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Beyond the Thyroid Gland: A Global Perspective on Triplex Ultrasound

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Abstract
Objective: To determine the triplex ultrasound features of thyroid disease that can help in discriminating between malignancy and benignity relative to histopathological results.
Patients: A total of 61 patients underwent triplex US of the thyroid and histopathological examination.
Methods: The number, size, location, echogenicity, echotexture, microcalcification, halo and margins, regional lymphadenopathy, peak systolic velocity and vascular flow pattern of thyroid lesions were determined on the basis of patient age, sex, and histopathological results.
Results: Eighty percent of patients had benign disease, and 11.4% had malignant disease. Nodules in four patients appeared to be inadequately diagnosed. Fifty-seven percent of patients with malignant thyroid nodules had papillary thyroid carcinomas, whereas forty-two had anaplastic carcinomas.

Keywords: Triplex Ultrasound, Thyroid, Malignancy, Benignity

I. Introduction

The largest endocrine gland (thyroid gland) in the body. The initial application of sonography for the evaluation of the neck, more than 40 years ago, was to differentiate cystic and solid thyroid nodules. With improvements in technology, ultrasound has been applied to characterize distinct features associated with the appearance of thyroid nodules. Thyroid nodules are very common. They are found in 4% to 8% of adults by means of palpation and in 10% to 41% of adults by means of US [(1)].

Important elements in patients' history that increase the likelihood of malignancy include a history of head and neck irradiation (especially during childhood, with a relative risk of 8.7 at 1 Gy for X-rays and gamma radiation); reports of rapid growth, dysphagia, dysphonia, male sex, and presentation at extremes of age (less than 20 years or more than 70 years); and a family history of medullary thyroid carcinoma or multiple endocrine neoplasia[(2,3)]. The thyroid gland appears as a homogenous, medium-level echotexture. Anatomic landmarks are best defined on transverse sections: the thyroid gland is located between the common carotid artery laterally and the trachea medially.

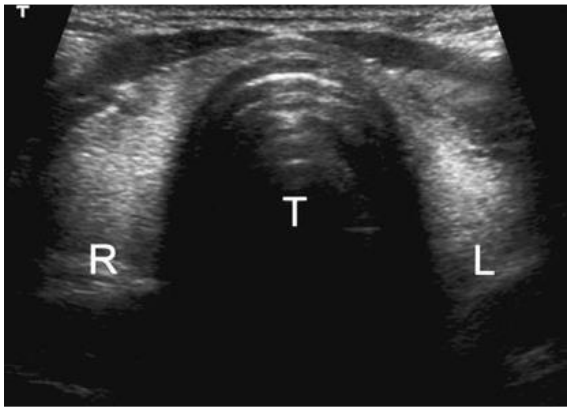

Fig 2 Ultrasound scanning. Transverse scan of a normal thyroid. R, right lobe; L, left lobe; T, trachea.

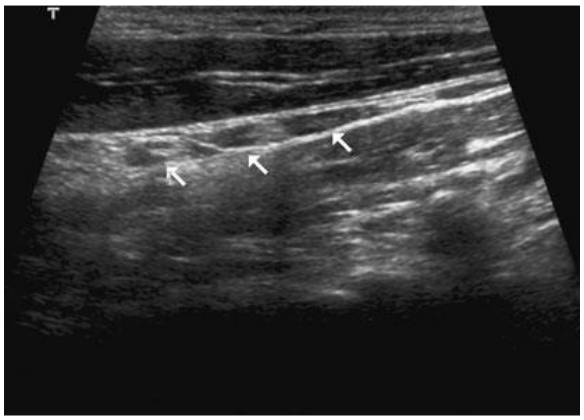

Fig 3 Ultrasonic scanning longitudinal scan of normal jugular lymph nodes (white arrows)

The risk of malignancy is similar in patients with multiple nodules and those with single nodules. The number of nodules present has not been shown to be correlated with the risk of malignancy. ([4, 5] Each nodule should be evaluated independently. In patients with more than one nodule greater than 1 cm, FNA should be guided by ultrasound characteristics suspicious for malignancy rather than size. ([6,7] Patients with Hashimoto's thyroiditis may have up to a 60-fold increase in the risk of developing lymphoma[8,9]. The ultrasound findings included ill-defined hypoechoic areas separated by echogenic septa. Purely cystic lesions are nearly uniformly benign; however, these comprise only 2% of all cystic lesions [10]. Approximately 15% of cystic nodules represent necrotic papillary cancers, most of which decrease in size over time or completely disappear[11]. MTC accounts for 5% of thyroid cancers. They arise from parafollicular C cells, which are primarily concentrated in the superior poles[12].

Lymphoma involving the thyroid gland is rare, accounting for less than 5% of all thyroid malignancies. [13] It may be primary or arise as part of a systemic lymphoma. Women are more often affected, and the age at diagnosis is usually greater than 50 years. Metastases to the thyroid gland are uncommon and usually arise from primary melanoma or breast, lung, or renal cell carcinoma. [14,15].

Ultrasonography is the imaging study of choice for thyroid nodules. It can identify nodules that are too small to be palpated, the presence of multiple nodules, and central or lateral neck lymphadenopathy, provides accurate measurements of nodule diameter, and recommends thyroid ultrasound for all patients with suspected thyroid nodules,[16,17] including patients with palpable abnormalities, nodular goiters, and thyroid lesions found incidentally on other imaging modalities.

II. Methodology

The study sample consisted of 61 patients with suspected thyroid nodules who presented at the imaging center at Sulaimani teaching hospital. Demographic information, including sex and age, was collected. A detailed history was taken, with special emphasis on enlarging the neck mass, voice changes, dysphagia, weight loss, a family history of thyroid illness and a history of neck and head irradiation. In patients with multiple nodules greater than 1 cm, each nodule was evaluated independently, and ultrasound-guided FNA was performed on the basis of ultrasound characteristics suspicious for malignancy rather than size. If multiple enlarged nodules were present and none of them displayed suspicious findings on ultrasound, the largest nodules were sampled. The ages of the patients in our study ranged from 20–80 years. The sample included 12 males and 49 females. Conventional and pulse-color-flow Doppler ultrasonography of the thyroid gland was performed in all patients by the same examiner via digital ultrasonography equipment (Medison, Sonace L 8000) with a 7.5 MHz linear transducer.

The patient should wear comfortable, loose-fitting clothing for ultrasound examination, and the patient may need to remove all clothing and jewelry in the area to be examined. No other preparation is needed. The method used to scan the thyroid (position of the patient) was as follows: supine position, no pillow or rolled towel behind with the chin up to extend the neck, and no hyperextension of the neck.

Full sweeps of the thyroid should be performed starting in the transverse plane and beginning midline transverse over the isthmus. Next, the images of both the right and left lobes were scanned from superior to inferior. Measurements should be taken at the middle portion of the thyroid. Longitudinal images of the right and left lobes from lateral to medial should be taken, followed by measurements taken at the middle portion of each thyroid lobe. The patients' heads should turn to the left and right to see the lower poles and substernal area. Angle below the sternum or clavicle.

Parameters such as the size of the lesion, solitariness, echogenicity, echotexture margin, presence of a halo, presence or absence of calcifications, vascular flow pattern, peak systolic velocity resistive index, and regional lymphadenopathy. The echogenicity of each lesion was classified as hypoechoic, hyperechoic, or isoechoic in comparison with the background thyroid tissue. The internal architecture was defined as solid, predominantly solid with cystic components, or predominantly cystic.

Cystic lesions are those containing cystic components that constitute more than 50% of a nodule. A smooth margin was considered when a clear demarcation with a normal thyroid was observed, and an irregular margin was considered when more than 50% of the border of the lesion was not clearly demarcated and/or when there was any focal irregularity. The perinodular hypoechoic halo represents the thyroid parenchyma

compressed by a slow-growing process and presumably benign. The presence of a complete or incomplete hypoechoic halo around each lesion was also examined. Microcalcifications are defined as punctuate echogenic foci measuring less than 1 mm (18). Because of their small size, they do not produce acoustic shadowing. The predominant flow pattern was classified as absence of flow, perinodular flow or intranodular flow. If a nodule showed both intranodular and perinodular blood flow, it was classified as having intranodular blood flow.

The inferior thyroid artery was examined in the oblique transverse plane, close to the transition between the middle and the inferior third of the thyroid, and the peak systolic velocity in the inferior thyroid artery was measured in all patients. The PSV values for the inferior thyroid artery ranged from 24.9–46 cm per second. A high peak systolic velocity was considered high when it was above 40 cm per second. Ultrasound is also useful in identifying cervical lymph nodes. Normal lymph nodes have a typical appearance with an echogenic central hilus surrounded by a hypoechoic cortex. When lymph nodes are involved in thyroid cancer, the normal architecture is converted to a heterogeneous texture with possible calcifications, cystic spaces, or peripheral vascularity.

Biopsies were performed with a 23-gauge needle. One to three passes were performed for each nodule. The aspirated contents were expelled onto glass slides. The aspiration samples were classified by a pathologist as malignant, benign, inadequate or suspicious. The ultrasonographic features of the benign and malignant nodules were compared and analyzed.

III. Results

The ages of the patients with benign and malignant nodules ranged from 20–65 and 36–80 years, respectively. The benign nodule group included 49 patients, 3 males and 46 females, and the malignant nodule group included 7 patients, 6 males and 1 female (Table 1).

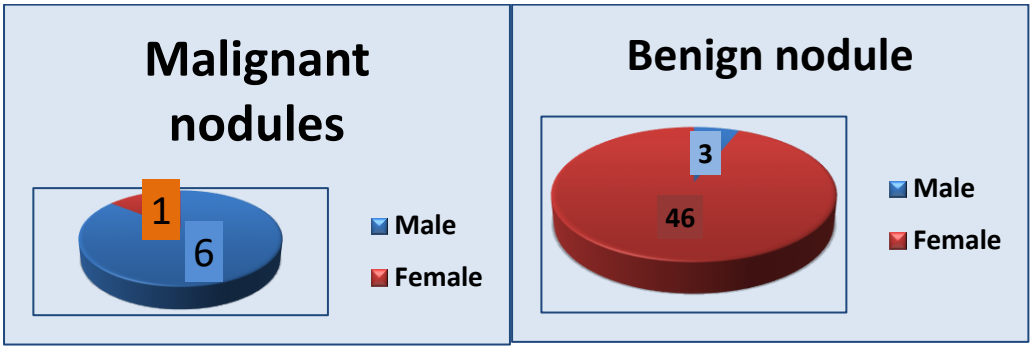

Table 1: Different results between solitary and multiple thyroid nodules

Number of lesion	Results				Total
	benign	malignant	suspicious	inadequate	
solitary	5	1	1	2	9
Multiple	44	6	0	2	52
Total	49	7	1	4	61

The nodules in four patients appeared to be inadequate for diagnosis. Finally, one patient appeared as a suspicious lesion. The age of the patients with thyroid carcinoma ranged from 36–80 years. In terms of sex, 6/7 (85.7%) of the patients with thyroid carcinoma were males, whereas 1/7 (14.2%) were males.

The sizes of the benign and malignant nodules ranged from 9–70 mm and from 14–60 mm, respectively. Among the 61 nodules, 9/61 (14.8%) were solitary, whereas 52/61 (85.2%) were multiples (Table 1). Among the 49 benign nodules, 5 (10.2%) were solitary, and 44 (89.7%) were nonsolitary. Among the 7 malignant nodules, 1 (14.2%) was solitary, and 6 (85.7%) were non-sentitary. Four nodules had inadequate diagnoses (6.5%), two were solitary, and the last two were multiple. One of the solitary nodules was suspicious (Table 1).

Table 2: Frequency of US features in benign and malignant nodules

US features	*Benign*		*Malignant*	
	NO	*%*	*NO*	*%*
Echogenicity				
Hypoechoic	9	18.3	5	71.4
Isoechoic	25	51	2	28.5
Hyperechoic	15	30.6	0	0
Echotexture				
Solid	10	20.4	6	85.7
Solid with cystic element	32	65.3	1	14.2
Predominantly cystic	7	14.2	0	0
Margin				
Smooth	44	89.7	1	14.2
Irregular	5	10.2	6	85.7
Calcification				
Absence of calcification	43	87.7	3	42.8
Microcalcification	0	0	4	57.1
Coarse calcification	2	4	0	0
Peripheral calcification	4	8.1	0	0
Flow pattern				
Absence of flow	27	55.1	2	28.5
Perinodular flow	14	28.5	1	14.2
Intranodular flow	8	16.3	4	57.1
Halo				
Absence of halo	14	28.5	6	85.7
Complete uniform halo	35	71.4	0	0
Incomplete halo	0	0	1	14.2

Among the 49 benign nodules, 9 (18.3%) were hypoechoic, and 40 (81.6%) were nonhypoechoic (25 isoechoic, 15 hyperechoic). Among the 7 malignant nodules, 5 (71.4%) were hypoechoic (Figure 3), and 2 (28.57%) were isoechoic. With regard to the frequency of hypoechogenicity (Table 2), there was a statistically significant difference between the groups. Among the 49 benign nodules, 10 (20.4%) were solid, 32 (65.3%) were predominantly solid, and 7 (14.28%) were predominantly cystic. Among the 7 malignant nodules, 6 (85.7%) were solid, and 1 (14.28%) was predominantly solid with a cystic element (Table 2). With regard to the frequency of solid echostructure (Table 2), there was a statistically significant difference between the groups. Among the 49 benign nodules, 5 (10.2%) had irregular margins, and 44 (89.7%) had smooth margins. Among the 7 malignant nodules, 6 (85.7%) had irregular margins, and 1 (14.28%) had a smooth margin. With respect to the frequency of irregular margins (Table 2), there was a statistically significant difference between the groups. In 43 (87.7%) of the 49 benign nodules, no calcification was present. In 4 (8.1%) of the benign nodules, peripheral calcification was detected, and in 2 (4%) benign nodules, coarse calcification was detected. In 3 (42.8%) malignant nodules, no microcalcifications were present, whereas microcalcifications were detected in 4 (57.1%) malignant nodules. With respect to the presence of microcalcifications (Table 2), there was a statistically significant difference between the groups.

Tables 3 and 4 **show the differences.**

Type	Halo				Flow pattern					
	Absent		Complete		Absent		Intranodular		perinodular	
	No.	%	No.	%	No.	%	No.	%	No.	%
Malignant	6	85.5	0	0	2	28.5	4	57.1	1	14.2
Benign	14	28.5	35	71.4	27	55.1	8	16.3	14	28.5

In 27 (55.1%) of the 49 benign nodules, no vascular flow was detected via color Doppler sonography. Perinodular

Type	Echogenicity						Echotexture					
	Hypoechoic		Isoechoic		Hyperechoic		Solid		Solid with cystic component		Predominantly cystic	
	No.	%	No	%	No.	%	No.	%	No.	%	No.	%
Malignant	5	71.4	2	28.5	0	0	6	85.7	1	14.2	0	0
Benign	9	18.3	25	51	15	30.6	10	20.4	32	65.3	7	14.2

flow and intranodular flow were detected in 14 (28.5) and 8 (16.3%) benign nodules, respectively. In 2 (28.5%) of the 7 malignant nodules, no vascular flow was present. Perinodular flow and intranodular flow were detected in 1 (14.2%) and 4 (57.1%) of the malignant nodules, respectively. With respect to the presence of intranodular flow (Tables 2, 4), the differences between the groups were statistically significant.

Tables 5 and 6: Comparison.

Echogenicity	Our results		Ameer et al results	
	No.	%	No.	%
Hypoechoic	9	18.3%	12	14.2%
Isoechoic	25	51%	21	25%
Hyperechoic	15	30.6%	51	60.7%
Total	49	100%	84	100%

Thyroid carcinoma	Our results		Ameer et al results	
	No.	%	No.	%
solitary nodule	1	11.1	4	12.5
Multiple nodules	6	11.5	1	3.8

In 14 (28.5%) of the 49 benign nodules, no halos were present. In the remaining 35 (71.4%) benign nodules, a uniform halo was present. In 6 (85.7%) malignant nodules, no halo was present. Only one (14.2%) malignant nodule had an incomplete halo. With respect to the absence of a halo (Tables 2, 4), the difference between the groups was statistically significant. In 1 of the malignant nodules (14.2%), invasion of the adjacent muscle was observed. Four of the malignant nodules (57.7%) were lymphadenopathies found at level 3, and these nodes were rounded in shape, with sizes ranging from 15–29 mm. microcalcifications and cystic changes were detected in 1 of them (25%). One benign nodule was lymphadenopathy, and the histopathological results revealed reactive sinus hyperplasia.

IV. Discussion

Thyroid nodules are common, and the majority are benign. Once detected, there is a need to distinguish benign from malignant nodules. A realistic goal is to utilize diagnostic tests that will either identify a cancer or reduce the probability of cancer to an acceptable level. To define what is acceptable, one first needs to consider the risk of

thyroid cancer in the general population. Given that there is no screening programme for thyroid cancer, an acceptable level cannot be lower than the risk for the general population (approximately 1:1000) (19,20).

The incidence of malignancy in our sample was 11.4%, whereas that of benign lesions was 80.3% (tables 7 and 8). In reference to Table 6, there is no difference in the incidence of malignancy between solitary and malignant nodules, in contrast to the Ameer et al. study; thus, our results are consistent with those of the Mandel SJ study (6). The incidence of malignancy was greater in males (85.7%) than in females (14.3%) (Table 7). This finding indicates that male sex may be a risk factor for thyroid malignancy. Our results revealed that the size of the benign nodules ranged from 9–70 mm, whereas the size of the malignant nodules ranged from 14–60 mm; therefore, the size of the nodule was not significantly predictive of malignancy; our results are concordant with the results of several studies, namely, Goong and Papini E (21–23). These studies revealed that the risk of malignancy for large thyroid nodules is approximately similar to the incidence of nodules smaller than 1 cm.

Two of the nodules involved the isthmus, whereas the rest involved the lobes Our results revealed that 5/49 of the benign nodules were solitary (10.2%) and that 1/7 of the malignant nodules were solitary (14.2%). Thus, when we compared our results with those of the Mandel SJ study regarding solitariness, there was no significant difference between the groups, and most of the thyroid nodules were benign, with approximately 10% of the nodules representing malignancy. The risk of malignancy of a nodule in a multinodular thyroid is similar to that of a solitary thyroid nodule. (6) In our study, the echogenicity of 5/7 malignant nodules (71.4%) was hyperechoic (Table 2), and in reference to Table 14, page 84, Ameer et al. (24) reported that the echogenicity was hyperechoic in 4 malignant nodules (80%). Thus, both results confirmed the significance of hypoechogenicity in the detection of malignant thyroid nodules, while the frequency of nonechoicity in benign thyroid nodules was 40/49 (81.6%). Our results revealed that 6/7 of the malignant thyroid nodules were solid (85.7%). Thus, a comparison of our results with those of Cappelli C, Castellano M, Pirola I, et al. (17), and Koike E, Noguchi S, Yamashita H, et al. (13) revealed that 121 of 148 (81.8%) histopathologically malignant nodules with solid malignancy were more closely associated with solid nodules. (21–25), compared with cystic or mixed nodules. One of the 7 malignant nodules (14.2%) had cystic components. Therefore, malignant thyroid nodules may have cystic components in the context of multinodular goiters (Table 2) (26). In 35/49 of the benign nodules (71.4%), a uniform halo was detected, whereas in 6/7 of the malignant nodules (85.7%), an absence of a halo was detected. Benign lesions are often associated with a hypoechoic circumferential halo, which is believed to represent a capsule and compressed thyroid tissue (23). Neoplasms may have a partial or absent halo (24) (Table 2). Among the benign nodules, 89.7% had smooth margins, whereas 85.7% of the malignant nodules had irregular margins. Irregularity or ill-defined margins have been associated with an increased risk of malignancy (21–29). Our results revealed that microcalcifications occurred in 4 malignant nodules (57.1%). By comparing our results with those of Kim EK, Park CS, Chung WY, et al. (21) and Bonavita JA, Mayo J, Babb J, et al. (28), 45% to 60% of the malignant nodules presented microcalcifications, whereas 7% to 14% of the benign nodules presented microcalcifications(21–29). Cappelli C, Castellano M, Pirola I, et al. (17) reported that microcalcifications are strongly associated with an increased risk of malignancy(17). Seiberling by KA, Dutra JC, Grant T, et al. (30) reported that approximately 60% of patients with microcalcifications have malignant disease. The presence of microcalcifications in malignant nodules is often attributed to psammoma bodies in papillary thyroid carcinoma (PTC). Asteria C, Giovanardi A, Pizzocaro A, et al. (31) and Iannuccilli JD, Cronan JJ, Monchik JM (32) reported that the overall specificity of microcalcifications for thyroid cancer and the overall specificity of microcalcifications for thyroid carcinoma ranged from 71% to 94%, with a sensitivity ranging from 35% to 72% (33–35). In our results, 43 benign nodules (87.7%) had no calcification, and 4 benign nodules (8.1%) were present. In reference to Table 15, page 86 of Ameer et al. (24) reported that 17 benign nodules (32%) had coarse calcification, and 2 (3.7%) benign nodules had peripheral calcification (eggshell calcification). Peripheral calcification (eggshell) is considered a benign feature that represents previous hemorrhage and degenerative changes.

Our results revealed that the frequency of perinodular flow14 (28.5%) was greater than that of intranodular flow8 (16.3%) among benign nodules, where the frequency of intranodular flow4 (57.1%) was greater than that of perinodular flow1 (14.2%) Papini E, Guglielmi R, Bianchini A, et al. (23), Frates MC, Benson CB, Charboneau JW, et al. (26), Rago T, Vitti P, Chiovato L, et al. (36) and Chan BK, Desser TS, McDougall IR, et al. intranodular flow is more common than perinodular flow and is found in 67–84% of malignant nodules (6,7,13,14). Therefore, our

flow pattern results are very concordant with the above results. It was observed in 1 case of malignant nodules (14.2%), so it is a pathognomonic feature of malignant nodules (37–39). Four of the 7 malignant nodules (57.1%) were enlarged and rounded with heterogeneous echogenicity and an absent central hilus at level III (Table 7). In one of them (25%), we detected microcalcification and cystic changes in the lymph nodes of patients with anaplastic carcinomas. The incidence of malignant lymph nodes is much greater in PTC than in anaplastic carcinomas (38–43). LeBoulleux S, Girard E, Rose M, et al. and Kuna SK, Bracic I, Tesic V, et al. (37) reported that the incidence of malignant lymph nodes is much greater in levels III, IV, and VI than in level II, and the sensitivity of a rounded shape, an absent hilus, and heterogeneous echogenicity raise the suspicion of malignancy (37,38). Therefore, our results are significant. One patient with PTC metastasized and presented with a sternal mass (Table 7) (44–46).

V. CONCLUSION

Thyroid nodules are common entities, and the majority of thyroid nodules are benign, and their incidence increases with age. Once they are detected, there is a need to distinguish benign from malignant nodules. The obtained results provide a rationale for using features from US examinations, such as hypoechogenicity, solid echotextures, irregular margins, microcalcification, intranodular flow patterns, and the absence of halos in selecting nodules for FNA. However, these features should be considered to have different predictive values in diagnosing malignancies. Our results revealed that the degree of malignancy in a nodule is similar between solitary and multiple thyroid nodules. Ultrasound features that raised the suspicion of malignancy were hypoechogenicity, solid echogenicity, irregular margins, the absence of a halo in the presence of microcalcification and an intranodular flow pattern. The common belief that the presence of multiple nodules decreases the likelihood of malignancy is contradictory. Color Doppler US can predict thyroid cancer when the flow is predominantly in the center portion of the nodule. US complements FNA, and vice versa. Nodule size is not predictive of malignancy. Pulse Doppler is not helpful.

Recommendations:

We recommend the following:

1. Routine use of color flow doppler in management of thyroid nodules .
2. The criteria for nodule selection for FNA were chosen on the basis of the risk of cancer associated with the US features.
3. A plan for a thyroid center.
4. Surgeons should consider new management strategies for thyroid nodules.
5. An epidemiological study for thyroid disease in sulaimani . As research continues and more information is obtained, recommendations regarding US-guided FNA of the thyroid may change.

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