Differentiation of Thyroid Nodules With Macrocalcifications

Role of Suspicious Sonographic Findings

Min Jung Kim, MD, Eun-Kyung Kim, MD, Jin Young Kwak, MD, Cheong Soo Park, MD, Woong Youn Chung, MD, Kee-Hyun Nam, MD, Ji Hyun Youk, MD

Objective. The purpose of this study was to determine which types of macrocalcifications are associated with thyroid carcinoma and to assess the role of other suspicious sonographic findings in thyroid nodules with macrocalcifications. ***Methods.*** Our Institutional Review Board approved this retrospective study, and informed consent was not required. We reviewed sonographic findings of thyroid nodules in 722 patients that underwent thyroid surgery in our institution between March 2006 and August 2006. Sonographic results were grouped into 3 types of macrocalcifications. Each lesion was evaluated on the basis of other suspicious sonographic criteria, including marked hypoechogenicity, irregular or microlobulated margins, and a taller-than-wide shape. Sensitivity and specificity based on sonographic criteria were calculated and compared among the subtypes of macrocalcifications. ***Results.*** One hundred seventy-four nodules showed macrocalcifications; 116 were malignant, and 58 were benign. Among the macrocalcification categories, solitary calcifications were more common in benign thyroid lesions, whereas coarse calcifications not otherwise specified were more common in malignant lesions ($P < .05$). Although the risk of malignancy was 17.2% in cases with no suspicious sonographic findings, the risk of malignancy was up to 82.8% in cases with at least 1 of the sonographic criteria ($P < .05$). On the basis of the suspicious sonographic criteria, the overall sensitivity was 82.8%. There was no statistically significant difference in sensitivity among the macrocalcification subtypes ($P > .05$). ***Conclusions.*** Suspicious sonographic features such as marked hypoechogenicity, irregular or microlobulated margins, and a taller-than-wide shape can play important roles in differentiating benign and malignant thyroid nodules with macrocalcifications. ***Key words:*** calcifications; sonography; thyroid.

Abbreviations
FNAB, fine-needle aspiration biopsy; NOS, not otherwise specified

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Address correspondence to Eun-Kyung Kim, MD, Department of Radiology, Yonsei University Heath System, 134 Shinchon-dong, Seodaemun-ku, Seoul 120-752, Korea.
E-mail: ekkim@yuhs.ac

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Calcifications, often described in sonography reports, can be detected in both benign and malignant thyroid nodules. Although it is well known that microcalcifications are associated with thyroid malignancy,[1–4] the results for macrocalcifications are controversial. Several recent reports have refocused attention on thyroid macrocalcifications.[5–10] Wang et al[5] and Seiberling et al[7] reported that detection of macrocalcifications as well as microcalcifications should increase the clinical index of suspicion for thyroid carcinoma. Taki et al[6] classified macrocalcifications into 3 subtypes and reported that any type of sonographically detected calcifications represents a risk of malignancy in 33% to 52% of cases. Consorti et al[10] reported no correlation between the presence of calcifications and their con-

sidered sonographic characteristics of nodules, including poorly defined margins, hypoechogenicity, and a solid structure, but they did not supply statistical data to support their conclusion. None of these reports addressed the role of other sonographic findings in assessing the risk of malignancy in thyroid nodules with macrocalcifications.

The purpose of this study was to determine which types of macrocalcifications are associated with thyroid carcinoma and to assess the role of other sonographic findings in diagnosing malignancy in thyroid nodules with macrocalcifications.

Materials and Methods

Our Institutional Review Board approved this retrospective study, and informed consent was not required.

Between March and August 2006, 722 patients underwent thyroid surgery in our institution. They consisted of 616 women (85.3%) and 106 men (14.7%). Their ages ranged from 9 to 82 years (mean age, 46 years). The reasons for thyroid evaluation were as follows: a palpable thyroid mass in 117 patients, a palpable lateral neck mass in 6 patients, hoarseness in 5 patients, and discomfort including dysphagia in 36 patients. The remaining 558 patients had incidentalomas. Preoperative sonograms obtained in our institution were available for 697 patients.

Preoperative sonographic evaluation was performed with an HDI 3000 or HDI 5000 system (Philips Medical Systems, Bothell, WA) or an Acuson Sequoia 512 system (Siemens Medical Solutions, Mountain View, CA) for evaluation of the thyroid gland and neck. With the use of the HDI 5000 machine, compound imaging was performed in all cases. Preoperative real-time sonography was performed by 1 of 3 board-certificated radiologists with an average of 6.7 years (4, 6, and 10 years, respectively) of experience in thyroid imaging. The time elapsed between sonography and surgery ranged from 27 to 63 days (median, 48 days).

One radiologist (M.J.K) blinded to the final pathologic diagnosis and the ratio of malignant to benign lesions retrospectively reviewed sonographic data for the 697 patients. We excluded 22 patients that underwent a second operation for tumor recurrence. Among the remaining 675 patients, each lesion was also evaluated for the presence of sonographically visible macrocalcifications. When microcalcifications, which were defined as multiple punctate bright echoes of less than 2 mm with or without acoustic shadowing, were present, the lesions were excluded from statistical analysis because the purpose of this study was to assess the role of sonographic macrocalcifications in evaluating thyroid nodules, and an analysis including microcalcifications would have detracted from the study. All calcifications that were not microcalcifications were regarded as macrocalcifications. If a thyroid nodule had a combination of microcalcifications and macrocalcifications, it was classified as a nodule with microcalcifications because it is well established that microcalcifications in thyroid lesions are more suspicious for malignancy than macrocalcifications.[2,4,5,11]

Among 675 patients, 174 nodules containing macrocalcifications constituted our study population. There were 116 malignant and 58 benign nodules. All of the malignant thyroid nodules were papillary carcinoma. Benign thyroid nodules included adenomatous hyperplasia in 56 nodules, follicular adenoma in 1 nodule, and lymphocytic thyroiditis in the remaining nodule.

The macrocalcification patterns were classified into 3 categories: type 1, solitary calcifications (linear or round hyperechoic structure >2 mm with or without acoustic shadowing in the middle of the nodule or along the margin of the nodule that encompassed less than 120° the circumference; Figure 1, A and B); type 2, eggshell calcifications (curvilinear hyperechoic structure parallel to the margin of the nodule that encompassed 120° or more of the circumference; Figure 1C); and type 3, all other coarse but not otherwise specified (NOS) calcifications (Figure 1D). If a patient had several thyroid nodules with macrocalcifications, each thyroid nodule with calcifications was classified separately.

Each lesion with macrocalcifications was also evaluated for other suspicious sonographic features according to published data,[1,2,12] including marked hypoechogenicity (decreased echogenicity compared with the surrounding strap muscle), irregular or microlobulated margins, and a taller-

than-wide shape (greater in its anteroposterior dimension than its transverse dimension), except for microcalcifications. We refer to this combination as the triple criteria. Each lesion was classified by the number of malignant sonographic features present.

Pathologic results were reviewed from surgical records and pathology reports. Sonographic findings and the pathologic diagnosis were correlated according to the size and location of the nodule and the calcification pattern described in the pathology report.

We determined the pattern and prevalence of macrocalcifications in resected thyroid lesions. The sensitivity and specificity were determined on the basis of the other sonographic features. We also compared the sensitivity and specificity according to the subtype of the calcifications. Statistical analyses were conducted with the χ^2 test for nonparametric variables and the t test for parametric inference. $P < .05$ was considered statistically significant. A 95% confidence interval was calculated. Statistical analyses were performed with SAS version 9.1 software for Windows (SAS Institute Inc, Cary, NC).

Results

The size of the 174 nodules ranged from 5 to 50 mm (mean, 15 mm). There was no statistical difference between the benign and malignant nodules with regard to size ($P > .05$). There were solitary calcifications in 60 nodules (Figures 2 and 3), eggshell calcifications in 81 (Figure 4), and coarse NOS calcifications in 33 (Figure 5 and Table 1). Among these macrocalcification subtypes, solitary calcifications were more common in benign thyroid lesions, and coarse NOS calcifications were more common in malignant thyroid lesions ($P < .05$). Table 2 shows the number of combined suspicious sonographic features in thyroid nodules with calcifications according to the triple criteria (hypoechogenicity, irregular or microlobulated margins, and a taller-than-wide shape). Although the risk of malignancy was 34.5% in cases with no suspicious sonographic findings (Figures 2 and 4), it was as much as 82.8% in cases with at least 1 of the triple criteria ($P < .05$; Figures 3 and 5). On the basis of the number of combined suspicious sonographic features among the triple criteria, the sensitivity was higher in the presence of 1 suspicious finding (82.8%) than in the presence of 2 or 3 suspicious findings (50% and 24.1%, respectively).

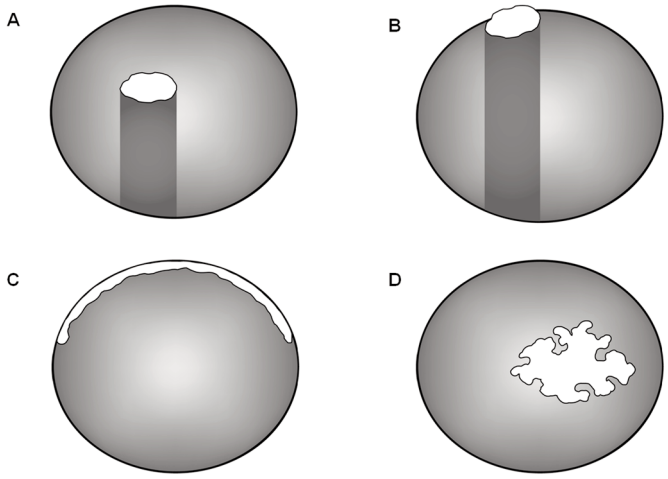
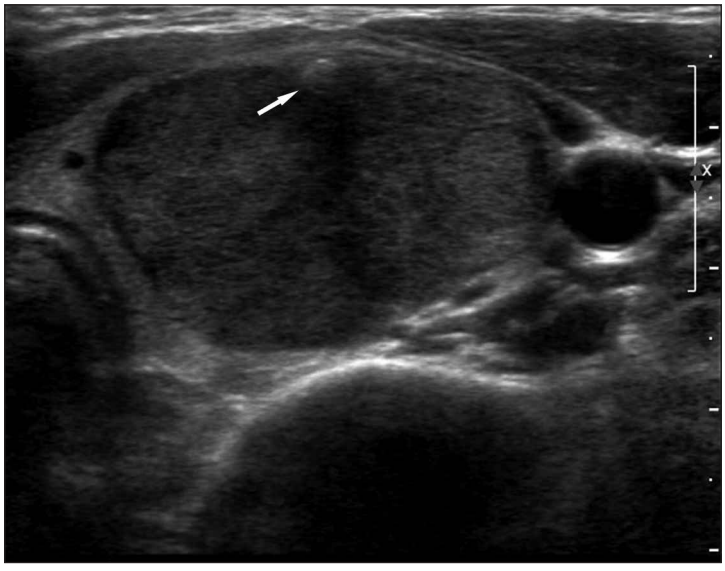


Figure 1. Schematic subtypes of calcifications on sonography. **A** and **B**, Type 1, solitary calcification: hyperechoic structure larger than 2 mm in the middle of a nodule (**A**) or along the margin of a nodule (**B**). **C**, Type 2, eggshell calcification: curvilinear hyperechoic structure parallel to the margin of a nodule encompassing more than 120° of the circumference. **D**, Type III, coarse NOS calcification: irregular macrocalcifications not specified in any other calcification subtype.

Figure 2. Transverse sonogram showing a round hyperechoic structure (>2 mm, type 1 solitary calcification; arrow) along the margin of an oval circumscribed nodule. It has no suspicious findings of the triple criteria. The pathologic result was adenomatous hyperplasia.



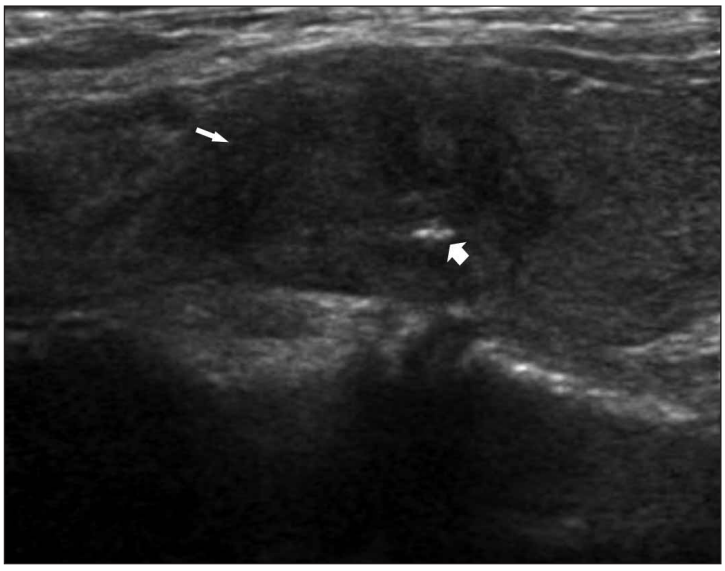


Figure 3. Sagittal sonogram showing a hyperechoic structure (>2 mm, type 1 central calcification; thick arrow) in the middle of a microlobulated hypoechoic nodule. It has 1 suspicious finding (microlobulated margin; thin arrow) among the triple criteria. The pathologic result was papillary carcinoma.

On the basis of the macrocalcification subtype, there were no significant differences in the sensitivity and specificity in the presence of at least 1 of the triple criteria ($P > .05$; Table 3).

Figure 4. Transverse sonogram showing a curvilinear hyperechoic structure (type 2 eggshell calcification; arrow), parallel to the margin of a nodule and encompassing more than 120° of the circumference. It has no suspicious findings of the triple criteria. The pathologic result was adenomatous hyperplasia.

Discussion

Many authors have reported sonographic criteria that facilitate differentiation of benign and malignant lesions,[2,8,13,14] but thyroid sonography has not been thought to allow such a distinction despite its widely accepted usefulness.[15,16] For accurate diagnosis, fine-needle aspiration biopsy (FNAB) with cytologic evaluation is the most important procedure and the most noninvasive and effective method for screening a thyroid nodule for cancer, especially with sonographic guidance.[6,7,10] However, the role of FNAB in thyroid lesions with calcifications is controversial[17] because one of the common causes of nondiagnostic sampling is calcified lesions. In addition, Khoo et al[8] reported that 25% of thyroid malignancies with calcifications in their study population had benign preoperative FNAB results. The importance of sonographic interpretation of thyroid nodules with calcifications deserves further attention for follow-up and treatment.

Although microcalcifications have a well-known association with thyroid malignancy,[2–4] a peripheral or eggshell calcification within a thyroid nodule is thought to be an indicator of benignity with just a few exceptions.[18] However, Taki et al[6] reported that 43% of the thyroid lesions with peripheral calcifications they examined were associated with cancer, and several recent investigations suggested that detection of macrocalcifications as well as microcalcifications should increase the clinical index of suspicion for thyroid carcinoma.[1,5–7,10] These reports detailed the prevalence of calcifications (including macrocalcifications) in benign and malignant thyroid lesions and correlated calcifications and malignancy in terms of the calcification size, location, and patient age. In a study by Wang et al,[5] microcalcifications were more significant than macrocalcifications ($P = .001$) for predicting thyroid malignancy, and the relative risk of malignancy was significantly higher in patients older than 45 years with macrocalcifications ($P = .03$). Moreover, Frates et al[1] reported that coarse or rim calcifications doubled the risk of malignancy compared with a similar nodule without calcifications, and the risk of malignancy increased when a nodule was solitary and solid. Although Consorti et al[10] reported no correlations between

the presence of calcifications and the sonographic characteristics of nodules considered, they did not present statistical data to support their conclusion. To our knowledge, no study before ours addressed the role of other sonographic findings in thyroid nodules with macrocalcifications in assessment of the risk of malignancy.

Our results showed that 82.8% of malignant thyroid nodules with macrocalcifications could be detected by the sonographic criteria outlined by Kim et al,[2] and the figures were relatively consistent across the macrocalcification subtypes. However, we found that the sensitivity of eggshell calcifications was comparatively lower than those of the other macrocalcification subtypes (solitary and coarse NOS), although it was not statistically significant. In some cases, it was difficult to apply these criteria to the thyroid nodules with eggshell calcifications because the calcification-lining margin of the nodule could obscure margin interpretation. Further modified criteria should be used to improve the sensitivity in thyroid nodules with eggshell calcifications.

One of the limitations of our study was the small percentage of benign nodules compared with previous reports in the literature. We reviewed consecutive surgical lesions over 6 months. Although we encountered benign calcified nodules frequently during FNAB, nodules referred for surgical excision are more likely to be malignant.[19] Considering the high sensitivity and specificity, FNAB should be recommended for nodules with macrocalcifications that have any suspicious sonographic findings. However, we did not assess how accurately FNAB could differentiate thyroid nodules with macrocalcifications prospectively, and further studies are warranted. The second limitation was that this study was retrospective. This could have had an effect on the results, but the degree of the effect on benign and malignant lesions seemed similar because the radiologist who reviewed the cases was blinded with respect to the final pathologic diagnosis and the ratio of malignant to benign lesions. A prospective analysis should be conducted. Last, we did not assess the role of macrocalcifications in evaluation of thyroid nodules in a case-control review, comparing macrocalcifications in nodules with noncalcified nodules and controlling for the presence of the triple criteria. This would also be an informative study of the importance of macrocalcifications as a stand-alone predictor of malignancy. We wanted to determine whether we could differentiate between benign and malignant thyroid nodules with macrocalcifications on the basis of sonographic findings suspicious for malignancy, and the result was that the sonographic findings were useful for differentiation. Further study of thyroid nodules with no suspicious sonographic findings but with macrocalcifications is needed.

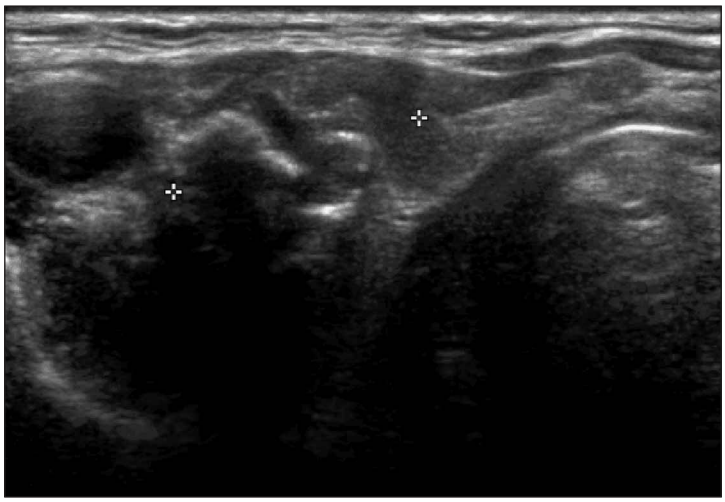


Figure 5. Transverse sonogram showing irregular macrocalcifications (type 3, coarse NOS calcifications; calipers) in a hypoechoic nodule. This lesion has 2 suspicious findings (microlobulated margin and a taller-than-wide shape) of the triple criteria. The pathologic result was papillary carcinoma.

Table 1. Macrocalcification Patterns and Prevalence of Malignancy in 174 Resected Thyroid Lesions With Macrocalcifications

Pathologic Type	Solitary	Eggshell	Coarse NOS	Total
Malignant	36 (60)	52 (64.2)	28 (84.8)	116
Benign	24 (40)	29 (35.8)	5 (15.2)	58
Total	60	81	33	174

Numbers in parentheses are percentages of the prevalence in the same calcification subtype.

Table 2. Triple Criteria Versus Pathologic Type

Suspicious Sonographic Features	Malignant	Benign
0	20 (17.2)	38 (65.5)
1	38 (32.8)	14 (24.1)
2	30 (25.9)	6 (10.4)
3	28 (24.1)	0 (0)
Total	116 (100)	58 (100)

Numbers in parentheses are percentages.

Table 3. Sensitivity and Specificity of Each Macrocalcification Pattern Based on Triple Criteria

Value	Solitary (n = 60)	Eggshell (n = 81)	Coarse NOS (n = 33)
Sensitivity	31/36 (86.1)	40/52 (76.9)	5/28 (89.3)
Specificity	16/24 (66.7)	21/29 (72.4)	1/5 (20)

Numbers in parentheses are percentages.

In conclusion, our study indicates that other sonographic criteria can play an important role in differentiating benign and malignant thyroid nodules with macrocalcifications.

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