

Diagnostic Value of Ultrasound-detected Calcification in Thyroid Nodules

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Abstract

Introduction: This study analyses the diagnostic value of ultrasonography (US) detection for calcification in thyroid nodules. **Materials and Methods:** We analysed the preoperative US findings and clinical characteristics of 577 malignant and 3434 benign thyroid patients who underwent surgery in our hospital. **Results:** The malignant rate in patients with microcalcification hyperechoic and tiny calcification foci ≤ 2 mm in diameter was significantly higher than the non-calcification and other calcification group ($P < 0.001$). The malignant rate in single calcification nodule was significantly higher than that in multiple nodule group ($P < 0.01$). Most of the patients (37/39) with lymph node calcification were malignant. The malignant rate of calcification and microcalcification was significantly higher in patients < 45 years old than in older patients ($P < 0.05$). **Conclusion:** Compared with other calcifications, microcalcification should be a better predictor of thyroid carcinoma. Malignancy should be highly suspected in patients with single calcification nodule, especially with lymph node calcification. Patients younger than 45 years of age with calcification or microcalcification have a greater risk for thyroid carcinoma.

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Key words: Age, Single nodule, Thyroid carcinoma, Ultrasonography

Introduction

Thyroid nodules which can be palpated are present in between 4% and 7% of the population. Solid nodules as small as 3 mm and cysts of 2 mm can be detected with high-frequency ultrasonography (US).¹ US has been also commonly used to differentiate malignant nodules from all thyroid lesions using several sonographic features. Both benign and malignant thyroid nodules can present with calcifications in thyroid images but the incidence of calcification (especially microcalcification) is higher in malignant thyroid nodules.²⁻⁵ Thus, the purpose of this study is to further evaluate the association of different types of calcifications detected on the ultrasound to thyroid carcinoma, and to evaluate the diagnostic accuracy of different calcification types, in a large cohort of Chinese patients.

Materials and Methods

Patients

We retrospectively evaluated the records of 4011 consecutive patients who received preoperative high-resolution US examinations for thyroid nodule and underwent thyroid surgery between January 2005 and January 2010 at our Hospital.

US Examination Technique

The US examination was performed with a scanner of Apolio-80 (Toshiba, Tokyo, Japan) and a 7- to 12-MHz linear-array transducer. All of the calcification characteristics were recorded. The location, size, shape, boundary, envelope, echo feature of the nodules and the characteristic of the lymph nodes were examined. The

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final neck US examination was performed within 1 month before surgery.

Thyroid Nodule Calcification and Pathological Result

Microcalcifications were defined as hyperechoic and tiny calcification foci ≤ 2 mm in diameter, either with or without acoustic shadows (Fig. 1); macrocalcifications were indicated by the presence of irregular calcifications with maximum diameter > 2 mm (Fig. 2); rim calcifications were defined when a nodule had egg-shell or peripheral curvilinear calcification (Fig. 3).^{6,7}

The diagnoses were confirmed by postoperative histopathology. Microcarcinomas were ≤ 10 mm in maximum diameter and macrocarcinomas were > 10 mm in maximum diameter.

Gender and Age

Malignant rates with different types of calcification were calculated in male and female patients. According to a previous study, there is a significant difference in prognosis between patients < 45 years old and ≥ 45 years old.⁸ Vini et al found that patients aged ≥ 70 years old were significantly more likely to have advanced disease and higher incidence of recurrence and mortality than younger patients.^{9,10} The cut-off points of 45 and 70 years old were chosen for the analysis of malignancy rate with calcification according to age.

Statistical Analysis

The chi-square test with the 95% confidence interval (CI) of odds ratio (OR) was deployed. A value of $P < 0.05$ was considered statistically significant. The sensitivities, specificities, positive predictive value, negative predictive value and accuracy of calcification, microcalcifications, macrocalcifications and rim calcification in the diagnosis of thyroid malignancy were calculated. Statistical analysis was performed using SPSS statistical software, version 16.0 (SPSS Institute, Chicago, USA).

Results

A total of 4011 patients aged between 7 and 83 years old (mean 51.99 ± 10.92 years) who received thyroid surgery were analysed in our study. Among these, 873 were male and 3138 were female, with a male-to-female ratio of 1 : 3.59. Medical history, physical and imaging examinations and fine needle aspiration biopsy results were considered before deciding whether or not to have surgery. Operation types included excisional biopsy, hemi/total thyroidectomy and lymph node dissection. The postoperation histopathological diagnosis included thyroid carcinoma, nodular goitre,



Fig. 1. A thyroid nodule (papillary thyroid cancer) with microcalcification (white arrow).



Fig. 2. A benign thyroid nodule with macrocalcification (white arrow).



Fig. 3. A benign thyroid nodule with rim calcification (white arrow).

thyroid adenoma and Hashimoto’s thyroiditis.

Calcifications were found in 39.37% (1579/4011) of all patients. Of the patients with calcifications, 33.69% (532/1579) had microcalcifications, 60.16% (950/1579) had macrocalcifications and 6.14% (97/1579) had rim calcifications. The incidence of malignancy was 56.02% (298/532) for patients with microcalcifications and 15.85% (166/1047) for patients with other calcifications including 16.11% (153/950) of macrocalcification and 13.40% (13/97) of rim calcification. The malignant rate in patients with calcifications were higher than that with non-calcification group ($P < 0.001$), with OR values of 8.54 (95% CI, 6.87 to 10.62). The malignant rate in patients with microcalcification was also significantly higher than that without microcalcification ($P < 0.001$), with OR value of 14.61 (95% CI, 11.84 to 18.03)(Table 1).

Of the 577 patients with malignant thyroid tumors, calcifications were detected in 80.42% (464/577): microcalcifications in 51.65% (298/577), macrocalcifications in 26.52% (153/577) and rim calcification in 2.25% (13/577). Ninety-six percent of the malignant thyroid tumours were papillary carcinomas in which 82.40% (440/534) had calcification, and 54.68% (292/577) had microcalcifications. The rate of calcification for other types of malignant tumours are summarised in Table 2.

In our group, the microcarcinomas were all micropapillary carcinomas histopathologically. The incidence of

microcalcification in microcarcinomas and macrocarcinomas were 52.23% (82/157) and 50.00% (210/420) respectively. There was no significant difference in the incidence of microcalcification in the 2 types of carcinomas (Table 2).

A total of 352 (22.29%) patients presented a single calcification nodule area in the 1579 patients with calcifications. Of them, 188 (53.41%) cases were malignant and 164 (46.59%) cases were benign. Of the 532 patients with microcalcifications, 174 (32.71%) showed a single calcification nodule area. Of these patients, 128 (73.56%) were malignant and 46 (26.44%) were benign. The incidence of malignancy was significantly higher in patients with single calcification nodule than in those with multiple calcification nodules ($P < 0.001$), with OR values of 3.95 (95% CI, 3.08 to 5.07). The malignant rate was also significantly higher in patients with single microcalcifications nodule ($P < 0.001$), with OR values of 3.08 (95% CI, 2.07 to 4.57) (Table 3).

Thirty-nine patients showed localised lymph node calcification. Thirty-seven of these patients were given a pathological diagnosis of metastatic papillary carcinoma while the other 2 were diagnosed with Hashimoto thyroiditis. Twenty-nine of these 37 patients had microcalcifications in the regional lymph nodes, whereas the others had macrocalcification in the lymph nodes.

There was no significant difference for the incidence of malignancy between male and female groups combined with calcification (31.61 % (98/310) vs 28.84 % (366/1269); P

Table 1. Calcification Types and Malignant Rates

Type of Calcification	Malignant cases	Benign cases	Malignant rate (%)	P value	Odds ratio	95% Confidence Interval
Microcalcification (n = 532)	298	234	56.02	<0.001	14.61	(11.84, 18.03)
Macrocalcification (n = 950)	153	797	16.11	0.084		
Rim calcification (n = 97)	13	84	13.40	0.78		
Calcification (n = 1579)	464	1115	29.39	<0.001	8.54	(6.87, 10.62)

Table 2. Pathological Diagnosis of 577 Malignant Thyroid Nodules with Different Calcifications

Pathological diagnosis	n	Microcalcification	Macrocalcification	P value
Papillary carcinoma	534	292	148	$P = 0.70$
Microcarcinoma (≤ 10 mm)	157	82	39	
Macrocarcinoma (> 10 mm)	377	210	109	
Medullary carcinoma	20	4	9	
Follicular carcinoma	2	0	0	
Anaplastic carcinoma	7	1	3	
Thyroid lymphoma	7	0	1	
Thyroid fibrosarcoma	3	0	2	
Others	4	1	3	
Total	577	298	166	

Table 3. Malignant Rates in Single and Multiple Nodule Combined with Calcifications

Single or multiple calcification nodule	n	Malignant Cases	Benign Cases	Malignant rate (%)	P value	Odds ratio	95% Confidence Interval
Single calcification	352	188	164	53.41	<0.001	3.95	(3.08, 5.07)
Multiple calcification	1227	276	951	21.67			
Single microcalcification	174	128	46	73.56	<0.001	3.08	(2.07, 4.57)
Multiple microcalcification	358	170	188	47.04			

Table 4. Malignant Rates in Different Age Status Combined with Calcifications

Age, years (n)	Age status combining with calcification (Malignant rate %)	P value	Age status combining with microcalcification (Malignant rate %)	P value
<45 years (1238)	49.20 (247/502)	< 0.001	74.90 (179/239)	< 0.001
45 to 70 years (2616)	20.18 (205/1016)	NA	40.43 (112/277)	NA
≥70 years (157)	19.67 (12/61)	NA	43.75 (7/16)	NA

Table 5. Diagnostic Value of Us Findings for Malignant Nodules According to Calcifications

Type of Calcification	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Calcification (n = 1579)	80.42	67.53	29.39	95.35	69.38
Microcalcification (n = 532)	51.65	93.19	56.02	91.98	87.21
Macrocalcification (n = 950)	26.52	76.79	16.11	86.15	69.56
Rim calcification (n = 97)	2.25	97.55	13.40	85.59	83.84

>0.05), as well as with microcalcification (51.69% (61/118) vs 57.25% (237/414); $P > 0.05$).

The malignant rates with calcifications in different ages were shown in Table 4. The malignant rate of calcification and microcalcification was significantly higher in patients < 45-years old compared with older patients ($P < 0.05$). There was no significant difference between the 45 to 70 years and ≥ 70 years groups ($P > 0.05$).

The sensitivities of calcification, microcalcification, macrocalcification and rim calcification for predicting malignancy were 80.42%, 51.65%, 26.52% and 2.25%, respectively; and the corresponding specificity were 67.53%, 93.19%, 76.79% and 97.55%, respectively. In addition, calcification, microcalcification, macrocalcification and rim calcification had positive predictive values of 29.39%, 56.02%, 16.11% and 13.40%, respectively, and negative predictive values of 95.35%, 91.98%, 86.15% and 85.59%, respectively (Table 5).

Discussion

Several studies reported the association of calcification and thyroid carcinoma. Lu et al found that calcification was presented in 49.6% (128/258) of malignant nodules and 15.7% (292/1864) of benign nodules.¹¹ Similar findings by Wang et al reported calcification present in 68 (63.55%)

of the 107 patients with malignant thyroid tumours.¹² Our studies show that 80.42% (464/577) of malignant thyroid nodules exhibited calcifications. The result is consistent with the calcification rate in the previous study. The presence of calcification was associated with an OR value of 8.54 for malignancy, suggesting that there was 8.54 times more relative risk of carcinoma than without calcification. The possible reason for higher calcification rate in the malignant group was the difference in formation of calcification in benign and malignant diseases. The fast proliferation of cancer cells and the hyperplasia mixed with necrosis of cancer tissue promote calcium deposition and calcification formation. But in benign thyroid lesions, macrocalcifications present on the wall of nodules after the hematoma absorption in a few cases.¹²

A number of studies focus on the relationship between thyroid nodule microcalcification and malignancy. Lu et al studied 2122 thyroid nodules and found that the incidence of microcalcifications was significantly higher in malignant than benign thyroid nodules. They were 33.7% (87/258) and 6.4% (120/1864) respectively.¹¹ Moon et al reported a microcalcification rate of 44.2% in malignant nodules which was much higher than that of in benign nodules.¹³ Shi et al found that the malignant rate was significantly higher in patients with microcalcifications (96.5%) compared with macrocalcifications (41.1%).¹⁴ We also have the

similar findings. The presence of microcalcifications was associated with an OR value of 14.61 for malignancy, suggesting that thyroid nodules with calcification had 14.61 times more relative risk of carcinoma than those without microcalcification. High specificity (93.19%) and accuracy rate (87.21%) suggest that compared to other calcifications, microcalcification should be a better predictor of thyroid carcinoma.

In the present study, the incidence of malignancy is significantly higher in patients with single calcification nodule than in those with multiple calcification nodules. The malignant rate was also significantly higher in patients with single microcalcification nodule, which was similar to other studies.¹⁵ Our studies also suggest that the association between single calcification nodule and malignancy is closer than the association between multiple calcification nodules and malignancy. So malignancy should be highly suspected in patients with single calcification nodule, especially with single microcalcifications nodule.

Wang et al reported that the relative risk of presence of microcalcification with carcinoma was higher in patients <45 years old than those >45 years old.¹² In our group, the malignant rate of calcification and microcalcification was significantly higher in patients <45 years old compared with older patients ($P < 0.05$), which is consistent with a previous report.¹⁴

Choi et al¹⁶ evaluated the diagnostic accuracy of preoperative US and computed tomography (CT) examination of the neck in 589 patients. The specificity of both methods was higher than 90% for cervical lymph node metastasis. In our study, the malignant rate of patients with localised lymph node calcification was 94.87% (37/39). Moreover, 78.38% (29/37) of these lymph nodes presented microcalcification as in the primary cancer lesion. We consider that the patient should be recommended for surgery if the localised lymph node calcification, especially microcalcification, was found with the primary nodule calcification.

Conclusion

In conclusion, the association between calcification in ultrasonography and malignancy is confirmed in this study. Compared with other calcifications, microcalcification has a higher diagnosis value for thyroid carcinoma. Malignancy should be highly suspected in patients with single calcification or microcalcification nodule. It is necessary to recommend surgery for patients younger than 45 years old with calcifications, especially with lymph node calcification.

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