Correlation between Thyroid Nodule Calcification Morphology on Ultrasound and Thyroid Carcinoma

C Shi, S Li, T Shi, B Liu, C Ding and H Qin

Fourth Department of Surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin, China

OBJECTIVE: This study investigated the detection of thyroid nodule calcifications on ultrasound and their relationship to thyroid carcinoma. METHODS: Microcalcifications (≤ 2 mm) and macrocalcifications (> 2 mm) on preoperative ultrasound examination of thyroid and lymph nodes were compared with postoperative pathological diagnoses in 4186 patients undergoing thyroid surgery.

RESULTS: Higher incidences of micro- and macrocalcifications were found in patients with thyroid carcinoma than in those with benign disease. The incidence of malignant disease was significantly higher in patients with microcalcifications than those with macrocalcifications, suggesting that the presence of microcalcifications is a better predictor of malignant thyroid carcinoma than other calcification types. The specificity of microcalcifications for a diagnosis of malignant thyroid carcinoma was 96.5%. Microcalcifications were significantly more frequent in patients aged ≤ 45 years, but there was no difference between genders. The incidence of malignancy was significantly higher in patients with single nodule calcifications than in those with multiple nodule calcifications. Lymph node calcifications were seen in 12 patients, all of whom had papillary carcinoma. CONCLUSIONS: Thyroid microcalcifications are strongly associated with thyroid carcinoma, especially micropapillary carcinoma. When cervical lymph node calcification is present, immediate surgery is required.

KEY WORDS: CALCIFICATION; THYROID NODULE; THYROID CARCINOMA; ULTRASOUND; LYMPH NODES

Introduction

With the widespread use of high-frequency ultrasonography and colour Doppler blood flow imaging, ultrasound has become one of the most important techniques for the preoperative screening of patients with thyroid disease. Intranodular calcifications are commonly seen in thyroid images in both benign and malignant diseases. The worldwide incidence of thyroid carcinoma is rising and accounts for roughly 1% of all new malignant disease.

Recognition of the correlation between thyroid malignant transformation and intragland calcification has led to ultrasonic examination becoming a crucial method for...
preoperative thyroid screening. The present study investigated the relationship between thyroid intranodular calcification, as revealed by ultrasound scan, and the incidence of thyroid carcinoma.

Patients and methods

STUDY POPULATION
All patients admitted for thyroid surgery to The Second Affiliated Hospital of Harbin Medical University, Harbin, China, between January 2005 and January 2010 were included in the study. The inclusion criteria were: (i) age 18 – 76 years old; (ii) preoperative diagnosis of thyroid disease; (iii) surgery for thyroid disease performed at The Second Affiliated Hospital of Harbin Medical University; and (iv) pathological confirmation of thyroid disease.

The study protocol was approved by the Ethics Committee of The Second Affiliated Hospital of Harbin Medical University, Harbin, China. Written informed consent was obtained from all study participants.

ULTRASOUND EXAMINATION
All patients underwent routine preoperative examination of the thyroid using high-frequency ultrasound (Vivid™ 7 colour Doppler ultrasound scanner, GE Healthcare Bio-Sciences, Piscataway, NJ, USA) with a probe frequency of 15 MHz. The size, location, morphology, boundary, envelope, echo behaviour, and intratumoural and peripheral blood flow of the lesion site were examined. The morphology and distribution of any calcification was recorded. Bright and granular calcification echo points ≤ 2 mm in diameter, with or without acoustic shadows, were considered to be microcalcifications (Fig. 1); all other calcifications with maximum diameter > 2 mm, including lumpy, irregular calcifications, with or without acoustic shadows, were defined as macrocalcifications (Fig. 2). The shape, echogenicity, size and location of calcification in the lymph nodes were noted. The final diagnosis was determined from pathology reports. A round hypoechoic nodule with a longitudinal/transverse ratio of < 2 was indicative of metastasis.

PATHOLOGICAL ASSESSMENT
Thyroid samples obtained during surgery were flash frozen for postoperative pathological examination. Micropapillary carcinomas were ≤ 10 mm in diameter and macropapillary carcinomas were > 10 mm diameter.

NODULAR CALCIFICATIONS AND AGE
The incidence of nodular calcifications according to age was examined based on the latest thyroid carcinoma data from the International Union Against Cancer, which
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indicates that the prognosis is significantly different in patients ≤ 45 years old compared with those > 45 years old. A cut-off point of 45 years old was, therefore, chosen for the analysis of nodular calcifications according to age.

STATISTICAL ANALYSES

The $\chi^2$-test or Fisher’s test was used for statistical comparisons. A $P$-value of < 0.05 was considered to be statistically significant. Data analyses were performed using SAS® statistical software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

A total of 4186 patients aged between 18 and 76 years (mean ± SD 47.6 ± 18.4 years) admitted for thyroid surgery were included in the study. Of these, 648 were male and 3538 were female (male : female ratio of 1.00 : 5.46). Thyroid diseases diagnosed at surgery included thyroid carcinoma, nodular goitre, thyroid adenoma, Hashimoto’s thyroiditis, hyperthyroidism and subacute thyroiditis.

The incidences of microcalcifications and macrocalcifications in benign and malignant thyroid disease are summarized in Table 1. There were 1391 malignant cases (225 males, 1166 females; male : female ratio 1.00 : 5.18) and 2795 benign cases (423 males, 2372 females; male : female ratio 1.00 : 5.61). Positive calcification signs were seen during preoperative ultrasound examination in a total of 1725 (41.2%) patients; of these, 916 (53.1%) cases were malignant and 809 (46.9%) cases were benign (not statistically significant). The incidence of malignancy was 96.5% (360/373) for patients with micro-

![FIGURE 2: Representative ultrasoundograph of the thyroid, showing a macrocalcification (arrow) which was regarded as a bright calcification echo point with maximum diameter > 2 mm](image)

<table>
<thead>
<tr>
<th>Disease status</th>
<th>$n$</th>
<th>Macrocalcification ($&gt; 2$ mm)</th>
<th>Microcalcification ($\leq 2$ mm)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign disease</td>
<td>2795</td>
<td>796 (28.5)</td>
<td>13 (0.5)</td>
<td>809 (28.9)</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>1391</td>
<td>556 (40.0)$^a$</td>
<td>360 (25.9)$^b$</td>
<td>916 (65.9)</td>
</tr>
<tr>
<td>Total</td>
<td>4186</td>
<td>1352 (32.3)</td>
<td>373 (8.9)</td>
<td>1725 (41.2)</td>
</tr>
</tbody>
</table>

Data presented as $n$ or $n$ (%).

$^aP < 0.0001$ compared with macrocalcification in benign disease, $\chi^2$-test or Fisher’s test.

$^bP < 0.0001$ compared with microcalcification in benign disease, $\chi^2$-test or Fisher’s test.
calcifications and 41.1% (556/1352) for patients with macrocalcifications (P < 0.01).

Of the 1725 patients with calcifications, 659 (38.2%) showed a single nodular area of calcification; of these, 193 (29.3%) were benign and 466 (70.7%) were malignant. The remaining 1066 patients (61.8%) had multiple nodular calcifications; of these, 543 (50.9%) were benign and 523 (49.1%) were malignant. The incidence of malignancy was significantly higher in patients with single nodular calcification than in those with multiple calcifications (P < 0.05).

A breakdown of the incidence of macro- and microcalcifications in patients with benign thyroid disease, according to pathological diagnosis, is given in Table 2. Calcifications were seen in 809 of 2795 patients with benign thyroid disease (28.9%). The incidence of microcalcifications in benign thyroid disease was 0.5%, which was significantly smaller than that in malignant cases (25.9%; P < 0.0001; Table 1).

A breakdown of the incidence of macro- and microcalcifications in patients with malignant thyroid disease, according to pathological diagnosis, is given in Table 3. Calcifications were seen in 916 of 1391 patients with malignant thyroid disease (65.9%). Of these 916 patients, 36 (3.9%) were found to have lymph node metastasis.

In thyroid carcinoma, the incidence of microcalcifications (25.9%; 360/1391 patients) was lower than that of macrocalcifications (40.0%; 556/1391 patients), but this difference was not statistically significant (Table 3). In micropapillary carcinomas, however, the incidence of microcalcifications (47.4%; 161/340 patients) was significantly higher than that for macrocalcifications (12.4%; 42/340 patients; P < 0.0001). The incidence of microcalcifications was significantly higher in micropapillary carcinomas (47.4%; 161/340 patients) than in macro-papillary carcinomas (19.9%; 192/963 patients; P < 0.0001).

The incidence of calcifications according to age and gender is given in Table 4. There was no significant difference in the overall incidence of calcifications in the two age groups; however, the incidence of microcalcifications was significantly higher in patients ≤ 45 years old compared with older patients (P < 0.0001; Table 4) and the incidence of macrocalcifications was significantly lower in patients ≤ 45 years old compared with older patients (P < 0.0001; Table 4).

### Table 2:

<table>
<thead>
<tr>
<th>Pathological diagnosis</th>
<th>n</th>
<th>Macrocalcification (&gt; 2 mm)</th>
<th>Microcalcification (≤ 2 mm)</th>
<th>Total</th>
<th>Statistical significancea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular goitre</td>
<td>2152</td>
<td>751 (34.9)</td>
<td>8 (0.4)</td>
<td>759 (35.3)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Adenoma</td>
<td>359</td>
<td>13 (3.6)</td>
<td>1 (0.3)</td>
<td>14 (3.9)</td>
<td>P = 0.0012</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>231</td>
<td>29 (12.6)</td>
<td>4 (1.7)</td>
<td>33 (14.3)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>38</td>
<td>2 (5.3)</td>
<td>0 (0.0)</td>
<td>2 (5.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Subacute thyroiditis</td>
<td>15</td>
<td>1 (6.7)</td>
<td>0 (0.0)</td>
<td>1 (6.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>2795</td>
<td>796 (28.5)</td>
<td>13 (0.5)</td>
<td>809 (28.9)</td>
<td>P &lt; 0.0001</td>
</tr>
</tbody>
</table>

Data presented as n or n (%).

NS, not statistically significant (P > 0.05)

aWithin-group comparison between macrocalcification and microcalcification incidence, χ²-test or Fisher’s test.
Table 4. There was no significant difference between males and females in the incidences of micro- or macrocalcifications, or in the overall calcification incidence (Table 4).

Localized lymph node calcification was seen in 12 patients. All of these patients had a pathological diagnosis of papillary carcinoma; eight patients (66.7%) had thyroid microcalcifications and four (33.3%) had macrocalcifications. No lymph node calcification was seen in patients with benign disease or other types of malignant disease.

**Discussion**

The incidence of thyroid disease can vary depending on factors such as the patient population and the examination technique used.\textsuperscript{13,14} In recent years, high-resolution ultrasonography has been widely used to screen for thyroid disease, but its value in differentiating benign from malignant disease is still under debate. A number of studies have shown a close relationship between calcification and thyroid carcinoma. For example, Kakkos \textit{et al.}\textsuperscript{15} reported that 54% of thyroid nodules with calcification were malignant, which is consistent with the 53.1% malignancy rate seen in cases with calcification in the present study. Similar findings were reported by Taki \textit{et al.}\textsuperscript{16} It is, therefore, apparent that calcification is correlated with thyroid carcinoma. In addition, the incidence of calcification in malignant thyroid carcinoma (65.9%) was higher than that in nodular goitre (35.3%) in the present study; this is consistent with the results of Consorti \textit{et al.},\textsuperscript{6} who reported incidences of 39.4% and 20.1% in thyroid carcinoma and goitre, respectively.

Ultrasound has been previously reported to have a specificity and sensitivity in detecting thyroid nodule calcifications of 91.3% and 43.1%, respectively,\textsuperscript{1} suggesting...
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that ultrasonography can be used as the first step in thyroid nodule calcification screening. Some previous studies, however, did not include the effect of different calcification forms on the correct prediction of malignant disease. In the present study, the incidence of malignancy was significantly higher in patients with microcalcifications (96.5%) compared with those with macrocalcifications (41.1%), suggesting that the occurrence of microcalcifications may be a reliable predictor of thyroid carcinoma. Wang et al. previously also reported a close correlation between microcalcifications detected on ultrasound and carcinoma, with a specificity of 96.7% and Chammas et al. reported similar findings, thereby indicating that the presence of microcalcifications may be a specific predictor for thyroid carcinoma.

In the present study the incidence of microcalcifications (25.9%) in malignant thyroid carcinoma was significantly lower than for macrocalcifications (40.0%); however, the fact that 96.5% of patients with microcalcifications had malignancy, means that the presence of microcalcifications is highly specific for malignancy and has important diagnostic value. The incidence of microcalcifications was only 0.5% in benign thyroid diseases, which is notably lower than the rate in thyroid carcinoma (25.9%); therefore the presence of microcalcifications can reduce the incidence of false-positive results. In the present study, patients with nodular goitre had the highest calcification incidence among all benign cases, consistent with the findings of others.

Calcifications can occur in metastasized lesion sites as well as in primary tumours. In the present study, the incidence of papillary carcinoma in the limited number of patients with localized lymph node calcification was 100%. This suggests that, once a patient with

<table>
<thead>
<tr>
<th>Disease status</th>
<th>n</th>
<th>Total</th>
<th>Statistical significance</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 45 years</td>
<td>1901</td>
<td>807 (42.5)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>&gt; 45 years</td>
<td>2285</td>
<td>918 (40.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>648</td>
<td>295 (45.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>3538</td>
<td>1430 (40.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data presented as n of patients, or n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS, not statistically significant (P &gt; 0.05)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Between-group comparison of calcification incidence (age ≤ 45 years versus &gt; 45 years; and male versus female); χ²-test or Fisher’s test.</td>
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</tbody>
</table>
thyroid disease is shown to have cervical lymph node calcification on ultrasound, immediate surgery is required. Of these patients, 66.7% had microcalcifications, further supporting microcalcification as a specific diagnostic indicator for papillary carcinoma.

A previous study found that patients < 40 years of age with calcification had a risk of thyroid carcinoma that was 1.52-fold higher than older patients (≥ 40 years), and the specificities of calcification for a malignant tumour diagnosis in the two age groups were 87% and 57%, respectively. In the present study, there was no difference in the overall incidence of calcification in patients younger or older than 45 years. The incidence of microcalcifications, however, was significantly higher in the younger group, which is consistent with a previous report. There was no difference in the calcification incidence between males and females, suggesting the same calcification mechanism occurs in both genders.

In the present study, the incidence of micropapillary carcinoma was significantly higher in patients with microcalcifications than in those with macrocalcifications and the incidence with which microcalcifications were associated with macropapillary carcinomas was significantly smaller than the association with micropapillary carcinomas. This suggests that an ultrasound finding of microcalcifications is of more value than a finding of macrocalcifications in the diagnosis of micropapillary carcinoma and that the detection of microcalcifications is of more clinical significance in the diagnosis of micropapillary carcinoma than in the diagnosis of macropapillary carcinoma. This is in contrast to an earlier report in which there was no difference between micro- and macropapillary carcinomas in their association with microcalcifications.

A previous study found that 50% of patients with single nodular calcifications had malignant thyroid disease. In the present study, a significantly higher percentage of patients with single nodular calcifications (70.7%) had malignant thyroid disease compared with those with multiple nodular calcifications (49.1%), suggesting that single nodular calcifications are more closely associated with malignancy than multiple nodular calcifications, and is in agreement with the findings of others.

More precise preoperative diagnosis of thyroid carcinoma would require a combination of ultrasound examination and other methods, such as needle aspiration cytology and other highly sensitive techniques. In particular, if the nodule is substantive, lacks the halo sign or a strong internal echo signal, or if the echoing structure is heterogeneous with ambiguous boundaries and no signs of microcalcifications are present, needle aspiration cytology is recommended.

In summary, microcalcifications detected by colour Doppler ultrasound are highly specific for the diagnosis of thyroid carcinoma, particularly papillary thyroid carcinoma, and have important clinical value in the diagnosis of micropapillary carcinomas. When cervical lymph node calcification is present, immediate surgery is required.

**Conflicts of interest**
The authors had no conflicts of interest to declare in relation to this article.
References


Author’s address for correspondence

Dr Huadong Qin
Fourth Department of Surgery, The Second Affiliated Hospital of Harbin Medical University, Xue Fu Road, Nangang District, Harbin 150086, Heilongjiang Province, China.
E-mail: aitiantang83@126.com