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Association of Ultrasonographic Findings and Thyroid Malignancy: A Cross-Sectional Study

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ABSTRACT

Objective: To determine the association of thyroid malignancy and the following ultrasonographic findings: presence of solid hypoechoic nodule, irregular margins (infiltrative, microlobulated, or speculated), microcalcifications or disrupted rim calcifications with small extrusive hypoechoic soft tissue component, taller than wide shape of the thyroid nodule, and evidence of extrathyroidal extension.

Methods:

Design: Cross-Sectional Study
Setting: Tertiary Government Training Hospital
Participants: Records of patients admitted to the Otorhinolaryngology- Head and Neck Surgery ward with a diagnosis of nodular non-toxic goiter, multinodular non-toxic goiter, and thyroid malignancy who underwent thyroid surgery between January 2017 and June 2018 were considered for inclusion.

Results: A total of 33 patients, 7 males and 26 females, were included in this study. Patients' age ranged from 26 to 69 years with an average of 46 years. Thirteen (39.4%) had malignant while 20 (60.6%) had benign histopathologic results. There was a significant association between presence of solid hypoechoic nodule (Fisher exact, n = 33, p = .0047), irregular margins and microcalcifications with malignant histopathology results (X^2 (df = 1, N = 33) = 8.57, p = .003). No significant difference was noted in the proportion of subjects with malignancy according to taller than wide nodules (Fisher exact, n = 33, p = 1.000) or presence of extrathyroidal extension nodules or presence of extrathyroidal extension (Fisher exact, n = 33, p = .276). On multivariate analysis using logistic regression, only microcalcification was found to be a significant predictor of malignancy (OR = 8.96, 95% CI: 1.02 – 87.19, p = .05).

Conclusion: There was a significant association between presence of solid hypoechoic nodule, margins and microcalcifications with thyroid carcinoma. Only microcalcification was found to be a significant predictor of thyroid malignancy on ultrasound, although our confidence interval was broad.

Keywords: *calcifications; thyroid; thyroid carcinoma; thyroid nodule; ultrasonography*

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Thyroid cancer accounts for approximately 0.5% of all malignancies.[1] Though most palpable nodules are benign, there is a 5-10% risk of having a malignancy.[2] The American Thyroid Association (ATA) strongly recommends thyroid ultrasonography (UTZ) for patients with suspected or incidentally-detected nodules. This modality is able to determine the presence of suspicious nodules, their character and location, and guide the accuracy of Fine Needle Aspiration Biopsy.[3]

A number of studies have been published associating specific sonographic findings with thyroid malignancy.[1,2,4-9] Many elucidate the role of nodule size and presence of microcalcifications.[2,4-9] The ATA listed presence of disrupted rim calcifications with small extrusive hypoechoic soft tissue component, evidence of extrathyroidal extension, nodule shape and features as determinants of malignancy. We initiated this study to determine whether these ultrasonographic features of malignancy are also present in, or if they differ in the local setting.

This study aims to determine the association of thyroid malignancy and the following ultrasonographic findings: presence of solid hypoechoic nodule, irregular margins (infiltrative, microlobulated, or speculated), microcalcifications or disrupted rim calcifications with small extrusive hypoechoic soft tissue component, taller than wide shape of the thyroid nodule, and evidence of extrathyroidal extension.

METHODS

With Institutional Review Board approval, this cross-sectional study was conducted from May to July 2018. Records of patients who were admitted to the Otorhinolaryngology- Head and Neck Surgery ward with a diagnosis of nodular non-toxic goiter, multinodular non-toxic goiter, or thyroid malignancy and underwent thyroid surgery from January 2017 to June 2018 were considered for inclusion. The following were excluded: post-surgery patients previously diagnosed with thyroid malignancy who were managed for tumor recurrence or relapse, and those with no ultrasonographic result or final histopathology results on record. A sample size of 24 was computed using this formula:

$$n = \frac{(Z\alpha\sqrt{2pq} + Z\beta\sqrt{P1Q1 + P2Q2})\ 2}{(P1\text{-}P2)\ 2}$$

where:

Z_α = 95% confidence level= 1.96

Z_β = 80% power of study= 0.84

P_1 = estimated proportion of malignant histopathological results among those with malignant ultrasound findings= 30/51 = 58.8 = 0.588

Q1= 1- P_1= 1- 0.588 = 0.412

P_2 = estimated proportion of malignant histopatholigical results among those with benign ultrasound findings
= 15/75= 20.0= 0.20

Q_2 = 1 - P_2 = 1- 0.20 = 0.80

$$p= \frac{P1+P2}{2} = \frac{0.588+0.20}{2} = 0.394$$

q= 1- p = 1 - 0.394 = 0.606

$$n = \frac{(1.96\sqrt{2(0.394)(0.606)} + 0.84\sqrt{(0.588\ (0.412) + 0.20\ (0.80)})\ 2}{(0.588 - 0.20)\ 2}$$

$$n = \frac{(1.35 + 0.53)2}{0.15} = 24$$

The clinical histories, physical examination, and histopathologic results recorded in the hospital charts were extracted by the researcher and collated using MS Excel for Mac 2011 version 14.4.2 (Microsoft Corp., Redmond, WA, USA).

A senior radiology resident blinded to the final histopathology viewed each ultrasound image and reviewed each printed report to ascertain the presence or absence of the parameters which may not be covered in the official interpretation of the ultrasound results. This was done to standardize the interpretation. If the feature/s were absent on the printed report, the image was reviewed; if both the printed report and the image was absent, then the parameter/s were ruled out. We tabulated the consolidated data using the same software. The presence and type of malignancy were included in the tabulation.

Analysis of data

Data were encoded and tallied in Statistical Package for Social Sciences (SPSS^X 3) version 10 for windows (SPSS Corp., Chicago, IL, USA). Descriptive statistics were generated for all variables. For nominal data frequencies and percentages were computed. For numerical data, mean ± SD were generated. Analysis of the different variables was done using the following test statistics: Chi-square test was used to compare/associate nominal (categorical) data, Fisher Exact test was used when there were expected frequencies <5, Logistic Regression was used in predicting a dichotomous outcome variable (i.e. malignant histopathology result).

RESULTS

Out of 45 records retrieved, a total of 33 were included in the study. Of the 12 excluded records, 9 had no histopathology result while 8 had no ultrasound report. Of the 33 included, 7 (21.2%) were males and

26 (78.8%) were females. The age ranged from 26 to 69 years with an average of 46 ± 13.6 years. The age of patients with malignant results (52.6 ± 15.6 years) was significantly higher (t (df = 31) = 2.42, p = 0.02) than those with benign histopathology (41.7 ± 10.4 years). On the other hand, no significant difference was noted in the proportion of males and females according to histopathology result (Fisher exact, n = 33, p = .58).

A solid hypoechoic nodule was present in 21 (63.6%), irregular margins in 9 (27.3%), microcalcifications in 15 (45.5%), taller than wide nodules in 29 (87.9%), and extrathyroidal extension in 4 (12.1%). *(Table 2)*

Of the 33 patients, 13 (39.4%) had thyroid carcinoma while 20 (60.6%) had benign lesions. Malignant histopathologies included 12 with papillary thyroid carcinoma and one with medullary carcinoma while benign lesions comprised 20 colloid adenomatous goiters. There were significant associations noted between histopathology results and the following ultrasonographic findings: 1. presence of solid hypoechoic nodule (Fisher exact, n = 33, p = .047), irregular margins and 2. microcalcifications (X^2 (df = 1, N = 33) = 8.57, p = .003). A significantly higher proportion (Fisher exact, n = 33, p = .047) of subjects with solid hypoechoic nodule had malignant histopathology results compared to those with nodules that were not solid with 11 (52.4%) and 2 (16.7%), respectively. Similarly, significantly higher proportions of nodules with irregular margins were malignant compared to those with regular margins with 6 (66.7%) and 7 (29.2%), respectively. Moreover, a significantly higher proportion (X^2 (df = 1, N = 33) = 8.57, p = .003) of nodules with microcalcifications yielded malignant results compared to those without microcalcifications with 10 (66.7%) and 3 (16.7%), respectively. On the other hand, no significant difference was noted in the proportion of subjects with malignancy according to taller than wide nodules (Fisher exact, n = 33, p = 1.000) or presence of extrathyroidal extension (Fisher exact, n = 33, p = .276).

On multivariate analysis using logistic regression, only microcalcification was found to be a significant predictor of malignancy. The risk of patients with microcalcification for thyroid malignancy was almost 9 times higher than those without microcalcification (OR = 8.96; 95% CI = 1.02 – 87.19; p = .05). *(Table 4)*

Table 1. Comparison of Demographic Characteristics According to Histopathology Results

	Histopath Result Malignant (n=13)	Benign (n=20)	Total	*p-value**
Age (in years)				
Mean ± SD	52.62 ± 15.61	41.70 ± 10.41	46.00 ± 13.60	.02 (S)†
Sex				
Male	3 (42.9%)	4 (57.1%)	7	1.00 (NS)‡
Female	10 (38.5%)	16 (61.5%)	26	

** p>0.05- Not significant; p ≤0.05-Significant*
Data presented as Mean ± SD, (medians) were computed as needed; or as frequency (%)
† T-test; ‡Fisher Exact test
** S- Significant; (NS)- Not Significant*

Table 2. Distribution According to Ultrasonographic Findings

	Frequency (n=33)	Percentage
Presence of solid hypoehoic nodule		
Solid	21	63.6
Not solid	12	36.4
Margins		
Irregular	9	27.3
Regular	24	72.7
Microcalcifications		
With	15	45.5
Without	18	54.5
Taller than wide nodules		
Taller than wide	29	87.9
Not taller than wide	4	12.1
Extrathyroidal Extension		
With extension	4	12.1
Without extension	29	87.9

DISCUSSION

This study revealed a significant association between malignant histopathologic results of the thyroid and the presence of solid hypoechoic nodules, irregular margins and microcalcifications on ultrasound. Conversely, no significant association was found between thyroid malignancy and taller than wide nodules or presence of extrathyroidal extension on ultrasound.

These findings are similar to those of Anil and colleagues wherein solid nodules on UTZ had the highest sensitivity (69-75%) for malignancy in comparison to cystic or spongiform appearance.[7] Cystic nodules were more likely benign (with only about 2% malignant),[8] similar to our findings. Solid nodules are a common ultrasound feature of papillary thyroid carcinoma in around 70% of cases,[4] anaplastic and medullary thyroid carcinoma also display this feature.[4]

Irregular margins may be infiltrative, microlobulated or spiculated.[3] Irregularity of margins is attributed to the nodule losing its pseudocapsule of fibrous connective tissues making the tumor and

Table 3. Distribution According to Ultrasonographic Findings and Histopath Results

	Histopath Result Malignant (n=13)	Benign (n=20)	Total	*p-value**
Presence of solid hypoehoic nodule				
Solid	11 (52.4%)	10 (47.6%)	21	.05 (S)‡
Not solid	2 (16.7%)	10 (83.3%)	12	
Margins				
Irregular	6 (66.7%)	3 (33.3%)	9	.05 (S)‡
Regular	7 (29.2%)	17 (70.8%)	24	
Microcalcifications				
With	10 (66.7%)	5 (33.3%)	15	.003 (S)§
Without	3 (16.7%)	15 (83.3%)	18	
Taller than wide nodules				
Taller than wide	11 (37.9%)	18 (62.1%)	29	1.00 (NS)‡
Not taller than wide	2 (50.0%)	2 (50.0%)	4	
Extrathyroidal Extension				
With extension	3 (75.0%)	1 (25.0%)	4	.28 (NS)‡
Without extension	10 (34.5%)	19 (65.5%)	29	

** p>0.05- Not significant; p ≤0.05-Significant*
Data presented as Mean ± SD, (medians) were computed as needed; or as frequency (%)
‡ Fisher Exact test; §Chi-square test
** S- Significant; (NS)- Not Significant*

Table 4. Multivariate Analysis of the Different Ultrasonographic Findings Predictive of Malignant Histopath Results

Variable	OR	95% CI	P value
Age	1.08	0.99 – 1.18	.07 (NS)
Sex (male)	0.53	0.03 – 9.79	.67 (NS)
Solid nodule	2.03	0.14 – 28.05	.60 (NS)
Irregular margins	1.83	0.17 – 19.79	.62 (NS)
Microcalcifications	8.96	1.02 – 87.19	.05 (S)
Taller than wide nodules	0.07	0.002 – 2.91	.16 (NS)
Extrathyroidal extension	9.50	0.49 – 182.82	.14 (NS)

Logistic Regression Analysis

the thyroid parenchyma indistinct.[7] Results of this study showed that significantly higher proportions of nodules with irregular margins were malignant compared to those with regular margins. This feature may also be found in benign nodules with a low sensitivity (48.3- 55%) but with high specificity (83-91%) and predictive value (60-81.3%).[7]

The ATA guidelines also implicated taller than wide thyroid nodules measured in transverse view having high specificity for detecting malignancy (>90%). In a study by Ren and colleagues (2015), taller than wide shape is a good predictor of papillary thyroid carcinoma in small nodules with high sensitivity and specificity (81.4% and 96.8%, respectively).[9] However, the sensitivity was significantly low and odds ratios were smaller (1.6-2.9) when assessed separately from other features.[3] In contrast, in this study, no significant association was observed between taller than wide shape and malignancy. The size of the nodule was excluded because this was not included in the parameters set by ATA. No qualifications were made as to large (>1cm) or small (<1); only the anteroposterior to transverse ratio was considered.

Extension to adjacent structures and metastasis to lymph nodes are specific signs of thyroid cancer.[7] Papillary thyroid cancer is known to metastasize to the pre/paratracheal group of lymph nodes.[4,7] Anaplastic carcinoma displays extracapsular and vascular spread (33%). Medullary carcinoma may present with lymph node and distant organ metastasis.[7] In this study, 3 had extrathyroidal invasion; 2 with extension to lateral cervical lymph nodes, and 1 to the submandibular region. However, no significant association was found between extrathyroidal invasion and malignancy. This may be due to the small number of subjects with extrathyroidal invasion which may differ in a larger population since sample size is inversely proportional to p value and CI.

In this study, only microcalcification proved to be a significant predictor of malignancy using multivariate analysis. The risk of those with microcalcifications for having malignancy was almost 9x higher than those without microcalcification. Microcalcifications were noted to have strong association with malignancy.[1,2] In a study by Sio *et al*., 86% of papillary thyroid carcinoma cases displayed microcalcification on thyroid UTZ.[2] This feature had the highest accuracy (76%), specificity (44-95%), and predictive value (77.9%) in detecting malignancy.[1] These sonographic findings are consistent with hyperechoic foci with or without shadowing, corresponding histopathologically to psammoma body clusters.[1,7]

The American Thyroid Association recommends ultrasonography in patients with known or suspected thyroid nodules. Asymptomatic nodules can be found in as many as 50% of adults[1,6] while thyroid malignancy affects 1/10,000 people annually.[1] The challenge lies in identifying whether a nodule is benign or malignant, and who among the population would necessitate early aggressive management or avoidance of unnecessary investigation.[4] At present, the ATA categorized nodules to be of high suspicion (malignancy risk >70% to 90%) if the following are present in thyroid ultrasonography: solid hypoechoic nodule, irregular margins (specified as either infiltrative, microlobulated, or speculated), microcalcifications or disrupted rim calcifications with small extrusive hypoechoic soft tissue component, taller than wide shape of the thyroid nodule and evidence of extrathyroidal extension.

Our study has several limitations. Although the required number of subjects of 24 was met, the study sample may not fairly represent the larger population because of our convenience sampling technique. Random or consecutive sampling with clearer inclusion and exclusion criteria in future studies may address this. Because this is an observational non-randomized study, our benign and malignant "groups" may also vary in prognosis due to different demographics, illness severity or other baseline characteristics. Moreoever, we have at least two potential sources of measurement or observer bias – the histopathologic readings (taken at face value from available reports), and the ultrasonographic readings (despite verification by a blinded senior radiology resident). Future studies can improve on this with random and concealed allocation of participants to groups and prospectively-obtained masked outcome assessment using objective and validated measures by independent, blinded observers.

In conclusion, our study found a significant association between malignant histopathologic results of the thyroid and presence of solid hypoechoic nodule, margins and microcalcifications but noted no significant difference with taller than wide nodules or presence of extrathyroidal extension on ultrasound. Only microcalcification was found to be a significant predictor of malignancy using multivariate analysis. The risk of patients with microcalcification for malignant result was almost 9 times higher than those without microcalcification, but this requires careful scrutiny, as our confidence interval was broad.

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