Ultrasound Predictors of Thyroid Cancer

Cholatip Wiratkapun MD*, Rapeechai Jaiyen MD*, Panuwat Lertsithichai MD, MSc**,
Banjongsak Wedsart MD*, Janjira Jatchavala MD*, Suphaneewan Jaovisidha MD*,
Prakasit Chirappapha MD**, Atcharaporn Pongtippan MD***, Rangsima Aroonroch MD***

** Department of Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
*** Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
**** Department of Pathology and Cytology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

Objective: *To identify ultrasound (US) features associated with cancer in thyroid nodules.*
Material and Method: *During a two and a half-year period, medical charts, US images, and pathological findings in 629 consecutive patients with thyroid nodules who underwent US examination as well as fine needle aspiration biopsy (FNAB) or surgical excision or both were retrospectively reviewed. Clinical and US findings associated with thyroid cancer were identified using statistical models.*
Results: *Unequivocal cytological or pathological findings were available for 578 patients. Forty-eight patients (8%) had thyroid cancer. Independent clinical and US features associated with thyroid cancer included younger age, symptoms other than palpable mass, solid nodules, fewer number of nodules, presence of calcifications, and enlarged cervical lymph nodes. The combination of all these features was most specific for the diagnosis of thyroid cancer. The absence of all these features could rule out all thyroid cancers.*
Conclusion: *The risk of the thyroid cancer in patients with thyroid nodules could be estimated by using relevant clinical and US features.*

Keywords: *Thyroid, Thyroid nodule, Ultrasound, Predictor, Cancer*

J Med Assoc Thai 2013; 96 (2): 225-30
Full text. e-Journal: *http://jmat.mat.or.th*

Thyroid nodules are a common finding in clinical practice[1-9]. Because of the superficial location of the thyroid gland, the thyroid nodule is easy to detect clinically[1]. Ultrasonography (US) plays a major role in the differential diagnosis of thyroid nodules. US can confirm the existence of the nodules, as well as provide useful diagnostic information for appropriate management[1-3].

High resolution US is the modality of choice for distinguishing between cysts and solid nodules of the thyroid. It is also a widely accepted and valuable tool in the diagnosis of thyroid cancer[1-3]. Many US features can be used as predictors of malignant thyroid nodules. These features include nodule size, shape (taller than wide), margin (spiculate or indistinct), echogenicity (marked hypoechogenicity), and the presence of calcifications (micro or macro-calcifications) with reported accuracies ranging from 59.5% to 73.4%[2]. Extra-thyroid findings such as the presence of enlarged cervical lymph nodes or tumor invasion into the strap muscles can also help in the diagnosis of the malignant nodule[2].

The purpose of the present study was to identify clinically important US predictors of thyroid cancer in a sample of Asian patients.

Correspondence to:
Wiratkapun C, Department of Radiology, the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama 6th Road, Rajthewee, Bangkok 10400, Thailand.
Phone: 0-2201-1260; Fax: 0-2201-1297
E-mail: cholatipp@gmail.com, racwr@mahidol.ac.th

Material and Method

The present study was approved by the institutional review board. The informed consent was waived because it was retrospectively conducted.

Data on 1,543 patients who underwent US thyroid at the Department of Radiology, the university-based hospital between June 1, 2007 and December 31, 2009, were reviewed. Patients were included in the present study if they had subsequent fine needle aspiration biopsy (FNAB) or surgical excision of the corresponding nodules. All pathological reports were reviewed by the pathologist-investigators. Patients with unsatisfactory or uncertain cytological or histopathological diagnosis were excluded.

Patients' symptoms, age, and gender were recorded and their US findings were retrospectively

reviewed by the investigators. The gland size, nodule size, echotexture, shape, margin, types of calcification, vascularity, and presence of halo or cysts were obtained. In cases of multiple thyroid nodules and cysts, morphology and size were recorded only for the lesion that had undergone an interventional procedure.

All US studies were performed with either an HDI 5000 (ATL Ultrasound, Bothell, WA, USA) or iU22 Ultrasound System CE 0086 (Bothell, WA, USA) instrument equipped with a 5 to 12 MHz or an 8 to 15 MHz linear-array transducer. The scanning protocol in all cases included both transverse and longitudinal real-time imaging of the thyroid gland. Seven radiologists performed the US examination.

Measurements and classification of US findings followed standard definitions[3,4]. The internal content of a nodule was categorized into five types according to the ratio of the solid and cystic portions in the nodule: solid nodule (100% solid component), predominantly solid nodule (more than 75% solid component), mixed solid cystic nodule (50 to 75% solid component), predominantly cystic nodule (25 to 50% solid component), and cystic nodule (less than 25% solid component).

The shape of the nodule was categorized as ovoid, round, and irregular. The margin of the nodule was categorized as well-defined, smooth, spiculated, or ill-defined. The presence of halo or hypoechoic rim was taken to mean a completely uniform halo around a nodule.

Echogenicity of the solid component of the thyroid nodule was assessed in relation to the thyroid parenchyma and strap muscles, and was classified as markedly hypoechoic (a relatively hypoechoic pattern in relation to the adjacent strap muscle), as hypoechoic (a relatively hypoechoic pattern in relation to the normal thyroid parenchyma), isoechoic (an echogenic pattern similar to that of the normal thyroid parenchyma), or hyperechoic (a relatively hyperechoic pattern in relation to the normal thyroid parenchyma).

Calcifications seen in the nodules were classified as microcalcification (tiny, punctate echogenic foci of 1 mm or less either with or without posterior shadowing), macrocalcification (punctate echogenic foci larger than 1 mm in size), or rim calcification (a peripheral curvilinear or eggshell calcification).

Vascularity of the nodule was evaluated by color or power Doppler US, and was categorized as intranodular flow (flow in the central part greater than that in the surrounding parenchyma), perinodular flow (the presence of vascularity of at least 25% of the circumference of a nodule), hypervascularity, hypovascularity, normal vascularity, and avascularity. US evaluation of the cervical lymph nodes in the internal jugular chain included measurement of size, presence of rounded bulging shape, replacement of fatty hilum, irregular margin, heterogeneous echo texture, calcifications, cystic areas, and presence of internal vascularity, all of which might be related to cancer metastasis. Local invasion was defined as the presence of infiltrating border of the node into the surrounding tissue.

Statistical analysis was performed using Stata version 9.0 (Stata Corp, College Drive, Texas, USA). Continuous variables were summarized using mean and standard deviation (SD) or median and range as appropriate. Categorical variables were summarized as counts and percentage. Statistical tests included unpaired t-test or rank test for continuous variables and chi-square test for categorical variables. Logistic regression was used for identifying significant predictors of thyroid cancer. Sensitivity, specificity, and discriminatory ability were used to measure the performance of a predictor. Discriminatory ability of a predictor was measured using the area under the receiver operating characteristic (ROC) curve (AUC). A two-tailed p-value of 0.05 or less was considered statistically significant.

Results

There were 629 patients in the present study. The majority, 558 patients, were women (89%) and 71 were men (11%). The mean age was 48.4 years (SD, 14.0 years). The most common presenting symptoms were palpable masses or nodules in 529 patients (84%). Other symptoms included tightness and pressure around the neck, hyperthyroidism, hoarseness of voice, dysphagia, and cervical lymphadenopathy.

FNAB was done in 591 of 629 patients (94%). Details of cytological results are shown in Fig. 1. Among 629 patients, 126 patients (20%) underwent surgery. These included lobectomy and isthmusectomy in 50 patients (40%), total thyroidectomy in 42 patients (33%), subtotal thyroidectomy in 17 (14%), excision of nodule in 14 (11%), and incision and drainage in three (2%). Surgical pathology results were benign in 82 and malignant in 48 lesions. (Four patients had concurrent benign and malignant foci in the specimen). For benign entity, 76 lesions were adenoma or cysts and six lesions were inflammatory lesions consisted with acute and chronic thyroiditis or granuloma.

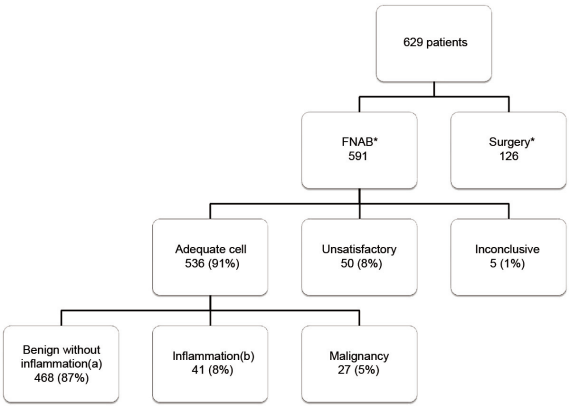

Fig. 1 Details of cytological results.
(a) Benign lesions without inflammation included goiter, cysts, intrathyroid lymphoid hyperplasia, thyroglossal duct cyst, and brachial cleft cyst.
(b) Lesion with cytologic findings of inflammation in acute and chronic thyroiditis, acute and chronic abscess.
* The sum of numbers of FNAB and surgery exceeded 629 because some patients underwent both FNAB and surgery.

Among the group of 578 patients used in the final analysis, who had unequivocal cytological or histopathological diagnosis, thyroid cancer was found in 48 patients (8%). Of these, papillary carcinoma was found in 41 patients (86%), follicular carcinoma in three (6%), anaplastic carcinoma in one (2%), lymphoma in two (4%) and squamous cell carcinoma in one (2%).

The age of the patients with cancer was younger than the noncancerous group (mean age 41.0 years, SD 16.8 versus 48.9 years, SD 13.7; p-value <0.001). Symptoms other than palpable mass (pressure effect, hyperthyroidism, hoarseness, dysphagia and cervical lymphadenopathy) were significantly associated with cancer (p-value 0.008). However, there was no clear difference in gender (p-value 0.876).

Univariable analysis for US features of benign and malignant lesions are in detail as follows. The patients with thyroid cancer were more likely to have a single nodule as opposed to multiple nodules (p-value 0.019) and more likely to have solid rather than cystic nodules (p-value <0.001). Malignant nodules were more likely to have ill-defined or spiculated borders (p-value <0.001), more likely to be markedly hypoechogenic (p-value 0.011), irregularly shaped (p-value 0.038), and to have micro- or macro-type calcifications (p-value <0.001), with predominantly perinodular vascularity (p-value 0.008). Thyroid cancers were also more likely to be associated with enlarged and detectable cervical lymph nodes (p-value <0.001).

Table 1 shows a multivariable logistic regression model with several independent clinical and US predictors significantly associated with thyroid cancer. There were 556 patients with complete data on all the predictors shown. Younger patients with symptoms other than palpable masses, and US findings of single solid nodule, evidence of calcification, and presence of cervical lymph nodes were more likely to have thyroid cancer. The discriminatory ability (AUC of the ROC curve) of the model to differentiate thyroid cancer from benign lesions was 0.816 (standard error, 0.036), which was very good.

Table 1. The set of independent predictive factors for thyroid cancer in the present study based on a multiple logistic regression model (n = 556)

Factors	Odds ratio (95% CI)	p-value*
Age (per year increase)	0.97 (0.95 to 0.99)	0.016
Pressure effect & other symptoms	2.72 (1.25 to 5.91)	0.011
Pure solid nodule	6.85 (2.74 to 17.1)	<0.001
Number of nodules (per nodule increase)	0.80 (0.67 to 0.96)	0.014
Calcification in nodule		
No calcification	1 (reference)	NA
Rim calcification	2.25 (0.44 to 11.7)	0.333
Microcalcification	3.66 (1.44 to 9.28)	0.006
Macrocalcification	3.94 (1.47 to 10.6)	0.007
Presence of cervical nodes	2.55 (1.25 to 5.20)	0.010

Area under the ROC curve for this model: 0.816 (standard error = 0.036)
* p-value by Wald's test

Table 2. Sensitivity, specificity and area under the ROC curve for some clinical, US and model predictors

Factor	Sensitivity (95% CI)	Specificity (95% CI)	AUC (SE)
Pressure effect & other symptoms	29.2 (17.0 to 44.1)	85.4 (82.1 to 89.3)	0.573 (0.034)
Pure single nodule	47.9 (33.2 to 62.8)	68.7 (64.5 to 72.6)	0.583 (0.038)
Irregular shape	22.9 (12.0 to 37.3)	89.0 (86.1 to 91.6)	0.560 (0.031)
Solid nodule	87.5 (74.8 to 95.3)	48.8 (44.4 to 53.1)	0.681 (0.027)
Ill-defined margin	41.7 (27.6 to 56.8)	81.5 (77.9 to 84.7)	0.616 (0.037)
Marked hypoechogenicity	27.1 (15.3 to 41.8)	86.6 (83.2 to 89.5)	0.569 (0.033)
Calcified nodule	37.5 (23.9 to 52.6)	85.6 (82.3 to 88.5)	0.615 (0.036)
Presence of cervical nodes	41.7 (27.6 to 56.8)	86.4 (83.1 to 89.2)	0.640 (0.037)
Multivariable model cut-off at probability = 0.5*	22.9 (12.0 to 37.3)	99.6 (98.6 to 99.9)	0.613 (0.031)

AUC = area under the ROC curve; SE = standard error; US = ultrasound
* Multiple logistic regression model in Table 1

The sensitivity, specificity and discriminatory ability for some clinical, US and model predictors are given in Table 2. All predictors, with single cut-off points, showed poor to fair discriminatory ability (AUC, 0.5 to 0.7). Most predictors have good specificity, with the multiple logistic model in Table 1 at cut-off probability of 0.5 having the highest specificity of 99.6%. However, these predictors were not very sensitive, except for the presence of a solid nodule on the US with a good sensitivity of 88%.

Patients with the absence of all the findings in Table 1 could be ruled out as having thyroid cancer. More precisely, in the present study, no patients older than 50 years, presenting only with palpable mass, with US findings of multiple cysts, no calcification and no cervical lymphadenopathy (n = 57) had thyroid cancer (0/57).

Discussion

Palpable nodules in the thyroid region are common[2,4]. US is often used as the first-line tool for investigating this abnormality. Except for the sonographic appearance of simple thyroid cysts, all complex cysts and solid nodules need careful evaluation due to the increased risk of malignancy.

In the present study, a pure solid nodule was the single most important and an independent predictor of thyroid cancer. The sensitivity and specificity of the finding of solid nodule, 88% and 49% respectively, were comparable to those of a previous study[6], reporting a sensitivity of 86% and a specificity of 40%. The presence of this finding might therefore be useful for screening for thyroid cancer. Once the radiologist has detected a pure solid thyroid nodule, he or she must carefully search for other features suggesting malignancy and perform a FNAB accordingly.

The degree of hypoechogenicity of the nodules has been shown to increase the accuracy of predicting thyroid malignancy[3]. In the present study, marked hypoechogenicity had a significant association with thyroid cancer on univariable analysis. This feature carried a high specificity (87%) but low sensitivity (27%), a finding similar to that of a previous study[3], which reported a specificity of 92% and a sensitivity of 41%. However, the degree of hypoechogenicity was not a significant independent predictor on multivariable analysis.

Margins of the nodule might be useful in predicting malignancy. Ill-defined or spiculate margins suggest nodular invasion into the surrounding tissues. The present study found that ill-defined or spiculated margin was significantly associated with thyroid cancer, with a high specificity (82%), but low sensitivity (42%). Although these findings were similar to those of previous studies[3,6], the nodule margin was not independently significant in predicting thyroid cancer.

It has been suggested that hypervascular nodules should be considered malignant until proven otherwise[4]. The present study agreed with the previous reports[3,4]. Moreover, the availability of color Doppler US could be useful for some thyroid nodules lacking other US characteristics of cancer. It is reasonable to inform that color Doppler should be applied to evaluate all thyroid nodules.

Calcifications associated with thyroid nodules have been shown to be one of the more

important predictors of thyroid cancer[2-8,10-12]. The present study showed that nodules with any type of calcification were significantly associated with thyroid cancer with a high specificity (86%) but low sensitivity (38%).

Similar to the previous studies[2,3,6,9,13] the finding of single as opposed to multiple nodules is a good predictor for thyroid cancer.

It is usually believed that a higher risk of thyroid cancer is associated with the male gender, increasing age, or the presence of pressure-effect symptoms[7,8]. The results of the present study supported the increased risk associated with the presence of pressure or similar symptoms, which was significant even on multivariable analysis, as opposed to the presence of only palpable nodules. In contrast, decreasing age was independently and significantly associated with thyroid cancer, while gender was not significant. This finding could be due to selection bias, as patients in the present series were overwhelmingly women and mostly young.

The presence of enlarged or abnormal cervical lymph nodes is known to be associated with thyroid cancer[2-6,8,13]. The present study supported this assertion. The presence of enlarged or abnormal lymph nodes was more common in the thyroid cancer group, and was an independent predictor of thyroid cancer. This finding was reasonably specific but not very sensitive in detecting malignancy, and was in agreement with that of previous studies[3,4].

There were several limitations in the present retrospective study. Real time sonographic assessment was not possible. This could have an influence on the interpretation of the US findings. Selection bias was also unavoidable as only higher risk patients or patients with suspicious thyroid lesions or those requiring tissue diagnosis were enrolled into the study. These limitations might have affected the validity of the present study.

The implications of the findings in the present study would be the confirmation of the clinical utility in the Asian population of some US characteristics shown to be associated with thyroid cancer in the European or American population, and the identification of a most specific set of clinical and US findings that could help diagnosing thyroid cancer. No single finding can be used alone without missing out on some thyroid cancers, but the whole set of characteristics in Table 1 and 2 should be used. At the very least, patients with any combination of these characteristics should undergo FNAB. On the other hand, patients with the absence of all findings in Table 1 would be unlikely to have thyroid cancer and might not require FNAB.

Conclusion

In the present study, younger age, symptoms other than purely palpable masses, solid nodule, markedly hypoechoic nodule, fewer numbers of nodules, presence of enlarged cervical nodes and presence of calcifications were independent predictors of thyroid cancer. Any combination of these findings should at least alert the clinician to the need for performing a FNAB. The absence of all these findings could rule out thyroid cancer.

Acknowledgement

The authors gratefully acknowledge Amnuay Thithapandha PhD for reviewing the manuscript and Rames Wacharasindhu MD for providing the US of the patients.

Potential conflicts of interest

None.

References

1. Solbiati L, Charboneau JW, Osti V, James EM, Hay ID. The thyroid gland. In: Wilson SR, Charboneau JW, Rumack CM, editors. Diagnostic ultrasound. St. Louis: Mosby, Elsevier; 2005: 735-70.
2. Hoang JK, Lee WK, Lee M, Johnson D, Farrell S. US Features of thyroid malignancy: pearls and pitfalls. Radiographics 2007; 27: 847-60.
3. Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, et al. Benign and malignant thyroid nodules: US differentiation—multicenter retrospective study. Radiology 2008; 247: 762-70.
4. Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, Coleman BG, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005; 237: 794-800.
5. McCartney CR, Stukenborg GJ. Decision analysis of discordant thyroid nodule biopsy guideline criteria. J Clin Endocrinol Metab 2008; 93: 3037-44.
6. Bastin S, Bolland MJ, Croxson MS. Role of ultrasound in the assessment of nodular thyroid disease. J Med Imaging Radiat Oncol 2009; 53: 177-87.
7. Polyzos SA, Kita M, Efstathiadou Z, Goulis DG, Benos A, Flaris N, et al. The use of demographic, ultrasonographic and scintigraphic data in the

diagnostic approach of thyroid nodules. Exp Clin Endocrinol Diabetes 2009; 117: 159-64.
8. Ghassi D, Donato A. Evaluation of the thyroid nodule. Postgrad Med J 2009; 85: 190-5.
9. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinol Metab 2009; 94: 1748-51.
10. Gulcelik NE, Gulcelik MA, Kuru B. Risk of malignancy in patients with follicular neoplasm: predictive value of clinical and ultrasonographic features. Arch Otolaryngol Head Neck Surg 2008; 134: 1312-5.
11. Choi YJ, Yun JS, Kim DH. Clinical and ultrasound features of cytology diagnosed follicular neoplasm. Endocr J 2009; 56: 383-9.
12. Kim MJ, Kim EK, Kwak JY, Park CS, Chung WY, Nam KH, et al. Differentiation of thyroid nodules with macrocalcifications: role of suspicious sonographic findings. J Ultrasound Med 2008; 27: 1179-84.
13. Kim MJ, Kim EK, Park SI, Kim BM, Kwak JY, Kim SJ, et al. US-guided fine-needle aspiration of thyroid nodules: indications, techniques, results. Radiographics 2008; 28: 1869-86.

ลักษณะคลื่นเสียงความถี่สูงที่ใช้ทำนายโอกาสเป็นมะเร็งต่อมไทรอยด์

ชลทิพย์ วิรัตกพันธ์, รพีชัย ใจเย็น, ภาณุวัฒน์ เลิศสิทธิชัย, บรรจงศักดิ์ เวชศาสตร์, จันทร์จิรา ชัชวาลา, สุภนีวรรณ เชาว์วิศิษฐ์, ประกาศิต จิรัปปภา, อัจฉราพร พงษ์ทิพพันธ์, รังสิมา อรุณโรจน์

วัตถุประสงค์: *เพื่อศึกษาลักษณะทางคลื่นเสียงความถี่สูงที่มีความสัมพันธ์กับมะเร็งต่อมไทรอยด์*
วัสดุและวิธีการ: *การศึกษาทำในผู้ป่วยที่ได้รับการตรวจคลื่นเสี่ยงความถี่สูงพบก้อนในต่อมไทรอยด์ และได้รับการเจาะตรวจเซลล์หรือ ผ่าตัดจำนวน 629 ราย ในระยะเวลา 2 ปีครึ่ง*
ผลการศึกษา: *ในผู้ป่วย 578 ราย ที่ผลเซลล์วิทยาและผลชิ้นเนื้อสรุปได้แน่ชัด พบมะเร็งต่อมไทรอยด์ ร้อยละ 8 พบว่า ปัจจัยที่มีความเกี่ยวข้องกับมะเร็งต่อมไทรอยด์อย่างมีนัยสำคัญทางสถิติ ได้แก่ อายุน้อย, อาการนอกเหนือจากการคลำพบก้อน, ลักษณะก้อนเป็นก้อนเนื้อ, ก้อนมีจำนวนน้อย, พบแคลเซียมภายในก้อน, และมีต่อมน้ำเหลืองบริเวณลำคอโต นอกจากนี้ยังพบว่ายิ่งมีลักษณะดังกล่าวหลายประการ โอกาสที่ก้อนนั้นจะเป็นมะเร็งเพิ่มสูงขึ้น และถ้าไม่พบลักษณะดังกล่าวแม้แต่ข้อเดียวสามารถให้การวินิจฉัยว่าก้อนนั้นไม่ใช่มะเร็ง*
สรุป: *มีลักษณะทางคลินิกและลักษณะทางคลื่นเสียงความถี่สูงที่สำคัญบางประการสามารถบ่งชี้ว่า ก้อนที่ตรวจพบมีโอกาสเป็นมะเร็งต่อมไทรอยด์*
