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Diagnostic Efficacy of Ultrasonography and Fine-needle Aspiration Cytology in Correlation with Histopathology in Euthyroid Patients Having Solitary Thyroid Nodule

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Abstract: *Objective:* In patients with solitary thyroid nodules, first approach is to confirm whether the nodule is benign or malignant. Commonly available investigations used in the evaluation include thyroid hormone assays, fine needle aspiration cytology (FNAC) and ultrasonography (USG) among others. These procedures are not without drawbacks. The present study was undertaken to compare the diagnostic efficacy of USG and FNAC in correlation with histopathology in euthyroid patients having solitary thyroid nodule. *Study Design:* A prospective study was carried out on 48 euthyroid cases of solitary thyroid nodule attending the Department of ENT, SMS Medical College & Hospital, Jaipur, during the period of March 2016 to November 2017. All patients underwent ultrasonography and fine-needle aspiration cytology. The results of FNAC and USG were correlated with post surgical histopathogical examination (HPE) of the specimens to evaluate their sensitivity and specificity by statistical methods. *Results:* Ultrasound was 87.5% sensitive & 92.50% specific in the detection of malignancy in solitary thyroid nodules while the fine needle aspiration cytology had a sensitivity of 87.50% & specificity of 100% in the same regard. *Conclusion:* It was found that FNAC is a safe, reliable and cost effective diagnostic modality with a high sensitivity and specificity and is the single best investigation for preoperative evaluation of solitary thyroid nodule to differentiate between benign and malignancy nodules.

Keywords: STN, USG, FNAC, Thyroid Malignancy

1. Introduction

Solitary thyroid nodule in the general population is very common with an estimated prevalence that ranges from 4% by palpation to 67% by ultrasonography. [1, 2] Autopsy studies reveal that 50% of adults had nodules, the majority of which were impalpable. [3] Thyroid nodules are four times more common in females than in men and increase in prevalence with increase in age. [3-5]

Few subjects in surgery have generated as much controversy as the management of solitary thyroid nodule (STN), the two major issues being the diagnostic workup and the extent of thyroidectomy. Because of the possibility of malignancy, some clinicians, especially those in the surgical subspecialties, recommend that all nodules should be removed weighing the risks and price to be paid for a malignancy. [6] On the other hand, endocrinologists recommend that FNAC be performed as the initial step of evaluation in order to avoid unnecessary surgery. Because thyroid nodularity is so common, it would be impossible to operate on every patient with a thyroid mass, as the incidence of malignancy is quite low compared with the overall incidence of thyroid nodularity. [7, 8]

Thyroid cancer incidence has been increasing over the last two or three decades in high-resource countries in which the disease is currently the second most frequent cancer, after breast cancer, among women younger than 45 years. In high-resource countries, papillary and follicular carcinomas, known collectively as differentiated thyroid carcinoma, account for approximately 75% and 13% of thyroid cancer, respectively. The well established risk factors for thyroid cancer include prior exposure to ionizing radiation for

childhood head and neck malignancy, history of goitre and thyroid adenoma. [9] The most common type of thyroid cancer is papillary thyroid cancer (PTC), comprising 80% of all cases. The second most common type is follicular thyroid cancer (FTC), which accounts for 10% to 20% of all cases. [10] Medullary thyroid cancer (MTC), however, arises from the parafollicular C cells. [11] This neuroendocrine thyroid tumor represents 6% to 8% of all thyroid cancer cases and occurs in both familial and sporadic forms. [12] Anaplastic thyroid cancer (ATC) is one of the most aggressive and rapidly fatal cancers. It can develop from DTC on dedifferentiation over time or it also arises de novo. [13]

It has been established from various studies that the majority of thyroid nodules are benign and only 10-20% of them are malignant. Hence unless indicated, to operate upon every thyroid nodule would be excessive and would relegate a large majority of patients to an unnecessary surgical procedure. So, the goal of diagnostic workup now is to select those patients for surgery who have a high likelihood of harbouring malignancy in the nodule. [14]

In patients with STNs, the first course of action is to determine whether the nodule is benign or malignant. Many investigations are used to differentiate between benign and malignant nodules so as to avoid unnecessary surgical excisions. Among these, FNAC and USG are commonly used in association with clinical features but there are drawbacks for each technique. [5] USG findings are largely subjective and are prone for errors in high-volume institutes. [15, 16] Although fine needle aspiration/ biopsy (FNAB) is the most commonly used diagnostic technique for the preoperative evaluation of thyroid nodules, there remains the issue of gray-zone nodules that need further diagnostic investigation. [14, 17] The present study was undertaken to compare the diagnostic efficacy of USG and FNAC in correlation with histopathology in euthyroid patients having solitary thyroid nodule.

2. Materials and Methods

A prospective study was carried out on 48 euthyroid cases of solitary thyroid nodule attending the Department of ENT, SMS Medical College & Hospital, India, during the period of March 2016 to November 2017. For the purpose of inclusion in this study, a solitary thyroid nodule (STN) was defined as a single clinically palpable discrete lesion involving either the lobe or the isthmus of the thyroid gland. All patients underwent FNAC, USG and thyroid function test. The results of FNAC were interpreted as benign, malignant, suspicious and inadequate aspirate. The nodules were evaluated for size, location, echotexture, margins, presence of halo, calcification, accessory nodules, associated cervical lymphadenopathy and consistency (solid, cystic or mixed) in order to differentiate between benign and malignant nodules on sonography following which all patients were subjected to surgery and histopathological examination (HPE) of the specimen. The histopathology reports were correlated with the findings of FNAC and USG in order to evaluate their sensitivity and specificity.

3. Results

Patient demographics, ultrasonography findings, FNA cytological reports, thyroglobulin and thyrotropin assays are summarized in Table 1. Table 2 shows the distribution of the cases based on ultrasonography findings with 38(79.17%) cases to be solid on echotexture and rest 10 cases (20.83%) cystic. It was observed that out of 48 cases, 10 cases were suspicious for malignancy on USG. Among these 10 suspicious cases, 7 cases were found to be malignant on gold standard HPE and 3 cases were benign on HPE (Table 3).

In this study, out of the 48 fine needle aspirates obtained, majority of cases revealed a benign nodule on cytology (n=34, 70.83%) followed by malignancy in five aspirates (10.42%), follicular lesion of undetermined significance in four cases (8.33%), non-diagnostic in three cases (6.25%) and suspicious follicular neoplasm in two cases (4.16%). Table 4 shows the distribution of FNAC findings based on Bethesda classification. Most of the nodules were grade II (70.83%) on Bethesda classification followed by grade VI (10.42%), grade III (8.33%), grade I (6.25%) and grade IV (4.16%) in that order. On comparing with final histopathological diagnosis, FNAC identified seven out of eight malignant cases with an overall accuracy of 97.91% (Table 6).

Sensitivity and specificity of USG to differentiate malignant from benign thyroid nodule was found to be 87.5% and 92.50% respectively with an overall accuracy of 91.67%. The overall sensitivity, specificity, PPV and NPV of FNAC was 87.50%, 100%, 100% and 97.50% (Table 6).

Table 1. *Patient Characteristics, USG, FNA and HPE findings.*

Patient Characteristics		Number (%)
Sample Size		48
Male		9 (18.75%)
Female		39 (81.25%)
F:M ratio		4.3:1
Mean Age		36.08±13.925
USG Findings		
	Solid	38(79.17%)
	Cystic	10 (20.83%)
Bethseda Classification		
	I	3 (6.25%)
	II	34 (70.83%)
	III	4 (8.33%)
	IV	2 (4.16%)
	V	5 (10.41%)
Histopathological Analysis		
	Benign	40(83.33%)
	Malignant	8(16.67%)
Incidence Of Malignancy		16.68%.
	Male	22.22%
	Female	15.38%

Table 2. Correlation of USG Echotexture with malignancy.

Echotexture	No. of Cases(%)	Histopathology		Percentage of Malignancy
		Benign	Malignant	
Cystic	10(20.83)	10	0	0
Solid	38(79.17)	30	8	21.05%
Total	48	40	8	16.68%

Table 3. Correlation of USG with Histopathology.

Suspected malignancy on USG histological assessment	HPR	
	Malignant	Benign
Suspicious for Malignancy (10 cases)	7(70%)	3(30%)
Benign(38cases)	1(2.63%)	37(97.37%)
Total(48 cases)	8(16.67%)	40(83.33%)

Table 4. Bethesda classification of FNAC aspirates.

Bethesda system	Number	Percentage%
I	3	6.25
II	34	70.83
III	4	8.33
IV	2	4.16
VI	5	10.42
Total	48	100.00

Table 5. Correlation of FNAC findings with HPR.

Suspected malignancy on FNAC	On HPE	
	Malignant	Benign
Malignant	7	0
Benign	1	40
Total	8	40

Table 6. Diagnostic Test Statistics of USG and FNAC for evaluation of STN.

Diagnostic Statistics	USG	FNAC
Sensitivity	87.50	87.50
Specificity	92.50	100.00
PPV	70.00	100.00
NPV	97.37	97.50
Accuracy	91.67	97.91

4. Discussion

National Comprehensive Cancer Network (NCCN) suggests all thyroid nodules be evaluated with thyrotropin and USG of thyroid and neck as a first step and prefers FNA (with or without sono-guidance) as an investigation of choice in only suspicious lesions. [18] Overall incidence of malignancy in STN varies from 9% to 30% according to various reports. This study finds an overall incidence of malignancy in STN of 16.67%. USG is a safe and effective method of determining the size and the presence of solid or cystic components within a thyroid nodule. High-resolution USG can be used to determine the presence of nonpalpable nodules as small as 1 mm within the thyroid tissue. The predictive value of several ultrasonic features of thyroid nodules, including calcifications, margins, and vascularity, have been examined by numerous studies. [19]

Elastosonography in combination with high-resolution USG can significantly improve the diagnostic accuracy to ultrasound which along with molecular markers now available for FNAB to distinguish a malignant from benign thyroid nodules. [20] In a review of published studies, use of conventional thyroid USG did not allow accurate prediction of the histology of STNs. In current practice, its main indications are the accurate measurement of size of the nodule, assessment for possible lymphadenopathy, and for sonoguidance of FNAB. [21] Katz & Kane et al also found USG to be very accurate in diagnosing adenomatous goitre but found it less reliable to differentiate thyroiditis from a malignant lesion. Out of 21 sonographic suspects, two were later found to be malignant follicular carcinoma. Halo sign was not characteristic of benign follicular adenoma as it was seen in only three out of four (75%) cases of follicular adenomas and when halo sign was absent in one case, histopathology revealed follicular adenoma. [22]

In the present series, out of 48 cases, ten cases were found suspicious for malignancy on USG. Among these 10 suspicious cases, seven cases were found to be malignant on gold standard HPE and three cases were benign giving an overall sensitivity and specificity of 87.50% and 92.50% respectively for USG to differentiate between benign and malignant nodules. These findings concurs with those of Watters et al who found that the sensitivity, specificity & positive predictive value of USG in suggesting a malignant disease were 74%, 83% & 51% respectively and they interpreted a solid or mixed solid-cystic and hypoechoic nodule with absence of halo on USG to be suggestive for malignancy. Further, they emphasized that USG has an added advantage in that it allows the whole gland to be examined rather than just the dominant nodule but at the same time, limited by the fact that no features are pathognonomic for malignancy. [23] Hence, USG should be regarded as complementary test rather than an alternative to FNAC for STNs. Jones et al found 75% sensitivity & 61 % specificity for USG in suggesting a thyroid nodule to be malignant and they added that whenever there is doubt about the possibility of malignancy, it is safer to operate. [24] Moon and colleagues categorized the internal composition of a nodule according to the ratio of the cystic portion to the solid portion into two groups; predominantly solid (<50% cystic) and predominantly cystic (≥50% cystic). [25] Kumar et al found 45% nodules to be solid, 6 % cystic & 49% mixed in his series with 14% of the solid nodules and 9 % of the mixed nodules to be malignant. None of the cystic nodules were malignant in his series. [26] Cox et al reported 6% incidence of malignancy in cystic nodules & emphasized that USG of the thyroid is accurate in determining the physical characteristic of isolated swellings but inaccurate in predicting the presence of neoplasia. [27]

Fine needle aspiration cytology appears to be a safe, reliable & cost effective method which provides valuable information to assist in selection of patients with solitary thyroid nodules for surgery. As it distinguishes the benign from malignant lesions quite effectively preoperatively, it has been proposed as a preoperative screening method of choice. [28]

Fine-needle aspiration biopsy (FNAB) has become the diagnostic tool of choice for the initial evaluation of solitary

thyroid nodule because of its accuracy, safety, and cost effectiveness. Fewer patients have undergone thyroidectomy for benign disease as a result of FNAB, with resultant decreased health care costs. Although needle biopsy can be performed easily, consistently obtaining adequate tissue and processing the specimens to achieve accurate cytopathological interpretation requires expertise and experience. [29] FNAC specimens are classified as malignant, benign, indeterminate (suspicious for follicular or Hürthle cell neoplasm), or insufficient for diagnosis. The effectiveness of FNAB of solitary thyroid nodules may be improved with the use of ultrasound guidance rather than simple palpation. [30]

Accuracy of FNAB is closely related to the histologic type of thyroid carcinoma that is being evaluated. Papillary thyroid carcinoma is readily identified using FNAB because of its unique cytological features. Diagnosis was correct for papillary thyroid carcinoma in approximately 90-100% of FNAB specimens when correlated with the histology of the final surgical specimen. Undifferentiated (anaplastic) carcinoma, medullary thyroid carcinoma, and primary thyroid lymphoma also have characteristic cytological features, which aid correct diagnosis in approximately 90% of FNAB specimens. [31]

In the present study, out of the 48 aspirates obtained, FNAC gave a diagnosis of benign lesion in 34 cases (70.83%), followed by malignancy in five cases (10.42%), follicular lesion of undetermined significance in four cases (8.33%), non-diagnostic in three cases (6.25%) and suspicious follicular neoplasm in two cases (4.16%) which on final histopathological examination found 83.33% of the thyroid enlargement to be benign (n=40) and rest 16.66% malignant (n=8).

Goellner and Gharib reported colloid goitre (40%) to be the most common histological diagnosis followed by follicular adenoma (18%) and adenomatous goitre in about 11% cases with a 16% malignancy rate. [32] This study found 16.67% cases (n=8) to be malignant on histological examination of which seven were rightly diagnosed positive for malignancy on FNAC. The overall accuracy was 97.91% in our series [Table 6], compared to 79% to 98% accuracy in other series.

A study by Kaliszewski et al indicated that FNAB rarely produces false-negative results in patients with solitary malignant thyroid tumors, while in contrast, the results in patients with multiple malignant thyroid tumors are often false negative. Compared with the thyroid cancer prediction rate for FNAB in patients with multiple malignant nodules, the prediction rate for those with cancer in single nodules was three times higher. [33] In this series, FNAC gave false negative diagnosis in one patient without any false positive cases.

Since the present study has included small number of cases (n=48), comparison with other studies is showing the difference of interpretation results. Accuracy rate of FNAC depends greatly on who prepares the cytology smears and how it is interpreted. Other possible reason for the misinterpretation could be the occurrence of hyperplastic nodules in the gland. The only way of reducing this would be to take more aspirates from solid areas. Cystic changes in STNs are a common cause for missed or wrong diagnosis. Altavila and Pascale reported in their series a 45.83% concordance between the histological & cytological diagnosis of papillary carcinoma. On including the suspect cases as cytologically positive, the concordance with histology was 70%. [34]

This study finds an overall sensitivity of 87.50% and specificity of 100% for FNAC in diagnosing a malignancy in a solitary thyroid nodule.

5. Conclusion

To conclude, even while chances of malignancy in a solitary thyroid nodule are less, keeping in mind the higher prevalence for STNs, it would be pragmatic to diagnose the malignant potential of STNs rather than a close observation protocol. Combining USG with FNAC proves to be a cost-effective method for screening thyroid malignancy in economically backward geographical areas till affordable and more definitive alternatives arise.

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