SONOGRAPHIC REVIEW OF THYROID LESION BASED ON ATA AND ACR-TIRADS CLASSIFICATION

DR DEIVIND KUMAR A/L NAGALINGAM

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (RADIOLOGY)

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BY

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ACR-TIRADS	American College of Radiology – Thyroid Imaging Reporting and Data System
AI TIRADS	Artificial Intelligence with Thyroid Imaging Reporting and Data System
ATA	American Thyroid Association
CDC	Centres for Disease Control
CI	Confidence interval
CT	Computed Tomography
FNAC	Fine Needle Aspiration Cytology
HPE	Histopathological examination
Hospital USM	Hospital Universiti Sains Malaysia
MNCR	Malaysia National Cancer Registry
NMCRR	National Mortality Case Record Review
NPV	Negative Predictive Value
OR	Odds ratio
PCR	Polymerase Chain Reaction
PPV	Positive Predictive Value
RIS	Radiology Information System
SPSS	Statistical Product and Service Solutions
TR	ACR-TIRADS category nodule
USG	Ultrasound
WHO	World Health Organization

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Kajian sonografi nodul kelanjar tiroid berdasarkan klasifikasi ATA dan ACR-TIRADS untuk mengesan nodul malignan

ABSTRAK

Latar belakang: Kanser kelenjar tiroid merupakan salah satu penyebab utama kanser di kalangan orang dewasa dengan purata kejadian 3-7%. Sonografi merupakan modaliti yang paling sensitif untuk mengesan nodul tiroid dan menstratifikasi nodul tiroid untuk mengenalpasti nodul yang malignan. Tujuan kajian ini adalah untuk membandingkan ciri-ciri sonografi nodul tiroid mengunakan ACR-TIRADS dan ATA klasifikasi serta mengenalpasti kesensitifan and kespesifikan klasifikasi tersebut.

Metod: Kajian kawalan kes secara retrospektif menggunakan imbasan sonografi yang telah dibuat sebelum pesakit- pesakit melalui pembedahan kelenjar tiroid. Nodul- nodul malignan telah dikenalpasti menggunakan penganalisaaan imej-imej nodul melalui sistem ATA dan pengiraan skor nodul telah dibuat menggunakan ACR-TIRADS. Pembolehubah seperti umur, jantina, sejarah keluarga, sejarah kanser telah dicatatkan dalam borang pengumpulan data. Untuk tujuan kajian ini, kategori ATA benign dan nodul tiroid yang disyaki malignan dalam kadar sangat rendah dan ACR-TIRADS TR2 ke bawah dianggap sebagai tumor yang tidak berbahaya. Manakala, nodul tiroid kategori ATA disyaki malignan dalam kadar rendah dan ACR-TIRADS kategori TR3 dan ke atas dianggap malignan.

Keputusan: Sejumlah 129 nodul dari 53 peserta telah digunakan dalam kajian ini. Segelintir nodul tiroid yang benign menunjukkan kategori benign berdasarkan ciri-ciri sonografi ATA menunjukkan 0% nodul tidak berbahaya dan 3% HPE malignan. Selain itu, nodul benign berdasarkan sonografi ACR-TIRADS, 0.8% menunjukkan HPE tumor yang tidak berbahaya dan 3.9% malignan HPE. Jumlah nodul malignan berdasarkan system klasifikasi ATA dan ACR-TIRADS adalah 93.0% dan 91.0%. Spesifikasi, NPV dan

ketepatan sistem ACR-TIIRADS mencatatkan peratusan yang tinggi (95.2%, 97.6% dan 93.0%). Statistik menunjukkan tiada perhubungan yang signifikan di antara setiap ciri-ciri ACR-TIRADS dengan nodul tiroid yang telah dikenalpasti dengan repot histopatologi. Sebanyak 28 nodul tiroid dalam kategori TR3, TR4, TR5 mencatatkan kadar malignan nodul 21.71%, 10.08% dan 6.98%.

Kesimpulan: Kajian ini menunjukkan tiada ciri-ciri spesifik sonografi nodul tiroid mempunyai hubungan yang signifikan dengan histopathologi malignan. Tetapi, gabungan segala ciri-ciri sonografi nodul tiroid mengunakan dua-dua klasifikasi ini dapat meramalkan nodul tiroid yang malignan. ACR-TIRADS merupakan sistem yang mudah dan praktikal untuk stratifikasi nodul tiroid dengan ketepatan yang tinggi.

Kata kunci: Kelenjar tiroid, Kanser tiroid, Sonografi, Nodul tiroid, Kanser tiroid papillary

Ultrasound review of thyroid nodules based on ATA and ACR-TIRADS classification to stratify malignant thyroid nodules

ABSTRACT

Background: Thyroid malignancy is one of the commonest cancers among adults with prevalence rate of 3-7%. High frequency ultrasound has been gold standard in detecting thyroid nodules and able to stratify malignant lesions. Research has been undertaken on these nodules with qualitative and quantitative manners to stratify these lesions. The purpose of this study is to compare stratification of thyroid lesions based on ACR-TIRADS and ATA in detecting malignant thyroid nodules and analyse the sensitivity and specificity of each scoring system.

Methods: A retrospective case-control study using sonographic images done prior to the patient's thyroidectomy. Identified thyroid nodules were analysed using ATA and ACR-TIRADS classification system for stratification and scoring. Variables such as age, gender, family history, previous malignancy history and previous irradiation history were documented in data collection form. For the purpose of our study, ATA benign and very low suspicion nodule were categorized as benign and TR2 and below category was taken as benign. On contrary to this, ATA low suspicion nodule with ACR-TIRADS TR3 category and above were taken as malignant.

Results: A total of 129 nodules from 53 participants were included in this study. The mean total identified benign thyroid nodule based on USG ATA classification showed 0% benign and 3% were malignant on HPE. Meanwhile, based on benign USG ACR-TIRADS features, 0.8% were benign and 3.9% were malignant. Malignant thyroid HPE based on ATA and ACR-TIRADS classification was 93.0% and 91.0% respectively. The specificity, NPV (Negative predictive value) and accuracy of ACR- TIRADS classification were high (95.2%,

97.6% and 93.0%) respectively. There was no significant association of each sonographic characteristics ACR-TIRADS with HPE proven malignant thyroid nodules. A total of 28 nodules of category TR3(TIRADS 3) was identified as HPE (Histopathological examination) proven malignancy with malignancy rate of 21.71%. in comparison to TR4 nodule and TR5 nodule of 10.08 % and 6.98% of detected malignancy rate.

Conclusion: Overall, this study showed that no single sonographic features of thyroid nodule have significant association with malignant histology outcome of thyroid nodule. However, combination of sonographic features improves predictability of malignancy. Concisely, ACR-TIRADS is simple and practical method for thyroid nodule stratification with high accuracy.

Keywords: *Thyroid gland, Thyroid cancer, Ultrasonography, Thyroid nodule, Papillary thyroid cancer*

CHAPTER 1: BACKGROUND

1.1 Introduction

Thyroid gland is a butterfly-shaped, endocrine organ in the neck which is composed of two lobes with interconnecting isthmus and completely enveloped by pre-tracheal fascia and lies in the visceral spaces of the neck (Bell *et al*, 2018).

Thyroid nodules are common clinical problem and are discovered on clinical examination in 3-7% of the adult population with detectable nodules on high resolution ultrasound are between 30% and 70% (Suhaimi *et al*, 2018). It is the most common endocrine malignancy with prevalence of thyroid cancer typically peaks in the third and fourth decades of life, typically three times higher in women than in men according to a study by Weir et al, from the US Centre's for Disease Control and Prevention (CDC). It is predicted that by 2020, the largest increases in the annual number of cancer cases in women will be for cancers of the lung, breast, uterus, and thyroid.

There has been a steady increase in the incidence rate of thyroid cancer in recent decades according to recent scientific papers, however, the causes of sudden increase in the number of cases have remained controversial (Vargas-Uricoechea *et al*, 2017).

It is clinically important to exclude thyroid malignancy from all the sonographically detected thyroid nodules and accordingly, optimization of long-term treatment must be determined to have better health outcomes and education about potential prognosis for individuals with thyroid neoplasm. This study aims to determine stratification of thyroid nodules and standard reporting system are important to avoid unnecessary invasive procedure or surgery and early intervention are feasible if indicated.

1.2 Objective

1.2.1 General objective

To determine the accuracy of ACR-TIRADS classification system compared to ATA classification system in categorizing malignant thyroid nodules.

1.2.2 Specific objectives

1. To compare individual ultrasound (USG) characteristics between thyroid nodules with benign and malignant outcomes (HPE)
2. To assess specificity and sensitivity between ACR-TIRADS and ATA ultrasound features for malignant thyroid nodule (HPE)
3. To compare negative predictive value and positive predictive value of ACR-TIRADS with ATA classification system

1.2.3 Problem statement

Ideally, sonographic features of malignant or benign thyroid nodules must be correlated with fine needle aspiration cytology (FNAC) findings. However, due to patient's refusal on invasive procedure, as thyroid nodules remain indolent for years. Due to this reason, this study was conducted in retrospective manner as most of the patient prefers for long term ultrasound (USG) assessment.

1.3 Hypothesis

Microcalcification, hypoechogenicity and irregular border of thyroid nodules are likely most sensitive and specific malignant thyroid nodule features. ACR-TIRADS classification system are likely more sensitive than ATA classification system in identifying sonographic features of malignant thyroid nodule for the decision of FNAC.

1.4 Research question

- What are most sensitive and specific USG features of malignant thyroid nodules?
- Is the ACR-TIRADS classification able to be used in daily practice for risk stratification?

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology of thyroid cancer in Malaysia and worldwide

According to National Mortality Case Record Review (NMCRR), there is increasing prevalence of thyroid cancer-causing health care burden in Malaysia with the incidence of thyroid cancer was highest among the Malay community involving more females than male patients (Lim *et al*, 2003). The lifetime risk is 1 in 884 in males and 1 in 336 for female (Lim *et al*, 2003).

The clinical importance of thyroid nodules rests with need to exclude thyroid cancer since the incidence rate depends on age, sex, ionizing radiation exposure history, family history, childhood exposure to head and neck irradiation and other factors (Sharma *et al*, 2020). In a European study of 86,690 patients with thyroid cancer between 2000 and 2007 by Dal Maso *et al* (2017), the relative thyroid cancer 5-year survival rates in men and women were 81% and 88%, respectively.

2.2 Aetiology, signs, and symptoms of thyroid cancer

Radiation exposure significantly increases the risk for thyroid cancer, particularly papillary thyroid carcinoma. Low-dose radiation therapy for benign disorders (for example acne, adenotonsillar hypertrophy) also causes increase in prevalence of the disease. However, low-dose radiation exposure from imaging studies and radiation therapy has not been found to have a tumorigenic effect (Sharma *et al*, 2020).

Low dietary intake of iodine does not increase the incidence of thyroid cancers overall (Sharma *et al*, 2020). However, populations with low dietary iodine intake have a higher proportion of follicular and anaplastic carcinomas (Sharma *et al*, 2020). Initial evaluation of thyroid malignancies includes history taking, physical examination,

laboratory investigation, and fine-needle aspiration biopsy remains mainstays in the evaluation of thyroid nodules.

Typical clinical manifestations are solitary nodules in patients older than 60 years and in patients younger than 30 years, rapid painless growth of existing thyroid nodules, hard and fixed nodules (Sharma *et al*, 2020).

2.3 Types of thyroid cancers

Thyroid carcinomas typically arise from the 2 cell types present in the thyroid gland (Sharma *et al*, 2020). The endodermally derived follicular cell gives rise to papillary, follicular, and anaplastic carcinomas (Sharma *et al*, 2020). In contrast, the neuroendocrine-derived calcitonin-producing C cell gives rise to medullary thyroid carcinoma (Sharma *et al*, 2020). Thyroid lymphomas arise from intrathyroid lymphoid tissue, whereas sarcomas arise from connective tissue in the thyroid gland (Sharma *et al*, 2020). Histological subtypes of thyroid malignancies are divided into papillary (80%) and follicular variant (10%), which comprises about 90% of all thyroid cancers (Haugen *et al*, 2016). Other subtypes include medullary thyroid carcinomas (5-10%), primary lymphoma and sarcomas (rare) (Cibas *et al*, 2009).

2.4 Pathophysiology of thyroid malignancy

Papillary thyroid carcinoma predominantly arises from follicular cells. Mutation to the RET (Rearranged during transfection) protooncogene which is located on the proximal arm of chromosome 10 and BRAF point mutation has been identified recently as pre-cursors for the thyroid malignancy. Multiple factors has been identified causing this derangement such as age, early radiation exposure, genetic mutation and low iodine levels in endemic regions. These factors cause RAS gene activation or peroxisome proliferator-activator receptor has been identified in development of follicular thyroid cancer which causes gradual loss of papillary and follicular growth pattern with simultaneous increase in solid pattern and progress with increase mitosis, necrosis with nuclear pleomorphism. These factors lead to development of papillary and follicular thyroid carcinoma. Meanwhile, parafollicular cell mutation leads to development of medullary thyroid carcinoma (Patel, Singh, 2006).

2.5 Relevant investigation and imaging findings in thyroid malignancy

Laboratory investigations include serum thyroid stimulating hormone concentrations which are sensitive for hyperthyroidism or hypothyroidism and for evaluation of solitary thyroid nodules (Sharma *et al*, 2020). Other blood parameters include serum calcitonin/ pentagastrin-stimulated calcitonin levels, typically elevated in medullary thyroid carcinoma (Sharma *et al*, 2020). Lastly, polymerase chain reaction (PCR) assay for germline mutations in the RET proto-oncogene for diagnosis of familial medullary thyroid carcinoma (Sharma *et al*, 2020).

According to ATA 2015, ultrasonography remains the most important imaging modality in the evaluation of thyroid cancer and should be used routinely to assess the primary tumour and all associated cervical lymph node involvement preoperatively (Haugen *et al*, 2016 and Mittal *et al*, 2020). Sonographic guided fine-needle aspiration of suspicious lymph nodes may be useful in guiding the extent of surgery (Haugen *et al*, 2016).

Cross-sectional imaging of computed tomography (CT) scanning with contrast or magnetic resonance imaging may be considered in selected circumstances for better characterization inferior tumour extension (Haugen *et al*, 2016).

Thus, high resolution thyroid ultrasound examination is considered the gold standard for initial stratification of thyroid lesions prior to invasive procedures (Grant *et al*, 2015).

Ultrasound features that predict increased likelihood malignancy include hypoechogenicity, microcalcification, taller than wide shape, irregular or microlobulated margins and increased intranodular vascularity (Grant *et al*, 2015). There is no single predictor has been found to have a high positive predictive value for cancer (Grant *et al*, 2015).

2.6 Analysis of thyroid nodules

ACR-TIRADS has proposed USG based risk stratification system, the Thyroid Imaging Reporting and Data System (ACR-TIRADS, whereby, a lexicon has been produced to describe all sonographic features of identified thyroid nodules and has developed management guideline for identified high-risk nodules (Grant *et al*, 2015). These nodules were categorized from TR1 (benign) until TR6 (malignant) (Grant *et al*, 2015).

With proposed USG features in combination with ACR-TIRADS category, thresholds for FNAC biopsy were decided (Grant *et al*, 2015). Obtained cytological sample was analysed and reported by experienced cytopathologists according to the Bethesda system for thyroid cytology reporting (Kim *et al*, 2011). These sample were classified ranging from Bethesda class I until VI (Kim *et al*, 2011). Out of those classification, Bethesda II were considered benign and Bethesda class VI were malignant (Kim *et al*, 2011). These were considered as diagnostic cytology reports and the remaining categories were Bethesda class I – inadequate; Bethesda class III – atypical cells or follicular cells of indeterminate significance; Bethesda class IV – follicular neoplasm; and Bethesda class V – suspicious for malignancy (Kim *et al*, 2011).

In contrast to ACR-TIRADS, the ATA classification system also stratifies the thyroid nodules qualitatively to predict the imaging features of malignant thyroid nodules (Haugen *et al*, 2016). Revised ATA guidelines propose five sonographic patterns related to increasing risk of malignancy: benign, very low, low, intermediate, and high suspicion (Haugen *et al*, 2016).

Both the guidelines eventually facilitated the selection of thyroid nodules for FNAC biopsy (Foley , 2019).

2.7 Rationale of study

Both ATA and ACR-TIRADS USG classification system facilitates clinicians in decision making for FNAC biopsy. However, ATA classification categorises suspicious thyroid nodule according to combination of USG features. In contrast, ACR-TIRADS combines USG features into more categorical fashion (TR1-TR6) and points were given in ascending order to help for decision-making for FNAC biopsy of these nodules.

From our study, we aim to build on the small existing body of evidence that ACR-TIRADS is more sensitive in detecting suspicious thyroid nodules in patients in a tertiary care teaching hospital in East-coast of Malaysia.

Eventually this could improve communication between radiologists and physicians through a standardized reporting format.

CHAPTER 3: METHODOLOGY

3.1 Study design

Retrospective data collection at the Department of Radiology, Hospital USM, Kubang Kerian, Kelantan, Malaysia for a period of 35 months from January 2017 to December 2019.

3.2 Sample population

i) Reference population - All USG neck done prior to thyroidectomy from January 2017 to December 2019 in Hospital USM, Kelantan

ii) Source population - All patients with known thyroid disease who underwent total, near total or hemithyroidectomy in Hospital USM

iii) Target population - All patients with thyroid nodules who underwent USG neck prior to their thyroidectomy surgery in Hospital USM.

iv) Sampling frame – Eligible patients according to the inclusion and exclusion criteria from the target population

3.3 Sample size calculation

For objective 1 and 3, the sample size is calculated using a single mean formula using Sample Size Calculator v2.0, prepared by Dr Wan Nor Ariffin, Unit of Biostatistics and Research Methodology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia.

Based on previous literature review by Chng *et al*, 2018 for diagnostic performance of ACR-TIRADS in prediction of thyroid malignancy, for standard deviation of 1.7, significance level of 0.001 and drop out 0%, the sample size was 127. Thus, 65 sample size for post thyroidectomy patients, and 65 sample size for patient underwent US

guided FNAC. Based on previous literature review by Chandramohan A *et al*, 2016 for TIRADS as practical and accurate system for use in daily clinical practise, for area under the curve of 0.761, confidence interval of 95% and significant p-value of <0.001, calculated sample size is 42.

Sample size for objective 2, sample size calculator sample size is still taken was 127 thyroid nodules and data sampling will be done using 2 by 2 tables.

3.4 Sampling method

Probability sampling was used either simple or systematic random from patients who underwent USG neck for past 35 months as per mentioned inclusion criteria. Set of data that was extracted from the subject's medical records using a research tool as below.

3.5 Inclusion criteria

1. Patients aged 18 years old and above with solitary or multinodular goitre.
2. Post thyroidectomy patients with available HPE results.

3.6 Exclusion criteria

1. Pregnant patients
2. Thyroid nodule less than 1cm

3.7 Research Tools

1) USG machines for image acquisition
    a) Samsung RS80A with Prestige
    b) Mindray DC-8 EXP
    c) Toshiba Aplio 500

d) Siemens Acuson S3000

2) Diagnostic Computer BARCO viewer to review USG images
3) GE Picture Archiving Communication System (PACS) in Hospital USM (PACS Universal Viewer Version 5.0 SP6) for USG image retrieval
4) LIS Pathology v2 HUSM for HPE data retrieval
5) IBM Statistical Product and Service Solutions (SPSS) (version 26)

3.8 Operational Definition

Thyroid nodules detected on the USG images are further characterized according to dedicated classifications. USG features of ATA classification has been depicted in Figure 1.

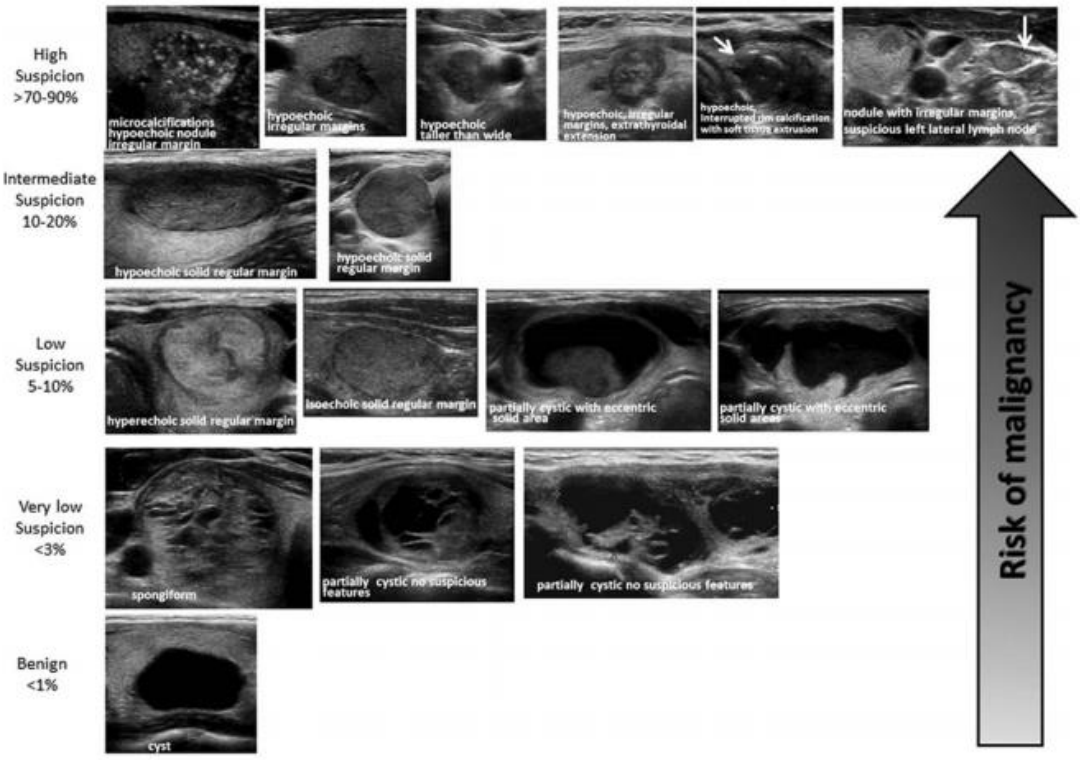

Figure 1: ATA nodule sonographic patterns and risk of malignancy (Image adapted from Haugen *et al*, 2016)

ACR-TIRADS Lexicon

1) Composition of thyroid nodules as depicted in Figure 2

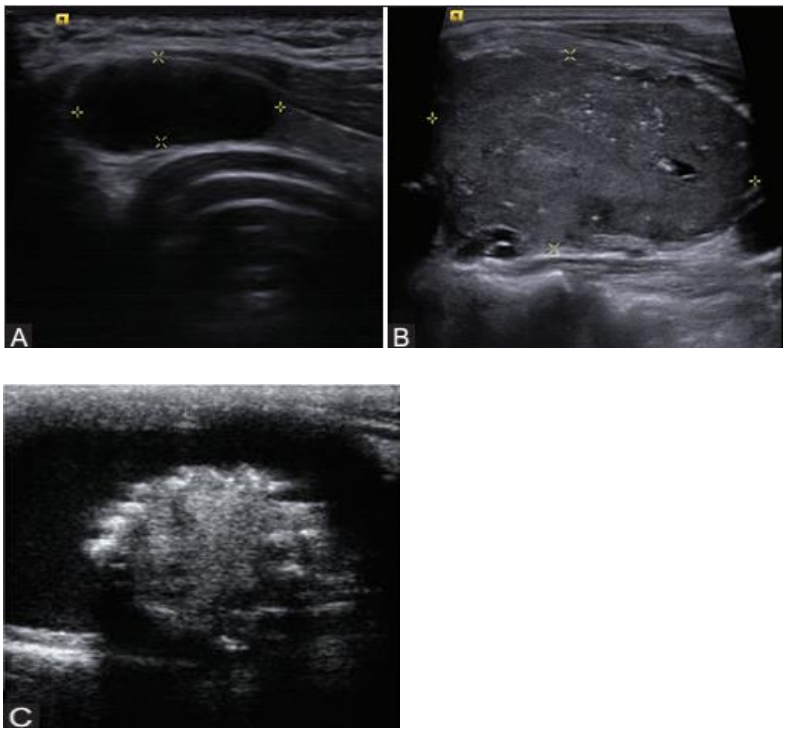

Figure 2: Composition of thyroid nodules (Image adapted from Chandramohan *et al*, 2016)

- describes the internal components of a nodule- presence of soft tissue or fluid and the proportion of each.

a) **Solid:** Composed entirely or nearly entirely of soft tissue, with only a few tiny cystic spaces

b) **Predominantly solid**: Composed of soft tissue components occupying 50% or more of the volume of the nodule

c) **Predominantly cystic:** Composed of soft tissue components occupying less than 50% of the volume of the nodule

d) **Cystic:** Entirely fluid filled

e) **Spongiform:** Composed predominately of tiny cystic spaces

2) Echogenicity of thyroid nodules as depicted in Figure 3

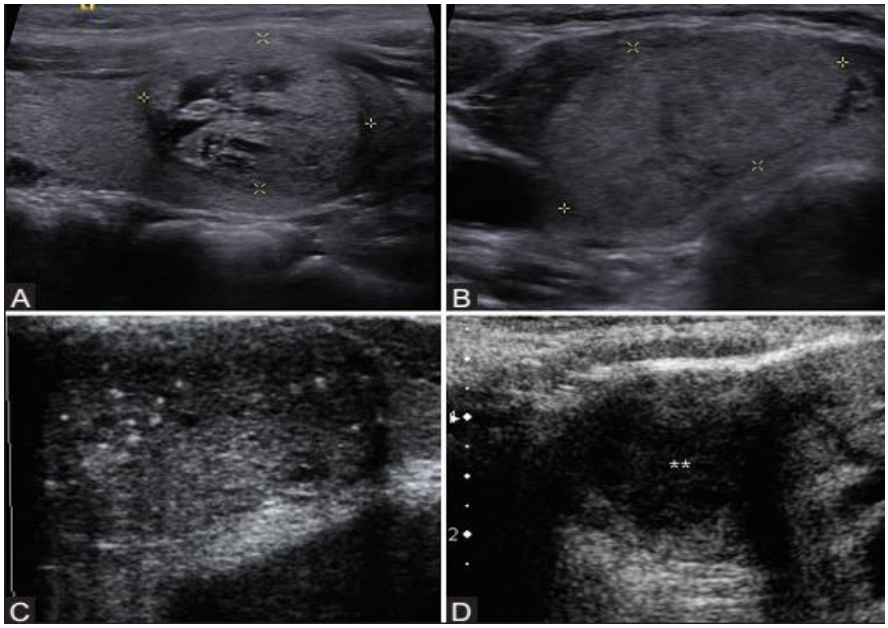

Figure 3: Echogenicity of thyroid nodules

(Image adapted from Chandramohan *et al*, 2016)

- Level of echogenicity of the solid component of a nodule (noncalcified areas) relative to surrounding normal thyroid tissue

a) **Hyperechoic**: Increased echogenicity relative to thyroid tissue

b) **Isoechoic**: Similar echogenicity relative to thyroid tissue.

c) **Hypoechoi**c: Decreased echogenicity relative to thyroid tissue

d) **Very hypoechoic**: Decreased echogenicity relative to adjacent neck musculature

3) Shape of thyroid nodules as depicted in Figure 4

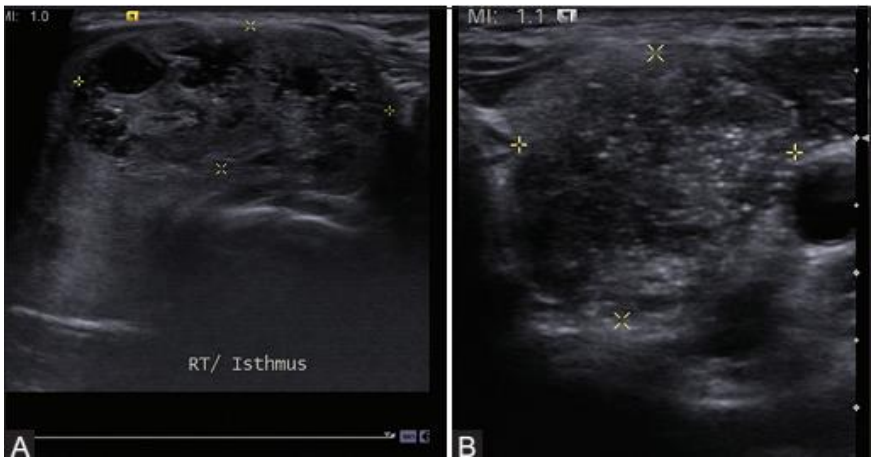

Figure 4: Shape of thyroid nodule

(Image adapted from Chandramohan *et al*, 2016)

a) Oval

b) Taller-than-wide

taller-than-wide shape is defined as a ratio of >1 in the anteroposterior diameter to the horizontal diameter when measured in the transverse plane.

4) Size of thyroid nodules as depicted in Figure 5

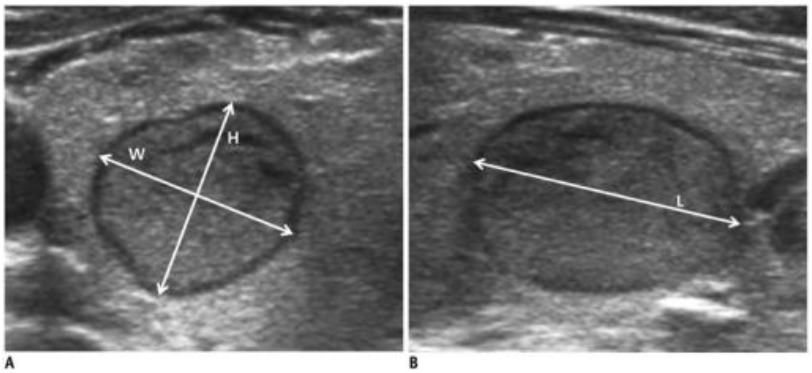

Figure 5: Size of thyroid nodules

(Image adapted from Choi *et al*, 2015)

The nodule should be measured at maximal diameter based on longitudinal, anteroposterior, and transverse measurements in centimetres.

5) Margins of thyroid nodules as depicted in Figure 6

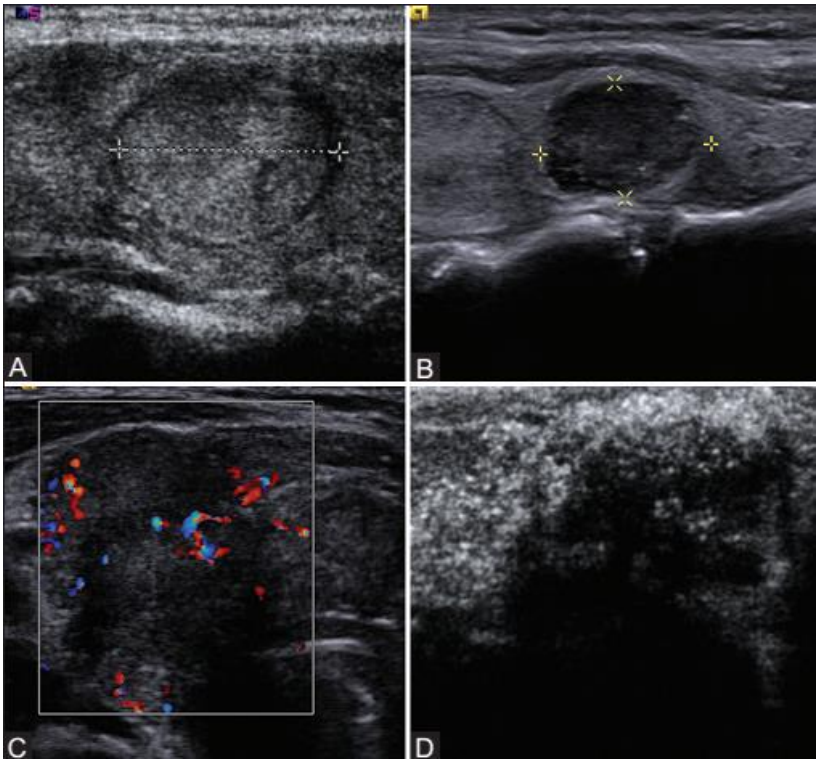

Figure 6: Margins of thyroid nodules

(Image adapted from Chandramohan *et al*, 2016)

- Refers to the border or interface between the nodule and the adjacent thyroid parenchyma or adjacent extrathyroidal structures.

a) **Smooth**: Uninterrupted, well-defined, curvilinear edge typically forming a spherical or elliptical shape

b) **Irregular margin:** The outer border of the nodule is spiculated, jagged, or with sharp angles with or without clear soft tissue protrusions into the parenchyma. The protrusions may vary in size and conspicuity and may be present in only one portion of the nodule.

c) **Lobulated:** Border has focal rounded soft tissue protrusions that extend into the adjacent parenchyma. The lobulations may be single or multiple and may vary in conspicuity and size (small lobulations are referred to as microlobulated)

d) **Ill-defined:** Border of the nodule is difficult to distinguish from thyroid parenchyma; the nodule lacks irregular or lobulated margins.

e) **Halo**: Border consists of a dark rim around the periphery of the nodule. The halo can be described as completely or partially encircling the nodule. In the literature, halos have been further characterized as uniformly thin, uniformly thick, or irregular in thickness.

f) **Extrathyroidal extension:** Nodule extends through the thyroid capsule

6) **Echogenic Foci**

- Refers to focal regions of markedly increased echogenicity within a nodule relative to the surrounding tissue. May vary in size and shape and may be encountered alone or in association with several well-known posterior acoustic artifacts.

a) **Punctate echogenic foci**: "Dot-like" foci having no posterior acoustic posterior artifacts.

Kwak et al defined punctate foci/microcalcifications as being <1mm.

b) **Macrocalcifications:** calcifications become large enough to result in posterior acoustic shadowing, they should be considered macrocalcifications. Macrocalcifications may be irregular in shape and >1mm.

c) **Peripheral calcifications**: These calcifications occupy the periphery of the nodule. The calcification may not be completely continuous but involves most of the margin. Peripheral calcifications are often dense enough to obscure the central components of the nodule.

d) **Comet-tail artifacts**: A comet-tail artifact is a type of reverberation artifact. The deeper echoes become attenuated and are displayed as decreased width, resulting in a triangular shape. If an echogenic focus does not have this feature, a comet-tail artifact should not be described.

Tabulated USG features of thyroid nodules with points for each USG features with further management plans are depicted with Table 1 and Table 2 as below.

Table 1: Thyroid USG features and points

USG characteristic	Points
Composition	cystic or completely cystic: 0 points spongiform: 0 points mixed cystic and solid: 1 point solid or almost completely solid: 2 points
Echogenicity	anechoic: 0 points hyper- or isoechoic: 1 point hypoechoic: 2 points very hypoechoic: 3 points
Shape	wider than tall: 0 points taller than wide: 3 points
Margin	smooth: 0 points ill-defined: 0 points lobulated/irregular: 2 points extra-thyroidal extension: 3 points
Echogenic foci	none: 0 points large comet tail artefact: 0 points macrocalcifications: 1 point peripheral/rim calcifications: 2 points punctate echogenic foci: 3 points

Source: Grant *et al*. Journal of the American College of Radiology 2015; 12 (12): 1272–79.

Table 2: Accumulative points and further recommendation

0 point	2 points	3 points	4-6 points	≥ 7 points	
TR 1	TR 2	TR 3	TR 4	TR 5	TR 6
Benign	Not suspicious	Mildly suspicious	Moderately suspicious	Highly suspicious	HPE Proven
No FNAC	No FNAC	≥ 1.5cm Follow up. ≥ 2.5cm FNAC	≥1.0cm Follow up. ≥1.5cm FNAC	≥ 0.5cm Follow up. ≥ 1.0cm FNAC	

Source: Grant *et al*. Journal of the American College of Radiology 2015; 12 (12): 1272–79.

For the purpose of our study, ATA benign and very low suspicion nodule were categorized as benign and ACR-TIRADS TR2 and below category was taken as benign.

3.9 Variable definition / Ascertainment

1. Independent variables: age, gender, family history, previous cancer history, previous irradiation therapy, presence of thyroid nodules and ultrasound findings.

2. Dependent variables: ATA and ACR-TIRADS thyroid nodule features on USG.

3.10 Data collection

Patient's registration number, age, gender, family history, presenting history, number of thyroid nodules, sonographic characteristics were recorded in a data collection sheet (Appendix D). Significant risk factors such as low iodine intake and prior radiation therapy were documented.

3.11 Image acquisition

This study retrospectively queried ultrasound reports between January 2017 to December 2019 from radiology records department Hospital USM, Kelantan. All USG were done at the fraternity USG facilities and reported. Using the USG report registration number, images are retrieved into GE PACS and viewed using Diagnostic Computer BARCO viewer. Each USG report was assigned a study identification number.

3.12 Image analysis and interpretation

All thyroid nodules were detected by reviewing previously done images from PACS. Thyroid nodules were categorised as done by Chng et al. These nodules were validated by Radiology Masters students and HPE findings were blinded prior to the analysis. Stratified thyroid nodules were correlated with final postoperative HPE findings. Collected data were analysed using IBM SPSS statistics (version 26).

3.13 Statistical analysis and hypothesis

Data were explored and analysed using SPSS software version 26.0. Each USG features of thyroid nodules were presented as n=frequency and percentage. Thyroid nodule sizes were presented in mean and standard deviation. The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of ATA and ACR-TIRADS with HPE were tabulated in 2 by 2 table. The association between each USG thyroid nodule features with benign or malignant nodule on HPE were tabulated. Independent t-test and Fisher's exact test were applied to test for statistically significant differences between ACR-TIRADS USG features and HPE findings. Statistical significance was defined by a p value of less than 0.05. All odd ratios were presented with 95% confidence intervals. TR3 (ACR-TIRADS category 3) to TR5 (ACR-TIRADS category 5) thyroid nodules were analysed for percentage of detection of malignancy rate based on USG ACR-TIRADS features in comparison to HPE outcome and were tabulated.

3.14 Confidential and privacy

Patient's USG report was labelled with an identification number in the data collecting sheet to maintain privacy and confidentiality. No identifiable data was expressed or shared to the public.

3.15 Ethical Consideration

The researcher has received ethical approval from the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM code: 9120944) which complies with the Declaration of Helsinki (Appendix E).

3.16 Study flowchart

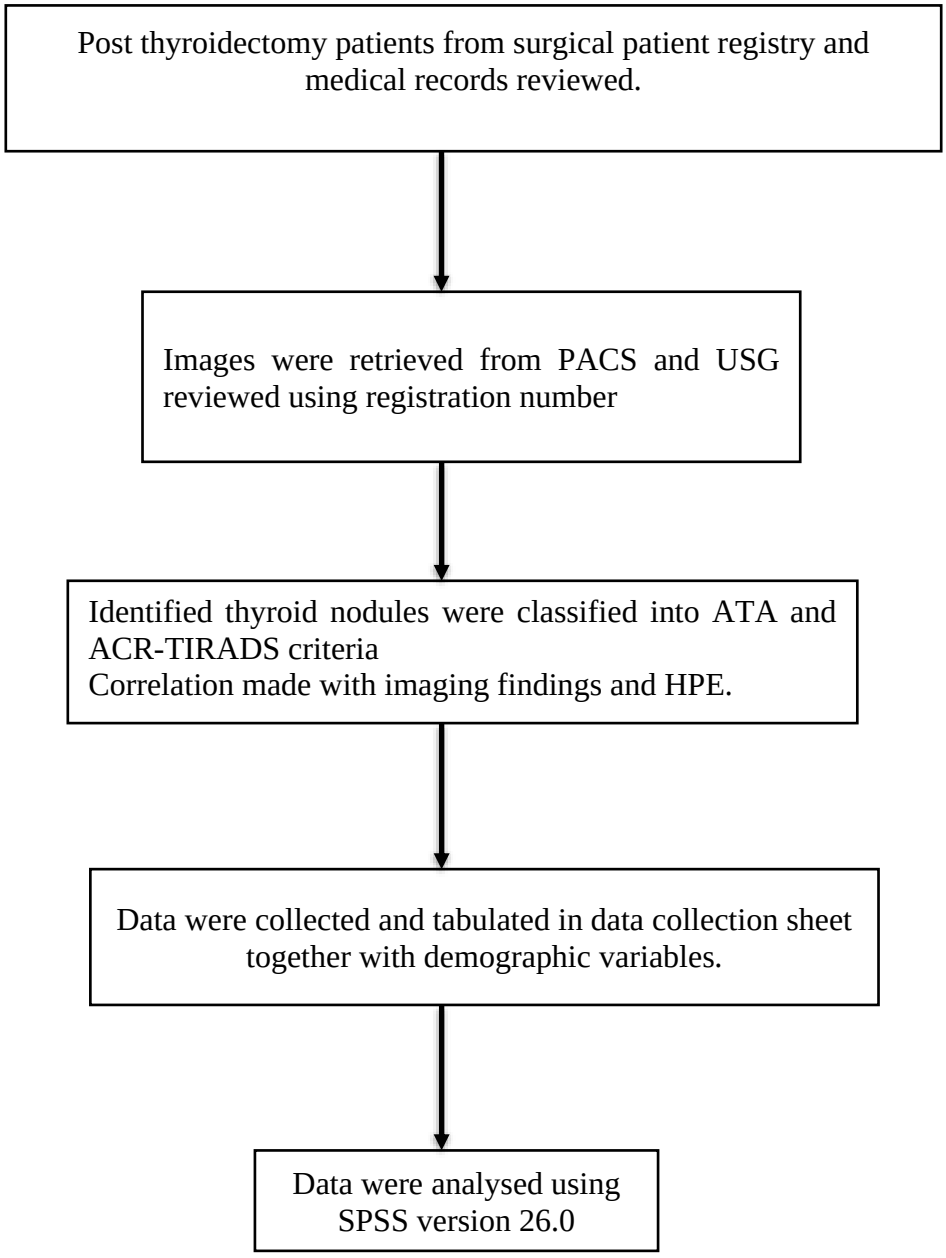

Figure 7: Study flowchart of recruitment of study participants

CHAPTER 4: MANUSCRIPT

Title: Sonographic Review Of Thyroid Lesion Based On ATA And ACR-TIRADS Classification

Deivind Kumar NAGALINGAM, MMed[1], Mohd Shafie ABDULLAH, MMed[1,3], Maya Mazuwin YAHYA, MMed[2,3]

[1]*Department of Radiology,* [2]*Department of Surgery, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia.*[3]*Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia.*

SONOGRAPHIC REVIEW OF THYROID LESION BASED ON ATA AND ACR-TIRADS CLASSIFICATION

ABSTRACT

Background: Thyroid malignancy is one of the commonest cancers among adults with prevalence rate of 3-7%. High frequency ultrasound has been gold standard in detecting thyroid nodules and able to stratify malignant lesions. Research has been undertaken on these nodules with qualitative and quantitative manners to stratify these lesions. The purpose of this study is to compare stratification of thyroid lesions based on ACR-TIRADS and ATA in detecting malignant thyroid nodules and analyse the sensitivity and specificity of each scoring system.

Methods: A retrospective case-control study using sonographic images done prior to the patient's thyroidectomy. Identified thyroid nodules were analysed using ATA and ACR-TIRADS classification system for stratification and scoring. Variables such as age, gender, family history, previous malignancy history and previous irradiation history were documented in data collection form. For the purpose of our study, ATA benign and very low suspicion nodule were categorized as benign and TR2 and below category was taken as benign. On contrary to this, ATA low suspicion nodule with ACR-TIRADS TR3 category and above were taken as malignant.

Results: A total of 129 nodules from 53 participants were included in this study. The mean total identified benign thyroid nodule based on USG ATA classification showed 0% benign and 3% were malignant on HPE. Meanwhile, based on benign USG ACR-TIRADS features, 0.8% were benign and 3.9% were malignant. Malignant thyroid HPE based on ATA and ACR-TIRADS classification was 93.0% and 91.0% respectively. The specificity, NPV (Negative predictive value) and