



Sonographic-pathologic correlation in an ultrasound-guided fine needle aspiration of a thyroid nodule: Concordant or discordant?

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ABSTRACT

Thyroid nodules are common medical problem caused by a variety of thyroid disorders. The aims of this study was to evaluate the sonographic-pathologic concordance and discordance of thyroid nodules and to demonstrate how ultrasound is integrated with the fine needle aspiration to provide valuable information that can be used to improve patient care. This prospective study was done on 76 patients with thyroid nodules referred for ultrasound examination. From 76 patients involved in this study and underwent ultrasound-guided fine needle aspiration cytology, 10 patients have inadequate aspirates and thus were excluded. Of the remaining 66 patients that were included in our study, only 6 patients had thyroid carcinoma (9%). Thyroid cancer was highest in age group of 50-59 years (50%). Five patients of thyroid carcinoma (83.3%) had solitary nodule more than 10 mm in largest dimension and only one patient (16.7%) had multiple thyroid nodules. After sonographic-pathologic correlation, the concordance and discordance rate presented as: (1) concordant benign (98.11%), (2) concordant malignant (71.42%), (3) discordant benign (14.28%), (4) discordant malignant (1.88%) and (5) borderline or high risk (30.76%). We conclude that careful sonographic-pathologic correlation and appropriated post-biopsy management will allow detection of a substantial number of false negative results immediately after needle biopsy by identifying discordant lesions prospectively, thereby avoiding delays in the diagnosis of cancer.

Keywords: Thyroid; Thyroid nodules; Thyroid carcinoma; Ultrasound.

INTRODUCTION

Thyroid nodules are common medical problem caused by a variety of thyroid disorders. They are found in 4%-8% of adults by means of palpation, in 10%-41% by means of ultrasound (US) and in 50% by means of pathologic examination at autopsy [1,2]. Given the high prevalence of thyroid nodules in the general population, it is essential to develop a method for identifying those nodules which require fine-needle aspiration due to suspicion for malignancy in order to avoid over- or under treatment of this disease [3]. Although the thyroid is the most common endocrine organ to undergo malignant degeneration, thyroid carcinoma accounts for only 1% of diagnosed neoplasms in the United States each year [4]. US plays a prominent role in the management of thyroid disease; it can detect clinically impalpable thyroid nodules and characterize them as cystic, solid, or complex but determining that a nodule is definitively benign or malignant is difficult, and so when indicated, it is used to guide fine needle aspiration (FNA) to determine whether the nodule is benign or malignant [5-7]. US and FNA cytology are advocated as first-line examinations for the assessment of thyroid nodules [8].

The low specificity of US is mainly due to the considerable overlap between the sonographic findings of benign nodules and thyroid cancer. Hence, most solid and complex cystic nodules require FNA to establish the true diagnosis. FNA can diagnose the nature of thyroid nodules with a sensitivity of 86% and a specificity of 85% [9].

Benign nodules typically present as well-defined cystic or solid masses with sharp edges. Solid nodules can be iso- or hyperechoic relative to the rest of the gland. If calcification is present, it is commonly curvilinear (eggshell calcification). There might be a thin halo (hypoechoic band) around the nodule. Benign solid nodules are generally multiple and hypovascular. Colloid nodules may demonstrate a comet tail artifact on US [10].

Malignant nodules most commonly have irregular, ill-defined margins, and are mostly solid and hypoechoic relative to the thyroid gland. Punctate psammomatous calcifications indicate malignancy with the highest degree of specificity [11]. An incomplete halo around the nodule and hypervascularity are other strong indicators of malignancy [12].

Benign thyroid lesions include adenomatous/colloid nodules, benign follicular adenomas, and Hashimoto thyroiditis while malignant nodules include papillary carcinoma, follicular carcinoma, medullary carcinoma, and anaplastic carcinoma.

The likelihood that a nodule is malignant is affected by a variety of risk factors. Malignancy is more common in nodules found in patients who are younger than 20 or older than 60 years of age than in patients between 20 and 60 years of age [2]. In addition, a history of neck irradiation or a family history of thyroid cancer increases the risk that a thyroid nodule is malignant [13].

FNA is safe, accurate, and inexpensive. The American Association of Endocrinologists (AAE) recommends performing fine needle aspiration on nodules over 1 cm in size [14]. FNA with cytologic evaluation has become the accepted method for screening a thyroid nodule for cancer. Cytologic specimens are typically classified as negative (or benign), suspicious for cancer or follicular neoplasm, positive (or diagnostic for cancer), or non-diagnostic. In general, the false-positive rate for aspirates classified as positive for cancer is less than 1%. Of the aspirates read as suspicious for cancer, 30%-65% will prove to be cancer at surgery [15]. Samples that are not suspicious or diagnostic for malignancy and that contain a smaller number of cells than required for diagnosis of a benign nodule must be considered non-diagnostic. Even in centers with substantial experience, the non-diagnostic rate may be as high as 15%-20% [16]. The rate of cancer in surgically resected nodules with non-diagnostic FNA results is 5%-9% [17].

Purposes of this study were: 1). to describe the sonographic findings of thyroid nodules that would help classify it as benign, suspicious or malignant and compare it with cytopathological results, to study the sonography- pathology concordance and discordance and to demonstrate how US is integrated with the FNA to provide valuable information that can be used to improve patient care. 2). to review derived categories and corresponding management for a sonography-pathology correlation after performing US-guided FNA and to illustrate the selected images for each category, which will provide guidance in the application of this post-biopsy assessment in practice.

MATERIALS AND METHODS

Between March 2013 and February 2015, this prospective study was done on 76 patients with thyroid nodules referred for US examination and US-guided FNA. Ten patients have inadequate or non-diagnostic aspirates and thus were excluded from the study; of remaining 66 patients, 13 were male, and 53 were females. Approvals of the local ethical and scientific committees were obtained before study onset and informed consent was obtained from all individual participants included in the study.

Prior to starting the examination, the patient's clinical history and any prior relevant imaging examinations were reviewed. After that, each patient underwent examination by US using a high-resolution sonography system (Siemens Acuson 150 ultrasound machine) equipped with a 7-12 MHz linear array transducer.

US characteristics that were evaluated included: Nodule diameter, number of nodules, echogenicity, consistency, halo sign, calcification, lesion margins, vascular pattern (Type 0: absence of flow, Type1:

peripheral flow, Type 2, internal flow). Hence, thyroid nodule categorized into three types: thyroid nodule of benign criteria includes (well-defined cystic or solid masses, sharp edges, iso- or hyperechoic relative to the rest of the gland, eggshell calcification, thin hypoechoic halo around the nodule, generally multiple and hypovascular or peripheral flow and comet tail artifact in colloid nodules). Thyroid nodule of malignant criteria includes (mostly solid, irregular, ill-defined margins, hypoechoic relative to the thyroid gland, punctate, psammomatous calcifications, incomplete halo around the nodule and internal hypervascularity). Thyroid nodule of suspicious criteria includes nodules of benign features but patients at high risk of malignancy.

After that, US guided FNA by the histopathologist using fine needle (gauge 20) was performed on thyroid nodules that measure more than 1.0 cm as recommended by American Association of Endocrinologists (AAACE). Smaller nodules were sampled in patients who received external radiation to the head or neck during childhood or in patients with a family history of medullary or papillary thyroid cancer and in patients who have had a hemithyroidectomy for thyroid cancer and micronodule found in the remaining lobe. Most other nodules 1 cm or less in size were observed over a period of time using US, and FNA not performed if there is no significant increase in size. The aspirated material was spread on 2 slides and fixed in 90% alcohol, stained by Hematoxylin and Eosin (H & E) and examined under light microscope. A sufficient sample was generally defined as when there was at least single slide that had six or more groups of >10 follicular epithelial cells [18-20]. Those aspirates that had yielded insufficient or inadequate materials for diagnosis were excluded from the study (10 patients).

Cytological material was classified as benign for (colloid nodules, lymphocytic thyroiditis, cystic goiters), malignant for (papillary carcinoma, medullary carcinoma, anaplastic carcinoma), suspicious for (follicular or Hurthle cell neoplasms) or non-diagnostic for (inadequate smears). All patients with suspicious or malignant cytology underwent surgery.

When the cytopathology result was received, the radiologist was compared the pathologic diagnosis with the expected result from the sonographic findings and imaging-pathology concordance assessed to classify the results into five categories include (concordant malignancy, discordant malignancy, concordant benign, discordant benign and borderline or high risk).

Data management and statistical analysis were performed by using the statistical package for social sciences (SPSS) version 19 for Microsoft Windows. Statistical significance was indicated by a *P* value of less than 0.05.

RESULTS

Of the 66 patients included in this study, 13 were male (19.7%), and 53 were females (80.3%). The age of patients ranged between 10-69 years. The mean age was 39 years and the maximum numbers of patients affected belong to the age group of 30 to 39 years (36.4%).

Among the 66 patients included in this study, only 6 patients (9%) had thyroid carcinoma while 56 patients (84.84%) had benign pathological results and 4 patients (6.16%) had suspicious pathological results.

Regarding the malignant thyroid nodules, the prevalence was highest in age group of 50-59 years (50%). Five patients of thyroid carcinoma (83.3%) had solitary nodule more than 10 mm in largest dimension and only one patient (16.7%) had multiple thyroid nodules. The rate of cancer in females with thyroid nodules (9.43%) was higher than in males with thyroid nodules (17.7%) ($P < 0.001$). The prevalence of thyroid cancer was higher in patients with a solitary thyroid nodule (20%) than in patients with multiple nodules (2.44%) ($P = 0.003$). The types of thyroid cancer were 66.7% papillary, 16.7% follicular and 16.7% undifferentiated carcinoma. The prevalence of thyroid malignancy was 25% of small nodules (<10 mm), 4.54% in thyroid nodules measure 10-19 mm, 6.66% in thyroid nodules measure 20-39 mm and 20% in thyroid nodules measure 40 mm or more. Table 1 listed all US characteristic of malignant thyroid nodule which revealed in this study.

Regarding the benign thyroid nodules, the prevalence was highest in age group of 30-39 years (35.71%). 32.14% of benign nodules had solitary nodule and 67.85% had two or more thyroid nodules, while 78.57% of benign thyroid nodules were in females and only 21.42% were in males. The prevalence of benign thyroid nodules was 75% of small nodules (<10 mm), 90.90% in thyroid nodules measure 10-19

mm, 86.66% in thyroid nodules measure 20-39 mm and 70% in thyroid nodules measure 40 mm or more. Table 2 listed all US characteristic of benign thyroid nodule which revealed in this study.

Regarding the suspicious thyroid nodules, the prevalence was highest in age group of 30-39 years (75%). Half of these nodules are solitary and all were in females. Table 3 listed all US characteristic of suspicious thyroid nodule which revealed in this study.

After sonographic-pathologic correlation, the concordance and discordance rate presented as follow: (1) concordant benign (98.11%), (2) concordant malignant (71.42%), (3) discordant benign (14.28%), (4) discordant malignant (1.88%) and (5) borderline or high risk (30.76%) as shown in tables 4 and 5.

DISCUSSION

The goal in evaluating a thyroid nodule is to determine whether it is benign or malignant so that patients with thyroid cancer can receive a diagnosis and undergo treatment at an earlier stage to reduce possible morbidity and mortality due to the disease, while avoiding unnecessary tests and surgery in patients with benign nodules.

In general, thyroid nodules are four times more common in women than in men [21]. In our patients: 13 were males (19.7%) and 53 were females (80.3%), F/M ratio is about 4:1. The rate of malignancy in the current study was 9% which is consistent with the proportion of thyroid cancers in reported series varies from 4% to 32% [21-26].

In our study, the rate of cancer in females (5 patients out of 53 or 9.43%) was higher than in males (1 patient out of 13 or 7.7%) ($P < 0.001$), these results were not comparable with those reported in previous studies [22, 26-28] and this result was in contrast to fact that puts male gender as a risk factor for thyroid carcinoma [29].

In our study, thyroid cancer was highest in age group of 50-59 years (50%) while benign thyroid nodules were highest in age group of 30-39 years (35.71%). The prevalence of thyroid cancer was higher in patients with a solitary thyroid nodule than in with multiple nodules (20% versus 2.4%) which is comparable to results obtained by other reported studies [25, 26, 29].

Our study did not show strong relation between size of the thyroid nodule detected by US and final pathological results and this agree with obtained by Ross L Titton *et al* and Amer AM Ali *et al* [4, 25]. The high percentage in small nodules less than 10 mm may be explained by highly selective patients sampled by fine needle aspiration.

The types of thyroid cancer were 66.7% papillary, 16.7% follicular and 16.7% undifferentiated carcinoma. These results are comparable statistically with those reported in other studies [20, 26].

Regarding the echogenicity, 35.71% of hypoechoic nodules in this study were confirmed malignant lesions by cytopathology while 83.3% of malignant nodules were hypoechoic and all hyperechoic nodules were benign and 95% of isoechoic nodules were benign. Brkljacic *et al* [30] stated that hypoechoic is associated with thyroid malignancy and is thought to represent a microfollicular structure on histology, whereas macrofollicular lesions may image as iso- or hyperechoic. These results in agreement with other literatures, that most of the malignant nodules are hypoechoic whilst most hyperechoic nodules are benign [29, 31].

This study reveals all cystic nodules were benign, 78.12% of solid nodules and 85% of heterogeneous mixed nodules were benign lesions; whereas, 12.5% of solid nodules and 10% of heterogeneous mixed nodules were malignant lesions while 66.6% of malignant nodules were solid.

Calcifications in this study was seen in 18 patients with thyroid nodules out of 66 (27.27%) and divided into different categories. Micro calcifications appear as small (<1 mm) echogenic foci without acoustic shadowing (3 patients out of 18 or 37.5%) and coarse or macro calcifications are larger than 2 mm and cause posterior acoustic shadowing (15 patients out of 18 or 83.5%). 66.6% of thyroid nodules that display micro calcifications were malignant while only 6.6% of thyroid nodules with macro calcifications were malignant. These findings are in accordance with other studies [31- 33].

The margins of a thyroid nodule may appear either regular and well defined or blurred and irregular, sometimes with a microlobulated appearance. Most patients (66.66%) of thyroid nodules in this study show irregular or ill-defined margin were malignant and 90% of well defined smoothly marginated thyroid nodules were benign. 66.6% of malignant nodules were irregular in outline; whereas, Amer AM Ali *et al* revealed that 80% of malignant nodules were irregular outline [25].

A halo is a sonolucent ring that surrounds a nodule and is thought to represent compressed perinodular blood vessels and divided into complete halo, incomplete halo and lack halo. In our study, most of patient (66.6%) with thyroid nodules that surrounded by incomplete hypoechoic halo were malignant and all thyroid nodules that surrounded by complete hypoechoic halo were benign in contrast to Propper *et al* [34] concluded that the halo sign is not specific.

The vascularity of a thyroid nodule is evident with color Doppler and categorized as absent (type I), peripheral (type II) or central (type III). 62.5% of thyroid nodules in the current study which show central internal vascularity on color Doppler imaging were malignant whereas 92.85% of thyroid nodules which show peripheral vascularity were benign and all thyroid nodules with absent flow were benign. Laith A. Khalaf study [35] found that pattern of central intrinsic hypervascularity seen in 62.5% within the malignant nodule rather than peri nodular flow seen in 16.7%.

Invasion of the surrounding structures can occasionally be seen with invasive thyroid cancers and the thyroid capsule is interrupted at the level of the tumor. Thyroid cancer may involve cervical lymph nodes in up to 35% of cases. Therefore, abnormal lymph nodes in the ipsilateral cervical chain may be apparent at the time of nodule diagnosis [30]. But in this study no thyroid nodule revealed local invasion or cervical lymphadenopathy of absent echogenic hilum.

FNA cytology is the initial and frequently the only tool for assessing the risk of malignancy in thyroid nodules and selecting patients for thyroid surgery. In experienced hands, the false negative rate is less than 5%, and the false positive rate less than 1% [4,26]. In our study, 10 patients (13.1%) have insufficient or non-diagnostic aspirates and were excluded from the study. Non-diagnostic smears occur when there are insufficient follicular cells to make a cytological diagnosis, aspirates of cystic nodules are a source of unsatisfactory specimens and are thought to be a result of sampling error. Other factors that influence the success of FNA cytology, including small nodule size, position of the nodule within the thyroid, and patient age and body built whether the patient is fatty with short neck or not [36].

One of main purpose of this study is to review derived categories and corresponding management for an sonography-pathology correlation after performing a sonography-guided fine needle aspiration and to illustrate the selected images for each category, which will provide guidance in the application of this post-biopsy assessment in practice. The sonographic and pathologic findings are considered to be concordant when the pathologic result provides an acceptable explanation for the imaging feature and discordant when they do not. After the assessment for concordance has been completed, a management plan can be provided. This study described five possible outcomes of imaging-pathology correlation and suggested corresponding management for each category.

Category 1. Concordant Malignancy (71.42%):

A lesion which showed a suspicious finding for malignancy on ultrasound images and is diagnosed to be malignant on a subsequent biopsy is a concordant malignancy (Fig.1). Within this category, appropriate action should be taken without any delay. The radiologist should communicate the biopsy result to the referring physician, and the patient should be informed of the results and referred to a surgeon or oncologist for proper treatment.

Category 2. Discordant Malignancy(1.88%):

A lesion which typically had benign imaging features but proves to be malignant at needle biopsy falls into this category (Fig.2). Case management should be identical to that for a concordant malignancy. The radiologist should notify the discordant result to the pathologist and ask the patient to review and confirm the diagnosis. Also, the images of the lesion should be reviewed for image quality, lesion characteristics, and missed associated features which may cause an underestimation of the severity of the lesion. The discrepancy between sonographic and pathologic results should be discussed thoroughly.

Category 3. Concordant Benign (98.11%):

A lesion which is initially thought to be benign sonographically and also demonstrates benign pathology at needle biopsy falls into this category (Fig.3). This result can offer both the physician and the patient reassurance. However, imaging follow-up should be recommended to patients because of delayed false-negative diagnoses at core biopsy. Although there is no standard follow-up guideline, a follow-up sonography at six months after biopsy and then annually for at least two years can be recommended.

Category 4. Discordant Benign (14.28%):

A lesion in this category is suspicious for malignancy at sonography, but demonstrates benign pathologic result after performing a needle biopsy (Fig.4). However, the radiologist should give special attention to discordant benign lesions from which a substantial number of missed cancers at needle biopsy can be detected without any delay in diagnosis. If there is concern regarding a discordant benign lesion, it is prudent for the radiologist to immediately contact the interpreting pathologist and thoroughly communicate with each other. According to the discussion, the radiologist should notify the result and discuss the need for a repeat biopsy to the referring physician or the patient. A surgical biopsy, rather than a core needle biopsy, is recommended for a repeat biopsy because of the inconclusive outcome from the first core biopsy.

Table (1) shows patients and ultrasound characteristics of malignant thyroid nodules

Category	Number (total= 6)	%
Age (years)	1-9	-
	10-19	1
	20-29	-
	30-39	1
	40-49	1
	50-59	3
60 or >	-	
Gender	Male	1
	Female	5
Number	Single	5
	Multiple	1
Size (mm)	< 10	1
	10 -19	1
	20 - 39	2
	40 or >	2
Lobe	Right	3
	Left	2
	Isthmus	1
Echogenicity	Hypoechoic	5
	Isoechoic	1
	Hyperechoic	-
Consistency	Solid	4
	Cystic	-
	Heterogeneous	2
Margin	Regular	2
	Irregular	4
Halo	Absent	4
	Complete	-
	Incomplete	2
Calcification	Absent	3
	Microcalcification	2
	Macrocalcification	1
Vascularity	Absent flow	-
	Peripheral flow	1
	Central or internal flow	5
Lymphadenopathy	Negative	5
	Positive (intact hilum)	1
	Positive (lack hilum)	-
Local invasion	Negative	6
	Positive	-

Table (2) shows patients and ultrasound characteristics of benign thyroid nodules

Category	Number(total= 56)	%
Age (years)	1-9	-
	10-19	5
	20-29	4
	30-39	20
	40-49	10
	50-59	8
	60 or >	9
Gender	Male	12
	Female	44
Number	Single	18
	Multiple	38
Size (mm)	< 10	3
	10 -19	20
	20 - 39	26
	40 or >	7
Lobe	Right	22
	Left	28
	Isthmus	6
Echogenicity	Hypoechoic	6
	Isoechoic	38
	Hyperechoic	12
Consistency	Solid	25
	Cystic	14
	Heterogeneous	17
Margin	Regular	54
	Irregular	2
Halo	Absent	44
	Complete	11
	Incomplete	1
Calcification	Absent	42
	Microcalcification	1
	Macrocalcification	13
Vascularity	Absent flow	15
	Peripheral flow	39
	Central or internal flow	2
Lymphadenopathy	Negative	52
	Positive (intact hilum)	4
	Positive (lack hilum)	-
Local invasion	Negative	56
	Positive	-

Table (3) shows patients and ultrasound characteristics of suspicious thyroid nodules

Category	Number (total= 4)	%	
Age (years)	1-9	-	
	10-19	-	
	20-29	-	
	30-39	3	75
	40-49	1	25
	50-59	-	-
Gender	Male	-	
	Female	4	100
Number	Single	2	50
	Multiple	2	50
Size (mm)	< 10	-	-
	10 -19	1	25
	20 - 39	2	50
	40 or >	1	25
Lobe	Right	2	50
	Left	2	50
	Isthmus	-	-
Echogenicity	Hypoechoic	3	75
	Isoechoic	1	25
	Hyperechoic	-	-
Consistency	Solid	3	75
	Cystic	-	-
	Heterogeneous	1	25
Margin	Regular	4	100
	Irregular	-	-
Halo	Absent	4	100
	Complete	-	-
	Incomplete	-	-
Calcification	Absent	3	-
	Microcalcification	-	-
	Macrocalcification	1	25
Vascularity	Absent flow	2	50
	Peripheral flow	2	50
	Central or internal flow	1	25
Lymphadenopathy	Negative	3	75
	Positive (intact hilum)	1	25
	Positive (lack hilum)	-	-
Local invasion	Negative	4	100
	Positive	-	-

Table (4) shows sonographic findings of thyroid nodules and pathological results correlation

Ultrasound	Pathology			Total
	Benign	Suspicious	Malignant	
Benign	52	-	1	53
Suspicious	3	3	-	6
Malignancy	1	1	5	7
Total	56	4	6	66

Table (5) shows classification of sonographic-pathologic concordance

Type	Ultrasound	Pathology	%
Concordant Benign	Benign	Benign	98.11
Discordant Malignant	Benign	Malignant	1.88
Concordant Malignant	Malignant	Malignant	71.42
Discordant Benign	Malignant	Benign	14.28
Borderline or high risk	Variable	Suspicious	30.76

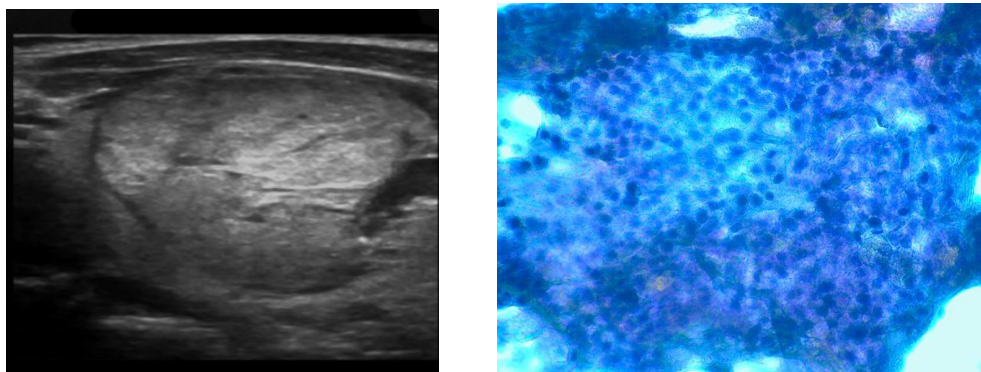


Fig. 1 Concordant malignancy: ultrasound examination reveals thyroid nodules with malignant criteria and pathological results reveals scattered epithelial follicular cells poorly cohesive with marked pleomorphism, nuclear angulation (papillary carcinoma)

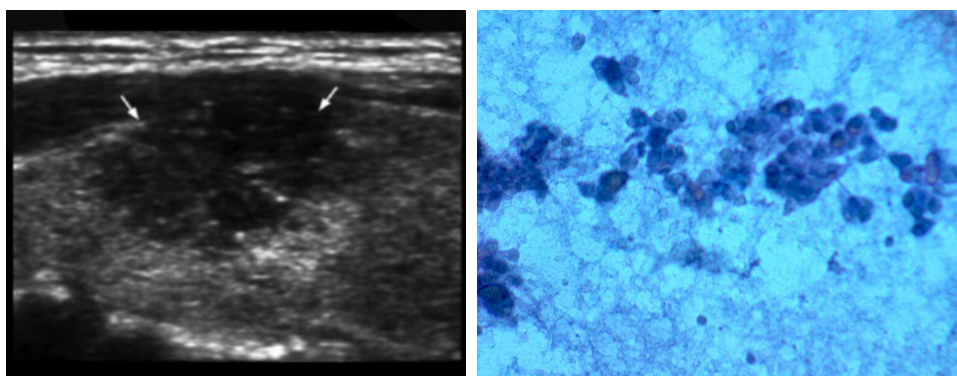


Fig. 2 Discordant malignancy: ultrasound examination reveals thyroid nodule of benign criteria and pathological results reveals sheets of follicular epithelium with marked pleomorphism and hyperchromasia in colloid background (follicular carcinoma)

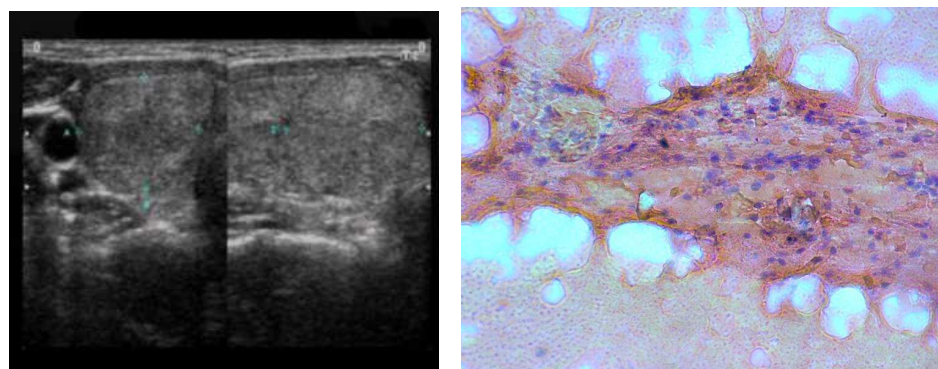


Fig. 3 Concordant Benign: ultrasound examination reveals thyroid nodule of benign criteria and pathological results reveals sheets of benign follicular cells

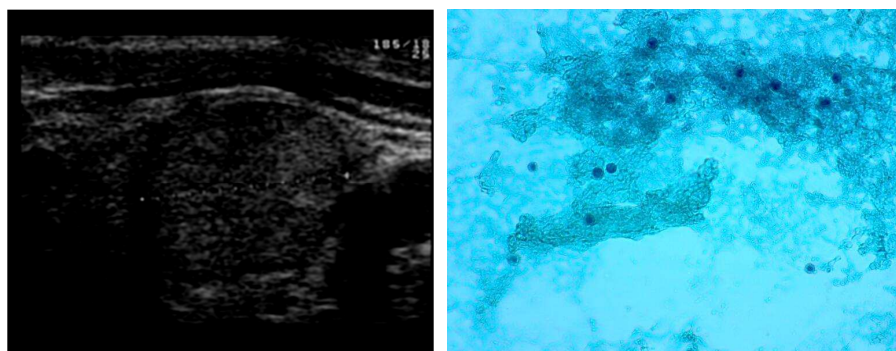


Fig. 4 Discordant Benign: ultrasound examination reveals thyroid nodules with malignant criteria and pathological results reveals scattered benign follicular epithelial cells

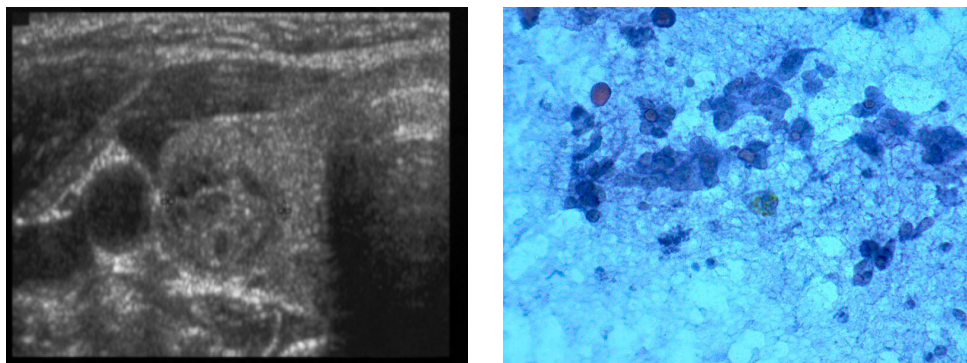


Fig. 5 Borderline or High Risk: ultrasound examination reveals thyroid nodules with indistinct criteria and pathological results reveals scattered benign follicular epithelial cells with mild to moderate atypia in colloid background (suspicious)

Category 5. Borderline or High Risk (30.76%):

A lesion in this category is not malignant but suspicious on biopsy and considered to have an increased lifetime risk for the development of thyroid cancer e.g. history of previous neck irradiation, family history of thyroid cancer, Hashimoto's thyroiditis...etc (Fig.5). A case-by-case approach is needed to manage the patient in accordance with the active discussion between different subspecialties. However, surgical excisional biopsy is usually recommended regardless of concordance, because of the relatively high upgrade rate to malignancy.

CONCLUSION

Careful sonographic-pathologic correlation and appropriated post-biopsy management will allow detection of a substantial number of false negative results immediately after needle biopsy by identifying discordant lesions prospectively, thereby avoiding delays in the diagnosis of cancer.

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