodules in general, it may have a diagnostic value for the increased risk of FTC in thyroid nodules.

Our study had several limitations. First, selection bias was possible because this study excluded some nodules without final diagnoses. However, this would not have a significant effect on the estimated malignancy risk of US features because of the large sample size. Second, the

 https://doi.org/10.3348/kjr.2020.0381

reference standards for benign and malignant diagnoses were based on the biopsy results as well as the post-surgical histopathological findings. This may have led to false-negative or false-positive results, although rare. Third, this study did not assess the interobserver agreement for US features. Fourth, it may not be easy to distinguish between macrocalcifications and clustered microcalcifications in US. When extensive psammomatous calcifications are formed, dense calcification can be observed on CT imaging [26,27]. However, to the best of our knowledge, no research evidence has shown that clustered microcalcifications can exhibit macrocalcification in US. Therefore, further studies are needed to address this issue.

In conclusion, macrocalcification was independently associated with malignancy and increased the malignancy risk in SH nodules and overall nodules. The presence of macrocalcification could stratify SH nodules without suspicious US features as upper- and lower-intermediate-risk nodules. The malignancy risks of nodules with macrocalcification were stratified from low to high according to their US patterns. Rim calcification was independently associated with malignancy and increased malignancy risk in PCIH nodules and the malignancy risks of nodules with rim calcification were stratified as low and lower-intermediate. However, the role of rim calcification in the risk stratification of thyroid nodules is uncertain.

Supplementary Materials

The Data Supplement is available with this article at https://doi.org/10.3348/kjr.2020.0381.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Dong Gyu Na, Hwa Seon Shin. Data curation: Dong Gyu Na, Wooyul Paik, So Jin Yoon, Hye Yun Gwon. Formal analysis: Dong Gyu Na, Hwa Seon Shin. Investigation: Dong Gyu Na, Hwa Seon Shin. Methodology: Dong Gyu Na. Project administration: Dong Gyu Na. Resources: Dong Gyu Na. Supervision: Dong Gyu Na. Writing—original draft: Hwa Seon Shin. Writing—review & editing: Byeong-Joo Noh, Won Jun Kim.

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REFERENCES

1. Ha EJ, Lim HK, Yoon JH, Baek JH, Do KH, Choi M, et al. Primary imaging test and appropriate biopsy methods for thyroid nodules: guidelines by Korean Society of Radiology and National Evidence-Based Healthcare Collaborating Agency. *Korean J Radiol* 2018;19:623-631
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, 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;26:1-133
3. Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, 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;17:370-395
4. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, 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. *Endocr Pract* 2016;22:622-639
5. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. E*ur Thyroid J* 2017;6:225-237
6. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS committee. *J Am Coll Radiol* 2017;14:587-595
7. Frates MC, Benson CB, Doubilet PM, Kunreuther E, Contreras M, Cibas ES, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on

sonography. *J Clin Endocrinol Metab* 2006;91:3411-3417
8. Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, et al. Benign and malignant thyroid nodules: US differentiation--multicenter retrospective study. *Radiology* 2008;247:762-770
9. Lu Z, Mu Y, Zhu H, Luo Y, Kong Q, Dou J, et al. Clinical value of using ultrasound to assess calcification patterns in thyroid nodules. *World J Surg* 2011;35:122-127
10. Seo H, Na DG, Kim JH, Kim KW, Yoon JW. Ultrasound-based risk stratification for malignancy in thyroid nodules: a four-tier categorization system. *Eur Radiol* 2015;25:2153-2162
11. Na DG, Baek JH, Sung JY, Kim JH, Kim JK, Choi YJ, et al. Thyroid imaging reporting and data system risk stratification of thyroid nodules: categorization based on solidity and echogenicity. *Thyroid* 2016;26:562-572
12. Zheng Y, Xu S, Kang H, Zhan W. A single-center retrospective validation study of the American College of Radiology Thyroid Imaging Reporting and Data System. *Ultrasound Q* 2018;34:77-83
13. Middleton WD, Teefey SA, Reading CC, Langer JE, Beland MD, Szabunio MM, et al. Multiinstitutional analysis of thyroid nodule risk stratification using the American College of Radiology Thyroid Imaging Reporting and Data System. *AJR Am J Roentgenol* 2017;208:1331-1341
14. Wang Z, Zhang H, Zhang P, He L, Dong W. Diagnostic value of ultrasound-detected calcification in thyroid nodules. *Ann Acad Med Singap* 2014;43:102-106
15. Na DG, Kim DS, Kim SJ, Ryoo JW, Jung SL. Thyroid nodules with isolated macrocalcification: malignancy risk and diagnostic efficacy of fine-needle aspiration and core needle biopsy. *Ultrasonography* 2016;35:212-219
16. Seo HS, Lee DH, Park SH, Min HS, Na DG. Thyroid follicular neoplasms: can sonography distinguish between adenomas and carcinomas? *J Clin Ultrasound* 2009;37:493-500
17. Kobayashi K, Fujimoto T, Ota H, Hirokawa M, Yabuta T, Masuoka H, et al. Calcifications in thyroid tumors on ultrasonography: calcification types and relationship with histopathological type. *Ultrasound Int Open* 2018;4:E45-E51
18. Kuo TC, Wu MH, Chen KY, Hsieh MS, Chen A, Chen CN. Ultrasonographic features for differentiating follicular thyroid carcinoma and follicular adenoma. *Asian J Surg* 2019;43:339-346
19. Kim BM, Kim MJ, Kim EK, Kwak JY, Hong SW, Son EJ, et al. Sonographic differentiation of thyroid nodules with eggshell calcifications. *J Ultrasound Med* 2008;27:1425-1430
20. Park M, Shin JH, Han BK, Ko EY, Hwang HS, Kang SS, et al. Sonography of thyroid nodules with peripheral calcifications. *J Clin Ultrasound* 2009;37:324-328
21. Malhi HS, Velez E, Kazmierski B, Gulati M, Deurdulian C, Cen SY, et al. Peripheral thyroid nodule calcifications on sonography: evaluation of malignant potential. *AJR Am J Roentgenol* 2019;213:672-675
22. Hoang JK, Middleton WD, Farjat AE, Teefey SA, Abinanti N, Boschini FJ, et al. Interobserver variability of sonographic features used in the American College of Radiology Thyroid Imaging Reporting and Data System. *AJR Am J Roentgenol* 2018;211:162-167
23. Malhi H, Beland MD, Cen SY, Allgood E, Daley K, Martin SE, et al. Echogenic foci in thyroid nodules: significance of posterior acoustic artifacts. *AJR Am J Roentgenol* 2014;203:1310-1316
24. Zayadeen AR, Abu-Yousef M, Berbaum K. JOURNAL CLUB: retrospective evaluation of ultrasound features of thyroid nodules to assess malignancy risk: a step toward TIRADS. *AJR Am J Roentgenol* 2016;207:460-469
25. Ha SM, Chung YJ, Ahn HS, Baek JH, Park SB. Echogenic foci in thyroid nodules: diagnostic performance with combination of TIRADS and echogenic foci. *BMC Med Imaging* 2019;19:28
26. Hiromura T, Tanaka YO, Nishioka T, Tomita K. Serous psammocarcinoma of the ovary: CT and MR findings. *J Comput Assist Tomogr* 2007;31:490-492
27. Ayala C, Healy GB, Robson CD, Vargas SO. Psammomatous calcification in association with a benign thyroglossal duct cyst. *Arch Otolaryngol Head Neck Surg* 2003;129:241-243

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