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Prediction of Malignancy in Thyroid Nodules; A Retrospective Comparative Study

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ABSTRACT

Aims This study assessed the potential of malignancy in patients presenting with clinically solitary thyroid nodules and compared the histopathology of excised samples and sonographic characteristics and fine-needle aspiration cytology results.

Participants & Methods This retrospective study was conducted over three years on data from 140 patients attended general surgery outpatient departments at Al-Sader Teaching Hospital and a private clinic with different complaints of solitary thyroid nodules. The collected data included initial diagnoses according to the results of clinical assessment, ultrasound evaluation, fine-needle aspiration cytology, and histopathological examination.

Findings As confirmed by histopathological examination, the prevalence of malignancy in clinical solitary thyroid nodules was 9.29% with male patients affected more than females (15% vs. 8.33%). Clinical assessment was a poor predictor for malignancy, as it was associated with a low sensitivity rate (69.23%), which means high false negative results, despite its high specificity rate (92.91%). According to the ultrasound examination, most malignancies were found in solid and mixed nodules (85% and 15%, respectively) with a significant association between the nature of nodules and malignancy potential. Fine-needle aspiration cytology was the most sensitive and specific investigation of thyroid nodules, it combined both high sensitivity and specificity for diagnosing malignant thyroid nodules (90.91% and 97.65%) respectively. Positive and negative predictive values were 79.83% and 99.06% respectively with an overall agreement of 97.02%.

Conclusion Fine-needle aspiration cytology is a minimally invasive diagnostic tool for the early detection of malignancy among patients with solitary thyroid nodules, which combines high degrees of both specificity and sensitivity with a high accuracy rate of 97.02% comparable to histological examination.

Keywords Ultrasonography; Thyroid Nodule; Cytology; Thyroid Gland

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Introduction

Thyroid nodules are quite prevalent in the general population, with up to 4-8% of adult people having palpable nodules. Thyroid nodules are common in clinical practice, which can be dominant within a multinodular goiter or solitary within a "normal" thyroid gland. There has been an increase in the incidence of thyroid nodules in recent decades. Several factors are involved in the development of thyroid nodules, such as age ≥60 years old (age more than 60 years is associated with malignancy in solitary thyroid nodule (STN)), male gender (thyroid nodules are four times more in females; however, the incidence of malignancy in males is about twice in females), solid echo structure, microcalcification, fixed and cervical lymphadenopathy [1]. Thyroid nodules are a diagnostic challenge due to the need to exclude thyroid malignancy. Thyroid malignant tumors are not commonly aggressive, but thyroid malignancies account for more deaths than all other endocrine system malignancies. Also, the majority of thyroid nodules are asymptomatic and clinically, excluding a thyroid malignancy is of great importance. A thyroid nodule >1cm in diameter is usually palpable; however, detecting a nodule by palpation depends on the structure of the patient's neck, its location within the thyroid, and the examiner's experience [2].

The differential diagnosis of a thyroid nodule is of great importance, because malignancy necessitates surgery, whereas careful patient follow-up is essential in the case of benignity. Ultrasound (US) increases the detectable rate to 19-67% [3]. It is applicable to determine alterations in the size of nodules during follow-up or to find recurrent lesions in patients suspicious of thyroid malignancy; however, there are no specific US results that suggest malignancy and its reliability remains a subject of debate, because it depends on the sensitivity of the equipment and the operator's experience with the certain method.

A common presentation of thyroid nodular disease is a clinically STN, which are 4-9 times more common in women compared to men. This is an apparently isolated lump in the thyroid, although 23% turn out, on imaging, to be multinodular [4]. The main aim of evaluating STNs is to identify nodules with malignant potential.

The primary goal of evaluating a thyroid nodule is to exclude malignancy, which affects 5-15% of STNs and typically does not require surgery for benign STNs [5]. Management of STNs begins with a thorough history search for signs that imply malignancy, such as a previous history of neck irradiation, hoarseness of voice possibly caused by recurrent laryngeal nerve infiltration, and a family history of thyroid cancer or other endocrine illnesses [6, 7]. Additionally, inquiries should be made for any hyperthyroid and obstructive symptoms, such as stridor and dysphagia [8, 9].

Thyroid nodules and glands should be the main focus of a clinical examination of the neck, along with any cervical lymphadenopathy that may be present [7].

Thyroid US can identify whether the STN is a dominant nodule within a multinodular goiter and distinguish between solid nodules and thyroid cysts (23% of clinically diagnosed STNs are dominant nodules within a multinodular goiter) [4]. The medical literature exhibits some diversity and overlap among the US parameters associated with malignancy, indicating that fine-needle aspiration cytology (FNAC) is required in many patients [10, 11].

FNAC has been one of the most useful techniques and a gold standard for diagnosing thyroid nodules since the 1950s. In recent years, the importance of FNAC has grown in terms of treatment strategies and identifying the malignancy potential of thyroid nodules. FNAC is a cost-effective, simple, and quick method to perform procedure in outpatient departments, which is associated with excellent patient compliance and aims to identify nodules requiring surgery and those benign nodules observable clinically and reduce the overall thyroidectomy rate in those with benign diseases. It also offers specific diagnosis rapidly with minimal complications.

None of the diagnostic techniques used to reach the final diagnoses of thyroid tumors (such as US, scintigraphy, radiography, and suppression therapy) are reliable enough to distinguish between benign and malignant thyroid nodules on their own [9, 12]. In many cases, it is sufficient to figure out sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) indices for FANC and the final histology results, respectively. The sensitivity and specificity for FNAC in previous studies range from 65% to 98% for sensitivity and 73-100% for specificity [13, 14]. In the study by Gupta *et al.* [15], the sensitivity, specificity, and accuracy of FNAC for STNs were respectively 80%, 86.6%, and 84%, while they were respectively 79%, 98.5%, and 87%, in a study by Kessler *et al.* [16]. Gupta *et al.* [15] recommended FNAC as the first line investigation for the diagnosis of STN. Factors, such as inadequate sampling, natural difficulties of differentiation of malignant and benign follicular lesions, and inexperience of the cytopathologist can reduce the efficiency of FNAC. In the literature, the nondiagnostic test rates have been reported between 1.6% and 20% [14]. It is believed that a benign FNAC diagnosis needs to be viewed cautiously because false negative results may occur and these patients should be followed up and each clinical suspicion of malignancy even for benign FNAC needs surgery.

Considering the increasing prevalence rate of STNs, as well as the importance of their accurate and timely diagnosis to start appropriate therapeutic approach to reduce mortality rate, this study aimed to assess the potential malignancy in patients presenting with

clinically STNs and correlated the histopathology of excised samples with sonographic characteristics and FNAC results.

Participants and Methods

This retrospective study was conducted in Basrah on 140 cases with clinically STNs examined at general surgery outpatient departments at Al-Sader Teaching Hospital and a private clinic, utilizing US, FNAC, and histological examination from November 2020 to November 2023.

The patients' health records were used to collect data, including age, gender, initial diagnoses based on clinical examination, laboratory investigations, diagnostic procedures, and final diagnoses. Data on FNAC performance, cytological, and histological results were collected from the hospital's database.

FNAC results were classified as benign, suspicious, malignant, and cases with inadequate aspirate

The sensitivity, specificity, and positive and negative predictive values were calculated as follows:

Sensitivity=true positive (TP)/(TP+false negative (FN))×100%

Specificity=true negative (TN)/(TN+false positive (FP))×100%

Positive predictive value=TP/(TP+FP)×100%

Negative predictive value=TN/(FN+TN)×100

The data were analyzed using SPSS 20.0 by the Chi-square and Fisher's exact tests. P-values ≤0.05 were considered significant.

The study included adult patients with clinically confirmed STNs, who underwent US examination, FNAC aspiration, and histological evaluation. Children below 18 years old, patients with apparently diffused multinodular goiter by clinical examination and those with inconsistent or incomplete medical records were excluded from the study.

Findings

The patients' ages ranged from 20 to 60 years. Out of 140 patients, 20 were male and 120 were female. The overall prevalence of malignancy in clinical STNs was 9.29% (13/140), with a higher prevalence in male patients (15% in males vs. 8.33% in females). However, the difference between males and females was not significant (p-value=0.341).

Regarding female patients, those older than 40 years had a considerably greater prevalence of malignancy (8/60) than those (2/60) below 40 years (p-value=0.047). For male patients, there was no significant difference in this regard (p-value=0.89; Table 1). Based on clinical examination, malignancy was suspected in 18 cases (9 malignant and 9 benign), and a final histology evaluation revealed that only 9 of them were malignant. Also, 122 cases (4 malignant and 118 benign) were found with benign thyroid nodules, of whom 4 cases were found to be malignant. The sensitivity of clinical examination was 69.23%, specificity was 92.91%, and the positive predictive value was 50%, while the negative predictive value was 96.72% with overall agreement equal to 90.71%.

Table 1. Relationship between the frequency of patients' age, gender, and the classification of thyroid nodules, and final histological diagnosis of solitary thyroid nodules

Diagnosis	Histological diagnosis		
	Benign	Malignant	Total
Histological diagnosis			
Female			
<40 years	58(45.67)	2(15.38)	60
>40 years	52(40.94)	8(61.54)	60
Male			
<40 years	5(3.94)	1(7.69)	6
>40 years	12(9.45)	2(15.38)	14
Total	127(91.1)	13(8.9)	140
Clinical examination			
Malignant	9	9	18
Benign	118	4	122
Total	127	13	140

According to the US results, the clinically STNs were true solitary in 43.57% (61/140) and dominant nodule (among multiple ones) in 56.43% of the cases. The frequency of malignancy was higher in dominant nodules in comparison to true solitary ones, but the difference was not statistically significant (p-value=0.696). Regarding the nature of the nodules studied by US, almost all cystic swellings were benign, and approximately 85% of malignancies were in solid nodules followed by mixed or complex nodules (15%), and there was a significant association between the nature of nodules and final histological examination (p-value<0.001; Table 2). Regarding the nature of STNs, according to US findings, 35(27.56%), 51(40.16%), and 41(32.28%) cases histologically diagnosed as benign were solid, cystic, and mixed, whereas 11(27.56%), 0(40.16%), and 2(32.28%) cases diagnosed as malignant were solid, cystic, and mixed, respectively.

Table 2. Relationship between the number and nature of nodules by ultrasound (US) and FNAC results, and final histological diagnosis

Diagnosis	Histological diagnosis		
	Benign	Malignant	Total
Frequency of nodule by US			
True solitary	56(44.09)	5(38.46)	61(43.57)
Dominant (multiple)	71(55.9)	8(61.54)	79(56.43)
Total	127	13	140
STN nature by US			
Solid	35 (27.56)	11 (84.62)	46 (32.86)
Cystic	51 (40.16)	0 (0)	51 (36.43)
Mixed	41 (32.28)	2 (15.38)	43 (30.71)
Total	127	13	140
FNAC results			
Benign	83 (65.35)	1 (7.69)	84 (60)
Suspicious	38 (29.92)	2 (15.38)	40 (28.57)
Malignancy	2 (1.57)	10 (76.92)	12 (8.57)
Inadequate	4 (3.15)	0 (0)	4 (2.86)
Total	127	13	140

The most important method for evaluating thyroid nodules in this investigation was FNAC. There were four benign, suspicious, malignant, and inadequate aspirate categories that were used to characterize

FNAC results (Table 3). The results were benign in 60% of cases, suspicious in 28.57% of cases, malignant in 8.57%, and inadequate in 2.86% of studied cases. There was a significant association between the results of FNAC and the final histological examination (p-value<0.001; Table 2).

The sensitivity of FNAC in this study was 90.91% and specificity of 97.65%. Positive and negative predictive values were 79.83% and 99.06%, respectively, with an overall agreement of 97.02%.

Discussion

This study aimed at investigating the potential malignancy in patients presenting with clinically STNs and correlated the histopathology of excised samples with sonographic characteristics and FNAC results.

Thyroid nodules are prevalent thyroid issues, potentially affecting around half of the global population, as determined through US [3]. Despite the thyroid being the endocrine organ most commonly prone to malignant transformation, approximately 5-15% of solitary thyroid nodules are malignant [5]. Clinical examination of the thyroid focuses on whether the nodule is dominant or solitary in a multinodular goiter. Various diagnostic methods, including US, thyroid nuclear scan, and FNAC, are accessible to clinicians for assessing thyroid nodules; however, FNAC is regarded as the gold standard diagnostic tool for this purpose. The superiority of ultrasound examination of the thyroid over clinical assessment has been documented, and it has been reported that US leads to a change in management of 44% of patients referring for a solitary nodule on physical examination

FNAC is a simple, cost-effective, and rapid procedure conducted in the outpatient department, with high patient compliance. Key factors for obtaining accurate results include obtaining a representative specimen from the goiter and having an experienced cytologist interpret the findings. In the adult population, only 4-8% of thyroid nodules identified by ultrasound are palpable, with women being more susceptible to thyroid disorders compared to men [17, 18]. In our study, 9.29% of the 140 cases of clinical STNs were found to be malignant, which is in agreement with a previous study [19].

History and clinical examinations may not serve as reliable diagnostic predictors of malignancy, as most nodules are typically asymptomatic and are often incidentally discovered by physicians during examinations for other issues [19].

The gender disparity in thyroid cancer incidence, prognosis and aggressiveness is well established, but our understanding of the molecular factors mediating this variation remains poorly understood. While reproductive factors would appear to be a logical hypothesis to account for the gender disparity, there is no conclusive evidence that they increase the risk of developing thyroid cancer. Recent estrogen receptor-status studies in thyroid cancer cells demonstrate a difference in the receptor subtypes expressed based on the histology of thyroid cancer [20]. Male gender, microcalcification, age ≥60 years old, solid echo structure, cervical and fixed lymphadenopathy are significantly associated with malignancy in patients. In terms of gender, our study revealed a higher occurrence of malignant nodules in male patients, aligning with the findings of a study by Jena *et al.* [18]. Conversely, among female patients, the likelihood of malignancy increased with age (over 40 years). Therefore, male gender [21] and advancing age [22] should be regarded as significant indicators warranting a high level of clinical suspicion for malignancy. Thyroid nodules have been reported more common in third, fourth and fifth decades of life. Individuals aged 20 to 50 years are vulnerable to hormonal fluctuations, leading to a peak incidence during this age range. Nevertheless, malignancy rates are elevated at the extremes of age. Therefore, nodules appearing in these age brackets necessitate a comprehensive evaluation for malignancy [20].

All patients in this study underwent US evaluation, a cost-effective, readily available, and non-invasive diagnostic procedure. Numerous studies have previously explored the advantages of thyroid ultrasonography over clinical assessment [10, 11].

In this study, based on US examinations, 56.43% of clinically suspected STNs were identified as dominant nodules within a multi-nodular goiter. The prevalence of malignancy was higher in multi-nodular goiters compared to true STNs (61.54% and 38.46%, respectively), although this difference was not statistically significant. These findings contradict a recent meta-analysis from 2022, which reported a higher incidence of thyroid cancer in true STNs compared to multi-nodular goiters [13]. However, a retrospective study by Ajarma *et al.* demonstrated that patients with multi-nodular goiter had almost the same risk of cancer as those with true STNs [23].

While there is not a single characteristic with both high sensitivity and high predictability for malignancy, several US features, when observed together, are associated with an increased risk of malignancy [10, 11]. Nodule size alone does not serve as a predictor of malignancy, as the risk of cancer in thyroid nodules remains consistent irrespective of their size on US [24]. It is demonstrated that cancer in nodules <10mm is not less frequent, and when using this value as a cutoff, a significant proportion of cancers will be missed

In the current investigation, nodules were classified through US examination into solid, cystic, mixed, or complex compositions. Our findings indicated that the majority of cystic nodules were benign, while malignancies were predominantly found in solid nodules. These results align with prior research that classified solid nodules as intermediate to high-risk factors and cystic nodules as low-risk factors [7].

FNAC is widely recognized as a sensitive, specific, and cost-effective diagnostic tool for determining the necessity of surgery for STNs. Studies have demonstrated that the routine application of FNAC not only decreases treatment expenses but also minimizes the need for unnecessary procedures [23]. In this study, FNAC results indicated benign aspirates in 60% of cases, suspicious findings in 28.57%, malignancy in 8.57%, and inadequate samples in 2.86% of cases, with notable sensitivity and specificity values of 90.91% and 97.65%, respectively.

Although FNAC is the gold standard for the diagnosis of STNs, it cannot be considered a definitive diagnostic tool, particularly in places with endemic goiters [25], and it is recommended that a mix of diagnostic techniques be used to distinguish between benign and malignant tumors.

Deciding between conservative management and surgery depends on careful analysis of the clinical findings, imaging, risk assessment, and diagnostic testing. The management challenge is to detect benign nodules and accurately diagnose and treat malignancy early. Clinically, if malignancy is strongly suspected, surgery should be performed to rule out the possibility of malignancy.

Conclusion

FNAC is the most reliable and safe, delivering more particular information than other techniques.

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Ethical Permission: The study was approved by ethical committee of College of Medicine, University of Basrah. In this study, the ethical standards of the Declaration of Helsinki were observed.

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