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Conventional Ultrasound and the Color Flow-doppler Mapping Function in Evaluation of Libyan Thyroid Tumors

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Authors' contributions

This work was carried out in collaboration between all authors. Author EAM participate in performed the US works and contributed to the design and preparation of the manuscript. Author AH also participate in performed the US works, and participated in the organizing of clinical data. Author GA conceived of the study, and participated in the organizing of clinical data. Author RM provided the samples and clinical data. Author ABF in addition to participate in performed the statistical analysis, he designed and coordinated the research and drafted the manuscript. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: Conventional Ultrasonography and (CFM) can be expected to improve the distinction between benign and malignant thyroid nodule gland. The aim of this study was to estimate the supporting value of a color flow-Doppler mapping function (CFM) of conventional Ultrasonography of the thyroid nodule, and do so by using different flow patterns and whether ornot, this technique can have a role in the diagnosis of malignant involvement.
Study Design: Prospective [analytic observational] study.
Place and Duration of Study: Department of Surgery and Department of Radiology, Misurata

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Cancer Center, Libya, between January 2007 and December 2009.
Methodology: This prospective study was based on 54 patients with an available histological diagnosis of the thyroid nodule 41 benign Follicular adenomas (FA) and 13 malignant papillary carcinomas (PC) were examined. Before thyroidectomies, the patients were submitted to US graphic in a two different assessment methods: (i) patients examined with conventional thyroid US and (CFM) method and (ii) then re-examined with CFM method. The CFM produced 3 vascular pattern [A; Peripheral ring of flow with minimal or no internal flow. B; Peripheral ring and small to moderate internal color flow. C; Extensive internal color flow with or without peripheral ring].
Results: The conventional ultrasonographic patterns showed significant differences between benign and malignant cases. The ill-defined and irregular edges of assessment nodules were especially significant. The type A or B blood flow pattern were not significant. However, All samples with type C blood flow pattern were malignant and with sensitivity 61.5%.
Conclusion: The study suggests that the conventional thyroid ultrasound with the color flow-Doppler mapping function can play a useful role in evaluation of the thyroid tumors, and the tumor features that analyzed by ultrasound should be considered at the time of surgical intervention. The method can be used to increase the effectiveness of cytological procedure in doubtful thyroid lesions.

Keywords: Thyroid nodule; conventional Ultrasonography; color flow-Doppler mapping function.

1. INTRODUCTION

Thyroid nodule is one of the most common pathological problems in the world particularly in population that living in iodine deficiency areas [1]. It is well known that the female gender has thyroid nodules four times greater than the male and the prevalence increases with age [1-3]. Majority of thyroid nodule patients' complain of midline neck swelling that may cause dysphagia and hoarseness of voice. Generally, the thyroid diseases can be classified into three classes: benign thyroid masses, malignant tumors of thyroid gland, and diffuse thyroid enlargement [4].

Thyroid malignancy in the euthyroid patient with a solitary thyroid nodule accounts for 5%–10%, whereas, the great majority of thyroid nodules are benign nodules (BN) [3–9]. The ability to distinguish benign from malignant nodules is essential to avoid unnecessary operations. The recent decades have shown development in the knowledge and understanding of the basic science of the thyroid disease. Today, the treatment of thyroid nodules improved from surgical therapy only to multidisciplinary management that needed surgeons, radiologists, pathologists and chemotherapists.

Early diagnosis is important because patients with early stage cancer have better survival than those with advanced disease. Fine-needle aspiration biopsy (FNAB) is minimally invasive and has high specificity and sensitivity particularly in papillary carcinoma. Nevertheless, the method can still potentially be improved by applying ultrasonography characteristics. Thyroid ultrasonography is simple to perform, commonly available, safely applicable and is easily combined with FNAB. Thyroid ultrasonography is non-invasive method and giving direct results. Several studies have been established the capability of thyroid ultrasound to distinguish the benign thyroid nodule from malignant one [6-9]. US also helps early detection of local invasion, regional nodal spread and presence of distant metastases.

Among the different patterns of conventional ultrasonography, hypoechogenicity of the nodule, micro calcifications and the absence of halo sign were confirmed to be a helpful in predicting thyroid cancer [10]. However, the effectiveness of color flow-doppler mapping function (CFM) scan in predicting malignancy of thyroid nodules is still controversial [11].

Although, pathology report is considered a final method for the diagnosis of lesion behavior, the time and energy put in it may lead to delay in the final diagnosis and treatment in many cases. There have been some reports over the last few decades dealing with color flow-doppler and conventional US examination of thyroid nodule, particularly the role of CFM in selection of patients requiring FNAB. Such investigation can support the diagnostic decisions in many cases, and improve the sensitivity and specificity of the preoperative clinical diagnosis.

The aim of current study was to evaluate the conventional thyroid ultrasound with color flow-doppler mapping function (CFM) can contribute to assess the thyroid tumours in a solitary thyroid nodule of Libyan patients and whether this technique can have a role in the diagnosis of malignant involvement.

2. MATERIALS AND METHODS

The prospective study was performed on Libyan thyroid cold nodule samples. All cases were diagnosed at the radiology and Pathology departments, National cancer Institute, Misurata, Libya and during years 2007- 2009. The patients were excluded from this study based on the following exclusion criteria: hypo or hyperthyroidism patients, non-solitary nodule, non-cold nodule, histopathology was done elsewhere than in our study centres, and pathological diagnosis was not follicular adenoma or papillary carcinoma. This left 54 samples for the study: 44 females and 10 males. No lesions had been biopsied earlier. A detailed history, clinicopathological features (age, duration of complain, tumor size, US features, stage grade, and lymph node status), were collected from patients files.

2.1 Conventional Thyroid Ultrasound and Color Flow-doppler Mapping Function (CFM)

It was performed using a modern high-resolution color Doppler apparatus (*Philips HD11 Ultrasound, USA*), with a 7.5 MHz linear transducer.

Data were collected as the following:

2.1.1 Conventional scan evaluated

Features of the nodule as (site, size, echo structure and echogenicity), presence of the cervical enlarged lymph nodes and the node's criteria of malignancy (including diameter of 1cm or more, clear hypoechogenic pattern or heterogeneous pattern, cystic appearance and presence of internal calcification).

The lesions carries low risk of malignancy when they have size equal or less than 1 cm, well defined, regular and smooth edges. Malignancy criteria of thyroid nodule (irregular edge nodule, hypoechoic solid nodule, presence of internal micro calcification as hyper echoic spots less than 2 mm with acoustic shadowing, and absence of the peripheral halo as transonic rim surrounding the lesion).

2.1.2 Color flow-doppler mapping function (CFM)

Color flow-doppler mapping function (CFM) scan evaluated the pattern of blood flow of the nodule and classified as follows:

Type A. Peripheral ring of flow with minimal or complete absence of internal flow signal.
Type B. Peripheral ring of flow with mild to moderate internal color flow signal.
Type C. Extensive internal color flow signal with or without peripheral ring of flow.

The malignant involvement of the nodule based on nodule characteristics found on the ultrasound scan classified as (low risk, median risk, and high-risk).The results confirm with histopathological reports

2.2 Statistical Analysis

Statistical analyses were performed by using SPSS for Windows, versions 19.0 (SPSS, Inc., Chicago, USA), software packages. The variables of the material were grouped into logical classes and descriptive statistics calculated for the continuous variables. P-values below 0.05 were regarded as significant. Comparison of numerical data was done by the chi-square test. Student t-tests and ANOVA were also used to test differences between the groups. Microsoft Excel 2007 was applied to drawn graphs and to evaluate relationships between variables.

3. RESULTS

A prospective study of forty four females of mean age 38.70±14.84 years (range 16– 65 years) and ten males of mean age 46.80±7.82 years (range 36 – 61 years) who had a single thyroid nodule (Figs. 1,2). Nodule size, as evaluated by US, ranged from 1.0 to 7.2cm (mean±s.d.: 3.7±1.3 cm);a diagnosis of carcinoma was histologically confirmed in 13 cases (24.1%); all are papillary carcinoma (PC) and with mean size of (3.08±1.01cm). The mean duration of compliant (7.9±5.0 months). However, 41 cases (75.9%) confirmed as benign nodules with diagnosed of follicular

adenoma (FA) and with mean size of (3.84±1.36 cm), while the mean duration of compliant (26.90±20.48 months) (Table 1).

Malignant features at histological examination were more frequent in female patients (84.6%) than in male patients (15.4%) at univariate analysis, with statistical significance (*P*<0.0001). Neoplastic lesions were not significantly associated with specific side localization (with frequency 57.4% in left side and 42.6 0% in right side; with *P* = 0.7).

Almost patients with papillary carcinoma, PC (92.3%) with short duration of compliant that ranged from 1 to 12 months which is significantly shorter than benign FA lesions.

Among 13 PC patients, 7 (53.8%) were complained of cervical lymph nodes involvement (P-value is <0.0001) (Figs. 3B and 4).

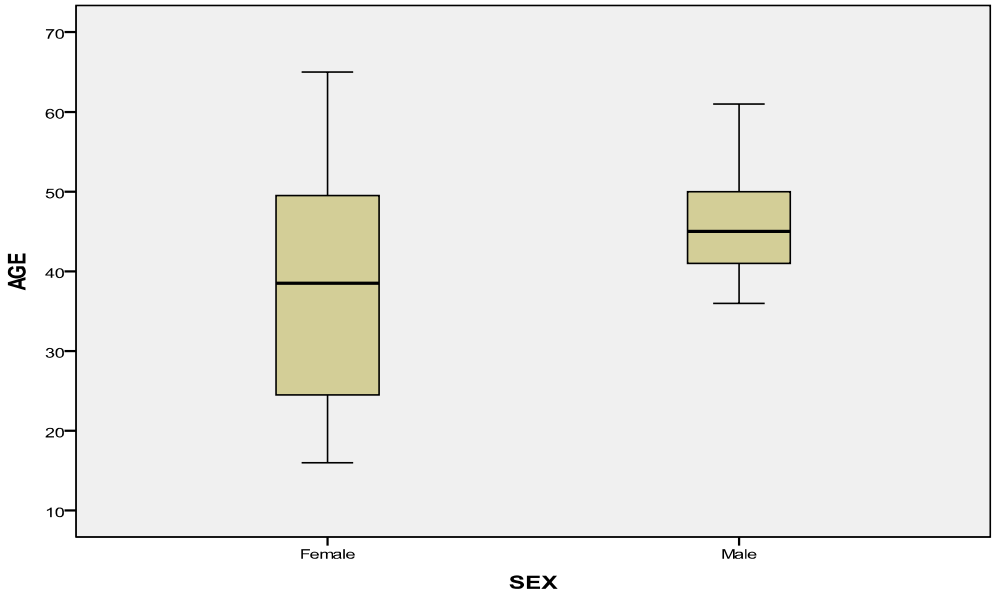
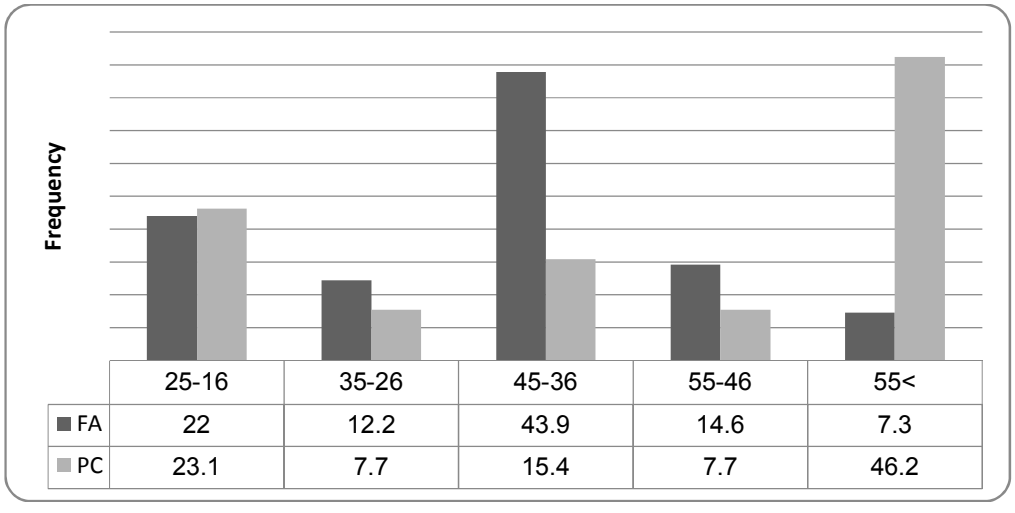


Fig. 1. Mean ± 2 SD of the age in histological section of thyroid tumors in different Libyan female and male patients. Clearly, the mean age is increased with the male gender



	25-16	35-26	45-36	55-46	55<
FA	22	12.2	43.9	14.6	7.3
PC	23.1	7.7	15.4	7.7	46.2

Fig. 2. Distributions and frequency of thyroid tumor type through age groups of Libyan patients

Table 1. The characteristics of 54 cases of Libyan thyroid tumors: Percent, mean and standard deviation of sex and histopathology

Clinical characteristics		Mean(S.D)	Frequency	Percent
Female	Age	38.70 (14.84)	44	81.5
	Duration in months	22.77 (20.48)		
	Diameter in cm	3.64 (1.36)		
Male	Age	46.80 (7.82)	10	18.5
	Duration in months	20.40 (16.07)		
	Diameter in cm	3.72 (1.17)		
FA	Age	38.02 (12.21)	41	75.9
	Duration in months	26.90 (20.48)		
	Diameter in cm	3.84 (1.36)		
PC	Age	47.08 (17.75)	13	24.1
	Duration in months	7.92 (5.02)		
	Diameter in cm	3.08 (1.01)		

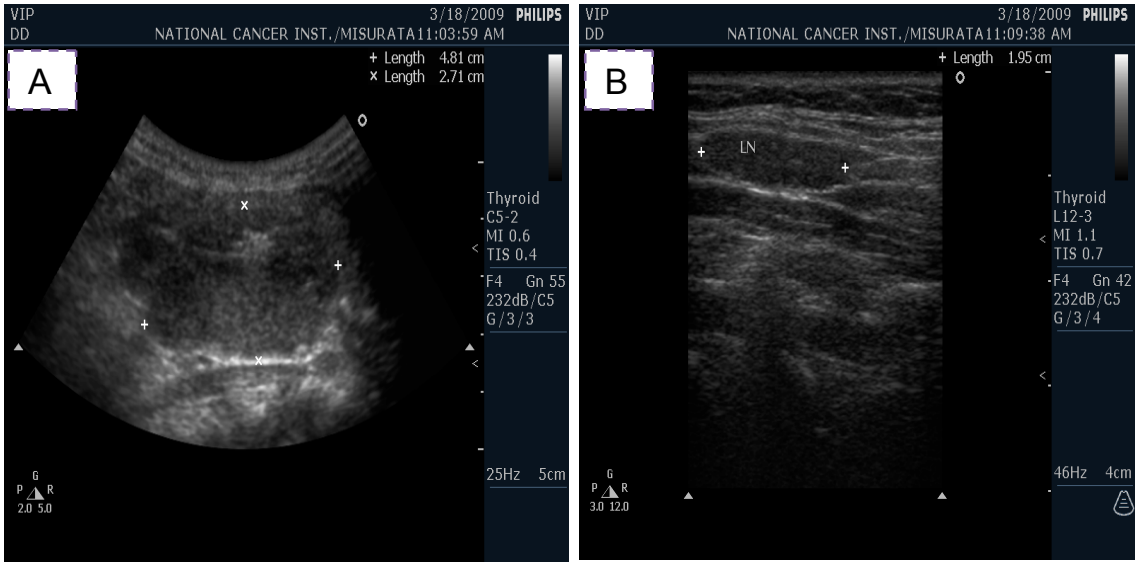


Fig. 3. Conventional ultrasound patterns. A: Absence of peripheral halo in thyroid papillary carcinoma (longitudinal section). With hetroechogenicity in papillary thyroid carcinoma (longitudinal section). B: regional LNs, with hetroechogenicity absence of peripheral halo and hypoechogenicity are also present in papillary thyroid carcinoma (longitudinal section)

3.1 The Result of Conventional Ultra-sonographic Patterns

Malignant PC lesions showed micro-calcifications more frequently than benign FA nodules (76.9 vs. 22.0%; *P*< 0.0001). Similarly, absence of peripheral halo (76.9 vs. 17.1%; *P*<0.0001), and solid hypo-echoic appearance (61.5 vs. 12.2%; *P*<0.0001) (Fig. 3). On the other hand, the most significant single sign for predicting malignancy is irregular edges (with frequency 84.6% in PC and 0% in FA) and if used as a sole predictive sign, it has a high specificity and sensitivity values (Table 2).

3.2 The Result of Color Flow Mapping Function Scan

In this study, The CFM patterns were Type A (found in 27 nodules; all are FA), Type B (found in 19 nodules; 14 are FA and 5 are PA), and Type C (found in 8 nodules). Particular the extensive internal color flow (Type C) (61.5% vs. 0.0%; *P*<0.0001) was significantly more frequent in malignant PC than in benign FA nodules (Fig. 5 and Table 3).

3.3 The Result of the Malignant Involvement of the Nodules Classification

The nodules were classified as low, medium, or high risk for malignant involvement, among the 54 thyroid nodules, 37 nodules were classified as low risk, 9 nodules as moderate risk and 8 nodules as high risk (Fig. 6).

All low-risk nodules 37(100%) were diagnosed as follicular Adenoma (FA). However, only 4 of 9 medium-risk nodules were diagnosed as FA nodules, whereas the most moderate risk nodules 55.6% were diagnosed as PC. On the other hand Among 13 patients with histological diagnosis of PC, 8 (61.5%) were had high-risk patterns (P<0.0001) (Table 4 and Fig. 6).

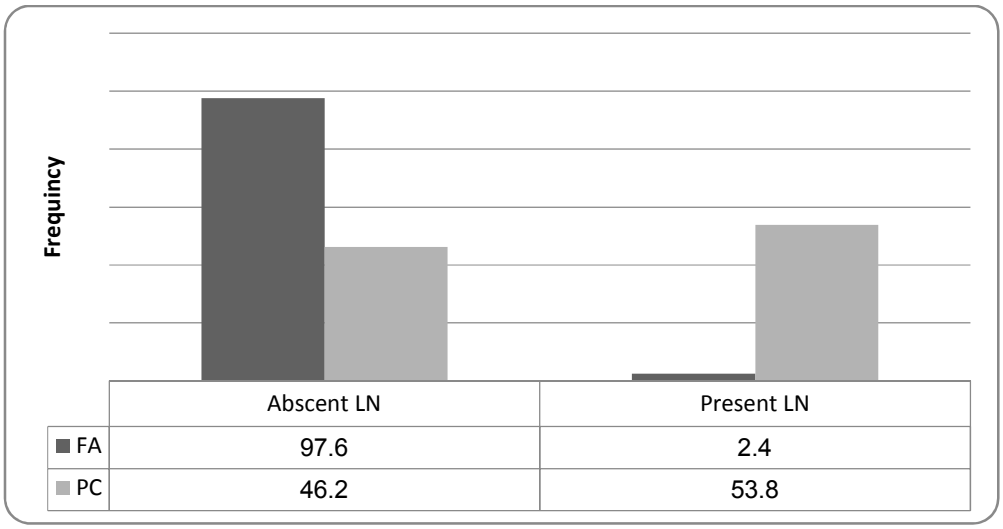


Fig. 4. The presence of cervical enlarged lymph node and histopathology

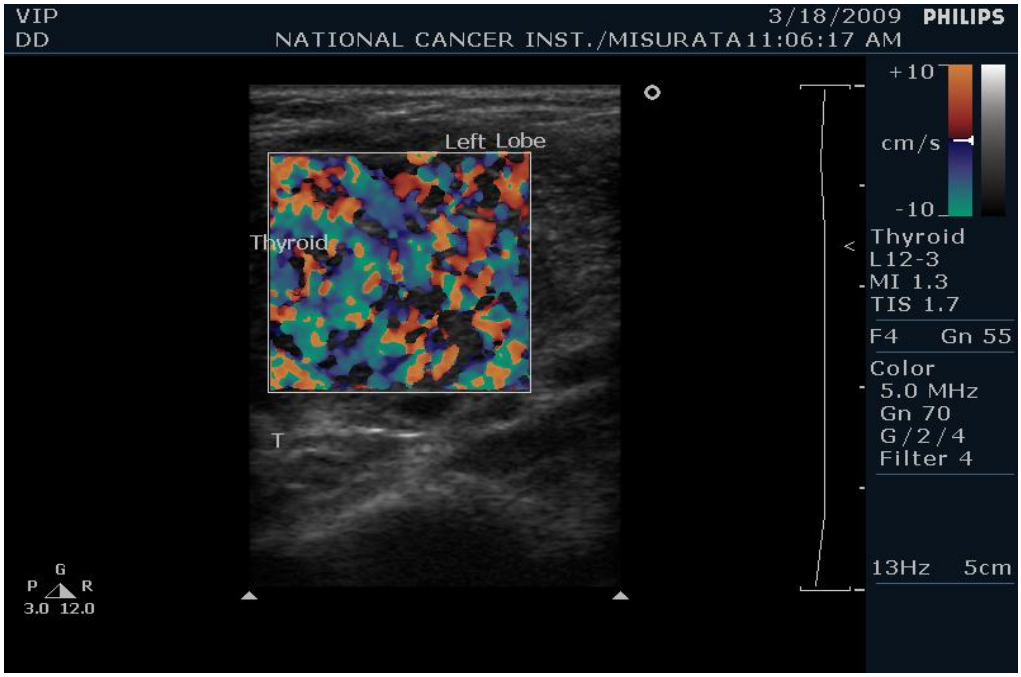


Fig. 5. Color flow mapping (CFM) most significant patterns: Extensive internal color flow

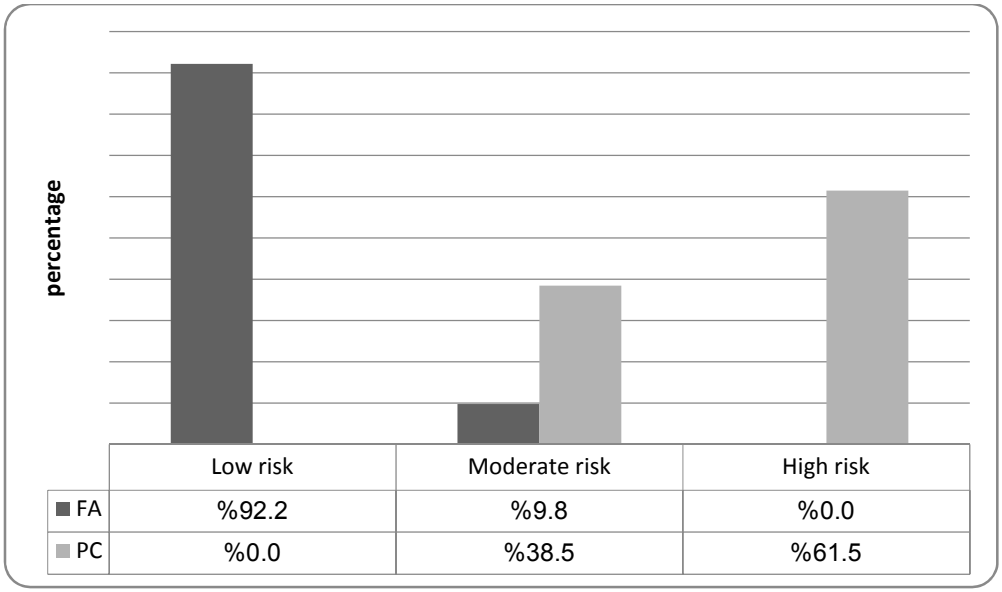


Fig. 6. Classification of the malignant involvement of the nodules and Histopathology. (*P* < 0.0001)

Table 2. The distribution of conventional ultrasonographic patterns among 54-thyroid lesion corresponding to histopathological type

Ultrasonographic pattern	PC	FA	p-value
irregular edge (IE)	11/13(84.6 %)	0(0 %)	<0.0001
Hypoechoic nodule	8/13(61.5 %)	5/41(12.2%)	<0.0001
Microcalcification	10/13(76.9%)	9/41(22.0%)	<0.0001
Absent peripheral halo	10/13(76.9%)	7/41(17.1%)	<0.0001

Table 3. Thyroid lesions samples studied with US graphic analysis. The Color flow mapping function (CFM) categories correspond to classes of A, B, C, respectively. The histological evaluation was based on the investigation by experienced pathologists, and confirmed in this study

CFM pattern category	No. of patients	Histological diagnosis	
		PC	FA
Type (A)	27	0	27*
Type (B)	19	5	14
Type (C)	8	8*	0
Total	54	13	41

*FA, Follicular adenoma; PC, papillary carcinoma; *, P < 0.0001*

Table 4. Classification of the malignant involvement of the nodules and HP

CFM pattern category	No. of patients	Histological diagnosis	
		FA	PC
Low risk (LR)	37	37*	0
Median risk (MR)	13	4	5
High risk HR	8	0	8**
Total	54	41	13

** Most numbers of FA (37/41) 90.2% with (LR) classification.*
*** Maximum numbers of PC (8/13) 61.5% with (HR) classification*

4. DISCUSSION

Several studies have been observed that the risk of malignancy in patients with thyroid nodules is low, about 5%, not including that patient who has a risk factor, such as an exposure to ionic radiation [2]. In current study, the majority of patients are female (81.5% F, 18.5% M). All malignant histological type are papillary carcinoma. Majority of papillary carcinoma patients'(92.3%) presented with short duration of compliant in rang of 1-12 months, which is similar to several other studies [12-14].

Some studies assisted the ultrasonographic features of thyroid nodules that can be useful indicators of histological malignancy. In general, these studies stated that only a few ultrasonographic features might have ability to identify the higher risk nodules.

Current study, recognized that the presence of microcalcifications, absent the hole sign (ill define margins), hypo-echoic pattern and internal vascular flow pattern were useful criteria of malignancy, as already stated by many studies [12,15-19,20]. For instance, Ragowith his colleagues found that 30/104 nodules were diagnosed as malignant. On US, the most predictive pattern for malignancy was the absent halo sign, which was found in 20/30 CA and in 17/74 BN (P <0.0001).

Seiberling et al. [7] recognized that 66/159 patients (41.5%) were diagnosed with cancer. Of those with malignancy, 52 (78.8%) had microcalcifications on thyroid US.

Moreover, this study confirmed that recently recognized by some authors [12, 21-22], that a nodule with an irregular shape is more powerful indicator for malignancy than the size of nodule. However, in present study the nodule size is not predictor of histological malignancy. This result online with results observed by other authors [15,18]. Therefore, the decision of FNAB to thyroid nodule should not dependent on just the size of nodule. The proper strategy is that the US-FNABshould be probably considered in all nodules, even those with small size less.

Bonavita et al. [23] stated that determination of specific morphologic patterns such as spongiform configuration, cyst with colloid clot, giraffe pattern, and diffuse hyperechogenicity, have an accurate method of identifying benign thyroid nodules that do not require cytological evaluation. Use of this approach may substantially decrease the number of unnecessary biopsy procedures.

4.1 Sensitivity and Specificity

The sonographic features analysis of thyroid nodules are successful application for preliminary diagnosis of malignant diseases and this is true of many cancer types [4-6]. However, for some patients with thyroid cancer, the identification of malignant risk was difficult (specificity is high but sensitivity is variable 55.5%. About 44.4% of moderate risk of malignant samples were benign in surgical biopsy according to the current study. Our results showed that image US features can have relatively high sensitivity in detecting malignancy (84.6%) in irregular edge feature that was seen via conventional and 61.5% in the extensive internal color flow (type c) on CFM. This seems to suggest that image features of US may improve the sensitivity and specificity of the cytological diagnosis and help in distinguishing between malignant and benign lesions, and might be help to determine optimal management of these lesions, by reducing the number of FNAB and the cost of healthcare.

Moon et al. [24] also recognized that most thyroid nodules were solid or predominantly solid rather than cystic or predominantly cystic. Moon et al also noted that sensitivity of these nodules was high (83.3%) most of which are papillary carcinoma (75%-80%).

4.2 Value of Color doppler US Graphic in Thyroid of Libyan Population

One of our aims was to determine the value of image *color dopplar US* in Libyan thyroid lesions. Our results showed that all benign thyroid no dual samples were either pattern A or B. Five out of 13 malignant cases also were either pattern A or B; all other available malignant cases had type C pattern CFM. These results indicate a clear diagnostic value of the type C pattern CFM. Neither micro follicular adenoma nor macro follicular adenoma gave type C pattern CFM. Comparison of the studies of Rago et al. [12], Cappelli et al. [22] and current study (type C pattern sensitivities: 50.0%, 61.6% and 61.5%, respectively) leads to a conclusion that the abnormal CFM is a marker for potential

malignancy. However, the presence of a type A and B pattern CFM cannot exclude malignancy. The results suggest a false-negative rate of 38.5% (in our study). If the clinician knows that there is a risk of false negatives, he will act accordingly and subject the patient to further investigations and follow-up. However, the situation with false positives is different: if CFM only is used as the basis for treatment decision, occasionally patients with a benign lesion will be subjected to cancer treatment, which is unnecessarily radical. Rago et al. [12] and Cappelli et al. [22] had false-positive cases among their benign samples. Although we did not have false positives, we think that the possibility of there being false positives must be taken into consideration. Hence, CFM diagnosis alone can only be preliminary, but is helpful for further management of the patient.

4.3 The Problem of Cost-effectiveness

However, since the problem of cost-effectiveness have always been important and have recently become even more applicable for clinical guidelines in many countries, it is attractive to outline a reasonable approach to the decision of performing FNAB when a thyroid nodule is detected on the US examination.

Papini et al. [15], concluded to limit the number of lesions that underwent to FNAB, suggested that FNABon non-palpable nodules characterized by hypo-echoic appearance and at least one of the three additional US features (intranodular vascular images, ill define margins and microcalcifications), would have missed only 13% of carcinomas, by performing FNAB in just 31% of patients. The same criterion applied to our series of nodules gives slightly worse results, with missing about 23.1% of carcinomas. However, when we have been applying the feature of irregular edges and type C pattern, we observed dramatically reduces the number of missed carcinoma to 0.0%.

We conclude that irregular edges and type C pattern with at least two additional US features may currently represent the best finding the middle ground between missing cancers and the problem of cost-effectiveness. However, because our material may be quite small for final conclusions. That may suggested being broader and further researches.

4.4 Diagnostic Limitation of Thyroid Ultrasound

There are some limitations to the application of different diagnostic tools of thyroid ultrasound. This is true even though quantitative estimations of different ultrasound characteristics are relatively sensitive methods. Selection of different type of ultrasound and the number of selected criteria will affect the results to a considerable extent. Careful examination of multiple solid cystic lesion still require some subjectivity and is quite unreproducible. In this study, exclusion of non-cold nodules and non-solitary nodules were quite enough to at least, partly avoid this problem. However, cystic components of thyroid malignant nodule or cystic lymph node metastases adjacent to the thyroid gland may be mistaken for solitary benign cyst or cystic degeneration in a benign nodule. A careful ultrasound assessment to demonstrate solid component with vascularity or detection of focal microcalcifications may help in differentiating these lesions. On other hand, diffusely infiltrative hyper-vascular thyroid carcinoma can be misinterpreted as autoimmune thyroiditis in addition, co‑existing autoimmune thyroid disease and thyroid carcinoma can be further complicate the interpretation [24,25].

On the other hand, some discrepancies in the results obtained in different studies has also been found because either the difference in the selection of ultrasound diagnostic criteria or variation in the work methodology among the different studies [26]. To minimize this possibility, should be introduce suitable methods rules in diagnostic features of different thyroid lesions, as a part of this efforts, current study tested a number of diagnostic criteria that may be diagnostically useful markers in guiding decision on future diagnosis and management of thyroid diseases.

5. CONCLUSION

This study demonstrates that the conventional thyroid ultrasound with the color flow-Doppler mapping function (CFM) can play a significant role in evaluation (diagnosis and management) of thyroid tumours especially papillary carcinoma.However, the reasons for the applying ultrasonography methods in the thyroid nodule analyzed at the time of surgical intervention are mainly down to the fact that

ultrasonography analysis methods are fairly simple, non-invasive, no radiation exposure, giving immediate information with high resolution(real-time approach), and relatively reasonable cost compared with other techniques. Furthermore, has high sensitivity in detection of cervical lymph node involvement and assessment of surrounding tissues invasion.

CONSENT

The proposed study has been examined and approved by the Research Council of Misurata Cancer Center and informed consent was obtained from the patients for publication of this research

ETHICAL APPROVAL

All authors hereby declare that all research processing in this study have been examined and approved by the ethics committee of Research Council of Misurata Cancer Center and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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