

# The Role of Ultrasound in the Diagnosis of Malignant Thyroid Nodules

DOI: <https://doi.org/10.32007/jfacmedbagdad.6231772>

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## Abstract

**Background:** Thyroid nodules are very common in clinical practice. Although most of thyroid nodules are benign, it is crucial to check out which nodules are more likely to be malignant. Ultrasound is a major diagnostic tool for screening and evaluating thyroid diseases because it is safe, non-invasive, non-radioactive and effective.

**Objective:** The aim is to identify the role of ultrasound in assessing thyroid nodules and to review various ultrasound criteria predicting malignancy.

**Patients and methods:** A case series study conducted during the period from January 2015 to February 2016 at the First Surgical Unit, Department of Surgery, Baghdad Teaching Hospital by a team of surgeons. One hundred eighty Patients who underwent surgical intervention for nodular thyroid disease were included in the study. The ultrasound features of these patients were analyzed with respect to the number of nodules (solitary or multiple), size, echogenicity, consistency, the presence of calcification, border definition, vascular pattern and whether there was lymphadenopathy and / or local invasion to adjacent structures. The final diagnosis was confirmed by histopathological examination after surgery. The ultrasound features of thyroid nodules were studied for their correlation with benign and malignant lesions.

**Results:** Among 180 patients with nodular thyroid disease, thyroid malignancy was found in 22 (12.2%) patients. Ultrasound features of thyroid nodules included significant echogenicity, consistency, calcification, border definition, vascular pattern and the presence of local invasion. Ultrasound features suggesting malignant nodules are solid and hypoechoic nodules, ill-defined borders, nodules with local invasion to adjacent structures, the presence of microcalcification and nodules that show increased vascularity on doppler study.

**Conclusion:** Ultrasound is useful in evaluating nodular thyroid disease and is valuable for identifying many malignant and potentially malignant nodules. Despite that, no single ultrasound feature is reliable in making the diagnosis of thyroid malignancy, combining ultrasound suggestive criteria could aid in predicting malignant nature of a given nodule.

**Key words:** Thyroid nodule, Multinodular goiter, Ultrasound, Thyroid malignancy

*JFac Med Baghdad*

2020; Vol.62, No. 3

Received: July 2020

Accepted: Sept. 2020

Published: Nov. 2020

## Introduction:

Thyroid malignancy is the fifth leading cause of cancer in women, is responsible for 5% of all newly diagnosed cancers, is the most common endocrine malignancy and is a rapidly rising cancer in both genders.<sup>1</sup> Its incidence is increasing worldwide. Approximately 5% of women will harbor a palpable thyroid nodule. Between 19 and 67% of patients will have an incidental thyroid nodule detected on ultrasound.<sup>2</sup> Thyroid nodules are pretty common, detected by palpation in 4-7% of the asymptomatic population. Most thyroid nodules are non-malignant,

while 4-14% are. Therefore, it is important to identify the nodules which are more likely to be malignant.<sup>3, 4, and 5</sup>

Ultrasonography is a crucial diagnostic tool for checking and evaluating thyroid disease,<sup>6</sup> and is the primal choice for detecting thyroid abnormality because it is safe, non-invasive, non-radioactive and effective.<sup>7</sup> The use of ultrasound for evaluation of the thyroid gland has led to the discovery of a large number of non-palpable thyroid nodules in the general population. In addition, ultrasonography of the carotid arteries and other structures in the neck has also led to incidental finding of thyroid nodules. When such non-palpable nodules are taken into account, the prevalence of thyroid nodules may reach 70% in the general adult population. Although only around 5% of these nodules will represent malignant disease upon further investigation, the main concern

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in evaluating thyroid nodule is the differentiation of whether a lesion is benign or malignant, as more aggressive therapy is needed for malignancies.<sup>8,9,10</sup> Thyroid ultrasonography can verify simple cysts from solid nodules, determining the size of nodules during follow-up, and allow fine needle aspiration cytology (FNAC). In addition, the non-invasiveness ultrasonography has increased clinical application of this method for the evaluation of thyroid nodules and the recently updated guidelines for thyroid nodule management suggests an initial and important role of this device.<sup>8</sup> Sonographic manifestations of potentially malignant thyroid nodules include microcalcifications, hypoechogenicity, ill-defined margins and increased vascularity. Although the individual ultrasonic outlines may be of limited value, but when multiple features appear in combination it is possible to make a rather accurate prediction and such nodules should be later assessed with FNAC.<sup>11</sup> However, ultrasound is still not sufficiently specific to determine malignancy.<sup>12</sup> A clearer understanding of the ultrasound features predictive of malignant or benign disease may avoid costly confirmatory investigations and have a large impact on both guideline recommendations and clinical practice.<sup>13</sup> Due to the increased use of ultrasonography and the more access to cytology analysis through FNAC guided by ultrasound, the number of small-sized thyroid gland malignancy diagnoses has increased. So, carcinomas less than 1 cm in diameter is being detected more frequently. They are usually diagnosed in an unexpected way (incidentalomas) by ultrasound or histopathology of surgically excised glands in cases with benign presentations, such as airway obstruction, large goiter, and uncontrolled hyperthyroidism.<sup>14,15</sup> Thyroid Imaging Reporting and Data System (TIRADS) has been introduced in 2009 by Horvath et al.<sup>16</sup> to group thyroid lesions in different categories with a percentage of malignancy similar to those accepted in the Breast Imaging Reporting and Data System (BIRADS). According to that, the BIRADS established a worldwide accepted clinical management. This system was modified in 2011 by Kwak et al.<sup>17</sup> to help categorize nodules and stratify their malignant risk.

The aim of the study is to address the role of ultrasound in assessing thyroid nodules and review various ultrasound criteria predicting malignancy, to avoid extensive and costly evaluation in most patients with benign disease without missing a minority of patients who have thyroid malignancy.

#### Patients and methods:

This 14-month case series study was conducted during the period from the January 2015 to February 2016 at the first Surgical Unit, Department of Surgery in Baghdad Teaching Hospital. One hundred and eighty-nine patients were subjected to surgery for different thyroid diseases. Exclusion criteria included patients with diffuse goiter (three patients) and those diagnosed preoperatively with thyroid malignancy by FNAC (six patients), so only 180 patients with

nodular thyroid disease were included in the study. All patients were subjected to preoperative thyroid ultrasound, thyroid function tests, FNAC, chest X-ray and indirect laryngoscopy to evaluate the mobility of the vocal cords. FNAC was performed by a cytologist either by palpation for palpable thyroid nodules or randomly for non-palpable ones (i.e. not under ultrasound guidance). All ultrasound examinations were done in the outpatient clinic in Baghdad Teaching Hospital, performed by specialist sonologists using ultrasound device (Philips HD 11xe 2011), with 5-7.5 MHz probe and vascularity was assessed using doppler study.

The surgical operations performed were total thyroidectomy, near total thyroidectomy, lobectomy and subtotal thyroidectomy. Ultrasound was interpreted in terms of:

Number of nodules: Either single or multiple. In case of multinodular goiter, in the present study the dominant or most suspicious nodule was included.

Size of nodules: Categorized into four groups, <1 cm, 1-1.9 cm, 2-4 cm,  $\geq$  4cm.

Echogenicity: Whether the nodule is isoechoic (compared to the normal tissue of thyroid), hypoechoic (compared to normal thyroid tissue) or hyperechoic.

Consistency: Whether solid, cystic or complex.

Calcification: If present, it is classified into microcalcification (tiny, punctate echogenic foci of  $\leq$ 1 mm with or without posterior shadowing), or macrocalcification (punctate echogenic foci >1 mm in size).

Border definition: Whether well-defined or ill-defined.

Vascular pattern: Hypervascular, hypovascular or normal thyroid tissue like vascularity.

Lymphadenopathy: Regional cervical lymph nodes that showed malignancy feature are included in present study, which are: Distorted hilar line, jugular deviation or compression, microcalcifications, cystic necrosis and chaotic vascularity.

Local invasion to adjacent structures.

The histopathological diagnosis after surgery was considered to be the gold standard reference test.

#### Statistical analysis

The Statistical Package for Social Science (SPSS) version 20 was used for data entry and analysis. Tables and graphs and were used to describe the data and suitable statistical tests were used accordingly. The Chi-Square test and Fisher's Exact Probability test were used to test the association between variables, the independent T test and ROC curve were also used. A P value of < 0.05 was considered to be statistically significant. The study had passed the ethical committee requirements in Baghdad Teaching Hospital and the Arab Board of Surgical Specialization committee agreement for conducting present study. All the patients have approved to be involved in the study.

#### Results:

The present study was a cohort of 180 patients who underwent surgical treatment for nodular thyroid disease with 146 (81.1%) females and 34 (18.9%) males. The results of histopathological examination revealed that 158 patients had benign nodules (87.8%) and 22 patients had thyroid malignancy (12.2%). Out of the 22 patients with malignant nodules, 19 patients (10.6%) had papillary carcinoma, two patients (1.1%) had follicular carcinoma and one patient (0.6%) had anaplastic carcinoma.

The mean age of patients with benign nodules was  $39.4 \pm 9.9$  years and that of patients with malignant nodules was  $44.7 \pm 10.8$  years with a statistically significant difference ( $p=0.03$ ). Gender showed no statistically significant association with the nodule being benign or malignant ( $p=0.3$ ).

Of patients with a single nodule 73.3% were benign and 26.7% were malignant, while in those with multiple nodules (multi nodular goiter), 92.6% were benign and 7.4% were malignant, ( $p=0.1$ ). The size of nodules, echogenicity, consistency, calcification, border definition and vascular pattern are depicted in the Table 1.

**Table 1: Distribution of ultrasound by histopathological findings**

Ultrasound Finding	Histopathology		Total	p-value
	Benign - No. (%) N=158	Malignant - No. (%), N=22		
Size (cm)	< 1	8 (72.7)	3 (27.3)	0.8
	1-1.9	31 (86.1)	5 (13.9)	
	2-4	61 (93.8)	4 (6.2)	
	>4	58 (85.3)	10 (14.7)	
Echogenicity	Isoechoic	28 (93.3)	2 (6.7)	0.001
	Hyperechoic	89 (100.0)	0 (0)	
	Hypoechoic	41 (67.2)	20 (32.8)	
Consistency	Solid	86 (86.9)	13 (13.1)	0.008
	Cystic	41 (100.0)	0 (0)	
	Complex	31 (77.5)	9 (22.5)	
Calcification	Absent	118 (89.4)	14 (10.6)	0.03
	Micro	25 (75.8)	8 (24.2)	
	Macro	15 (100.0)	0 (0)	
Border definition	Well	145 (91.2)	8 (8.8)	0.01
	Ill	13 (61.9)	14 (38.1)	
Vascular pattern	Hyper	27 (73.0)	10 (27.0)	0.006
	Similar	67 (89.3)	8 (10.7)	
	Hypo	64 (94.1)	4 (5.9)	
Lymphadenopathy	Present	12 (75.0)	4 (25.0)	0.1
	Absent	146 (89.0)	18 (11.0)	
Local invasion	Present	0 (0)	3 (100.0)	0.001
	Absent	158 (89.3)	19 (10.7)	

The sensitivity and specificity of each ultrasound findings as compared to histopathology results are summarized in (Table 2).

**Table 2: Sensitivity and specificity of ultrasound criteria as compared to histopathology results**

Ultrasound Test Variable(s)	Result	Sensitivity %	Specificity %
Number		45	79
Size		63	75
Echogenicity		90	82
Consistency		40	19
Calcification		66	65
Border Definition		76	80
Vascular Pattern		74	82
Lymphadenopathy		41	62
Local Invasion		86	90

Ultrasound features suggesting that malignant nodules are solid, hypoechoic nodules, those with ill-defined borders and nodules with local invasion to adjacent structures, in addition to the presence of microcalcification and nodules that show increased vascularity on Doppler study.

The frequency of patients having malignant nodules according to number of ultrasound supporting criteria is shown in (Table 4). The ultrasound findings results have revealed that only (13.6 %) of patients having malignant nodules have had five malignancy supporting criteria and just over a third (36.4%) had three criteria. In patients having benign nodules, the ultrasound results have revealed that (46.9%) had a single supporting criterion and (26.6%) had two criteria. One fifth of patients having benign nodules (19.6%) have not shown any malignancy supporting criteria according to ultrasound findings (Table 3).

**Table 3: Distribution of patients with malignant and benign nodules according to number of ultrasound supporting criteria**

Number of ultrasound supporting criteria	Patients with Malignant Nodules (%)	Benign Nodules (%)
5	3 (13.6)	0 (0.0)
4	5 (22.8)	1 (0.6)
3	8 (36.4)	10 (6.3)
2	3 (13.6)	42 (26.6)
1	3 (13.6)	74 (46.9)
0	0 (0.0)	31 (19.6)
Total	22	158

**Discussion:**

Although ultrasound findings of malignancy have low sensitivity and specificity, but the existence of hypoechoic nodule, ill-defined border, increased vascularity and the presence of microcalcification are considered to be the dependable predictors of malignancy.<sup>2</sup> Age and gender are the non-sonographic features included in the present study. There is no evidence of thyroid malignancies incidence being affected by age and gender<sup>3,8,18,19</sup>. It was accepted previously that solitary thyroid nodules are more likely to be malignant as compared to nodules in multinodular goiter, but many studies<sup>20,21</sup> denied this belief. The present study found that the occurrence of malignancy was not significantly associated with the nodule being a solitary one or otherwise, a multinodular goiter. The present study has shown that nodule size does not appear to be a significant predictor of malignancy. These results are similar to the results of Frates et al<sup>19</sup> who divided nodules into categories of size by 5 mm increments, but failed to demonstrate a significant relationship between nodule size and the likelihood of thyroid malignancy. Kim et al<sup>22</sup> found no significant difference in the incidence of malignancy among small thyroid nodules that were incidentally discovered by ultrasound examination. However, McHenry et al<sup>23</sup>, found that the mean size for benign thyroid nodules was larger than the malignant nodules, although not significantly so. This finding holds true across other studies.<sup>2,3,4,13,18</sup> In the present study, it was found that completely cystic nodules were never malignant. On the other hand, it was found that most of the benign nodules, as well as malignant nodules, were vastly solid. So, this component alone cannot be a useful criterion for the differentiation of malignant from benign nodules. This matches other studies<sup>19,24</sup> such as Frates et al.<sup>19</sup>, who stated that the more cystic a nodule the less likely it is malignant. Typically, malignant nodules are hypoechoic. In the present study the frequency of hypoechogenicity was significantly different between malignant (90.9%) and benign (26.0%) nodules. While (56.3%) of benign nodules were hyperechoic, none of malignant nodules were hyperechoic. The findings are in concordance with previous studies.<sup>4,19,22</sup> Different conclusions were found by Yoon et al.<sup>3</sup> and Iannuccilli et al.<sup>25</sup> An ill-defined or

irregular border is a general finding of malignancy. In the present study, border definition of thyroid nodules was categorized into well-defined and ill-defined, which was considered to be significant with a sensitivity of (76%) and specificity of (80%) in which an ill-defined border was found in (63.3%) of malignant nodules and just (8.2%) of benign conditions, while the majority of benign nodules had a well-defined border. Yunus et al<sup>11</sup> noticed that sensitivity ranges widely (53% to 89%) and Moon et al.<sup>24</sup> suggested that ill-defined borders are in favour of a diagnosis of malignancy. However, Frates et al<sup>19</sup>, did not find any correlation between margin definition and risk of malignancy.

Microcalcifications studied by ultrasound are generally accepted as the most reliable and sharp indicator of malignancy, because they mostly represent Psammoma's bodies<sup>6</sup> which are the general findings in papillary cancer and is a pathognomonic finding in malignant nodules compared to other malignant sonographic findings<sup>8</sup>. On the other hand macrocalcifications are usually irregularly shaped concretions secondary to tissue necrosis, also known as dystrophic calcifications, and are related to fibrosis and degeneration especially with long disease duration and usually related to benign conditions<sup>6,22</sup>.

Microcalcification was present in (15.8%) of benign nodules and (36.4%) of malignant nodules in the present study, while macrocalcification was present in benign nodules only. This difference was statistically significant and its sensitivity and specificity was around (65%). Yunus et al<sup>11</sup> stated that calcification had a specificity of (86%). A good number of studies have also shown a strong relationship between calcification and thyroid carcinoma. Kakkos et al<sup>26</sup> wrote that (54%) of thyroid nodules with calcification were malignant. Similar findings were reported by Taki et al<sup>6</sup> and Consorti et al<sup>27</sup> who reported an incidence of calcification of (39.4%) and (20.1%) in thyroid malignancy and benign goiter, respectively. Wang et al<sup>28</sup> also reported a close correlation between microcalcifications, detected by ultrasound, and carcinoma, with a specificity of (96.7%) and Chammas et al<sup>12</sup> reported a similar finding, thereby indicating that the presence of microcalcifications may be a specific predictor for thyroid carcinoma.<sup>29</sup> Color Doppler ultrasound is widely available and is a useful imaging technique for assessing the vascularity of thyroid nodules. In the present study, most of the malignant nodules have shown increased vascularity, while most benign nodules were either hypovascular or showed no change in vascularity compared with the surrounding thyroid tissue, this was statistically significant with a sensitivity of (74%) and a specificity of (82%). These findings are consistent with those revealed by other studies, as Yunus et al<sup>11</sup> showed that predominantly central blood flow patterns in solid nodules are indicators of malignancy. Papini et al<sup>20</sup> declared that in nonpalpable thyroid tumors, increased intra-nodular vascularization on color Doppler sonography as an individual feature

with a sensitivity of (74.2%) and a specificity of (80.8%) for thyroid cancer diagnosis, which were close to the results of the present study. Others 21,30 have noted that malignant thyroid nodules predominantly had central vascularization, whereas benign nodules predominantly had peripheral vascularization.

Involvement of regional lymph nodes is a specific sign of malignancy, which is seen most commonly with papillary carcinoma. Lymph node metastases in follicular thyroid carcinoma are very rare, even in highly invasive cases. Examination of the internal jugular chain of cervical lymph nodes, particularly on the ipsilateral side of a suspicious thyroid lesion, should be a routine part of ultrasound evaluations of the thyroid. Suspicious features of lymph node metastases include distorted hilar line, the presence of jugular deviation or compression, the presence of microcalcifications, the presence of cystic necrosis and those with chaotic vascularity. 31,32 In the present study the ultrasound features were not significant, in contrast to the study of Yoon et al. 33 who conducted their study on nodules 3cm or larger in size. This could be due to the limitation of nodule size and the involvement of a larger number of patients in their study.

Local invasion is an important sign of malignancy, suggestive clinical symptomatology includes dyspnea, hoarseness of voice, and dysphagia caused by direct invasion of the trachea or larynx, the recurrent laryngeal nerve, or the esophagus, respectively<sup>31</sup>. Ultrasound features of local invasion to adjacent structures was present only in malignant thyroid nodules, which was found to be statistically significant.

The majority of patients (72.8%) with malignant nodules had three or more sonographic predictors of malignancy, compared to only (6.9%) of patients with benign nodules. So ultrasound was useful, although not diagnostic, in predicting malignancy.

Using ultrasound guidance is the finest recommended method for FNAC, regardless of whether the nodule is palpable or not, and is mandatory for non-palpable nodules. Nodules lesser than 8 mm may not be aspirated because of the low rates of successful FNA. The use of ultrasound-guided FNAC allows precise aspiration of the nodule, reducing sampling error, and ensures that the solid portion of the mixed solid/cystic lesion is aspirated. The use of ultrasound guided FNAC decreases the rate of non-diagnostic aspirates from (20%) to (1–10%), enabling more accurate preoperative diagnoses, which would spare patients with benign lesions excisional surgery and allow more accurate planning of surgical procedures for patients with malignant disease<sup>21</sup>. FNAC of thyroid nodule has replaced blind surgical intervention as the procedure of choice in the diagnosis of thyroid nodule.<sup>4</sup> In addition, ultrasound guided FNAC can be used to aspirate abnormal lymph nodes and measuring the thyroglobulin in aspirates of abnormal lymph nodes has also been found to be of a sensitive adjunct to cytology<sup>21</sup>

One of the limitations in the diagnosis of thyroid malignancy in our hospital is that FNAC is performed either by palpation or done randomly without ultrasound guidance.

#### Conclusions:

Ultrasound is useful in evaluating nodular thyroid disease and is of value for recognizing many malignant and potentially malignant nodules. Despite that, not a single ultrasound feature is sufficiently reliable in making the diagnosis of thyroid malignancy, combining ultrasound suggestive criteria could aid in predicting the malignant nature of a given nodule.

#### Authors' contributions:

Tharwat Sulaiman: Study conception, Study design and Critical revision

Maan Sarsam: Acquisition of data, Analysis and interpretation of data and Drafting of manuscript

Ammar Noori: Analysis and interpretation of data and Drafting of manuscript

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## دور الفحص بالموجات فوق الصوتية في تشخيص عقيدات الغدة الدرقية الخبيثة

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الخلاصة

**الخلفية:** عقيدات الغدة الدرقية شائعة جدا في الممارسة السريرية. على الرغم من أن معظم العقيدات الدرقية هي حميدة، فمن المهم تحديد أي العقيدات أكثر احتمالية ان تكون خبيثة. الموجات فوق الصوتية هي أداة تشخيصية رئيسية لفحص وتقييم أمراض الغدة الدرقية.

**الهدف:** هو معرفة دور الفحص بالموجات فوق الصوتية في تقييم العقيدات الدرقية واستعراض صفات الموجات فوق الصوتية المختلفة لتوقع الاورام الخبيثة للغدة الدرقية.

**طرائق البحث:** أجريت هذه الدراسة المستقبلية خلال الفترة من بداية كانون الثاني 2015 إلى نهاية شباط 2016 في الوحدة الجراحية الاولى - مستشفى بغداد التعليمي من قبل نفس الفريق الجراحي. خضع 180 مريضا ومريضة لتدخل جراحي لأمراض الغدة الدرقية العقيدية وتم ادراجهم في الدراسة. وقد تم تحليل ميزات الموجات فوق الصوتية لهؤلاء المرضى. تم تأكيد التشخيص النهائي عن طريق الفحص النسيجي بعد الجراحة. وقد تم تحليل ميزات الموجات فوق الصوتية وعلاقتها مع الاورام الحميدة والخبيثة.

**النتائج:** من بين 180 مريضا يعانون من مرض الغدة الدرقية العقيدية، تم العثور على الورم الخبيث للغدة الدرقية في 22 مريضا (12.2%). كانت ميزات الموجات فوق الصوتية من العقيدات الدرقية التي تظهر دلالة إحصائية هي الكثافة، طبيعة الصدى، التكلس، وجود الاوعية الدموية، تعريف الحدود و الغزو المحلي.

**الاستنتاج:** الموجات فوق الصوتية مفيدة في تقييم أمراض الغدة الدرقية العقيدية وهي قيمة للتعرف على العديد من العقيدات الخبيثة. وعلى الرغم من ذلك، ال يوجد ميزة واحدة للموجات فوق الصوتية موثوقة في تشخيص الأورام الخبيثة للغدة الدرقية، والجمع بين هذه المعايير للموجات فوق الصوتية يمكن أن تساعد في توقع طبيعة هذه العقيدات.

**كلمات المفاتيح:** عقيدات الغدة الدرقية، مرض الغدة الدرقية العقيدية، الموجات فوق الصوتية، الاورام الخبيثة للغدة الدرقية.