Original Research Paper

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ULTRASOUND FEATURES OF THYROID NODULE IN PATIENT WITH DIFFERENTIATED THYROID CANCER

Medicine

KEYWORDS:

Amani Alhozali

Department of Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

ABSTRACT

Diagnostic tests can determine if a thyroid nodule is benign or malignant ; this information can help to guide treatment decisions. There are several diagnostic tests and each provides unique information about the thyroid nodule. Thyroid nodules are common and occur in up to 50% of the adult population; however, less than 7% of thyroid nodules are malignant. High-resolution ultrasonography (US) is commonly used to evaluate the thyroid gland, but US is frequently misperceived as unhelpful for identifying features that distinguish benign from malignant nodules. Microcalcifications are one of the most specific US findings of a thyroid malignancy. Other useful US features include a marked hypoechogenicity, irregular margins, and the absence of a hypoechoic halo around the nodule. Lymphadenopathy and local invasion of adjacent structures are highly specific features of thyroid malignancy but are less commonly seen. The number, size, and interval growth of nodules are nonspecific characteristics. Suspicious US features may be useful for selecting patients for fine-needle aspiration biopsy when incidental nodules are discovered and when multiple nodules are present. This study done to assess retrospectively ultrasound features of thyroid nodule in patient having differentiated thyroid cancer.

INTRODUCTION

Thyroid nodules are common in clinical practice. They may be solitary within a "normal" thyroid gland or dominant within a multinodular goiter. The incidence of thyroid nodules has been on the rise in recent decades, mainly due to the wider use of neck imaging. Therefore, the incidental finding of a thyroid nodule in an asymptomatic patient is not rare. The differential diagnosis of a thyroid nodule is crucial, as malignancy necessitates surgery, while strict patient follow-up is necessary in the case of benignity. Fine-Needle Aspiration biopsy is considered to be the "gold standard" in the selection of patients for surgery. However, Ultrasonography (US) can be used to determine changes in the size of nodules during follow-up or to detect recurrent lesions in patients suspected for thyroid malignancy, although there are no specific US findings that suggest malignancy. Surgery is mandatory in cytologically malignant nodules or in cases suspicious for malignancy. The definite diagnosis and consequent therapy is based on the histological findings after surgery(Polyzos et al., 2007).

Most thyroid nodules cause no symptoms at all. They are usually found by patients who feel a lump in their throat or see it in the mirror. Occasionally, a family member or friend will notice a strange lump in the neck of someone with a thyroid nodule. Another common way in which thyroid nodules are found is during a routine examination by a physician.

Occasionally, nodules may cause pain, and even rarer still are those patients who complain of difficulty swallowing when a nodule is large enough and positioned in such a way that it impedes the normal passage of food through the esophagus (which lies behind the trachea and thyroid).

Sometimes, a thyroid nodule is found because the patient is undergoing a CT scan, MRI scan, or ultrasound scan of the neck for some other reason (such as parathyroid disease, carotid artery disease, or cervical spine pain). Thyroid nodules found this way (by accident) is cancerous far less than 1% of the time(Norman, 2016b).

Thyroid nodules occur in 4-15% of the adult population by palpation and in 10-41% by ultrasound (Sachmechi et al., 2000; Frates et al., 2005). The prevalence of thyroid nodules increases with age and can be found in up to 90% of women over the age of 60 years (Sachmechi et al., 2000; Frates et al., 2005). The vast majority of these nodules are benign- only 2-7% of all thyroid nodules, 6-9% of non-palpable nodules, and 9-13% of nodules selected for fine-needle aspiration are malignant (Schoder & Gonen, 2007; Nachiappan et al., 2014). The major challenge that faces a clinician is to determine whether a thyroid nodule is benign or malignant. Malignancy is more common in nodules found in patients who are younger than 20 years or older than 60 years (Frates et al., 2005). A history of neck irradiation or a family history of thyroid cancer is also associated with an increased risk for malignancy (Frates et al., 2005). Although certain aspects of the history and physical examination may suggest an increased risk for malignancy, in most cases these are nonspecific and are of no predictive value. Additionally, the presence of multiple nodules (MNG) does not decrease the likelihood that one of them is a carcinoma, as was once thought (Utiger, 2005; Cooper et al., 2006; Frates et al., 2005). Additional tests that may be helpful in establishing a diagnosis include thyroid function tests, thyroid scan, thyroid ultrasound and fine needle aspiration biopsy (FNAB).

A serum TSH level and thyroid function tests should be obtained for any thyroid nodule larger than 1-1.5 cm (Cooper et al., 2006). The thyroid function tests will reveal whether a patient with a thyroid nodule is euthyroid, hypothyroid, or hyperthyroid. If the TSH is suppressed, nuclear medicine imaging can be performed to document an autonomously functioning nodule(Cooper et al., 2006). Most patients with thyroid cancers are euthyroid, therefore hypothyroid (i.e. Hasimoto's disease) or hyperthyroid patients (autonomously hyper functioning nodules) with thyroid nodules are more likely to have a benign process. However, there are exceptions to this as patients with Graves' disease and a dominant cold nodule may have underlying thyroid cancer that behaves in a more aggressive manner (Belfiore et al., 1990). Hypothyroid patients with Hashimoto's disease and a dominant nodule or a rapidly enlarging goiter may also have lymphoma of the thyroid and require FNAB. Thyroid ultrasound can document the size of a thyroid nodule and provide an objective parameter for assessing response to hormone suppression.

A thyroid ultrasound should be performed in all patients with a suspected thyroid nodule or nodular goiter on physical examination or with nodules incidentally noted on other imaging studies (carotid ultrasound, computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [PET] scan). Thyroid ultrasonography is used to answer questions about the size and anatomy of the thyroid gland and nearby structures in the neck. Thyroid ultrasound findings can be used to select nodules that require FNA biopsy(Ross et al., 2016).

Thyroid ultrasound US is noninvasive, relatively inexpensive, and can identify nodules not apparent on physical examination, isotope scanning, or other imaging techniques. It should be performed in all patients with a suspected thyroid nodule, a nodular goiter on physical examination, or with nodules incidentally noted on other imaging studies (carotid ultrasound, CT, MRI, or 18-fluorodeoxyglucose [FDG]-PET scan).

Thyroid ultrasonography is used to answer questions about the size and anatomy of the thyroid gland and adjacent structures in the

neck. Sonographic characteristics of a thyroid nodule associated with a higher likelihood of malignancy include hypoechogenicity, increased intranodular vascularity, irregular margins, microcalcifications, absent halo, and a shape taller than wide measured in the transverse dimension (Leenhardt et al., 1999a; Papini et al., 2002; Nam-Goong et al., 2004b; Cappelli et al., 2007; Moon et al., 2008b; Frates et al., 2006).

A Papillary Thyroid Cancer (PTC) is generally solid or predominantly solid and hypoechoic, often with infiltrative irregular margins and increased nodular vascularity. Micro-calcifications, if present, are highly specific for PTC, but may be difficult to distinguish from colloid. Conversely, follicular cancer is more often iso- to hyperechoic and has a thick and irregular halo, but does not have microcalcifications (Jeh et al., 2007). Follicular cancers that are <2 cm in diameter have not been shown to be associated with metastatic disease (Machens et al., 2005).

Certain sonographic appearances may also be highly predictive of a benign nodule. A pure cystic nodule, although rare (<2 % of all nodules), is highly unlikely to be malignant (Frates et al., 2006). A spongiform appearance, defined as an aggregation of multiple microcystic components in more than 50 % of the nodule volume, is 99.7 % specific for identification of a benign thyroid nodule (Moon et al., 2008a, 2009; Bonavita et al., 2009).

The presence of a considerable overlap of the US features between benign and malignant nodules still hampers the diagnosis of thyroid carcinoma by US examination. However, as evidenced by several large-scale studies (Kim et al., 2002; Khoo et al., 2002; Nam-Goong et al., 2004a; Peccin et al., 2002; Alexander et al., 2004; Wienke et al., 2003; Lee et al., 2011; Frates et al., 2005; Moon et al., 2008a), certain US features appear reliably associated with a higher risk for malignancy in thyroid nodules (Hegedüs et al., 2003)(2). A taller-than-wide shape and centrifugal growth across the tissue planes are indicators of malignancy. But, and importantly, their sensitivity is low because small papillary carcinomas frequently present with a well-defined round shape. The presence of irregularly microlobulated or spiculated margins, suggestive of an infiltrative neoplastic growth into the surrounding parenchyma, may be clearly depicted by current US equipment.

Most slightly hypoechoic nodules are benign, but a marked hypoechogenicity (similar to cervical muscles) represents a suspicious feature. Finally, intranodular microcalcifications, albeit occasionally difficult to distinguish from comet-tail colloid interfaces, strongly indicates papillary carcinoma. The demonstration of aggressive growth (extension of the lesion beyond the thyroid capsule, invasion of the strap muscles or infiltration of the tracheal cartilage) or that of pathologic adenopathy (absence of hilum, cystic changes and/or microcalcifications) are obvious signs of thyroid neoplasia. Finally, even a chaotic intranodular neovascularisation may be indicative of malignancy (Leenhardt et al., 1999b).

Smith-Bindman et al. (2013) conducted a study to quantify the risk of thyroid cancer associated with thyroid nodules based on ultrasound imaging characteristics. This study took into account of retrospective case-control study of patients who underwent thyroid ultrasound imaging from January 1, 2000, through March 30, 2005. Thyroid cancers were identified through linkage with the California Cancer Registry. Thus, 8806 patients participated where they went through 11 618 thyroid ultrasound examinations. It was identified from the study results that thyroid nodules were common in patients diagnosed as having cancer (96.9%) and patients not diagnosed as having thyroid cancer (56.4%).

Moreover, three ultrasound nodule characteristics—micro-calcifications (odds ratio [OR], 8.1; 95% CI, 3.8-17.3), size greater than 2 cm (OR, 3.6; 95% CI, 1.7-7.6), and an entirely solid composition (OR, 4.0; 95% CI, 1.7-9.2)—were the only findings associated with the risk of thyroid cancer. If 1 characteristic is used as an indication for biopsy, most cases of thyroid cancer would be detected (sensitivity, 0.88; 95% CI, 0.80-0.94), with a high false-positive rate (0.44; 95% CI, 0.43-0.45) and a low positive likelihood ratio (2.0; 95% CI, 1.8-2.2), and 56 biopsies will be performed per cancer diagnosed. If 2 characteristics were required for biopsy, the sensitivity and false-positive rates would be lower (sensitivity, 0.52; 95% CI, 0.42-0.62; false-positive rate, 0.07; 95% CI, 0.07-0.08), the positive likelihood ratio would be higher (7.1; 95% CI, 6.2-8.2), and only 16 biopsies will be performed per cancer diagnosed. Compared with performing biopsy of all thyroid nodules larger than 5 mm, adoption of this more stringent rule requiring 2 abnormal nodule characteristics to prompt biopsy would reduce unnecessary biopsies by 90% while maintaining a low risk of cancer (5 per 1000 patients for whom biopsy is deferred). It could be concluded that thyroid ultrasound imaging could be used to identify patients who have a low risk of cancer for whom biopsy could be deferred.

Study objectives

- To find out the ultra sound features of thyroid nodule in patient affected with thyroid cancer
- To diagnose the appropriate thyroid nodule treatment
- To identify the exact nodule responsible for harboring cancer

Research Gap

The study was in context to Saudi Arab and non-Saudi Arab nationalities. However, it has not taken into consideration of thyroid nodule cancer in other parts of the world. Moreover, the challenging is aspect is determining a thyroid nodule in terms of benign or malignat. This study also provides the treatment through US features but has not covered the availability of other types of treatments. As per the study result, it was onserved that adult population were mostely afected with thyroid cancer. However, there is no clarity over the specific age group of people. Considering all these aspects, this study is attempt to find out more insights related to thyroid cancer treatment.

Problem statement

As per the study, ultrasound imaging is the major tool for selecting thyroid nodules to determine whether a nodule is benign or malignant. Therefore, the signficance is choosing the specific nodule on the basis of ultrasound characteristics. Thus, the statement of the problem is to identify the ultrasound imaging characteristics related to malignant nodules to develp a standardized system for predicting the risk of cancer in a thyroid nodule.Methodology In this regard, ATA Thyroid Nodules and Differentiated Thyroid Cancer guidelines were reviewed and revised in 2009 (25). Since there is rapid growth of the literature on this topic, past 4 years publications were reviewed before initiating this study. Guidelines were followed as per ATA policy. Moreover, methodologic elements were considered such as recruitment of patients involving clinical practice, target population of interest, testing procedures representing clinical practice, and precision of diagnostic accuracy measures like sensitivity, specificity, and consistency of results. In most of the cases, the outcome of interest for the diagnostic test was the diagnosis of thyroid cancer. However, prognostic studies were also graded using the diagnostic study critical appraisal framework. In terms of strength of recommendation for use of diagnostic studies, approach was initiated for conducting therapeutic studies. However, the target outcome was the accuracy in establishing a definitive diagnosis, mostly related to the diagnosis of new or recurrent malignancy. An important limitation of our diagnostic test appraisal system is that it does not specifically examine the clinical utility of a test in improving long-term health outcomes by execution of the test as part of an intended therapeutic strategy. However, mostly, the effort was to separate recommendations on the diagnostic accuracy of a test from therapeutic management based on the test result. It is signficant to note that diagnostic test grading system is a body of well-executed nonrandomized diagnostic accuracy.

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In additon, this study applied qualitative methodology, where selected number of patients from Saudi Arabia and non Soudi Arbaia patients were considered.

RESULTS

Table 1: Demographic details of study participants

Demographic details	Saudi	Non-Saudi
	n (%)	
Gender		
Male	7 (18.4)	5 (14.3)
Female	31 (81.6)	30 (85.7)
Total	38 (100.0)	35 (100.0)
Age group		
Below 20	3 (7.9)	1 (2.9)
21-30	8 (21.1)	11 (31.4)
31-40	7 (18.4)	9 (25.7)
41-50	8 (21.1)	8 (22.9)
Above 51	12 (31.6)	6 (17.1)
Total	38 (100.0)	35 (100.0)

Totally, 73 patients participated in the research. Among the patients, 38 were Saudi people and remaining 35 were non-Saudi people. When the gender based classification was considered, a maximum number of female patients agonized from thyroid cancer in both nationalities. In the Saudi patients, the majority of 51 and above age group patients were affected by thyroid cancer followed by, respectively, 8 patients who aged 21-30 years and 41-50 years were affected by thyroid cancer. Analogously, the majority of the 21-30 age group patients were suffered from thyroid cancer in the non-Saudi patients which is followed by, 31-40 age group (9 patients), 41-50 age group (8 patients) and above 51 age group (6 patients) patients agonized from thyroid cancer.

Table 2 : Association between age group and number of nodules of patients

No. of nodules	Age group					Total
	Below 20	21-30	31-40	41-50	51+	
	n (%)					
0	1 (1.4)	0 (0)	1 (1.4)	0 (0)	0 (0)	2 (2.8)
1	2 (2.8)	8 (11.3)	5 (7.0)	5 (7.0)	4 (5.6)	24 (33.8)
2 - 3	1 (1.4)	6 (8.5)	5 (7.0)	7 (9.9)	7 (9.9)	26 (36.6)
> 3	0 (0)	3 (4.2)	5 (7.0)	4 (5.6)	7 (9.9)	19 (26.8)
Total	4 (5.6)	17 (23.9)	16 (22.5)	16 (22.5)	18 (25.4)	71 (100.0)

Chi-square value: 14.319; p-value: 0.281

Table 2 shows the association between age group and number of nodules of patients. From the figures, it is observed that the majority of the patients who aged less than 30 years, possessed only one nodule while patients (n=7) who aged 41-50 years had 2-3 nodules and the patients (n=7) who aged above 51 years had more than 3 nodules. It indicates that number of nodules is increased on the basis of increase in age of patients. However, the association between age group and number of nodules is not statistically significant (p=0.281>0.05).

Table 3 : Association between nodule size and histopathology

Nodule size	Histopathology		Total
	non-PTC	PTC	
Small nodule (<10mm)	0 (0)	5 (7.4)	5 (7.4)
Large nodule (>10mm)	13 (19.1)	50 (73.5)	63 (92.6)
Total	13 (19.1)	55 (80.9)	68 (100)

Chi-square value: 1.276; p-value: 0.259>0.05

Association between nodule size and histopathology of patients is depicted in table 7. The nodule size is classified as a small nodule (<10 mm) and large nodule (>10 mm). From the findings, it is inferred that a maximum number of PTC and non-PTC patients possessed large nodule. However, nodule size and histopathology of the patients are not associated. Since, the p-value is above 5 percent level of significance.

Table 4 : Association between number of nodules and histopathology

Number of nodules	Histopathology		Total
	non-PTC	PTC	
0	0 (0)	2 (2.8)	2 (2.8)
1	6 (8.5)	18 (25.4)	24 (33.8)
2 - 3	6 (8.5)	20 (28.2)	26 (36.6)
> 3	1 (1.4)	18 (25.4)	19 (26.8)
Total	13 (18.3)	58 (81.7)	71 (100)

Chi-square value: 3.724; p-value: 0.293

From the above table, it is noticed that a maximum number of PTC and non-PTC patients possessed 2-3 nodules followed by, 18 PTC and 6 non-PTC patients had only one nodule and finally, 18 PTC patients and one non-PTC patient had more than three nodules. In addition, there was an association between nodule size and histopathology of patients.

Table 5 : Association between ultra sound features like hypo echogenicity and histopathology

Hypo echogenicity	Histopathology		Total
	non-PTC	PTC	
No	10 (14.5)	35 (50.7)	45 (65.2)
Yes	1 (1.4)	23 (33.3)	24 (34.8)
Total	11 (15.9)	58 (84.1)	69 (100.0)

Chi-square value: 3.808; p-value: 0.051*

Table 5 shows the association between the ultra sound features like hypo echogenicity and histopathology of the patients. In the research, around 33 percent of PTC patients and 1 percent of non-PTC patients had the hypo echogenicity when using ultra sound. But, the majority of the PTC and non-PTC patients did not have the hypo echogenicity. Further, the significance value (p-value<=0.05) specifies that the ultra sound features like hypo echogenicity and histopathology are associated with each other.

Table 6 : Association between calcification and histopathology

Calcification	Histopathology		Total
	non-PTC	PTC	
No	8 (11.6)	47 (68.1)	55 (79.7)
Yes	4 (5.8)	10 (14.5)	14 (20.3)
Total	12 (17.4)	57 (82.6)	69 (100.0)

Chi-square value: 1.528; p-value: 0.216

Table 6 depicts the association between the presence of calcification and histopathology of patients. The findings clearly indicate that a

maximum number of PTC and non-PTC patients did not have the calcification. Hence, calcification is not the main factor of thyroid cancer. However, 10 PTC and 4 non-PTC patients had the calcification in their thyroid gland. But, the presence of calcification and histopathology are not associated. Because of the p-value is above 5 percent level of significance ($p>0.05$).

Discussion

This study has so far presented on ultrasound features of thyroid nodule in patient having differentiated thyroid cancer. To assess the ultrasound features of thyroid nodule, study was conducted among 73 respondents, i.e. patients. The study was among Saudi Arabian (38) and people from other nationalites (35). It was analysed that more number of female patients were affected with thyroid cancer by both Saudi Arabians and non-Saudi Arabians. An interesting development came out of this study was that patients having 51 years and above are the mostly affected with thyroid cancer. However, patients in the age group of 21 to 30 and 41 to 50 were least affected. This is the scenario for Saudi nationals.

In the case of non- Saudi Arabians, patients in the age group of 21 to 30 were highly affected. However, patients beyond this age group witnessed less number of cases, i.e. with increase in age, the number of thyroid cancer affected patients got reduced. It is what analysed that there were only 9 patients in the age group of 31 to 40 followed by 8 patients in the age group of 41 to 50 and mere 6 numbers of patients by those exceeding 51 years. This reflects that with increase in age, Saudi Arabians are more prone to get affected with thyroid cancer. On the contrary, there is more number of patients affected in lower age group. However, there is no clarity over between age group and number of nodules. Further, other studies reflect that thyroid nodules occur in 4-15% of the adult population by palpation and in 10-41% by ultrasound. The prevalence of thyroid nodules increases with age and can be found in up to 90% of women over the age of 60 years .

Therefore, to assess further clarity in this regard, the examination was carried out to find out the relationship between size of nodule and histopathology of patients. Here, nodule size was taken into consideration in terms of a small nodule (<10 mm) and large nodule (>10 mm). It could be inferred from the study findings that majority of the patients both PTC and non-PTC were having large nodule. However, there was no relation between nodule size and histopathology.

Moreover, it was observed that majority of PTC patients were having 2-3 nodules. On the contrary, non-PTC patients also were having 2-3 nodules. The same is the scenario for patients having more than 3 nodules. Again, it could be inferred from histopathology findings that maximum number of PTC patients were having 1 nodule and less number of patients were having a single nodule in the case of non-PTC patients. This gives an indication that there is a relationship between size of nodule and histopathology of patients.

Another study carried out in this regard was to find out the relationship between the ultrasound features between hypo echogenicity and histopathology of the patients. It was observed that 33% of patients were having hypo echogenicity; whereas, it was only 1% for non-PTC patients, who were subjected to treatment through ultrasound. However, the hypo echogenicity was not observed in the case of both the PTC and non-PTC patients. Hence, it could be inferred that the hypo echogenicity has relationship with histopathology.

To induce further information in context to the study, assessment was done among the PTC and non-PTC patients to find out the role of calcification. It was observed that majority of the PTC patients were having no calcification in thyroid gland; whereas, less number of non-PTC patients were having without any calcification. However, 10 PTC and 4 non-PTC patients were found to be with the calcification in their thyroid glands. This reflects there is no relationship between calcification and histopathology.

It could be concluded that generally adult populations are having thyroid nodule. The most common type of thyroid cancer is papillary thyroid cancer. Thus, the general practice to treat thyroid nodule is through ultrasound examination.

Conclusion

It could be concluded that thyroid nodules are the entities that requires medical evaluation. Nodules are identified through physical exam or by resorting to imaging modalities. Most of the thyroid nodules are benign. However, they require surgical excision if the nodules are very large to be symptomatic or concern for malignancy. Ultrasound is the basic study to image the thyroid gland. Nodules having length of one centimeter or more require cytologic analysis by the application of Fine Needle Aspiration Biopsy (FNAB). The same is application even in the case of sonographically suspicious sub-centimeter nodules. In both case, the purpose of examination is to determine the risk of malignancy. However, molecular biomarkers have shown enough interest to detect malignancy in FNAB specimens thereby serves as a powerful adjunct to cytology, provided they are available. Identification of malignancy prior to operation is the key as it ensures comprehensive thyroidectomy in a single operation without dependency on frozen section or removal of the thyroid remnant in a second surgery. Thus, biomarkers into cytology and molecular are the primary diagnostic modalities to which a surgeon leverages the advantage to ascertain the process of thyroid surgery.

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