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Association between computed tomography-detected calcification and thyroid carcinoma

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This study aimed to investigate the diagnostic value of calcification detected by computed tomography (CT) for the differentiation of benign and malignant thyroid nodules. This is a retrospective study of 930 consecutive patients (709 women, 221 men; mean age 51 years) with pathologically proven thyroid nodules. The characteristics of calcification on CT images were correlated with the pathological results. A total of 168 patients were pathologically diagnosed with thyroid carcinomas and 762 patients with benign thyroid nodules. Calcification was found in 231 cases (24.84%). The incidence of calcification was significantly higher in patients with thyroid carcinoma (52.38%) than in those with benign nodules (18.77%; $P < 0.001$). Detection of calcification in diagnosing thyroid carcinoma had a sensitivity of 52.38% (88/168) and specificity of 81.23% (619/762). No significant difference was noticed in the incidence of microcalcification (≤ 2 mm) between malignant and benign nodules ($P = 0.305$). Calcification is more frequently found in thyroid carcinomas than benign nodules. CT detected-calcification may suggest malignant disease. Further confirmation of the suspected malignancy with fine-needle aspiration or surgery is still needed.

Key words: thyroid neoplasm, thyroid nodule, calcinosis, computed tomography

Thyroid neoplasm include nodular goiter, thyroid adenoma, and thyroid carcinoma. Differentiating between benign and malignant thyroid nodules can be tricky with clinical manifestation and image findings. Calcification is a common finding in thyroid imaging, and can occur in both benign and malignant thyroid lesions [1-4]. It has been found that the thyroid carcinoma has a higher incidence of calcification than benign thyroid nodules [5, 6]. Most of these calcified thyroid nodules were detected with ultrasonography. However, computed tomography (CT) detected-calcification has rarely reported [7]. Here we report our results with an increased sample size compared with Wu *et al* [7] (930 vs. 383).

In this study, we retrospectively reviewed 930 patients with thyroid nodules that underwent thyroidectomy and pathological examination. The calcification pattern, size, and location were analyzed and correlated with the pathology of the thyroid nodules.

Patients and methods

Patients. From January 2005 to November 2013, 930 patients with thyroid nodules underwent thyroidectomy in our hospital. The diagnosis was made pathologically. The patients included 221 men and 709 women (man: woman ratio, 1: 3.2). Their ages ranged from 13 to 82 years with a median age of 51 years. The initial symptom in most patients was goiter with disease courses from 2 days to 6 years. This study was approved by the Ethics Committee of our hospital.

Imaging study. CT images were obtained with the patients in the prone position with hyperextension of the neck (GE BrightSpeed, LightSpeed, 32 slice). The slice thickness and interslice interval were both 3 to 5 mm. Plain and enhanced scanning was performed from the upper borderline of the hyoid gland to the aortic arch. The contrast was OMNIPAQE (300 mg/ml) 80-100 ml injected via the ulnar vein at a rate of 2-3 ml/s. Dual-phase enhanced scanning was performed at 35 s and 50 s after contrast injection. The CT images were interpreted independently by two experienced radiologists. When different opinions occurred, the two readers discussed to reach agreement.

Classification of the calcification. Microcalcification has a diameter ≤ 2 mm. Coarse calcification has a diameter > 2 mm or irregular eggshell calcification. Only one calcification was solitary and > 1 calcification was multiple. The calcification

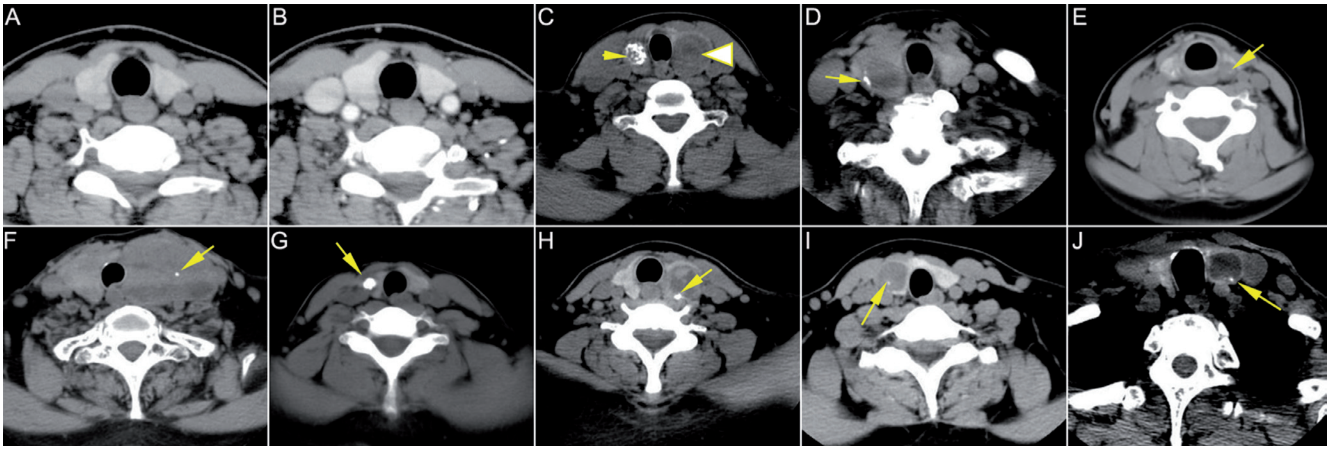

Figure 1. CT images of the thyroid nodules.
A) The thyroid CT image of a healthy patient in the plain scanning. B) The thyroid CT image of a healthy patient in the enhanced scanning. C) Calcification (arrow) was noticed in the right thyroid, which was pathologically diagnosed as papillary carcinoma. A cyst (arrow head) was found in the left thyroid, with a pathological result of follicular adenoma. D) CT detected coarse calcification (arrow) in the right side, which was pathologically diagnosed as nodular goiter with lymphocyte infiltration. E) CT detected microcalcification (arrow) in the left thyroid with a pathological result of papillary carcinoma. F) CT showed bilateral thyroid goiter and left-sided calcification (arrow). Pathological examination found adenoma with calcification. G) A CT-detected right-sided coarse calcification (arrow) was pathologically diagnosed as microcarcinoma. H) CT detected a coarse calcification in the left thyroid (arrow), which was shown by pathological examination as follicular adenoma with calcification. I) A microcalcification (arrow) in the right thyroid detected by CT was shown by pathological examination as papillary carcinoma. J) CT found left-sided peripheral calcification (arrow), which was pathologically proven to be adenoma with calcification.

was also classified as intranodular calcification and peripheral calcification. The diagnosis of nodular goiter did not exclude thyroid adenoma. The diagnosis of thyroid adenoma included follicular adenoma and acidophilic adenoma. The diagnosis of Hashimoto thyroiditis did not exclude nodular goiter and adenoma.

Statistical analysis. The data were analyzed using SPSS software (SPSS 21.0, IBM, US). The comparisons were made with χ^2 test and $P < 0.01$ was considered statistically significant.

Results

Pathological results. Of all the cases, 18.06% (168/930) were malignant thyroid nodules and 81.94% (762/930) were benign thyroid nodules. Among the 168 malignant cases, 91 patients had papillary carcinomas, 7 had follicular carcinomas, 6 had medullary carcinomas, and 63 had microcarcinomas. The 762 benign cases contained 293 nodular goiter cases, 402 cases of thyroid adenoma, 62 cases of Hashimoto thyroiditis and 5 cases of subacute thyroiditis (Table 1). Besides, in 66.67% of the patients with thyroid carcinoma, benign nodules were also found, including 40 cases of nodular goiter, 41 cases of adenoma, and 31 cases of Hashimoto thyroiditis (Fig. 1). Metastases to the neck lymph nodes were seen in 6 cases of thyroid carcinoma.

Table 1. Pathological diagnosis of the thyroid nodules

Pathology	Values (n, %)
Malignant thyroid nodules	168 (18.06%)
Papillary carcinoma	92 (54.76%)
Follicular carcinoma	7 (4.17%)
Medullary carcinoma	6 (3.57%)
Microcarcinoma	63 (37.50%)
Benign thyroid nodules	762 (81.94%)
Nodular goiter	293 (38.45%)
Thyroid adenoma	402 (52.76%)
Hashimoto thyroiditis	62 (8.14%)
Subacute thyroiditis	5 (0.65%)

Calcification detected by CT. Calcification was found in 231 cases of all patients (24.84%). The incidence of calcification was significantly higher in patients with thyroid carcinoma than those with benign nodules (52.38% vs 18.77%; $P < 0.001$) (Table 2). In patients with calcified nodules, no significant differences in the incidences of microcalcification (≤ 2 mm) ($P = 0.31$) and solitary calcification ($P = 0.46$) were noticed (Table 2). However, the incidence of intranodular calcification was significantly higher in patients with thyroid carcinoma than those with benign nodules ($P < 0.01$) (Table 2), with a sensitivity of 79.55% and a specificity of 67.83%. In patients with various malignant thyroid nodules, no significant difference was found between the incidence of microcalcification and coarse calcification (Table 3).

Sex and age relationships with thyroid nodules. The incidence of thyroid carcinoma did not differ significantly between males and females ($P > 0.05$). In patients with either benign or malignant thyroid nodules, there was no significant

Table 2. Correlation of CT-detected calcification patterns with the thyroid nodular nature

Items	Malignant (n, %)	Benign (n, %)	χ^2	P
Calcification			83.31	< 0.01
Positive	88 (52.38%)	143 (18.77%)		
Negative	80 (47.62%)	619 (81.23%)		
Calcification size			1.05	0.31
Microcalcification	45 (51.14%)	83 (58.04%)		
Coarse	43 (48.86%)	60 (41.96%)		
Calcification numbers			0.55	0.46
Solitary	53 (60.23%)	79 (55.24%)		
Multiple	35 (39.77%)	64 (44.76%)		
Calcification distribution			41.30	< 0.01
Intranodular	70 (79.55%)	56 (36.60%)		
Peripheral	18(20.45%)	97(63.40%)		

Table 3. Incidence of microcalcification and coarse calcification in patients with various malignant thyroid nodules

	n	Coarse calcification (> 2 mm)	Microcalcification (≤ 2 mm)	Calcification rate (%)	χ^2	P
Papillary carcinoma	91	27	27	59.34	3.815	0.258
Medullary carcinoma	6	1	3	66.67		
Follicular carcinoma	7	2	0	28.57		
Microcarcinoma	63	17	10	42.86		
Total	167	47	40	52.10		

Fisher's exact test.

Table 4. Comparison of the calcification rate between males and females in malignant and benign thyroid nodules

Items	Malignant (n, %)		Benign (n, %)	
	Calcification (n = 80)	Non-calcification (n = 88)	Calcification (n =143)	Non-calcification (n = 619)
Male	18(46.15%)	21(53.85%)	29(15.93%)	153(84.07%)
Female	72(55.81%)	57(44.19%)	114(19.66%)	466(80.34%)
P-value	0.26		0.29	

difference in the incidence of calcification between males and females ($P > 0.05$) (Table 4). The mean age of male patients with malignant thyroid nodules was significantly lower than of those with benign nodules (49.12 ± 12.31 vs 53.86 ± 11.72, $P < 0.05$). However, the mean age did not differ significantly between female patients with malignant and benign thyroid nodules (51.18 ± 12.80 vs 52.12 ± 13.71, $P = 0.539$).

Discussion

It is critically important to distinguish malignancy when facing thyroid nodules in clinical practice. Both malignant and benign thyroid nodules can develop calcifications, with higher incidence of calcification detected in malignant nodules (42%-72.3%) compared with that in benign nodules (13.1%-23.0%) [5-7]. At present, the major preoperative tool for diagnosing thyroid lesions is ultrasonography, because this method is relatively inexpensive, sensitive and easy-operating [8]. In contrast to ultrasonography, CT is uncommon in clinical practice due to high expense, more radiation exposure and doubtful utility in private clinical practice. However, CT could give additional information for restrosternal goiters, cervical metastatic illness, and so on, which may be useful in guiding further operation planning preoperatively. According to our experience, there is a united standard for the diagnosis of calcification on CT, while the diagnosis of calcification on ultrasonography depends on the senior doctors' experience to a great extent. In addition, calcification is also a common finding in thyroid nodules on CT, suggesting that CT-detected calcified thyroid nodules may have the potential value for predicting possible malignancy in thyroid nodules. This study found that CT-detected calcification, especially intranodular calcification, is associated with thyroid carcinoma (Table 2).

At ultrasonography, the reported incidence rate of calcification in thyroid nodules was 37.75% [9]. Wu *et al* have reported that the rate of calcification in thyroid nodules observed on CT was 35% [7]. In our study, the results showed that calcification was noted in 24.84% of the thyroid nodules, which was lower than the above results. The possible reason may be that ultrasonography has a higher detecting ability of calcifications < 1 mm than CT and the different technical setting or types of CT machines compared with the study of Wu *et al* [7]. Besides, our study included a larger population than that in the study of Wu *et al* [7]. Previous studies have demonstrated that the incidence of calcification in malignant thyroid nodules is higher than that in benign thyroid nodules whatever on ultrasonography or CT [7, 10-12]. Similar to the above results, it was found in our study that the incidence of calcification was significantly higher in patients with malignant nodules than those with benign nodules ($P < 0.01$) (Table 2).

It has been found that microcalcification is associated with thyroid carcinoma and coarse calcification is associated with benign nodules [7, 13-15]. Microcalcification indicates the histological pattern of "psammoma bodies" [16], which are typically found in thyroid papillary carcinomas. However, ultrasonography-detected microcalcification and the associated psammoma bodies do not cover the several calcification types found histologically [17, 18]. The reported microcalcification incidence ranged from 29.0% to 38.2% in malignant thyroid nodules with calcification [3, 19]. On CT, Wu *et al* also reported a strong correlation of micro-calcification with malignant thyroid nodules [7]. In this study, the microcalcification incidence rate was 51.14% in malignant nodules and no significant difference in the size of calcification was found between malignant and benign thyroid nodules. Most of the previous studies used ultrasonography to investigate the size of calcification (Table 2). The possible reasons were listed as follows. Most of the previous studies used ultrasonography to investigate the size of calcification, and ultrasonography has a higher detecting ability of calcifications < 1 mm than CT. In addition, we also found calcification by pathological examination in 10 cases of thyroid carcinoma, but the preoperative CT was negative. This also indicates the suboptimal detection of microcalcification by CT.

It has been shown that ultrasonography-detected intranodular calcification suggests malignant thyroid nodules while peripheral calcification suggests benign thyroid nodules [2]. We found similar results with CT detection of thyroid nodule calcification. It was found that 79.55% of the intra-nodular calcification was associated with malignancy, and significant correlation was found between CT-detected intra-calcification and malignant thyroid nodules (Table 2). Besides, some studies have shown that the solitary calcified thyroid nodule is associated with malignancy both on ultrasonography and CT imaging [7, 12, 20]. However, our results showed no significant correlation of solitary calcified thyroid nodule with the incidence of malignancy (Table 2). The specific mechanisms underlining the different calcification patterns between malignant and benign thyroid nodules remain unclear. Further investigation is needed to elucidate problem.

In addition to calcification, there are several other imaging features for the differentiation of benign and malignant thyroid nodules. Malignant nodules can demonstrate ultrasonography features such as taller than wide, spiculated margin, and hypoechogenicity, which have an overall sensitivity of 83.3% and specificity of 74.0% [6]. While benign nodules show ultrasonography features of isoechogenicity and spongiform appearance, with sensitivity of 56.6% and 10.4% and specificity of 88.1% and 99.7%, respectively.

Moon *et al* analyzed 1083 thyroid nodules and found that central flow is the most common distinction between benign and malignant nodules [21]. Of the 1083 nodules studied, 814 were benign and 269 were malignant. Intranodular vascularity was frequently observed in the benign nodules, and vascularity was more often absent in the malignant nodules. Baier *et al* evaluated the ultrasonography and the clinical and laboratory characteristics of 944 patients with thyroid nodules and noted an association between malignant solid nodules and patient age younger than 45 years [22]. In contrast, Choi *et al* found no association between age and malignancy in nodules with indeterminate cytology [23]. The authors studied the cases of 165 patients who had been diagnosed with follicular tumors and found no significant associations between malignancy and sex, age, diameter, or ultrasonography characteristics, although there was a significant association with central flow by Doppler study. We also found no association between sex and thyroid malignancy (Table 4).

Our study has some limitations, of which we are aware. This study was a retrospective study, which was limited by the nature of retrospective study itself with selection bias. On the another hand, micro-calcification of some patients may be neglected because 3- to 5- mm slice thickness of CT images was used, which may affect our results in some extent. The technical details should be improved in the future study.

In conclusion, this study found that CT-detected calcification, especially intranodular calcification, may suggest an increased risk of thyroid carcinoma. However, the sensitivity and specificity of these two diagnostic parameters are not high enough. Fine-needle aspiration or surgical pathological examination is still needed to confirm the suspected thyroid malignancies.

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