Utility of Gray Scale Ultrasound and Color Flow Doppler Versus Histology in Cold Solitary Thyroid Nodule

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Abstract: Background: Nodular thyroid disease is detected in 3-7% of the adults. Ultrasonography (US) is the most common way to image the thyroid gland and its pathology. **Objectives:** The objective of study was to assess the utility of color flow criteria alone or in combination with Gray scale sonography criteria for differentiation between benign and malignant cold solitary solid thyroid nodule and to correlate the characteristics of benign and malignant nodules with pathological diagnosis .**Subjects and Methods:** Twenty six patients with cold solitary solid thyroid nodule were selected from 93 patients with thyroid swelling after full history taking, complete clinical examination, laboratory and radiological investigations. Gray scale ultrasonography findings that suggested malignancy included micro-calcification, an irregular or microlobulated margin, marked hypo-echogenicity, a shape that more tall than it was wide and type III color flow Doppler(CFD)pattern were recorded. If even one of these sonography features was present the nodule was classified as positive (malignant) and if a nodule had none of the features described, it was classified as negative (benign). Hemi-thyroidectomy was done for all the cases with solitary nodule. The final diagnosis of a feature as benign or malignant was confirmed by histopathological examination to excised specimens. **Results:** This study included 44 females and 8 males with age range from 23 to 65 years. Histopathological results showed 18 malignant (34.65%) lesions and 34 benign (65.4%).All malignant lesions were papillary carcinoma (100%) (34.2% from total).The benign lesions were 14 simple nodules (41.2%) (26.9% from total) and 20 follicular adenoma (58.8%) (38.5% from total)**.**Sonographic results: The size of the 52 nodules ranged from 3 to 18 mm (mean size, 10.5 mm).The sonographic characteristics of malignant lesions were detected in 16 cases out of histopathologically malignant 18 cases and in 12 cases out of histopathologically benign 34 cases. The correlation of sonographic categorization with histological findings showed: In these 52 nodules, our sonographic classification method resulted in a sensitivity of 88.9% (16/18), specificity of 64.7% (22/34), and accuracy of 73% (19/26).Regarding to sonographic finding in 18 histopathologically malignant cases, there were 12 cases with CFD type III (A), 12 with micro calcification (B), 10 with irregular margin (C), 8 with marked hypoechogenicity (D) and 8 more tall then wide (E). while in 34 histopathologically benign cases there were 12 with CFD type III, 4 with microcalcification, 6 with irregular margin, 4 with hypoechogenicity and 4 more tall than wide. The accuracy of A, B, C, D, & E were 65.38%, 80.8%, 73.1%, 73.1% & 73.1% respectively**.** The accuracy of combination of CFD with gray scale patterns ranged from 69.2% to 80.8% with the mean of 74.3% .The results showed that there was no single sonographic item with accuracy of 100% can differentiate malignant from benign solitary nodule. The sensitivity, specificity and accuracy were calculated:Of 17 histopathologically benign cases, 6 were classified as positive. The accuracy of color Flow Doppler (CFD) alone was 65.4% while in combination with gray scale parameters the mean accuracy was 74.3%.**Conclusions:** No single US criterion is reliable in differentiating benign from malignant nodule. The color Doppler alone cannot reliably distinguish benign from malignant thyroid nodule and also when added to gray scale parameters did not increase the accuracy. We recommend more studies on larger scale to assess utility of this technique before any final conclusion can be drawn as regard to its accuracy in diagnosis of thyroid carcinoma.

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1. Introduction:

Nodular thyroid disease is detected in 3-7% of the adult population worldwide. The majority of these cases are clinically occult but readily detected by high-resolution Ultrasonography (USG)[1-4]. Many thyroid diseases can present clinically with one or more thyroid nodules. Solitary nodule is more common than multinodular goiters. Solitary thyroid nodule may be neoplastic, toxic, simple and very rarely inflammatory. Solitary nodule considered to be more likely to harbor malignant disease[5,6]**.** The main objective of evaluating solitary thyroid nodule is to exclude malignancy. Solitary thyroid nodule may be cystic, mixed or solid. Solid one is highly suspicious of malignancy[7]**.** Thyroid cancer is rare and accounts for <1% of all malignant neoplasms. It has a good

long-term prognosis after surgical excision. The high prevalence of thyroid nodules in the general population calls for a clear strategy to identify patients in whom surgical excision is genuinely indicated as opposed to those who can be managed conservatively[2]. Current management guidelines (American Thyroid Association) state that diagnostic USG should be performed in all patients with thyroid nodules and fine needle aspiration (FNA) in potentially malignant nodules[3].Preoperative assessment of solitary thyroid nodule includes sonography, CT, MRI and FNAC.CT and MRI are more costly than sonography, not as efficient in detecting small lesions and are best used selectively when sonography is inadequate to elucidate a clinical problem[8]**.** For differential diagnosis of thyroid nodule, US were found to be better than Multi-slice CT (MSCT). However, MSCT could be useful for the evaluation of advanced cases with suspicion of extra capsular extension[9].

FNAC of the thyroid gland is now firmly established as important diagnostic test for evaluation of goiter and accounts for the most effective test for preoperative diagnosis of solitary thyroid nodule. It also permits one stage surgical procedure[10]**.** Traditionally, the main indication for FNA biopsy of the thyroid has been the presence of a solitary nodule[11]**.** The accuracy of FNAC is about 90% [12] and about 98%[13]. FNAC carries some complications such as bleeding, infection, necrosis, cystic formation, release of thyroglubulin into the blood stream and implantation of malignant cells along the puncture canal, so it is considered as an invasive procedure[12]**.** Among the several imaging techniques that provide clinically useful anatomic information about the thyroid gland, sonography has become the method that is most commonly employed due to the superficial location of thyroid gland and its economical cost. The superficial location helps sonography to demonstrate normal thyroid anatomy and pathologic conditions with remarkable clarity. Sonography can supply clues about nature of a thyroid lesion. Rather, sonography can elucidate cryptic findings on physical examination, assess the comparative size of nodules on patient who are under observation or therapy, detect non palpable thyroid lesion, identify the solid component of a complex nodule, facilitate fine needle aspiration biopsy and evaluate for recurrence of a thyroid mass after surgery[8]**.**Hypo-echogenicity, blurred margin, absence of halo sign and microcalcifications has already been reported as single patterns suggestive of malignant thyroid nodule in observation of many authors[14,15].Color Doppler ultrasonography has been applied to the evaluation of thyroid nodules. It evaluates the presence and pattern of blood flow i.e. allows the evaluation of nodular and peri-nodular blood flow. The 2 main categories of vessel distribution are nodules with peripheral vascularity. About 95% of hyperplastic goitrous, adenomatous nodules display peripheral vascularity with or without a peripheral component[16]. The purpose of this study was to assess the accuracy of Color Doppler ultrasonography either alone or in combination with gray scale one in differentiation of benign from malignant cold solitary solid thyroid nodule and to correlate the characteristics of benign and malignant nodule with the pathological diagnosis.

2.Patients and methods:

Patients:

Consecutive eighty five patients with palpable thyroid swelling and 21 patients with non palpable thyroid swelling discovered during US for non thyroid causes e.g. Carotid Doppler or investigation of neck mass, were recruited prospectively from Internal Medicine Department at Benha university Hospitals between Juli 2011 and Decembre 2012. Investigations to be performed were explained to each patient and inC formed consent was taken.All patients were subjected to:A thorough clinical history taking; complete general and local examination(to exclude toxic and inflammatory goiter and also to select the cases with solitary thyroid nodule if palpable); laboratory investigations (thyroid function tests) for all patients to exclude toxic nodule and radiological investigations(radioiodine scans for selection of cold nodule and thyroid sonography.

Sonography:

Gray scale and color power Doppler were preformed with Toshiba Core Vision Model SSA-320A equipped with a linear probe 5 / 7.5 mHz. Malignant sonographic criteria:1-Microcalcifications: were defined as tiny, punctate hyperechoic foci either with or without acoustic shadows. Peripheral eggshell-like calcifications were not considered malignant.2-An irregular or microlobulated margin: it was defined as the presence of many small lobules on the margin.3-Marked hypoechogenicity: decreased echogenicity compared with the surrounding strap muscles.4-A nodule with a Shape more tall than wide: greater in its antero-posterior dimensions than its transverse dimension. We consider this finding to be positive for malignancy if any part of the nodule was more tall than wide.5-Type III color flow pattern defined as marked intranodular and absent or slight perinodular blood flow.6-The presence of a halo sin (anechoic or hypoechoic rim surrounding the nodule) was also recorded. Nodules were prospectively classified as positive or negative. If a single feature suggestive of malignancy was present, the nodule was classified as positive. If a nodule had no suspicious features, it was classified as negative (benign).Sensitivity, specificity

and accuracy were calculated for individual sonographic characteristics. After previous clinical examinations, and investigations, we detected 52 cases with cold solitary thyroid nodule. These 52 cases were included only in this study.

Histopathology:

All cases in this study were subjected to:I-Preoperative assessment: Indirect laryngoscopic examination and routine laboratory investigations for preparation to operation were done for all patients preoperatively.II-Operative procedures:All cases underwent hemithyroidectomy under general anesthesiaIII-Post operative assessment: Histopathological study for all excised specimens was done and the result was compared to the result of US examination for detection of the accuracy of US in differentiation between benign and malignant cold solitary solid thyroid nodule.

3.Results:

This study included 44 females (84.6%) and 8 males (15.4%) with age range from 23 to 65 years. **Histopathological** results showed 18 malignant (34.65%) lesions and 34 benign (65.4%).

All malignant lesions were papillary carcinoma (100%) (34.2% from total). The benign lesions were 14 simple nodules (41.2%) (26.9% from total) and 20 follicular adenoma (58.8%) (38.5% from total) (Table 1)**. Sonographic results:** The size of the 52 nodules ranged from 3 to 18 mm (mean size, 10.5 mm).The sonographic characteristics of malignant lesions were detected in 16 cases out of histopathologically malignant 18 cases and in 12 cases out of histopathologically benign 34 cases (Tables 2& 3). The correlation of sonographic categorization with histological findings is shown in table 4. In these 52 nodules, our sonographic classification method resulted in a sensitivity of 88.9% (16/18), specificity of 64.7% (22/34), and accuracy of 73% (19/26). Regarding to sonographic finding in 18 histopathologically malignant cases, there were 12 cases with CFD type III (A), 12 with micro calcification (B), 10 with irregular margin (C), 8 with marked Hypoechogenicity (D) and 8 more tall then wide (E). while in 34 histopathologically benign cases there were 12 with CFD type III, 4 with microcalcification, 6 with irregular margin, 4 with Hypoechogenicity and 4 more tall than wide. The accuracy of A, B, C, D, & E were 65.38%, 80.8%, 73.1%, 73.1% & 73.1% respectively (Table 5**).** The accuracy of combination of CFD with gray scale patterns ranged from 69.2% to 80.8% with the mean of 74.3% (Table 6).The results showed that there was no single sonographic item with accuracy of 100% can differentiate malignant from benign solitary nodule. Figures 1, 2, 3, 4 & 5 showed sonographic pattern to some cases in this study.

Table 1 : Postoperative histopathological patterns:

	Malignant nodules		**Benign nodules**		**Total**	
	number	**%**	**number**	**%**	**number**	**%**
	18	34.6	34	65.4	52	100
Papillary carcinoma	18	100	-	-	9	34.6
Simple nodule	-	-	14	41.2	7	26.9
Follicular adenoma	-	-	20	58.8	10	38.5
Total	18	100	34	100	52	100

Table (2): Malignant sonographic characters detected in cold solitary thyroid nodule:

Cases	**CFD type III (A)**	**Micro-calcification (B)**	**Irregular margin (C)**	**Marked Hypoechogenicity (D)**	**More tall than wide (E)**
1	Positive	Positive	Positive	Positive	Positive
2	Positive	Positive	Positive	Positive	Positive
3	Positive	Positive	Positive	Positive	Positive
4	Positive	Positive	Positive	Positive	Positive
5	Positive	Positive	Positive	Negative	Negative
6	Positive	Positive	Positive	Negative	Negative
7	Positive	Positive	Negative	Negative	Negative
8	Positive	Positive	Negative	Negative	Negative
9	Positive	Negative	Positive	Positive	Positive
10	Positive	Negative	Positive	Positive	Positive
11	Positive	Negative	Positive	Positive	Positive
12	Positive	Negative	Positive	Positive	Positive
13	Negative	Positive	Negative	Negative	Negative
14	Negative	Positive	Negative	Negative	Negative
15	Negative	Positive	Negative	Negative	Negative
16	Negative	Positive	Negative	Negative	Negative

Table (3) : Benign sonographic characters detected in cold solitary thyroid nodule:

Cases	**CFD type III (A)**	**Micro-calcification (B)**	**Irregular margin (C)**	**Marked Hypoechogenicity (D)**	**More tall than wide (E)**
1	Positive	Positive	Negative	Negative	Positive
2	Positive	Positive	Negative	Negative	Positive
3	Positive	Positive	Negative	Negative	Negative
4	Positive	Positive	Negative	Negative	Negative
5	Positive	Negative	Negative	Positive	Positive
6	Positive	Negative	Negative	Positive	Positive
7	Positive	Negative	Positive	Negative	Negative
8	Positive	Negative	Positive	Negative	Negative
9	Positive	Negative	Positive	Negative	Negative
10	Positive	Negative	Positive	Negative	Negative
11	Positive	Negative	Positive	Positive	Negative
12	Positive	Negative	Positive	Positive	Negative

Table (4): Comparison of sonographic and final histopathologic findings:

Sonographic category	Histologic findings		
	Malignant	Benign	Total
Malignant	16	12	28
Benign	2	22	24
Total	18	34	52

Table (5): Diagnostic index for individual malignant sonographic criteria of solitary thyroid nodule:

Sonographic characteristics	Malignant nodule n=18	Benign nodule n=34	Sensitivity (%)	Specificity (%)	Accuracy (%)
Type III color flow pattern (A)	12(66.7%)	12(35.3%)	12/18(66.7%)	22/34(64.7)	34/52(65.4)
Microcalcification(B)	12(66.7%)	4(11.8%)	12/18(66.7%)	30/34(88.2)	42/52(80.8)
Irregular or microlobulated margin (C)	10(55.6%)	6(17.6%)	10/18(55.6%)	28/34(82.4)	38/52(73.1)
Marked Hypoechogenicity	8(44.4%)	4(11.8%)	8/18(44.4%)	30/34(88.2)	38/52(73.1)
More tall than wide (E)	8(44.4%)	4(11.8%)	8/18(44.4%)	30/34(88.2)	38/52(73.1)

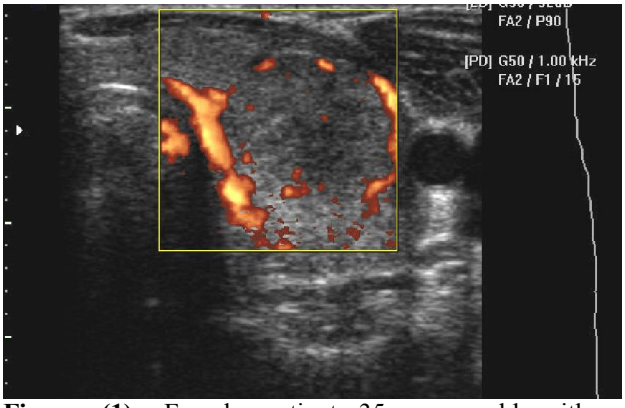

Figure (1): Female patient 35 years old with histopathological follicular adenoma left thyroid lobe. Gray scale and color Doppler US showed an isoechoic, solid nodule with type II color flow signals (peri-nodular without intranodular flow signals). No microcalcifications.

Table (6): The accuracy of combination of CFD with Gray scale patterns:

Sonographic pattern	Accuracy %
A+B	38/52(73%)
A+C	38/52(73%)
A+D	38/52(73%)
A+E	38/52(73%)
A+B+C	40/52(76.9%)
A+B+D	38/52(73%)
A+B+E	36/52(69.2%)
A+C+D	40/52(76.9%)
A+C+E	42/52(80.8%)
A+D+E	40/52(76.9%)
A+B+C+D	38/52(73%)
A+B+C+D+E	38/52(73%)
Mean	74.3%

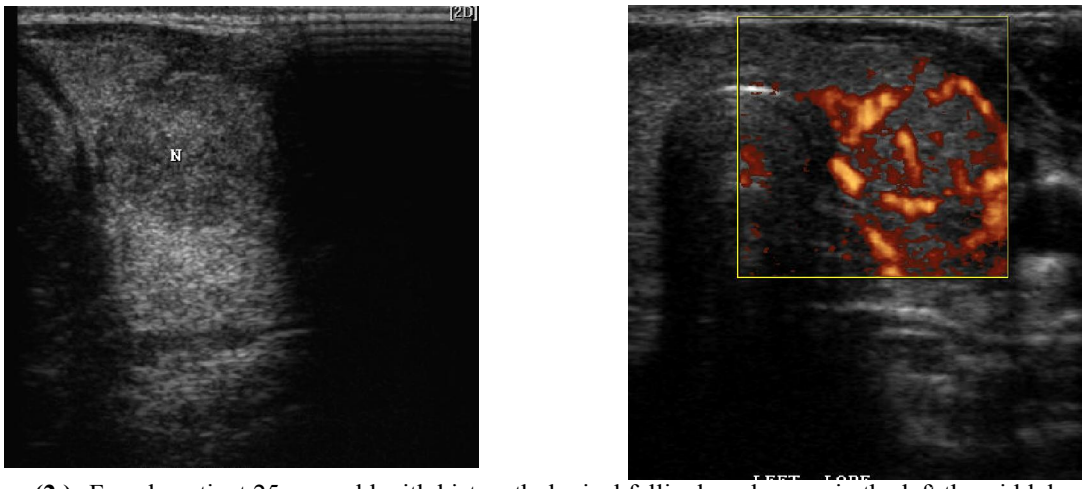

Figure (2): Female patient 25years old with histopathological follicular adenoma in the left thyroid lobe. Gray scale image shows hypoechoic solid nodule with a well defined margin, halo sign, intra and peri-nodular flow signals (type III). This lesion was categorized as malignant lesion on the base of US criteria but its benign nature was proved by histopathological examination.

4.Discussion:

Thyroid nodular disease is characterized by the presence of one or more palpable or nonpalpable nodules within the substance of the thyroid gland. A thyroid nodule is defined as a discrete lesion within the thyroid gland that is distinguishable from the adjacent parenchyma at USG[8]. Many thyroid diseases can present clinically with one or more thyroid nodules. Such nodules represent common clinical problems. Palpable thyroid nodules occur in 4-7% of population, but nodules found incidentally on US suggest a prevalence of 19-67%. The majority of thyroid nodules are asymptomatic[5].The great majority of thyroid nodules are benign, less than 5% are malignant. The main objective of evaluating thyroid nodules is to exclude malignancy[17].Several studies have been performed to establish the ability of US to differentiate benign from malignant thyroid nodules. Indeed, compared with FNAB, thyroid US has the advantage of being a non invasive procedure and giving immediate information[17,18].As the FNA cytology more accurate than Gray scale sonography but it is considered invasive procedure, so the **aim of this study** was to assess the accuracy of CFD sonography either alone or in combination with Gray scale one in differentiation of benign from malignant cold solitary thyroid nodule.

In our study, the malignant sonographic criteria mainly microcalcifications, marked echogenicity, shape (more tall than wide), irregular margin and type III color flow pattern were assessed in 52 solitary thyroid nodule. The sonographic results were compared to histopathological results for detection of accuracy of ultrasonography in detecting benign and malignant lesions. Microcalcification is a common finding in patients with palpable thyroid papillary carcinoma. It is not often seen in a non palpable nodule. Sonography is not highly sensitive in revealing micro calcification unless they occur within masses. At pathology, tiny, punctuate micro calcifications are correlated with the calcification of psammoma bodies. The detection of micro calcification in thyroid nodules with high-frequency sonography, although uncommon, can be considered nearly specific for malignancy[19]**.** In our study, microcalcifications were the most accurate (80.8%) ultrasonographic finding.

In our study, the presence of irregular or microlobulated margin was considered positive index for a malignant lesion that requires further evaluation although; it was about 55.6% sensitive and 73.1% accurate. Microlobulation was more common than an ill-defined margin in non palpable thyroid malignancy, and it may be associated with smaller mass and a less invasive character. Our results were lower than that reported by other study[20]**.** The difference may be due to that their study were on non palpable nodules only and larger patient sample in their study.

Hypoechogenicity was considered a finding suggestive of malignancy. However, most solid thyroid nodules are hypoechoic and most of those are benign[21]. In this study, it was attempted to differentiate markedly hypoechoic lesion from other hypoechoic lesions, and only markedly hypoechoic lesions were considered a finding indicative of malignancy. Marked Hypoechogenicity is considered when a solid nodule is much less echogenic than the medium-level echogenicity of the strap muscles. Normally, the healthy thyroid gland shows

homogeneous hyperechogenicity compared with the surrounding muscles. Because most thyroid nodules show Hypoechogenicity when compared with the parenchyma of the thyroid, this comparison does not provide much useful information. The strap muscle is uniformly present in all patients; therefore, it was used as the comparative standard for the evaluation of the echogenicity of solid nodules. A nodule shape taller than wide was regarded as a finding suggestive of malignancy. Researchers have documented that nodules in the breast that are taller than they are wide are more likely to be malignant[22]**.** This finding was applied in thyroid nodules and showed that it was not a sensitive (44.4%) but a very specific (88.2%) finding, and thus it could be used as an ancillary finding particularly of non palpable thyroid malignancies.

Color Doppler US has been applied to the evaluation of thyroid nodules, but again, many similarities were noted between the appearances of malignant nodules. No consistent correlation has been found between the pathologic findings and either the presence of internal flow or its amount. Color Doppler finding depend more on lesion size than on the histological features[23]**.** In our study; type III flow pattern on color-power Doppler was used as predictive criteria for malignancy. However according to accuracy of CFD alone in this study was 65.4% while in combination with other Gray scale parameters the mean accuracy was 74.3%. The CFD did not add any increase in the accuracy of Gray scale parameters, so Color Doppler cannot reliably distinguish benign from malignant thyroid nodule. Our results regarding to CFD coincide with that reported by other study [24], who reported that the diagnostic value of Doppler sonography in the differentiation of benign and malignant thyroid nodules is not established yet. Other investigators [25] compared color Doppler with powered sonography in a large study included more than 300 cold nodules (including 20 papillary cancers) and had results similar to this study, with a hypervascular color Doppler pattern common in but not diagnostic of papillary carcinoma.

Another study[26] showed that although the degree of vascularity as determined by color Doppler imaging differs in malignant and benign nodules, the role of color Doppler sonography in the evaluation and treatment of thyroid nodules is limited.In another smaller series study that included 7 malignancies, when color Doppler sonography was used in conjunction with gray scale sonography, it aided in the differentiation of neoplastic lesions from colloid nodules but was not sensitive enough to distinguish benign from malignant neoplasm[27]**. Conclusions:** Gray-scale USG features of thyroid nodules are useful to identify patients with clinically significant thyroid nodules from those with innocuous nodules. In our study, the USG features of poorly defined margins, marked hypoechogenicity, and taller-than-wide shape were found to have high diagnostic accuracy for identifying malignant thyroid nodules.Color Doppler sonography results alone or in combination with Gray scale one has a limited role in differentiation between Benign and malignant thyroid nodule. We recommend more studies ,on larger scale, to assess this technique before any final conclusions for its utility in diagnosis of thyroid carcinoma.

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