CT Features of Thyroid Nodules with Isolated Macrocalcifications Detected by Ultrasonography

Abbreviated Title: CT features of Thyroid Isolated Macrocalcification

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**Type of manuscript:** Original article

**Running title:** CT features of Thyroid Isolated Macrocalcification

**Type of manuscript:** Original research

**Word count for the manuscript:** 2093

**Acknowledgements:** None

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Funding:** This research was supported by the Medical Research Promotion Program through the GangNeung Asan Hospital funded by the Asan Foundation (2018-C03).
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ABSTRACT

Purpose: A thyroid nodule with an isolated macrocalcification is a calcified nodule with complete posterior shadowing on ultrasonography (US). This study aimed to determine the computed tomographic (CT) features of isolated macrocalcifications detected by US.

Methods: This study included 20 patients who had thyroid nodules with isolated macrocalcifications and underwent neck CT or chest CT. Those patients were enrolled from 82 patients with isolated macrocalcifications detected by US out of 7142 consecutive patients who underwent thyroid biopsy in two institutions. We evaluated the CT features of nodules with isolated macrocalcifications and categorized them as central or rim type calcifications. We assessed the nodule size, nondiagnostic fine-needle aspiration (FNA) results, and frequency of malignant tumors according to the CT features of isolated macrocalcifications.

Results: CT images showed central type calcifications in 18 nodules (90.0%) and rim type calcifications in 2 (10.0%) of 20 nodules with isolated macrocalcifications. Among the 18 nodules with central type isolated macrocalcifications, complete compact calcification was found in 6 nodules and partial coarse calcification in 12 nodules. In 18 nodules with central type isolated macrocalcifications, the nondiagnostic FNA rate and frequency of malignant tumors were not significantly different between complete and partial central type calcifications (P=0.620 and P=0.999, respectively). Malignant tumors were found only in nodules with central type isolated macrocalcifications.

Conclusion: The majority of nodules with isolated macrocalcifications showed central type calcifications on CT. Thyroid nodules with isolated macrocalcifications detected by US should not be classified as a type of rim calcification.

Keywords: Thyroid nodule; Calcinosis; Diagnosis; Ultrasonography; Computed Tomography, Multidetector
Introduction

Ultrasonography (US) has an essential role in estimating the malignancy risk and management of a thyroid nodule (1). Although a macrocalcification may increase the risk for malignancy, it presented a variable malignancy rate and was not highly specific for malignancy (2-5). An isolated macrocalcification is defined as a calcified nodule with complete posterior acoustic shadowing in which any soft tissue component is not identified due to dense shadowing on US (6). The US lexicon for isolated macrocalcifications is not established and nodules with isolated macrocalcifications have only been considered for risk stratification of nodules in the Korean Thyroid Imaging Reporting and Data System (K-TIRADS) (7, 8) and in the American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS) (8-10). Previous studies (11-14) classified an isolated macrocalcification as a type of rim or peripheral calcification. However, the detail of an isolated macrocalcification cannot be evaluated using US alone due to dense posterior shadowing, which causes challenges in categorizing nodules with isolated macrocalcifications in the risk stratification of thyroid nodules (7-10).

Meanwhile, computed tomography (CT) has the advantage of enabling detailed evaluation of an isolated macrocalcification. A previous study (6) reported that isolated macrocalcification may show an entirely calcified nodule on CT; however, there has been little investigation on CT features of isolated macrocalcifications. Therefore, this study aimed to determine the CT features of thyroid nodules with isolated macrocalcifications detected by US.

Materials and Methods

The institutional review board approved this retrospective study, and the requirement to
obtain informed consent was waived.

**Patients**

This study included 20 patients (17 women, 3 men; mean age 61.1 ± 11.6 years) who had thyroid nodules with isolated macrocalcifications and underwent neck CT or chest CT (Fig. 1). Thyroid nodules with isolated macrocalcifications were defined as isolated calcified nodules with complete posterior acoustic shadowing in which any solid component was not obviously identified within the nodules on US (Fig. 2-4). The enrolled patients were selected from 82 patients with isolated macrocalcifications detected by US at two institutions. Forty-four patients with isolated macrocalcifications were found in the cohort data (dataset 1, n=4081) of patients with thyroid nodules in one institution, which has been previously published (14). Thirty-eight patients with isolated macrocalcifications were found in the cohort data (dataset 2, n=3061) of patients with thyroid nodules in whom fine-needle aspiration (FNA) or core needle biopsy (CNB) was performed from January 2011 to June 2018 in another institution. In dataset 1, nodules with isolated macrocalcifications were retrospectively determined by reviewing thyroid US images of 408 patients for which the word “macrocalcification” was used in the radiology report of the thyroid US (6). In dataset 2, nodules with isolated macrocalcifications were retrospectively determined by reviewing US images of all patients. Among 82 patients with isolated macrocalcifications detected by US at two institutions, 62 patients who did not undergo neck or chest CT were excluded from this study (Fig. 1).

FNA or CNB was routinely performed for large (≥ 1 cm) isolated macrocalcifications and was selectively performed for small (< 1 cm) isolated macrocalcifications in the case of previous inconclusive FNA results, evaluation of the contralateral lobe for thyroid lobectomy, patients suspected of having lymph node metastasis, and by the request of referral physicians.
(in most cases). Final diagnoses of malignant tumors were determined by surgery or malignant diagnosis of FNA or CNB, and final diagnoses of benign nodules were determined by surgery or benign diagnosis of FNA or CNB.

US and CT Examinations

High-resolution US examinations were performed using a 10–12 MHz linear-array transducer (ApioXG, Toshiba, Otawarashi, Japan) and 5- to 12-MHz linear-array transducers (iU22 or EPIQ7, Philips Medical System, Bothell, WA, USA). Neck CT images were obtained in 11 patients and chest CT images in 9 patients. For CT examinations, 64-channel multidetector CT scanners were used. Unenhanced neck CT was performed to evaluate the calcified mass before biopsy in 7 patients, and both unenhanced and contrast-enhanced neck CT were performed for the preoperative evaluation in 4 patients diagnosed as thyroid cancers. Unenhanced chest CT was obtained in 4 patients and contrast-enhanced chest CT in 5 patients for the evaluation of lung lesions. The neck CT images were reconstructed into axial images with scan parameters of 2 to 4 mm slice thickness, 512 x 512 matrix, and 22-25 cm field of view (FOV). The chest CT images were reconstructed into axial images with scan parameters of 2.5 to 5 mm slice thickness, 512 x 512 matrix, and 33-43 cm field of view (FOV). The unenhanced neck and chest CT images were reviewed for the evaluation of isolated macrocalcifications in 15 patients and enhanced chest CT images were reviewed in 5 patients.

US-guided FNA and CNB Procedures

US-guided FNA was performed with a conventional method using a 21- to 23-gauge needle and at least two samplings were performed for each nodule (15). Direct smears or liquid-based cytology (LBC) was used for the preparation of FNA specimens. The specimen was
smeared on a slide and immediately fixed in 95% ethanol in the direct smear method. In the liquid-based cytology method, the specimen was prepared using the ThinPrep 2000 processor (Hologic Co., Marlborough, MA, USA).

US-guided CNB was performed using a free-hand technique and a disposable 18-gauge, double-action spring-activated needle (1.1 cm excursion; TSK Acecut; Create Medic, Yokohama, Japan) as described previously (6, 16). The specimen was immediately fixed in 10% neutral buffered formalin solution and stained in the standard manner for a histopathologic examination. The interpretation of FNA or CNB was based on the Bethesda system for reporting thyroid cytopathology (17) and 6 categories of a CNB pathology reporting system (18). After the patients underwent biopsy, we immediately compressed the biopsy site, and the patients were observed with self-manual compression of the biopsy site for 20-30 minutes.

**Image Analysis and Statistics**

US images were retrospectively reviewed by one experienced radiologist (D.G.N) with 21 years of experience in performing thyroid US and interventional procedures. A reviewer who had no previous knowledge of FNA result or final diagnosis determined the presence of isolated macrocalcifications from the US image database of patients. The CT features of included nodules with isolated macrocalcifications were retrospectively evaluated by the consensus of two radiologists (D.G.N and W.P) in a blind fashion. The CT features of an isolated macrocalcification were categorized into central and rim type calcifications. The central type calcification was defined as a calcified nodule with intranodular macrocalcification located in the center of calcified nodules. Central type calcification was further subcategorized as either complete calcification (compact entire calcification) or partial calcification (coarse partial calcification with obvious non-calcified soft tissue component
within the calcified nodule). The rim (peripheral) type was defined as a calcified nodule with complete or incomplete curvilinear rim calcification. The CT features of central type isolated macrocalcifications were evaluated on axial CT images with a wide window width (1500 Hounsfield unit) for assessing the internal architecture of calcified nodules.

We assessed the nodule size, nondiagnostic FNA results, and frequency of malignant tumors according to the CT features of isolated macrocalcifications. The Mann–Whitney U test was used to compare the mean nodule size and Fisher’s exact test was used to compare the rate of nondiagnostic FNA rate between complete and partial central type calcifications. Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). A significant difference was defined as a P-value of < 0.05.

Results

Demographic Data

The CT images were obtained in 20 (24.4%) of 82 patients with isolated macrocalcifications. The sizes of the 20 nodules ranged from 6 to 20 mm (mean size, 12.3 ± 3.4 mm). Among the 20 nodules with isolated macrocalcifications, both FNA and CNB were performed simultaneously in 9 (45.0%), FNA alone in 10 (50.0%), and CNB alone in 1 (5.0%) for the initial biopsy procedure. The initial FNA results of the 19 nodules were nondiagnostic (n=9, 47.4%), benign (n=6, 31.6%), atypia of undetermined significance/follicular lesion of undetermined significance (n=2, 10.5%), suspicious for malignancy (n=1, 5.3%), and malignant (n=1, 5.3%). The initial CNB results of the 10 nodules were nondiagnostic (n=1, 10.0%), benign (n=4, 40.0%), indeterminate (n=4, 40.0%), and malignant (n=1, 10%). Final diagnoses were obtained in 12 (60.0%) of 20 nodules and 8 nodules showed inconclusive FNA or CNB results. Malignant tumors were found in 4
(20.0%) of 20 nodules, of which 3 were conventional papillary thyroid carcinomas (PTC) and 1 was found to be invasive encapsulated follicular variant PTC.

**CT Features of Isolated Macrocalcification**

Central type calcification was found on CT images in 19 (90.0%) and rim type calcification was in 2 (10.0%) of 20 nodules with isolated macrocalcifications (Table 1). Among the 18 nodules with central type calcifications, complete calcification was found in 6 nodules (Fig. 1) and partial calcification in 12 nodules (Fig. 2). The 2 nodules with rim type calcification showed incomplete rim calcifications, and no complete rim calcification was observed (Fig. 3).

**Nodule Size, Nondiagnostic FNA Results, and Frequency of Malignant Tumors According to Isolated Macrocalcification Type**

In the 18 nodules with central type isolated macrocalcification, the mean size of nodules with partial calcification subtype was larger than that of nodules with complete calcification subtype, but statistically insignificant (P=0.098) (Table 2). Nondiagnostic FNA results were found in 9 (47.4%) of 19 nodules which underwent FNA. The nondiagnostic rate was similar in central type calcifications (47.1%) and rim type calcifications (50%), and there was no significant difference of nondiagnostic rate between complete and partial central type calcifications (P=0.620) (Table 2). The malignant tumors were only found in 4 (22.2%) of 18 nodules with a central type isolated macrocalcification. There was no significant difference in the frequency of malignant tumors between complete and partial central type calcifications (P=0.999).

**Discussion**
Our study demonstrated that the majority (90.0%) of nodules with an isolated macrocalcification showed central type calcifications on CT, which suggests that thyroid nodules with an isolated macrocalcification should not be classified as a type of rim or peripheral calcification. Our study also showed that 3 types of macrocalcifications (central complete, central partial, and rim) may have a similar US feature of isolated macrocalcification.

US lexicon of macrocalcification is defined as echogenic foci larger than 1 mm with posterior acoustic shadowing, which has consistent definitions in Korean Society of Thyroid Radiology (KSThR), European Thyroid Association (ETA), and American College of Radiology (ACR) guidelines (7, 9, 19). However, isolated macrocalcifications were not clearly defined in the published guidelines and were categorized as a type of rim or peripheral calcification in previous studies (11-14). Based on our study results, an isolated macrocalcification should be differentiated from a rim calcification, which is defined as a peripheral curvilinear echogenic rim with or without posterior shadowing. Rim calcifications with posterior shadowing should be determined when any part of the internal content can be visualized even though there is accompanying dense posterior shadowing.

The distinction of isolated macrocalcification from rim calcification may be useful in the diagnosis and management of thyroid nodules. First, the clarified definition of rim calcification may improve the interobserver agreement in the interpretation of calcified nodules because the interobserver variability is closely related to the clarity of an US lexicon. Second, the malignancy risk and diagnostic value of rim calcification might be better clarified. The previous studies (2, 3, 5, 20) showed conflicting results of malignancy risk and association of rim calcification with malignancy, which might have been affected by the difference in definition of rim calcifications. Third, more cautious FNA or application of CNB is necessary for nodules with isolated macrocalcification because the nondiagnostic
FNA rate is very high (6).

The US lexicon has an important role in malignancy risk stratification of thyroid nodules. An isolated macrocalcification was categorized as an intermediate suspicious nodule in the Korean Thyroid Imaging Reporting and Data System (K-TIRADS) (7, 8) and a moderately suspicious nodule in the American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS) (8-10). However, it is not specified for risk stratification of thyroid nodules in other thyroid society guidelines. A previous study (6) reported that malignancy risk ranged from 11.4% to 16.1% in all nodules with isolated macrocalcifications, and 16.7% in nodules (≥ 1 cm) with final diagnoses. A recent study (14) reported that the malignancy risk of nodules with a completely shadowed peripheral calcification was 38.5%.

In our study, the CT patterns of central type isolated macrocalcifications showed a similar frequency of malignant tumors. However, our study had limited ability to assess the malignancy risk of each CT calcification pattern due to small number of patients. In our study, the nondiagnostic FNA rate was similar between complete and partial central type isolated macrocalcifications. However, there may remain a possibility that completely calcified nodule might increase the risk of a nondiagnostic FNA result because needle penetration may be more difficult in a totally calcified nodule compared with a partially calcified nodule.

There are several limitations to this study. First, the included number of patients is small and there exists a selection bias because CT images were not obtained in many of the isolated macrocalcifications. Second, the statistical results are limited because of the small sample size of our study. Third, the retrospective assessment of US images by one interpreter has an inevitable limitation in the interpretation of isolated macrocalcifications. Third, further investigation is necessary to determine whether nondiagnostic FNA rate and malignancy risk may differ according to the CT features of isolated macrocalcifications.

In conclusion, the majority (90.0%) of thyroid nodules with isolated macrocalcifications
showed a central type calcification on CT. Therefore, thyroid nodules with isolated macrocalcifications detected by US should not be classified as a type of rim or peripheral calcification.
References


Figure legends

Fig. 1
Flow diagram of patient enrollment.

Fig. 2
Thyroid nodule with isolated macrocalcification in a 70-year-old woman. Transverse US image (A) shows a calcified nodule (6 mm) in the left lobe and the posterior margin of the calcified nodule is not visualized by strong posterior acoustic shadowing. Axial unenhanced CT image (B) shows a complete compact central type calcification of isolated macrocalcification detected by US.

Fig. 3
Thyroid nodule with isolated macrocalcification in a 59-year-old woman. Transverse US image (A) shows a calcified nodule (12 mm) with strong posterior acoustic shadowing in the right lobe. Axial unenhanced CT image (B) shows a partial coarse central type calcification of isolated macrocalcification detected by US.

Fig. 4
Thyroid nodule with isolated macrocalcification in a 50-year-old woman. Longitudinal US image (A) shows a calcified nodule (10 mm) with strong posterior acoustic shadowing in the right lobe. Axial unenhanced CT image (B) shows a curvilinear incomplete rim type calcification at the right margin of isolated macrocalcification detected by US.
<table>
<thead>
<tr>
<th>Type of calcification</th>
<th>No. of nodules (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central type</td>
<td>18 (90.0)</td>
</tr>
<tr>
<td>Complete</td>
<td>6</td>
</tr>
<tr>
<td>Partial</td>
<td>12</td>
</tr>
<tr>
<td>Rim type</td>
<td>2 (10.0)</td>
</tr>
</tbody>
</table>

Table 1. CT features of isolated macrocalcifications (n = 20)

메모 [a1]: R1-1.
Revised by updated patient data.
Table 2 | Nodule size, nondiagnostic FNA results, and frequency of malignant tumors according to CT types of isolated macrocalcification.

<table>
<thead>
<tr>
<th>Type of calcification</th>
<th>Nodule size (mm)</th>
<th>Nondiagnostic FNA result (%)</th>
<th>No. of malignant tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 20)</td>
<td>12.3 ± 3.4</td>
<td>9 (47.4) b)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Central type (n = 18)</td>
<td>12.3 ± 3.5</td>
<td>8 (47.1) b)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Complete (n = 6)</td>
<td>10.5 ± 3.4</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Partial (n = 12)</td>
<td>13.3 ± 3.4</td>
<td>6 (54.4) b)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Rim type (n = 2)</td>
<td>11.5 ± 2.1</td>
<td>1 (50)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

b)Mean ± standard deviation. b)FNA was not performed in one nodule.

메모 [a2]:
R1-1.
Revised by updated patient data.
FIG1

Flow diagram of patient enrollment.
Thyroid nodule with isolated macrocalcification in a 70-year-old woman. Transverse US image (A) shows a calcified nodule (6 mm) in the left lobe and the posterior margin of the calcified nodule is not visualized by strong posterior acoustic shadowing.
Axial unenhanced CT image (B) shows a complete compact central type calcification of isolated macrocalcification detected by US.
FIG3A

Thyroid nodule with isolated macrocalcification in a 59-year-old woman. Transverse US image (A) shows a calcified nodule (12 mm) with strong posterior acoustic shadowing in the right lobe.
FIG3B

Axial unenhanced CT image (B) shows a partial coarse central type calcification of isolated macrocalcification detected by US.
Thyroid nodule with isolated macrocalcification in a 50-year-old woman. Longitudinal US image (A) shows a calcified nodule (10 mm) with strong posterior acoustic shadowing in the right lobe.
Axial unenhanced CT image (B) shows a curvilinear incomplete rim type calcification at the right margin of isolated macrocalcification detected by US.