

Accuracy of Ultrasonic Thyroid Nodules' Calcifications in Detection of Malignancy in Northern Iran

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ABSTRACT

BACKGROUND AND OBJECTIVES: The study aimed to evaluate the morphology of thyroid nodules' calcifications by ultrasound and its relationship with the type of pathology to determine whether the characteristics of calcifications on ultrasound

have a predictive value for malignancy of thyroid nodules.

MATERIALS AND METHODS: In the diagnostic study, included 390 patients with thyroid nodules underwent ultrasound sonography. FNA (fine-needle aspiration biopsy) was performed on all 413 nodules, and the 97 cases with calcifications were separated from the study and matched to the type of pathology. Each echogenic particle with or without posterior shadow was considered calcification; those < 2 mm were considered microcalcification and those > 2 mm macrocalcification. Other forms of calcification were also identified.

RESULTS: A total of 413 nodules were examined, of which 97 cases had calcification, including 70 cases (73.7%) macrocalcification and 27 (26.3%) microcalcification. Pathology revealed 80 benign nodules (82.5%) and 17 malignant nodules (17.5%). There was a significant difference between macro-calcification and micro-calcification pathologically, so that nodules with microcalcification had higher rates of malignancy than nodules with macrocalcification ($p < 0.001$). The Sensitivity and Specificity of microcalcification and macrocalcification were 65%, 80% and 35%, 35% respectively. But the difference between central and peripheral calcifications was not significant regarding malignancy ($p = 0.07$).

CONCLUSION: Observation of microcalcification in the thyroid nodules is important and the probability of malignancy is higher in these nodules.

Key words: Thyroid nodules; Calcifications; Ultrasound; Fine-needle aspiration biopsy; Malignancy

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INTRODUCTION

Thyroid nodules are a common clinical findings and its prevalence, based on the palpable thyroid nodules on physical examination, includes 3% to 7% of cases^[1]. The prevalence of non-palpable

thyroid nodules in the United States ranges from 20% to 76% in the general population, and a similar prevalence were reported according to the autopsy reports^[2]. The prevalence of palpable nodules is 2.5% in Iran; 3.5% in women and 1.3% in men^[3]. The prevalence of thyroid nodules on ultrasound in central Iran is reported 22.4%^[4], but it is more in the northern Iran with coastal and mountainous area, thus, its prevalence is a challenge to diagnose benign and malignant nodules^[5,6].

However, only 7% of the thyroid nodules are malignant and it is critical that they are accurately identified^[7].

Thyroid nodules are more common in the elderly, in women, in those who suffer from iodine deficiency and in those with a history of exposure to radiation^[8]. Both benign and malignant disorders can cause thyroid nodules. Thus, the clinical importance of newly diagnosed thyroid nodules, is primarily ruling out malignant thyroid lesions. High resolution ultrasound is the most sensitive test to evaluate thyroid nodules^[9,10]. The challenge of imaging thyroid nodules is to reassure most patients who have benign disease and to diagnose the minority of patients who will prove to have a malignancy^[11]. Calcification may be observed in 30% of thyroid nodules that is divided into different types^[12-16]. Microcalcification defined as prominent echogenic focus with or without posterior shadowing less than 2 mm. Macrocalcification has a size of more than 2 mm^[17]. With the help of ultrasound images, the risk of malignancy can be predicted. The value of ultrasonic findings in predicting cancer is low because of low sensitivity and there are no signs in ultrasound images that can definitely predict a malignant lesion. Presence of coarse or rim calcifications in nodules with ≥ 10 mm diameter also increases the risk of malignancy of thyroid nodules^[14].

In the study by Wang and colleagues, calcification in single nodule of thyroid in young patients was associated with greater malignancy rates^[18]. In the study by Lu *et al.*, calcification was reported in 49.6% of malignant nodules and 15.7% of benign nodules, and microcalcification type was associated with malignancy, but alone was limited in the prognosis of nodules^[19]. However, there have been controversies about the interpretation of calcifications. The present study aimed to find the sensitivity and specificity of the type of calcification in thyroid nodules and its association with malignancy that can have predicting value for benign or malignant tumors in thyroid nodules.

MATERIALS AND METHODS

In our study 390 consecutive patients who received US examinations for thyroid nodules and underwent thyroid surgery between Jan 2015 and May 2017 at Imam Hospital in Sari, Mazandaran. The Patients were enrolled in the study, if they wished, after completing the consent form. Inclusion criteria included patients with thyroid nodules who were diagnosed by an endocrinologist or by routine ultrasonography. Ultrasound was performed for patients with thyroid nodules and the obtained data was recorded in a checklist. Ultrasound was performed with Zonar, Aloka device with a linear probe of 7.5 MHz. The ultrasound were performed by one radiologist (Alaee).

And all thyroid nodules with suspicious sonographic findings underwent FNA by the one radiologist (sakhae). Nodules less than 1 cm were also excluded from the study, since the recommended minimum size for ultrasound guided FNA (fine-needle aspiration biopsy) is 1.5 cm^[8]. Purely cystic nodules were not subjected to FNA. Nodules with calcifications were separated from the study and were matched to the type of pathology. FNA was performed with syringe

5 or 10 and needle 21 or 22 and after the slides were prepared, Pathofix liquid was sprayed on the slides and the samples were sent for Papanicolaou staining. Then samples were cytopathologically evaluated by a pathologist. Positive malignancies of the nodules in the FNA were confirmed by histologic examination after surgery.

Statistical analysis was performed using spss 20 statistical software. Descriptive statistics was used to analyze the qualitative variables, and mean \pm SD for age and other quantitative variables such as size. To analyze the data, chi-square test and Fisher's exact tests were used. To compare age and size of nodules in patients with malignancy and other variables, t-test was used. In all statistical tests, p -value < 0.05 was considered as the significance level. The study was approved by the Ethics Committee of University.

RESULTS

In our study 413 nodules were examined, of which 97 cases had calcification and entered the study, belonging to 89 patients (8 patients had two nodules) 21 cases (23.6% of them) were male and 68 (76.4%) were female. Mean age of patients was 49.29 ± 12.25 . The minimum age of participants in this study was 24 years and the maximum age was 73 years. Mean age of male patients was 52.71 ± 12.66 and that of females were 48.23 ± 12.28 . The age difference between the sexes was not statistically significant ($p = 0.151$). 97 cases of calcification were observed in ultrasonography that included 70 cases (72.2%) of macrocalcification and 27 cases (27.8%) of microcalcification. Also, 18 cases (18.6%) of nodules with macrocalcification had rim calcifications. In 2 cases (2.1%) calcification was Coarse. In 33 cases (34%), central calcification and in 64 cases (66%) peripheral calcification was observed. The difference between microcalcification and macrocalcification was not significant ($p = 0.697$) (Table 1) (Figure 1).

Among the 97 studied nodules, 80 nodules (82.5%) were benign (belonging to 73 patients) and 17 nodules (17.5%) were malignant (belonging to 16 patients). At first, the pathology result of 3 patients was unclear, which underwent FNA that determined the exact pathology. In the study, there was no significant relationship in gender between macrocalcification and microcalcification ($p = 0.166$). The sensitivities and specificities for calcification of thyroid nodules were determined. The microcalcification was found to have a high diagnostic accuracy for distinguishing malignant from benign thyroid nodules that had Sensitivity of 65% and Specificity of 80% (Table 2).

Also, no significant difference was observed in rim calcification between men (24%) and women (17.6%) ($p = 0.288$). Coarse calcifications were observed in the two patients who were female. Also, the relationship between the type of calcification in terms of central and peripheral calcification and gender was not significant ($p = 0.358$). In the study, no significant relationship was observed between macrocalcification and microcalcification ($p = 0.109$). The mean age of patients with rim calcifications was 53.05 ± 10.66 years that had no significant relationship with rim calcification ($p = 0.154$). In the study, there was a significant difference between macrocalcification and microcalcification in terms of pathology, so that the rate of malignancy was significantly higher in nodules with microcalcification than nodules with macrocalcification ($p < 0.001$). But the difference between central and peripheral calcification was not significant regarding malignancy ($p = 0.07$). The rim calcifications were also benign ($p = 0.03$). Coarse calcifications were observed in two patients aged 50 and 24 years. Both cases of coarse calcification were also benign (Table 3).

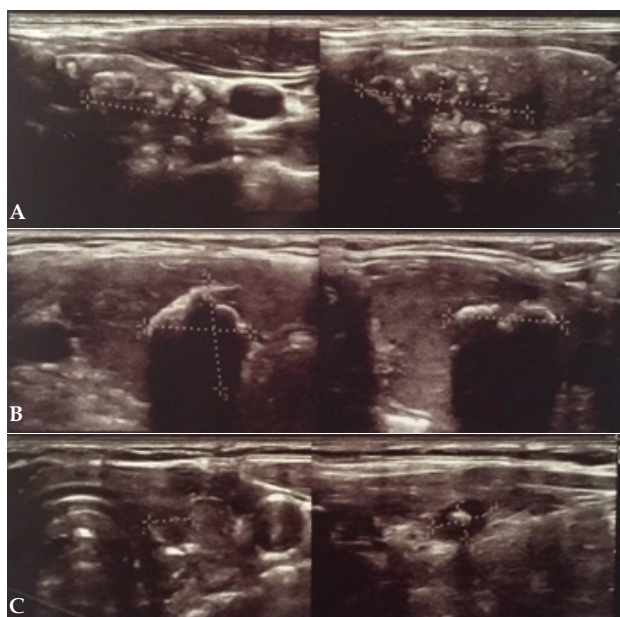


Figure 1 Types of calcifications in thyroid nodules ultrasound. A: Microcalcification and macrocalcification (central). B: Microcalcification and macrocalcification (peripheral). C: Rim and coarse calcifications (peripheral, central).

DISCUSSION

In the study, 97 nodules with calcification were found on ultrasonography, 72.8% of which were microcalcification. Also, regarding pathology, approximately 18% were malignant. There was a significant difference between macrocalcification and microcalcification in terms of pathology, so that the rate of malignancy was significantly higher in nodules with microcalcification than nodules with macrocalcification (40% vs 8%). A thyroid nodule is a common manifestation of thyroid diseases and it is important to recognize reliable criteria for malignancy in a thyroid nodule when using imaging methods. The exact nature of thyroid nodule is ultimately established by histopathological examination. FNAC cannot be done on all incidentally detected thyroid nodules as it is expensive and not practical.

The possible reason for higher calcification rate in the malignant group was the difference in formation of calcification in benign and malignant diseases. 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^[18].

A number of studies focus on the relationship between thyroid nodule calcification and malignancy.

In the study by Consorti and colleagues, the risk of calcification in thyroid malignancies (papillary carcinoma of thyroid 40% and multinodular goiter 20.7%) was reported to suggest in the overall process of surgical decision making^[20].

When calcification is noted within a solitary thyroid nodule, the risk of malignancy is very high. The detection of thyroid calcifications by sonography is diagnostically valuable, especially in cases involving a solitary nodule or a young person. The presence of calcifications in these cases should raise the suspicion of malignancy^[21,22].

Shi and colleagues reported the incidence of malignancy in nodules

Table 1 Comparing the frequency of calcification.

Calcification	Microcalcification	Macrocalcification	p-value
Central	10(37%)	23(32.9%)	0.697
Peripheral	17(63%)	47(67.1%)	

Table 2 Diagnostic accuracy of ultrasonic calcifications types of malignant nodules.

Variable	microcalcification	macrocalcification
Sensitivity	17/11 (65%)	17/6 (35%)
Specificity	80/64 (80%)	80/16 (35%)
Positive predictive values	27/11 (41%)	70/6 (35%)
Negative predictive values	70/64 (91%)	27/16 (35%)
Accuracy	97/75 (77%)	97/22 (35%)

Table 3 The relationship between calcifications on ultrasound and patholog.

Variable	Microcalcification	Macrocalcification	Central	Peripheral
Benign	16 (59.3%)	64 (91.4%)	24 (72.7%)	56 (87.5%)
Malignant	11 (40.7%)	6 (8.6%)	9 (27.3%)	8 (12.5%)
p-value	< 0.001		< 0.07	

with microcalcification was 96.5% although in their study the rate of malignancy was higher in nodules with microcalcification, the rate of malignancy was much higher in their study than our study. This issue can be assumed to be due to the high statistics of malignancy in that area. Also in that study, the incidence of microcalcification in benign nodules was 5%^[23].

In a study conducted by Taki and his colleagues, 82% of nodules with microcalcification were diagnosed as cancerous nodules^[16]. Frates *et al* argued that the presence of microcalcification increased the risk of cancer up to three-folds^[24].

Popli and colleagues showed in a study that the presence of microcalcification has a sensitivity of 65.9% and specificity of 97.9% for malignancy of thyroid nodules^[25]. Kwak *et al* stated that existence of microcalcification has positive predictive value in the investigation of malignant nodules^[15]. In the study by Wu *et al*, the risk of malignancy was higher in thyroid nodules with microcalcification^[26]. Microcalcification was specific in 61% of malignant nodules in the study by Chammas *et al*^[27].

Kim and colleagues also showed that microcalcification is one of the most important and independent factors for investigation of papillary thyroid cancer in large and small lesions^[28]. However, Moon and colleagues said that despite the significant relationship between microcalcification and malignancy, the presence of microcalcification in nodules smaller than 2 mm may not be a reliable predictor of malignancy^[29].

Moreover, from the results of this study and similar studies, it can be concluded that microcalcification can be an important factor in the prediction of malignant nodules that serves as a priority for biopsy or treatment.

There are also a few reports suggesting that a considerable portion of the macrocalcified nodules are malignant.

In the study by Arpaci and colleagues, contrary to the general thinking, 5.8% and 40.5% macrocalcifications were reported in two modes egg-shell and parenchymal, respectively, with higher rates of malignancy^[30,31].

Sonographic characteristics of macrocalcification such as interruption, irregular thickness and the presence of soft tissue rim were associated with malignancy in thyroid nodules with macrocalcifications^[32]. In the study by Lee *et al*, macrocalcification

was not a reliable criterion of malignancy^[33]. In the study, about 18% of calcifications were rim, which were all benign, while Frates *et al* stated that rim calcifications increase the risk of malignancy^[11].

Even though, in a study by Moon *et al*, it was noted that the relationship between rim calcifications and malignancy is not yet conclusively proven and its existence is not statistically significant in differentiating benign from malignant nodules^[29]. Therefore, it seems that, although all cases of rim calcifications in the present study were benign, rim calcification that is a category of macrocalcification, cannot definitely predict malignancy and further study is required in this regard. Also, there were 2 cases of coarse-type calcification that both belonged to patients who had macrocalcifications and pathologic result of both cases was benign.

In a study by Taki *et al*, 52% of nodules with coarse calcifications were diagnosed as cancerous nodules. The study also stated that coarse calcifications with microcalcification or in the center of a hypo-echoic nodule may be suggestive of malignancy^[16]. Frates *et al* also stated that the presence of coarse calcifications increases risk of cancer up to two-folds^[24]. But Solbiati stated that coarse calcifications are often seen with benign nodules and represent the long period of disease^[9].

However, some studies have shown that the presence of coarse or rim calcifications, especially in nodules ≥ 10 mm increases the risk of malignancy of thyroid nodules^[34,35]. In the study, the prevalence of coarse calcification was too small and appropriate conclusions could not be made.

In the study also about 34% of calcifications were central and 66% were peripheral, but 27% of central and 12% of peripheral nodules were malignant and the difference between central and peripheral calcifications with malignancy was not significant.

In the study by Yoon *et al*, 18.5% of thyroid nodules with peripheral calcifications were malignant that was somewhat similar to our study^[36]. But Taki *et al* reported that 43% of nodules with peripheral calcification were diagnosed as malignant a cancerous nodule that was higher than the statistics of the present study. This study suggested that peripheral calcifications can be found in benign and malignant nodules. So, peripheral calcification that was once thought to be seen only in benign nodules, may also be found in malignant nodules.

In the study, no significant relationship was observed between macrocalcification and microcalcification or central and peripheral calcification regarding age and gender. Also, there was no significant relationship between age and rim and coarse calcifications.

However, the probability of observing thyroid nodules by ultrasonography increased with increasing age^[37]. But, in the research and similar research, no specific age or gender was identified for calcification of thyroid nodules and the frequency of types of calcifications were same in different ages and genders.

Thyroid nodules are a common clinical finding with 7.3% risk of malignancy^[37].

Ultrasonography is more sensitive and reliable than other imaging, in diagnosis of calcification thyroid nodules^[38]. Ultrasound is routinely used to assess thyroid gland and some sonographic features may help in diagnosis of benign and malignant nodules. However, the main method for detection of thyroid malignancy is FNA that it is not affordable for all nodules. Many studies have tried to determine sonographic features (large nodule size (≥ 3 cm), Lobulated margin, extra- thyroidal extension, calcification, solid composition, very hypoechogenicity, taller than wide in shape), which are high risk for malignancy^[39-50]. In the study, all nodules with rim and coarse calcifications were benign, but they could not decisively show benign

nodules and this issue requires further studies in future, investigating this specific type of calcification with a larger number of samples.

CONCLUSION

In the study suggested microcalcification as an important ultrasound finding in thyroid nodules that increases the possibility of malignancy. Therefore these nodules are preferred for sampling and have a predictive value. Both peripheral and central calcifications, whether of microcalcification or macrocalcification, are associated with both benign and malignant nodules. Also, in case of prediction of ultrasound for malignancy, may be in future can reduce the rate of FNA with certainty and proof.

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