ASSOCIATION OF SONOGRAPHICALLY DETECTED CALCIFICATION WITH THYROID CARCINOMA

Ning Wang, PhD, Yuanhong Xu, PhD, Chunlin Ge, PhD, Renxuan Guo, PhD, Kejian Guo, MD, PhD

General Surgery Department II, The First Affiliated Hospital, China Medical University, Shenyang 110001, People's Republic of China. E-mail: wn232@hotmail.com

Accepted 14 March 2006
Published online 4 October 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20481

Abstract: Background. Calcification can be detected in both benign and malignant nodules and is often neglected by clinical physicians. The purpose of this study was to investigate the association of thyroid nodule calcification detected on ultrasound with thyroid carcinoma.

Methods. One hundred seven cases of thyroid carcinoma and 215 cases of benign thyroid nodules were selected from the records of inpatients of our hospital who had high-resolution ultrasonography preoperatively and pathologic diagnosis postoperatively between 2001 and 2004. The case numbers and percentage of calcification, fine stippled psammomatous (FSP), and non-FSP calcification in benign nodules and thyroid carcinoma, sex, and age groups (<45 years and ≥45 years) were retrospectively reviewed. Statistical analysis was performed using chi-square test and odds ratio. Sensitivity and specificity of calcification and FSP calcification on ultrasonography were also calculated.

Results. The incidence of calcification, non-FSP calcification, and FSP calcification were significantly higher in thyroid carcinoma than in the benign group (p < .001, p = .03, and p < .001, respectively). However, FSP calcification was more significant than the non-FSP calcification (p = .001) for predicting thyroid cancer. The incidence of non-FSP calcification and FSP calcification did not differ significantly between the sexes (p = .50 and p = .83, respectively). The relative risk of malignancy incidence was significantly higher in those younger than 45 years old with FSP calcification (p < .001). The incidence of non-FSP calcification was significantly higher in the older group (p = .03). The sensitivity of calcification and FSP calcification for the detection of malignancy was 63.55% and 24.30%, respectively; the specificity was 69.77% and 96.77%, respectively.

Conclusions. The detection of calcification on ultrasonography should increase the clinical index of suspicion for thyroid carcinoma and alert the physician. FSP calcification is valuable and has a very high specificity for predicting thyroid carcinoma, particularly for those younger than 45 years old or with calcified regional lymph nodes. To increase the sensitivity for the diagnosis of thyroid carcinoma, tests such as fine-needle aspiration cytology should also be performed. The use of these modalities could result in earlier detection of thyroid carcinoma. The use of ultrasound to detect calcification and FSP calcification is as efficient as thyroid papillary macrocarcinoma in predicting microcarcinoma.

Keywords: calcification; ultrasonography; thyroid nodule; thyroid carcinoma

In adults, clinically palpable thyroid nodules are present in 5% to 10% of the population and increase with age. High-resolution (7–13 MHz) ultrasonography has a high sensitivity for detecting thyroid nodules. Cysts as small as 2 mm and solid nodules measuring 3 mm can be detected with high-frequency transducers. High-resolution ultrasound can detect thyroid nodules in approximately 50% of the population over 50 years of age. It is important to identify which
nodules are malignant, although only 10% of solid nodules are malignant. Although ultrasonography cannot distinguish between benign and malignant exactly, it is commonly used in the initial evaluation because it is cost-effective, convenient, and noninvasive.

Calcification, often described in sonography reports, can be detected in both benign and malignant nodules. Because most thyroid nodules are benign, calcification seemingly appears more in benign nodules. Therefore, it is frequently neglected by clinicians. Thus, the purpose of this study was to investigate the association between thyroid nodule calcification detected on ultrasound and thyroid carcinoma.

**PATIENTS AND METHODS**

We retrospectively evaluated 322 patients at our hospital who, between 2001 and 2004, had undergone preoperative high-resolution ultrasonography (with a scanner of Apolio-80; Toshiba, Tokyo, Japan, with a 7.5- to 12-MHz linear-array transducer), and then thyroid surgery, with a pathologic diagnosis obtained from evaluation of paraffin-embedded slides.

The size, location, configuration, and echogenic pattern of the nodules were described in the sonography reports. Bright and sandy hyperechogenic dots of calcification, with or without shadow, sized 2 mm or less, were considered to be fine stippled psammomatous (FSP) calcifications (Figure 1). Other calcifications, including hyperechogenicity of nodular, piece-like, rim-like, and irregular shapes with shadow, that were larger than 2 mm were considered to be non-FSP calcifications (Figures 2–4). By comparing ultrasonography with the surgical record within the multinodules of the malignant group, calcification in the malignant nodules was considered to be positive, excluding the calcification in the benign nodules such as nodular goiters or in normal thyroid tissue.
We determined the distribution of cases and percentage of calcification, non-FSP calcification, and FSP calcification in the benign and malignant groups according to sex and age (<45 years and ≥45 years). Statistical analysis was performed using the chi-square test, and the 95% confidence interval (CI) of odds ratio (OR) was calculated. A p value <.05 was considered statistically significant. The sensitivities and specificities of calcification, non-FSP calcification, and FSP calcification in the diagnosis of thyroid malignancy were calculated.

RESULTS

Of the 322 cases, 107 cases were malignant, with a male-to-female ratio of 1:5.29 (Table 1); 215 cases were benign, with a male-to-female ratio of 1:4.12 (Table 2).

One hundred thirty-three (41.30%) of the 322 patients had positive ultrasound findings consistent with calcification: 100 (31.06%) had non-FSP calcification, and 33 (10.25%) had FSP calcification. Sixty-eight (51.13%) of the 133 patients with calcifications had malignancy: 42 (42.0%) of the 100 with non-FSP calcification and 26 (78.79%) of the 33 with FSP calcification. For predicting thyroid cancer, FSP calcification was more significant than non-FSP calcification (p = .001).

Thus, of the 107 patients with malignant thyroid tumors, calcification was present in 68 (63.55%); non-FSP calcification in 42 (39.25%) and FSP calcification in 26 (24.30%).

Ninety-six of the malignant thyroid tumors were papillary carcinomas. Sixty-three (65.62%) of the 96 papillary carcinomas had calcification, and 25 (26.04%) had FSP calcification. Twenty-four of the 96 papillary carcinomas were microcarcinomas. Fourteen (58.33%) of the 24 papillary microcarcinomas were calcified and 5 (20.83%) were FSP calcified. Among the other subtypes, 0% (0/1), 100% (2/2), 50.00% (2/4), 0% (0/1), and 33.33% (1/3) of follicular, anaplastic, medullary, thyroid malignant lymphoma (TML), and other carcinoma, respectively, had calcifications. FSP calcification was found in only 1 (25%) of 4 medullary carcinomas (Figure 5).

In the benign group, calcification occurred in 65 (30.23%) of 215: non-FSP calcification in 58 (26.98%) of 215, and FSP calcification in 7 (3.25%) of 215. Calcification occurred in 30.37% (41/135), 26.92% (14/52), and 35.71% (10/28) of nodular goiters, thyroid adenomas, and Hashimoto’s disease, respectively; of these, 0.74% (1/135), 9.615% (5/52), and 3.57% (1/28), respectively, had FSP calcifications (see Figure 6).

In addition, 5 of 8 patients with papillary carcinomas and FSP calcification in the primary cancer nodules had enlarged and FSP-calcified regional lymph nodes, whereas the others had enlarged.

Table 1. General conditions of the patients with thyroid malignancy.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th></th>
<th>Female</th>
<th></th>
<th>Total no. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Mean age (range), y</td>
<td>No. of cases</td>
<td>Mean age (range), y</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>13</td>
<td>40 (16–58)</td>
<td>83</td>
<td>41 (18–67)</td>
<td>96</td>
</tr>
<tr>
<td>follicular</td>
<td>0</td>
<td>–</td>
<td>1</td>
<td>33 (33)</td>
<td>1</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>1</td>
<td>47 (47)</td>
<td>1</td>
<td>68 (68)</td>
<td>2</td>
</tr>
<tr>
<td>Medullary</td>
<td>2</td>
<td>41 (22–60)</td>
<td>2</td>
<td>54 (41–68)</td>
<td>4</td>
</tr>
<tr>
<td>TML</td>
<td>0</td>
<td>–</td>
<td>1</td>
<td>65 (65)</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>72 (72)</td>
<td>2</td>
<td>62 (49–76)</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>43 (16–72)</td>
<td>90</td>
<td>42 (18–76)</td>
<td>107</td>
</tr>
</tbody>
</table>

Abbreviation: TML, thyroid malignant lymphoma.
and non-FSP-calcified regional lymph nodes. The lymph nodes of all the 8 patients showed a pathologic diagnosis of metastatic papillary carcinoma. No calcifications were present in the lymph nodes in the other malignant cases or in the benign group.

The sensitivity of calcification, non-FSP calcification, and FSP calcification for the detection of malignancy was 63.55% (68/133), 39.25% (42/100), and 24.30% (26/109), respectively; the specificity was 69.77% (73/103), 73.02% (43/52), and 96.74% (208/215), respectively. In addition, calcification, non-FSP calcification, and FSP calcification had positive predictive values of 51.13% (68/133), 42% (42/100), and 78.79% (26/33), respectively, and negative predictive values of 79.36% (150/189), 70.72% (157/222), and 71.97% (208/289), respectively.

Statistical analysis by the chi-square test indicated that both calcification and FSP calcification status differed significantly between the malignant and benign groups (p < .001 and .001), with OR values of 4.02 (95% CI, 2.40–6.67) and 9.54 (95% CI, 3.76–25.22). Calcification and FSP calcification on ultrasound had 4.02 and 9.54 times more relative risks of cancer than without calcification or FSP calcification. Non-FSP calcification status also has significant differences between the malignant and benign groups (p = .03), with OR values of 1.75 (95% CI, 1.04–2.94).

Non-FSP calcification and FSP calcification occurred in 35.59% (21/59) and 11.86% (7/59) of the men, respectively, and in 30.04% (79/263) and 9.885% (26/263) of the women, respectively. The differences between the sexes were not significant (p = .50, .83).

Calcification occurred in 42.465% (62/146) of patients <45 years of age and in 40.34% (71/176) of patients ≥45 years of age; this difference was not significant (p = .79). FSP calcification occurred in 17.81% (26/146) of those <45 years of age and 3.98% (7/176) of those ≥45 years of age; this difference was statistically significant (p < .001). The OR of presence of FSP calcification with cancer status was 11.00 (95% CI, 3.28–40.67) and 4.16 (95% CI, 0.75–24.66) in the younger and older groups, respectively. On the other hand, non-FSP calcifications were identified in 24.66% (36/146) and 36.36% (64/176) of patients in different age

Table 2. General conditions of patients with benign thyroid disease.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>Mean age (range), y</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Nodular goiter</td>
<td>30</td>
<td>53 (38–70)</td>
</tr>
<tr>
<td>Thyroid adenoma</td>
<td>10</td>
<td>42 (30–69)</td>
</tr>
<tr>
<td>Hashimoto’s disease</td>
<td>2</td>
<td>41 (32–50)</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>50 (30–70)</td>
</tr>
</tbody>
</table>

FIGURE 5. Calcification in thyroid malignant tumors. Papillary microcarcinoma and macrocarcinoma have similar non-FSP calcification and FSP calcification rates. Besides papillary carcinoma, FSP calcification was seen in only 1 case of medullary carcinoma. *TML, Thyroid malignant lymphoma; FSP, fine stippled psammomatous.
groups. Non-FSP calcifications were significantly higher in the older group ($p = .03$), with OR value of 1.75 (95% CI, 1.04–2.92).

**DISCUSSION**

Fine-needle aspiration cytology (FNAC) is quick and inexpensive. In reports, when adequate material is aspirated, including repeated FNAC, it has a sensitivity of 71% to 93% and specificity of 96%\(^2,5\) and is regarded as the “gold standard.” However, more than 85% of thyroid carcinomas are differentiated, and without enough FNA material, it is difficult to get information of capsular and vascular invasion. It was reported that FNAC had a false negative rate of 11% to 25%, and 5% to 30% of results were unsatisfactory or non-diagnostic.\(^5-7\) Moreover, FNAC cannot distinguish between benign and malignant follicular neoplasms.\(^8\)

Thyroid nodules can be found at an earlier stage with use of high-resolution ultrasonography.\(^2\) Nowadays, it is used in many institutions for a first-line investigation of thyroid disease, but its value for distinguishing malignant from benign is still controversial. Recently scholars have become aware of the importance of the association between calcification and thyroid cancer.\(^2,4,6\) Seiberling et al found that 78.8% of 66 thyroid cancers and 38.7% of 93 benign nodules had calcifications.\(^2\) Kakkos et al\(^4\) found that 54% of 37 malignant thyroid nodules and 32% of 151 benign thyroid nodules had calcifications. Our results were similar. However, excluding mirocarcinoma to be cancer, Khoo et al\(^6\) found only 26.1% of 111 malignant thyroid nodules and 8.0% of 250 benign thyroid nodules had calcifications. It is well known that ultrasonography is operator dependent and reader dependent, which usually lacks identical recognition and description of calcification patterns. To increase the accuracy of ultrasonography, it should be operated by one with expertise in sonography.

Intrathyroid calcification patterns include coarse dense nodular, piece-like, and rim-like calcifications as well as FSP calcifications. Tiny ones are often concealed by coarse calcification, dense fibrosis, and condensed colloid. Furthermore, dense fibrosis and condensed colloid can mimic microcalcification on ultrasonography\(^6,9\) (see Figure 7). FSP calcification consists of multiple fine calcified stipules. It is easy to observe and judge. Therefore, we classified calcification as unambiguous non-FSP calcification and FSP calcification.

Seiberling et al,\(^2\) Kakkos et al,\(^4\) and Khoo et al\(^6\) failed to find the difference between different calcification patterns for predicting malignancy. In our study, for predicting thyroid cancer, non-FSP calcification and FSP calcification were significantly different ($p = .001$). Moreover, FSP calcification is thought to be a familiar ultrasonographic characteristic of papillary carcinoma and represents psammoma bodies of papillary carcinoma. It not only occurs in the primary tumor but also may be seen in metastatic deposits of papillary carcinoma.\(^10\) In our patients, most had papillary carcinoma (89.72%), and other malignant tumors were relatively few; however, FSP calcification was still seen in 25.00% (1/4) of the medullary carcinomas.

![Image](head hed 1081 1401904434)

**FIGURE 7.** Condensed colloid. The mimicked calcification is shown (arrow).
It is reported that either coarse calcification or FSP calcification can be noted in papillary, medullary, and anaplastic carcinomas. In the study by Kakkos et al, calculation is also found in 0 of 2 thyroid malignant lymphomas. In our limited follicular carcinomas, no calcifications were found. But in the research of Seiberling et al, one third of follicular carcinomas had calcifications. Although the calcification rate is not described in the report of Kakkos et al, it is thought that another diagnostic criterion, sonographically detected calcification to suggest malignant follicular neoplasm, would be helpful.

Perhaps because of cancer cells' fast proliferation, cancer tissue hyperplasia, and hyperplasia mixed with necrosis, calcium is apt to deposit and lead to calcification. But in benign lesions of the thyroid, after hematoma absorption, only coarse calcification presents on the wall of nodules or fibrosis spacing in fewer cases. Therefore, in our study, calcification appeared in both benign and malignant thyroid nodules, but the rates of non-FSP calcification and FSP calcification in malignant nodules were still significantly higher than those of benign nodules. The positive rate of FSP calcification (24.30%) in malignant nodules was obviously lower than that of non-FSP calcification (39.25%), but its specificity was very high, and higher than the specificities of FNAC described earlier.

Seiberling et al, Kakkos et al, and Khoo et al believe that thyroid nodular goiter had the highest calcification rate in benign lesions. In our study, it had the second highest calcification rate (30.37%) after Hashimoto's disease (35.71%). Considering that FSP calcification has the highest specificity, and FSP calcification only occupies 0.74% of nodular goiters, FSP calcification could decrease the false positive rate. Hashimoto's disease has the highest calcification rate in the benign group, but preoperative examinations of anti-thyroglobulin, anti-thyroperoxidase, and function tests of thyroid could imply this. Thyroid adenoma had the highest FSP calcification rate. Moreover, it is hard to distinguish from solitary nodular goiter preoperatively. Although it is benign, it is apt to cause hyperthyroidism and carcinoma. Surgery is the principle therapy; therefore, diagnosis cannot alter the therapeutic choice of operation.

Similar to other research, neither non-FSP calcification nor FSP calcification showed significant differences between the sexes, indicating that the mechanism of calcification is the same. In the research of Kakkos et al, patients younger than 40 years old with calcified nodules constituted a high-risk group, with a relative risk of 3.8 versus 2.5 in patients older than 40 years old. The specificities were 87 and 57%. In the literature, there are different age standards for classification.

According to latest standard of the Union Internationale Contre le Cancer (UICC) for differentiated thyroid carcinoma, prognosis differs significantly by age at approximately 45 years. Therefore, we classified patients by age younger than 45 years and 45 years of age or older. In our research, non-FSP calcification differed significantly between age groups (p = .03). It was apt to appear in the older group. FSP calcification also differed significantly between age groups (p < .001). FSP calcification was more reliable in the diagnosis of thyroid carcinoma in the younger group than it was in the older group.

A cancer nodule with its largest diameter less than 10 mm is defined as microcarcinoma. It is hard to be suspicious of cancer by palpable hard nodules. Therefore, ultrasonography appears more useful for it. In our data, calcification and FSP calcification rates of papillary microcarcinoma are similar to those of papillary macronodules. Therefore, calcification and FSP calcification on ultrasonography for papillary microcarcinoma is as valuable as papillary macronodules and seems to be more important.

Calcifications in regional lymph nodes were few in our limited data, and the accuracy of diagnosis of carcinoma was 100% (8/8). Moreover, in 62.50% (5/8) of the lymph nodes, calcification patterns were the same as in the primary cancer lesion. It shows that FSP calcification is the specific characteristic of papillary carcinoma.

Either calcification or FSP calcification, with sensitivities of 63.55% and 24.30%, is limited as a sole marker for thyroid carcinoma. Thus, to further support a preoperative diagnosis of thyroid carcinoma, ultrasonography should be combined with other well-established diagnostic tests such as FNAC or other known risk factors. FNAC is recommended for nodules with absent halo sign, solid or hypoechoigenicity, heterogeneous echo structure, irregular margin, and without FSP calcification to make more carcinoma diagnosed preoperatively.

In conclusion, the presence of calcification on ultrasonography should alert the physician to the possibility of thyroid carcinoma. FSP calcification for carcinoma in the group younger than 45 year old is very valuable; it has a very high specificity for thyroid carcinoma. When FSP calcification appears, especially with calcified regional lymph nodes, surgery should be recommended immediately.
ately. To further support a preoperative diagnosis of thyroid carcinoma, ultrasonography should be combined with other well-established diagnostic tests such as FNAC or other known risk factors. Calcification and FSP calcification for diagnosis of thyroid papillary microcarcinoma have similar value with macrocarcinoma and seems more important.

REFERENCES
8. Tuttle RM, Lemar H, Burch HB. Clinical features associated with an increased risk of thyroid malignancy in patients with follicular neoplasia by fine-needle aspiration. Thyroid 1998;8:377–383.