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A Cross Sectional Study on the Value of Ultrasonography in Predicting the Risk of Thyroid Malignancy

Isaac David E. Ampil II, M.D., F.P.C.S. and Rafael R. Azares, M.D.

Department of Surgery, University of the East Ramon Magsaysay Memorial Medical Center

This study aimed to determine the accuracy of ultrasonography in differentiating malignant thyroid nodules/ lesions. It also aimed to identify the ultrasound features that would highly suggest thyroid malignancy and validate the scoring system proposed by Ampil, et al. (2007) that would predict thyroid malignancy based on the said ultrasonographic features.

Methods: A retrospective, cross sectional study of 278 patients with thyroid pathology were included in this study comparing ultrasound characteristics and pathologic results from 2004 to August 2011. The main outcome measure is to identify ultrasound features that predict malignancy by means of multiple logistic regression analysis.

Results: For patients with thyroid malignancy, all those with invasion to contiguous structures turned out to be malignant ($P<0.0001$), while the other statistically significant common ultrasonographic findings were negative halo sign, irregular shape, ill-defined margins and hypoechogenecity. In this study, a score of 0-3 have a negligible risk of malignancy, a score of 4 has an intermediate risk of cancer and a score of 5-8 has the highest chance of being malignant.

Conclusion: Ultrasonography is a useful diagnostic tool in identifying the presence of thyroid nodules. Moreover, some features are identified to predict the probability of a malignancy. The presence of invasion, irregular margins, homogeneity and absence of halo sign are the main predictors of thyroid malignancy.

Key words: Ultrasound, thyroid, cancer, risk stratification

Since the advent of high-resolution ultrasonography, it is sometimes possible to establish the diagnosis of a well-differentiated thyroid cancer.[1]

Ultrasound of the neck is a useful imaging technique in the evaluation of the thyroid gland for patients with a confirmed or suspected thyroid nodule on physical examination. It is safe, non-invasive, relatively inexpensive and easily available for point-of-care evaluation in the clinic or the operating room. The portable equipment provides an immediate 2-dimensional gray scale image of the neck through high resolution and frequency transducers. Qualitative features, such as contents, calcifications, borders, shapes, echotexture, and vascularity, when evaluated, in combination, can provide information about the malignancy potential of thyroid lesions and should be documented.[2]

The latest American Thyroid Association (ATA) Management Guidelines strongly recommend the use of ultrasonography in all patients with known or suspected thyroid nodules.[3] Numerous reports have already been done showing certain ultrasound characteristics that are associated with a higher likelihood of malignancy. These include nodule hypoechogenicity compared to the normal thyroid parenchyma, increased intranodular vascularity, irregular infiltrative margins, the presence of microcalcifications,an absent halo, and a shape taller than the width measured in the transverse dimension. The ATA stated, however, that no single sonographic feature or combinations of features is adequately sensitive or specific to identify all malignant nodules.

Locally studies and the Philippine College of Surgeons also recommend the use of ultrasonography in patients with suspicious nodule for cancer in the background of multinodular goiter, high-risk patients, those with adenopathy suggestive of a malignant lesion and for

evaluation of the patient with nodular goiter.[4] As of the moment, the General Surgery I (Head and Neck, Upper GI) service of this hospital adapts these recommendations and in line with this, a pilot study (A Cross Sectional Study on the Use of Ultrasonography in Detecting Thyroid Malignancy) done by Ampil, Arellano (2007) concluded that the presence of invasion, irregular margins, homogeneity and absence of halo sign are the main predictors of thyroid malignancy. However, the proper combination of ultrasound characteristics that could increase the sensitivity and specificity in predicting thyroid malignancy has not been established.[5]

This study aimed to determine the ultrasound features that would be highly suggestive of malignancy and validate the scoring system proposed by Ampil, et al.

Methods

This was a cross sectional study conducted at UERMMMCI involving patients from both Pay and Service wards who sought consult due to a thyroid disease and underwent thyroidectomy, from January 2004 to August 2011. Data from the pilot study done last 2007 (Ampil, Arellano) were included, as well as data from the Thyroid Registry of the Department of Surgery; all of which were retrieved from the Department's monthly Census files. Additional data were then gathered from clinical abstracts/ discharge summaries submitted to the Records Section of the hospital. All ultrasound examinations were performed using GE Logiq 500 (2004-2009), and GE Logiq 7 (2009 onwards). The sonographic characteristics evaluated were based on previously published criteria and the recommendation of American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE) and the Associazione Medici Endocrinologi (AME), consisting of size of the nodule, shape, margin, echogenicity, presence or absence of calcification, peripheral halo, extracapsular growth or invasion to adjacent structures and internal echo. All ultrasound plates were reviewed by a sonologist, who was blinded as to the case and the final histopathology of the thyroid specimen (which was used as the gold standard for diagnosis in determining whether the nodule was benign or malignant).

Sensitivities and specificities were calculated, as well as the positive and negative predictive values, and positive and negative likelihood ratios, to determine the accuracy of ultrasound in predicting malignancy. A scoring system previously formulated to predict malignancy was used to validate these ultrasound findings.

Results

A total of 278 patients who have a preoperative ultrasound and subsequently underwent thyroidectomy from 2004 to 2011 were included. The average number of thyroidectomies done per year was 35 (Table 1). There were 193 benign lesions (69%) and 85 (31%) malignant lesions based on the final pathologic report (Table 2).

Table 1. Distribution of 278 patients diagnosed per year.

2004		2005		2006		2007		2008		2009		2010		2011	
n	Freq%	n	Freq %	n	Freq %	n	Freq %	n	Freq %	n	Freq %	n	Freq %	n	Freq %
32	12%	26	9%	30	11%	35	13%	39	14%	37	13%	51	18%	28	10%

Table 2. Distribution of patients based on the presence or absence of malignancy.

Malignancy	2004		2005		2006		2007		2008		2009		2010		2011		Total	
	n= 32	%	n= 26	%	n= 30	%	n= 35	%	n= 39	%	n= 37	%	n= 51	%	n= 28	%	n= 278	%
+Cancer	12	13%	5	6%	9	12%	11	13%	11	13%	12	14%	15	18%	10	11%	85	31%
–Cancer	20	10%	21	11%	21	11%	24	13%	28	14%	25	13%	36	18%	18	10%	193	69%

The most common malignancy was papillary cancer (85%), followed by follicular cancer (13%), then the less common variants medullary (2%) and anaplastic (<1%) cancer.

Table 3. Histopathologic outcome of the 85 patients with thyroid cancer.

Type of Tumor	Number of Patients	%
Papillary carcinoma	72	85%
Follicular carcinoma	11	13%
Medullary carcinoma	2	2%
Anaplastic carcinoma	1	<1%
Total	85	100%

The sensitivities, specificities, positive and negative predictive values, and positive and negative likelihood ratios of the different ultrasonographic findings were computed. The findings with highest sensitivities and specificities were negative halo sign (95% and 98%), irregular shape (82% and 88%), homogenous internal echo (82% and 85%) and hypoechoic (82% and 82%). The presence of invasion was only 9% sensitive, but was 100% specific. Absence of halo sign had the highest (+) likelihood ratio (47), followed by ill-defined margins (9.08) and irregular shape (6.62). (Table 4)

Univariate analyses of the identified ultrasonographic characteristics were done using Fisher exact t-test. In all of the benign thyroid lesions, no invasion was noted on ultrasound. For patients with thyroid malignancy, all of those exhibiting invasion to contiguous structures turned out to be malignant, while the other statistically significant common ultrasonographic findings were negative halo sign, irregular shape, ill-defined margins and hypoechogenecity (Tables 5-12).

Table 4. Ultrasonographic features and computed sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios

USG Features	Sensitivity	Specificity	PPV	NPV	(+)LR	(-)LR
Ill-defined Margins	75	92	80	89	9.08	0.027
Irregular Shape	82	88	75	92	6.62	0.2
Solid or Predominantly Solid	75	52	41	83	1.56	0.48
Hypoechoic	82	82	67	91	4.56	0.22
Homogenous	82	85	71	92	5.47	0.21
Absence of Halo Sign	95	98	96	98	47	0.05
Presence of Calcifications	56	83	60	81	3.29	0.53
Presence of Invasion	9	100	100	72	-	0.91

Table 5. Tabulation of margins (well-defined and ill-defined) as to the final histopathology.

			Final Histopath		Total
			Benign	Malignant	
Margins	Well defined	n	177	21	198
		%	89%	11%	
	Ill defined	n	16	64	80
		%	20%	80%	
Total		n	193	85	278

P <0.0001

* A thyroid nodule is considered ill-defined when more than 50% of its border is not clearly demarcated.[9]

Table 6. Tabulation of shape (regular and irregular) as to the final histopathology.

			Final Histopath		Total
			Benign	Malignant	
Shape	Regular	n	169	15	184
		%	92%	8%	
	Irregular	n	24	70	94
		%	25%	75%	
Total		n	193	85	278

P <0.0001

Table 7. Tabulation of consistency (cystic and solid) as to the final histopathology.

			Final Histopath		Total
			Benign	Malignant	
Consistency	Cystic	n	101	21	122
		%	83%	17%	
	Solid	n	92	64	156
		%	59%	41%	
Total		n	193	85	278

P <0.0001

Table 8. Tabulation of echo structure (hyperechoic and hypoechoic) as to the final histopathology.

			Final Histopath		Total
			Benign	Malignant	
Echo Structure	Hyperechoic	n	159	15	174
		%	91%	9%	
	Hypoechoic	n	34	70	104
		%	33%	67%	
Total		n	193	85	278

P <0.0001

Table 9. Tabulation of internal echo (heterogenous and homogenous) as to the final histopathology.

			Final Histopath		Total
			Benign	Malignant	
Internal Echo	Heterogenous	n	164	15	179
		%	92%	8%	
	Homogenous	n	29	70	99
		%	29%	71%	
Total		n	193	85	278

P <0.0001

Table 10. Tabulation of halo sign (present and absent) as to the final histopathology.

			Final Histopath		Total
			Benign	Malignant	
Halo	Present	n	190	4	194
		%	98%	2%	
	Absent	n	3	81	84
		%	4%	96%	
Total		n	193	85	278

P <0.0001

* The halo or hypoechoic rim around a thyroid nodule is produced by a pseudocapsule of fibrous connective tissue, a compressed thyroid parenchyma and chronic inflammatory infiltrates (indicative of a benign entity).[9]

Table 11. Tabulation of calcification (absent and present) as to the final histopathology.

			Final Histopath		Total
			Benign	Malignant	
Calcification	Absent	n	161	37	198
		%	81%	19%	
	Present	n	32	48	80
		%	40%	60%	
Total		n	193	85	278

P <0.0001

* Microcalcifications appear as punctate hyperechoic foci without acoustic shadowing.[9]

Table 12. Tabulation of invasion (absent and present) as to the final histopathology.

			Final Histopath		Total
			Benign	Malignant	
Invasion	Absent	n	193	77	270
		%	72%	28%	
	Present	n	0	8	8
		%	0%	100%	
Total		n	193	85	278

P <0.0001

Multivariate analysis (logistic regression) of the different ultrasonographic characteristics was done using an internet-based software (http://faculty.vassar.edu/lowry/odds2x2.html). Based on the analysis, the presence of invasion and absence of halo sign was the highest predictors of malignancy (Table 13).

Table 13. Multivariate analysis of the ultrasound features.

	OR	95% CI	P value
Margins	33.7	17.57 - 68.61	<0.001
Shape	32.9	16.27 - 66.35	<0.001
Consistency	3.3	1.90 - 5.91	<0.001
Echogenicity	21.8	11.17 - 42.62	<0.001
Internal echo	26.39	13.33 - 52.26	<0.001
Calcifications	6.5	3.68 - 11.57	<0.001

The previously published scoring system done by Ampil and Arellano (2007) was utilized in this study to analyze the risk of cancer.

Table 14. Cancer score and final histopath cross tabulation.

CA Score	Final Histopathology		Total
	Benign	Malignant	
0	75	0	75
1	44	0	44
2	39	0	39
3	28	0	28
4	6	12	18
5	1	22	23
6	0	25	25
7	0	24	24
8	0	2	2
Total	193	85	278

Score of 0 – 3: no chance of CA

4: there is 67% chance of CA (12 out of 18 patients)

5: there is 96% chance of CA (22 out of 23 patients)

6 – 8: there is 100% chance of CA

Table 15. Recommendations in the management of thyroid nodules based on ultrasonographic features.

Score	Risk of CA	Recommendation
0 - 3	Low	Serial monitoring / observation
4	Intermediate	FNAB is recommended
5 - 8	High	Surgery is recommended
1 - 5 BUT with presence of invasion or absence of halo		

Discussion

Ultrasonography remains to be the imaging procedure in documenting thyroid pathology. In the general population, the over-all incidence of thyroid cancer is about 4-7 percent. Benign thyroid disease makes up the majority of any thyroidal pathology (adenoma, thyroiditis, multinodular non-toxic goiter), as shown in this study (69% versus 31% for cancer). Likewise, the incidence of well-differentiated thyroid cancer greatly outweighs its poorly differentiated counterpart. Papillary cancer is the most prevalent, followed by the follicular variant (98% for the combined papillary and follicular). As stated in the literature, the incidence of both the medullary and the anaplastic variants are rare, as shown in this study.

Tissue diagnosis is still the gold standard in establishing whether the pathology is benign or malignant. All patients with a palpable thyroid nodule or with clinical risk factors should undergo ultrasound examination.[6] Certain ultrasonographic features are used to predict the probability of malignancy (irregular margins, invasion, increased vascularity, calcification, anechoic, absent halo). The reported specificities for predicting malignancy are 41.4 to 92.2 percent for marked hypoechogenicity, 44.2 to 95.0 percent for microcalcifications (small, intranodular, punctate, hyperechoic spots with scanty or no posterior acoustic shadowing), 48.3 to 91.8 percent for irregular or microlobulated margins, and about 80 percent for chaotic arrangement or intranodular vascular

images. The value of these features for predicting cancer is partially blunted by the low sensitivities, however, no ultrasonography sign independently is fully predictive of a malignant lesion. The coexistence of 2 or more suspicious ultrasound criteria greatly increases the risk of thyroid cancer.[7,8] The presence of invasion and absence of halo sign have the highest predictors of malignancy, followed by hypoechoic nodules, homogeneity and irregular shape. Almost all known thyroid cancers are solid except when associated with necrosis, thereby making it unspecific for malignancy.

The previously published pilot study (Ampil, Arellano) formulated a scoring system in which ultrasound features can predict malignancy, and subsequently derived recommendations for the management of thyroid nodules based on the said features. Using the mentioned criteria, this study validates this proposed scoring system with high accuracy. In this study, a score of 0-3 has a negligible risk of malignancy, a score of 4 has an intermediate risk of cancer and a score of 5-8 has the highest chance of being malignant.

It can never be emphasized, however, that the decision of a physician in managing patients with thyroid pathology should be based on the over-all picture, not relying in ultrasound alone. This study should serve to be a guide and as an adjunct in the treatment of thyroid diseases.

Conclusion

Ultrasonography is a useful diagnostic tool in identifying the presence of thyroid nodules. Moreover, some features are identified to predict the probability of a malignancy. The presence of invasion, irregular margins, homogeneity and absence of halo sign are the main predictors of thyroid malignancy.

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