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Calcifications in Thyroid Ultrasonography and Thyroid Carcinoma

ABSTRACT

Background: Thyroid nodules are a common disease entity occurring in 5-10% of the general population and increasing with age. Their detection on ultrasonography ranges from 13% to 67%. Calcifications on ultrasound may occur in both benign and malignant diseases but have been cited for increased risk of thyroid carcinoma.

Objective: To determine the association of calcifications found on thyroid ultrasonography and the different types of calcifications with thyroid carcinoma.

Methods:

Design: Retrospective Study
Setting: Tertiary Private Hospital
Participants: 126 patients with pre-operative thyroid or neck ultrasonography who subsequently underwent thyroidectomy (total or subtotal, with or without frozen section) were selected from a database covering a one-year period from January to December 2012. The presence and type of calcification on ultrasonography was correlated with the final histopathologic report for a diagnosis of thyroid carcinoma. Sensitivity, specificity, positive and negative predictive values were obtained.

Results: 51 out of 126 studies (40%) were observed to have calcifications of any description in both histologically benign (41%) and malignant (59%) nodules. Calcifications seen in malignancy arose from papillary carcinoma (86%). Follicular carcinoma and others (Plasmacytoma and Lymphoma) accounted for 7% each. The peripheral type of calcification was most prevalent accounting for 37% (11 out of 30). The sensitivity of detecting calcifications on ultrasonography is 58.82%, specificity 81.33%, positive predictive value 68.18% and negative predictive value 74.38%. Chi square test computed was 21.54 ($P < 0.05$).

Conclusion: There was an association between calcification found on ultrasonography and thyroid carcinoma and 86% of the calcifications were peripheral patterns mostly found in papillary thyroid carcinomas. Ultrasonography alone is not sufficient in diagnosing thyroid carcinoma but may increase the suspicion of malignancy depending on the type of calcification.

Keywords: *Thyroid carcinoma, papillary carcinoma, calcifications, ultrasonography*

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Thyroid nodules are common and occur in 5-10% of the general population with increasing age.[1] They have a relative frequency of 4-7% by palpation alone and 13-67% by sonography.[4] The incidence of thyroid nodular disease is quite high spontaneously occurring at a rate of 0.08% per year starting in early life and extending into the eighth decade. Although thyroid nodules represent a wide spectrum of disease, most are colloid nodules, adenomas, cysts and focal thyroiditis with only a few (5%) being carcinoma.[2]

The most recent ATA guidelines for the evaluation of thyroid nodules and cancer emphasize the use of thyroid ultrasound to guide the clinician on which nodule requires biopsy to exclude malignancy. Microcalcifications are frequently cited with increased risk of thyroid malignancy specifically papillary thyroid carcinomas.[7]

Diagnosis of thyroid carcinoma includes a comprehensive history, physical examination and the aid of diagnostic tests. High-resolution ultrasonography is commonly used but frequently misperceived as unhelpful for identifying features that distinguish benign from malignant nodules. Although individual ultrasonographic findings may be of limited value, multiple signs of thyroid malignancy that appear in combination can make a more accurate prediction.

Calcifications on ultrasound may occur in both benign and malignant diseases.[5] According to the literature, microcalcifications are one of the most specific ultrasound findings suggestive of a thyroid malignancy.[3] Thyroid calcifications can be classified as microcalcification, coarse calcification or peripheral.[3]

Because most thyroid nodules are benign, calcifications may seem to appear more in benign nodules, thus being neglected by clinicians. This study aims to determine the association of calcifications found in thyroid or neck ultrasonography and of their types with thyroid carcinoma. This study will also determine the predictive value for malignancy of calcifications determined by thyroid ultrasonography.

METHODS

Subjects

This is a retrospective study analyzing 126 thyroidectomy patients selected from a database covering a one-year period between January to December 2012 at our institution. All patients included in the study underwent pre-operative thyroid or neck ultrasound in the same institution. Patients who underwent thyroidectomy where ultrasonography was done at a different institution were excluded.

All data was retrieved from the Healthcare Database System, which included official results of the procedures including the final histopathological report after each operation. Board-certified radiology and pathology consultants interpreted the ultrasonographic and histopathologic studies.

Calcifications on Ultrasonography

These studies were stored at the Picture Archiving and Communication Systems (PACS) system and were reviewed using the BARCO Coronis Fusion 6 MegaPixel DL (MDCC-6130) system (Barco Pte Ltd, Singapore). Its technical specifications include the following: TFT AM Color LCD Dual Domain IPS-Pro, Native 6 MegaPixel 3280 x 2048 display, 654 x 409 mm active screen size and 800 cd/m2 maximum luminance (500 cd/m2 DICOM calibrated).

Each ultrasound result had already been officially tandem-read by two radiology consultants (reader A) and then re-read by the co-author, a senior radiology resident (reader B) to ascertain the presence or absence of calcifications and to describe the types of calcifications with the reviewer blinded to the final histopathology.

Calcifications were defined as hyperechoic signals observed in the periphery or within a thyroid nodule or mass. Calcifications were further subdivided into (1) probably benign (inspissated colloid calcifications with typical reverberation artifacts) and (2) probably malignant. Subtypes of the latter include (2.a) microcalcifications (round laminar and punctate hyperechoic focus), (2.b) coarse (larger hyperechoic structures, either spicule or granular) and (2.c) peripheral (either rim or arc and further described as stippled, curvilinear smooth and irregular).

Statistical Analysis

A certified statistician at our institution then analyzed the data using Statistical Package for the Social Sciences SPSSv16.0 (IBM, New York, USA). Sensitivity, specificity, positive predictive and negative predictive values were then calculated.

RESULTS

Out of the 126 patients with thyroid mass who underwent ultrasonography, 17 were male, 109 female, with ages ranging from 10 to 73 years old (median age 45). There were 81 benign and 45 malignant final diagnoses by histopathology. *Table 1* summarizes the findings.

Table 1. Summary of the histopathologic findings

Benign	Number of patients
Multiple Colloid Adenomatous Goiter (MCAG)	58
Follicular Adenoma	4
Nodular Hyperplasia	11
Hashimoto's Thyroiditis	5
Tuberculosis	1
Hurthle Cell Adenoma	1
Unremarkable	1
Total	81

Malignant	Number of patients
Papillary Carcinoma	34
Papillary Microcarcinoma	6
Follicular Carcinoma	3
Hodgkin's Lymphoma	1
Plasmacytoma	1
Total	**45**

Of the 126 patients included, 51 studies (40%) were observed to have calcifications of any description in both histologically benign and malignant nodules. Out of the 51 studies with calcifications, 30 (59%) studies were seen in malignancies and 21 (41%) in benign conditions. *(Figure 1)*

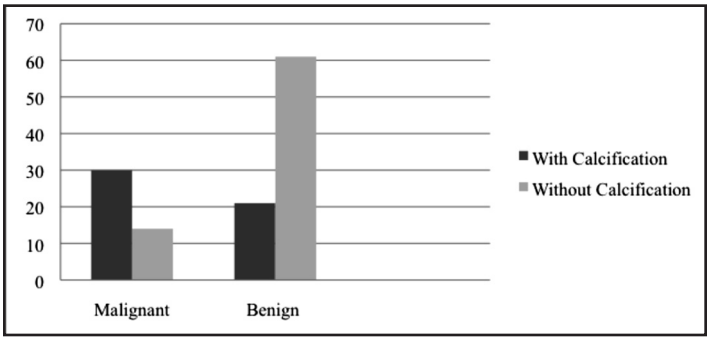

Figure 1. Breakdown of malignant and benign cases with and without calcifications

Majority of the calcifications in malignant cases were seen in those diagnosed with Papillary Carcinoma (26 out of 30 malignancies, 86%). The rest were seen in Follicular Carcinoma (2 out of 30 malignancies, 7%) and other cancers-- Hodgkin's lymphoma and Plasmacytoma (2 out of 30 malignancies, 7%).

Calcifications secondary to inspissated colloid were described and all five examinations with this type of calcification were proven benign (multiple colloid adenomatous goiter). It should be noted that out of all the calcifications under the umbrella of malignant subtypes, there were more of the peripheral type of calcification seen in 37% followed by microcalcifications 33% and lastly the coarse types which accounted for 30%. *(Figure 2)*

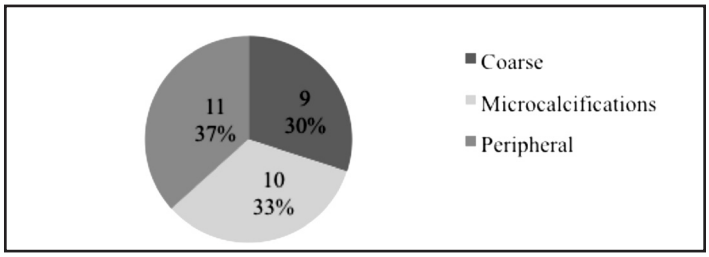

Figure 2. Types of calcifications seen in malignant cases

The studies reviewed by the co-author revealed reader disagreement in 14 studies or only 11%. They differed in the types of calcification reported (ex. peripheral, coarse or microcalcification). The co-author based the description of the type of calcification reported from literature published by Hoang and his colleagues.[3] These discrepant readings are listed in *Table 2* with the final histopathology results.

Table 2. Reader discrepancy between Reader A and Co-author with final histopathology

Reader A	Reader B (Co-author)	Final Histopathology	Presence or Absence of Calcification
Calcification	Peripheral calcification	Papillary Thyroid Carcinoma	Present
Calcification	Coarse calcification	Multiple Colloid Adenomatous Goiter	Present
Calcification	Peripheral calcification	Papillary Thyroid Carcinoma	Present
Peripheral Calcification	Microcalcification	Multiple Colloid Adenomatous Goiter	Present
Peripheral Calcifications	Coarse calcifications	Multiple Colloid Adenomatous Goiter	Present
Peripheral Calcifications	Coarse calcifications	Multiple Colloid Adenomatous Goiter	Present
Calcifications	Microcalcifications	Papillary Thyroid Carcinoma	Present
Calcifications	Coarse and microcalcifications	Multiple Colloid Adenomatous Goiter	Present
Calcifications	Coarse microcalcifications	Multiple Colloid Adenomatous Goiter with Nodular Hyperplasia	Present
Calcifications	Coarse and microcalcifications	Multiple Colloid Adenomatous Goiter	Present
Calcifications	Microcalcifications	Multiple Colloid Adenomatous Goiter	Present
Calcifications	Coarse calcifications	Papillary Microcarcinoma	Present
Peripheral calcifications	Coarse calcifications	Multiple Colloid Adenomatous Goiter	Present
Calcifications	Coarse calcifications	Multiple Colloid Adenomatous Goiter	Present

The sensitivity of the type of calcification in predicting malignancy on ultrasonography was calculated to be 58.82%, specificity was 81.33%. On the other hand, predicting thyroid malignancy based on

the type of calcification had a positive predictive value of 68.18% and negative predictive value of 74.39%. *(Table 3)*

Table 3. Statistical analyses of calcification found on ultrasonography

Parameter	Percentage
Sensitivity	58.82%
Specificity	81.33%
PPV	68.18%
NPV	74.39%

Chi square test to determine the association of presence or absence of calcifications with benign and malignant disease was statistically significant at 21.54 ($P < 0.05$).

DISCUSSION

Calcifications detected on thyroid ultrasonography may appear coarse or dense as microcalcifications or peripheral rim-like.[6] Among these, the microcalcification and coarse types are known to be associated with increased likelihood of malignancy.[6] Based on the study by Hoang *et al*. in 2007, microcalcifications are found in 29% to 59% of all primary thyroid carcinomas, most commonly in papillary thyroid carcinoma. This subtype is one of the most specific features of thyroid malignancy with a specificity of 85.8%–95% and a positive predictive value of 41.8%–94.2%.[3]

In our study, there were more peripheral types of calcification at 33%. Similar studies were published by Yoon *et al.* in 2007 and Park *et al*. in 2011 on peripheral calcification seen on ultrasonography, its pattern and association with thyroid malignancy.

On histopathology, thyroid calcifications are divided into psammomatous and dystrophic types. Psammomatous calcifications consist of laminated round calcium deposits in the epithelium which are formed in papillary thyroid carcinomas. These are detected as microcalcifications on ultrasonography. In contrast, dystrophic calcifications consist of non-laminated amorphous deposits in fibrous tissue septa. This type of calcification is thought to correspond to coarse calcifications on ultrasonography, which can occur in both benign and malignant conditions. Peripheral calcifications on the other hand, are patterns of dystrophic calcification located around nodules. They were generally thought to be more frequently associated with benign conditions but cases of papillary thyroid carcinoma associated with this type of calcification have been reported.[6] The results of the this study are congruent with these reports.

Based on statistical analysis, the presence of calcification on thyroid ultrasound will yield a positive result 59% of the time in patients with thyroid carcinoma. However, it will yield false positive results in 19% of patients without thyroid carcinoma. On the other hand, the study tells us that 81% of patients who do not have thyroid carcinoma will test negative for the test (calcification on ultrasonography). Therefore a positive result from this means a high probability of the presence of the disease. Sixty-eight (68) % of those with calcification detected on thyroid ultrasonography will actually have a thyroid carcinoma (whether papillary or follicular). Lastly, the probability of not having thyroid carcinoma given a negative thyroid ultrasound test is 74%.

This study can guide clinicians in diagnosing thyroid nodules particularly in pre-operative evaluation and counseling patients and relatives. Ultrasound can help direct the biopsy toward areas of calcification with a high probability of disease. The limitation of this study is small sample size.

In conclusion, there was an association between calcifications found on ultrasonography and thyroid carcinoma and 86% of the calcifications were peripheral patterns mostly found in papillary thyroid carcinomas. Ultrasonography alone is not sufficient in diagnosing thyroid carcinoma but may increase the suspicion of malignancy depending on the type of calcification.

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