ORIGINAL ARTICLE

Diagnostic accuracy of ultrasound in classifying solitary thyroid nodules in comparison to fine needle aspiration cytology

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Abstract

Introduction: According to United Nations International Children's Emergency Fund (UNICEF) about 70% of the total population in Pakistan is at risk of developing thyroid diseases due to iodine deficiency. In Pakistan thyroid cancer is responsible for 1.2% cases of all malignant tumours. Ultrasound (U/S) is helpful in detecting cancer in thyroid nodules based on different features. Correct diagnosis of thyroid disease can minimize unnecessary surgery and removal of benign nodules.

Objectives: To determine the ability of Fine Needle Aspiration Cytology (FNAC) and US independently and in combination in classifying thyroid nodules, keeping histopathology as gold standard.

Study Design: Validation, cross-sectional study.

Setting: Khyber Teaching Hospital, Peshawar, Surgical Department.

Duration: From September 21, 2020, to March 20, 2021

Material and Methods: This was a cross sectional, validation study of 234 patients. After taking approval from ethical committee of the hospital. Informed written consent was taken from the patients. Patients referred to Radiology Department, meeting the inclusion criteria were enrolled in the study after taking brief history and examination. Ultrasound followed by FNAC were performed and the biopsy was sent for histopathology.

Results: 234 patients with solitary thyroid nodule diagnosed clinically and on ultrasound were observed, in which 52(22.22%) were male and 182(77.78%) were female patients. Average age was 41.18 years + 12.38SD. Accuracy of ultrasound, FNAC and their combination to detect malignancy in solitary thyroid nodule was 76.92%, 81.2% and 83.76% respectively.

Conclusion: FNAC is superior in accurately identifying malignant thyroid nodules compared to ultrasound. The accuracy is increased when both modalities are used in combination.

Keywords: Solitary thyroid nodule, malignant, FNAC, Histopathology

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Introduction:

Globally thyroid nodules occur in 30-60% of the population.[1] In general, the reported prevalence of thyroid nodules varies greatly amongst different populations and the techniques used for their detection.[2] For instance, studies conducted show that the prevalence of thyroid nodules on ultrasound comes out to be 34.2%.[3]

Commonly thyroid nodules are benign, but about 15% of them have malignant potential.[4] The gold standard for diagnosis of thyroid nodules is histo-pathology. Nevertheless, it is imperative to accurately diagnose the disease in its initial stages for management plans.[5] The available investigations for diagnosing thyroid nodules, other than histo-pathology are biochemistry (TFTs etc.), cytology and imaging. Among these, the predominant procedure for evaluation of thyroid nodules is ultrasound, presumably due to its cost-effectiveness, safety and general acceptability.[6] Surveys show that thyroid ultrasound has a sensitivity of 70.6% and speci-

Table 1: Accuracy of Ultrasound in diagnosis of malignant thyroid nodule

		Malignancy on Histopathology		
		Yes	**No**	**Total**
Malignancy on Ultrasound	Yes	42	37	79
		17.90%	15.80%	33.80%
	No	17	138	155
		7.30%	59%	66.20%
Total		59	175	234
		25.20%	74.80%	100%
Sensitivity	71.19%			
Specificity	78.86%			
Positive Predictive Value	53.16%			
Negative Predictive Value	89.03%			
Diagnostic Accuracy	76.92%			

Table 2: Accuracy of FNAC in diagnosis of malignant thyroid nodule

		Malignancy on Histopathology		
		Yes	**No**	**Total**
Malignancy on FNAC	Yes	51	36	87
		21.80%	15.40%	37.20%
	No	8	139	147
		3.40%	59.4%	62.80%
Total		59	175	234
		25.20%	74.80%	100%
Sensitivity	86.44%			
Specificity	79.43%			
Positive Predictive Value	58.62%			
Negative Predictive Value	94.56%			
Diagnostic Accuracy	81.20%			

Table 3: Accuracy of FNAC and US in diagnosis of malignant thyroid nodule

		Malignancy on Histopathology		
		Yes	**No**	**Total**
FNAC and Ultraound	Yes	54	33	87
		23.10%	14.10%	37.20%
	No	5	142	147
		2.10%	60.7%	62.80%
Total		59	175	234
		25.20%	74.80%	100%
Sensitivity	91.53%			
Specificity	81.14%			
Positive Predictive Value	62.07%			
Negative Predictive Value	96.60%			
Diagnostic Accuracy	83.76%			

ficity of 90.4%.[7] However, studies also reveal that ultrasound is ultimately an operator dependent technique, and its accuracy is restricted by the skill of the ultrasonologist.[8] In comparison, FNAC is not operator dependent and is regarded as an accurate diagnostic test for assessing thyroid nodules.[9] Despite that, FNA cytology is restricted in accuracy due to 10-40% of the nodules which exhibit indeterminate cytology.[10] In addition to that, FNA cytology is more expensive and invasive, carrying a small risk of harm to the patient.[11]

Rationale of study: In our set-up thyroidectomy is still considered a high-risk surgery with potential to develop serious complications.[12] Due to the limited use of genetic and immunohistochemical tests in Pakistan, we rely heavily on Ultrasound and FNA cytology for diagnosing thyroid disease. The limitations of both ultrasound and FNA cytology can be overcome if used in combination. Correct diagnosis of thyroid disease could minimize unnecessary surgery and removal of benign nodules.

Material and Methods:

This validation, cross-sectional study was conducted at Khyber Teaching Hospital, Peshawar, Surgical Department from September 21, 2020, to March 20, 2021, on 234 patients with solitary thyroid nodules, selected according to the inclusion and exclusion criteria through non-probability consecutive sampling.

Both males and females with age above 15 years having a thyroid nodule clinically and on ultrasound were included in this study. Patients who had previously undergone thyroidectomy or with diffuse, uniform enlargement of the thyroid gland, toxic nodules and patients with bleeding diathesis were excluded from the study.

The study was conducted after approval from the ethical board and research committee of the institution. Strict exclusion criteria were followed to control cofounders and bias in the study results. All patients fulfilling the inclusion criteria from indoor and outdoor department of Khyber Teaching Hospital were studied after

Table 4: Stratification with respect to age

		Malignancy on Histopathology		Sen, Spec.	
FNAC & US		**Yes**	**No**	**PPV, NPV**	**Accuracy**
Age(in years)<=35	Yes	17	9	80.95%	84.71%
		65.4%	34.6%	85.94%	
	No	4	55	65.38%	
		6.8%	93.2%	93.22%	
36 -55	Yes	31	19	100%	83.76%
		62.0%	38.0%	77.91%	
	No	0	67	62%	
		.0%	100.0%	100%	
56+	Yes	6	5	85.71%	81.25%
		54.5%	45.5%	80%	
	No	1	20	54.55%	
		4.8%	95.2%	95.24%	

taking informed consents. These patients were interviewed (age, sex, race, family history of thyroid disease, personal history of radiation exposure, nodule size).

All these patients were thoroughly investigated (complete blood count, liver function tests, renal function tests, thyroid function tests were conducted). The data was recorded in a predefined proforma listed below. The ultrasound neck for detecting thyroid nodules was conducted by two radiologists who were blind to the clinical course and were fellows of College of Physicians and Surgeons, Pakistan. Each sample of the fine needle aspirate taken by the two radiologists was sent to two cytologists for the most accurate results.

The results of Ultrasound and FNAC were analyzed with respect to the histo-pathological confirmed diagnosis of the thyroid nodules. The out-comes were categorized as True Positive, True Negative, False Positive and False Negative. The paired measures of diagnostic accuracy i.e., sensitivity, specificity, positive and negative predictive values were calculated with the standard formula.

Statistical analysis of the data was performed using the SPSS software version 20. Mean+Standard deviation was calculated for continuous variables like age and thyroid nodule size. Frequencies and percentages were calculated for categorical variables like gender and presence of thyroid nodules. The ultrasound risk stratification for each nodule was determined based on the average rating of 2 experienced ultra-sonographers. The data was labelled via the histo-pathological confirmed diagnosis and paired measures of ultrasound and FNAC were calculated as per the standard formulas of sensitivity, specificity, positive predictive value, and negative predictive value. The standard 2x2 table design was drawn to determine diagnostic accuracy. All results were presented in the form of tables and graphs.

Results:

In this study, 234 patients with solitary thyroid nodule diagnosed clinically and on ultrasound were observed, in which 52(22.22%) were male and 182(77.78%) were female patients. Male to female ratio was 1:3.19). Patient age was divided in four categories, out of which most presented in middle age i.e., 36-55 years: which were 117(50%), while 85(36.3%) patients were in the age range of less than 35 years and 32(13.7%) presented at age more than 56 years. The study included age ranged from 15 up to 70 years. Average age was 41.18 years±12.38SD.

Majority of the patients 179(76.50%) were having personal history of exposure to ionizing radiation while 55(23.5%) were free of ionizing radiation effect. Ultrasound sound (US) played a key role in diagnosis of malignant thyroid nodule. The sensitivity and specificity of ultrasound in diagnosis of thyroid malignancy was 71.19% and 78.86% respectively. It had positive predictive value of 53.16% and negative predictive value is 89.03%. Overall, the diagnostic accuracy of ultrasound in diagnosis of thyroid malignancy is 76.92%. (Table 1)

Fine needle aspiration cytology is another invasive tool and show 81.2% diagnostic accuracy using histo-pathology as gold standard. (Table 2)

The combined accuracy of FNAC and ultrasound shows high accuracy compared to that

Table 5: Stratification with respect to age

FNAC & US			Malignancy on Histopathology Yes	No	Sen, Spec. PPV, NPV	Accuracy
Gender	Male	Yes	16	6	88.89%	84.62%
			72.7%	27.3%	82.35%	
		No	2	28	72.73%	
			6.7%	93.3%	93.33%	
	Female	Yes	38	27	92.68%	83.52%
			58.5%	41.5%	80.85%	
		No	3	114	58.46%	
			2.6%	97.4%	97.44%	
Exposure to Ionizing Radiation	Yes	Yes	29	28	93.55%	83.24%
			50.9%	49.1%	81.08%	
		No	2	120	50.88%	
			1.6%	98.4%	98.36%	
	No	Yes	25	5	89.29%	85.45%
			83.3%	16.7%	81.48%	
		No	3	22	83.33%	
			12.0%	88.0%	88%	
Family History	Yes	Yes	16	7	84.21%	83.87%
			69.6%	30.4%	83.72%	
		No	3	36	69.57%	
			7.7%	92.3%	92.31%	
	No	Yes	38	26	95%	83.72%
			59.4%	40.6%	80.3%	
		No	2	106	59.38%	
			1.9%	98.1%	98.15%	

Table 6: Stratification of FNAC using histopathology as gold standard with respect to age

		Malignancy on Histopathology Yes	No	Sen, Spec. PPV, NPV	Accuracy
Age(in years)<=35	FNAC-Yes	15	10	71.43%	81.18%
		60.0%	40.0%	84.38%	
	No	6	54	60%	
		10.0%	90.0%	90%	
36 -55	FNAC-Yes	30	19	96.77%	82.91%
		61.2%	38.8%	77.91%	
	No	1	67	61.22%	
		1.5%	98.5%	98.53%	
56+	FNAC-Yes	6	7	85.71%	75%
		46.2%	53.8%	72%	
	No	1	18	46.15%	
		5.3%	94.7%	94.74%	

of individual accuracy which was recoded as 83.76%. (Table 3)

Stratification of age shows significant effect in younger age while the accuracy was reduced in older age group. (Table 4). Stratification of gender shows that accuracy was a little bit high in male compared to that of female. Similarly, accuracy was less in patients expose to ionizing radiation and patients having family history of thyroid nodule. (Table 5)

Stratification of FNAC and ultrasound with respect to age, gender, exposure to ionizing radiation and family history are given in table 6-9.

Discussion:

Thyroid nodules are very common. They are found in 4%–8% of adults by means of palpation, in 10%–41% by means of ultrasound,[19-23] and in 50% by means of pathologic examination at autopsy.[24] The prevalence of thyroid nodules increases with age. The likelihood that a nodule is malignant is affected by a variety of risk factors. Malignancy is more common in nodules found in patients who are younger than 20 or older than 60 years of age than in patients between 20 and 60 years of age.[25]

Many studies have been published in which the ability to predict whether a thyroid nodule is benign or malignant based on ultrasound findings was assessed.[26-31] Nodule size is not predictive of malignancy, because the likelihood of cancer in a thyroid nodule has been shown to be the same regardless of the size measured at ultrasound.[26-29]

Thyroid nodule is more common in female than male and our study there were 57-female and 25-males, with female:male ratio of 2.28:1, which is comparable to the studies conducted nationally and internationally.[26-28] The exact reason of female preponderance cannot be established from this study, probably iodine deficiency and hormonal changes may play rule.

The combination of factors improves the positive predictive value of ultrasound to some extent.[28] A predominantly solid nodule (25%

Table 7:Stratification of FNAC with respect to gender, exposure to ionizing radiation and family history

			Histopathology		Sen, Spec.	
			Yes	No	PPV, NPV	Accuracy
Gender	Male	FNAC-Yes	16	6	88.89%	84.62%
			72.7%	27.3%	82.35%	
		No	2	28	72.73%	
			6.7%	93.3%	93.33%	
	Female	FNAC-Yes	35	30	85.37%	80.22%
			53.8%	46.2%	78.72%	
		No	6	111	53.85%	
			5.1%	94.9%	94.87%	
Exposure to Ionizing Radiation	Yes	FNAC-Yes	12	8	85.71%	82.46%
			60.0%	40.0%	81.4%	
		No	2	35	60%	
			5.4%	94.6%	94.59%	
	No	FNAC-Yes	39	28	86.67%	80.79%
			58.2%	41.8%	78.79%	
		No	6	104	58.21%	
			5.5%	94.5%	94.55%	
Family History	Yes	FNAC-Yes	5	5	83.33%	73.91%
			50.0%	50.0%	70.59%	
		No	1	12	50%	
			7.7%	92.3%	92.31%	
	No	FNAC-Yes	46	31	86.79%	81.99%
			59.7%	40.3%	80.38%	
		No	7	127	59.74%	
			5.2%	94.8%	94.78%	

Table 8: Stratification of ultrasound using histopathology as gold standard with respect to age

		Histopathology		Sen, Spec.	
Ultrasound		Yes	No	PPV, NPV	Accuracy
Age(in years)<=35	Yes	12	11	57.14%	76.47%
		52.2%	47.8%	82.81%	
	No	9	53	52.17%	
		14.5%	85.5%	85.48%	
36 -55	Yes	24	19	77.42%	77.78%
		55.8%	44.2%	77.91%	
	No	7	67	55.81%	
		9.5%	90.5%	90.54%	
56+	Yes	6	7	85.71%	75%
		46.2%	53.8%	72%	
	No	1	18	46.15%	
		5.3%	94.7%	94.74%	

cystic) with micro-calcifications has a 31.6% likelihood of being cancer, as compared with a predominantly cystic nodule (75% cystic) with no calcification, which has a 1.0% likelihood of being cancer.[29]

FNAC is the most effective and reliable procedure for the diagnosis of malignant thyroid nodules.[32] Yokozawa et al. and Rosen et al. report 88% and 68% accuracy of Ultrasound guidance, respectively.[33,34]

In our study, we achieved, with reasonable interviewer reliability, a diagnostic accuracy up to 78.0% when the presence of one of the malignant ultrasound findings was applied for a diagnosis of malignant thyroid nodules. Traditionally, a predominantly solid component is regarded as being suggestive of a malignant nodule rather than a benign nodule.[35,36] In some reports, however, 60%–83% of benign nodules were predominantly solid.[37,38] In our study, most of the benign nodules, as well as the malignant nodules, were predominantly solid. Therefore, a predominantly solid component alone cannot be a useful criteria for the differentiation of malignant from benign nodules.

Our findings support previous study results[39,40] that suggest a taller than-wide shape is very specific for differentiating malignant thyroid nodules from benign ones. This result conveys the fact that malignant nodules (taller than wide) grow across normal tissue planes, while benign nodules grow parallel to normal tissue planes.[39-41]

In results of a previous study,[35] the presence of a micro-calcification in a pre- dominantly solid nodule increased cancer risk by threefold, and coarse macrocalcifications increased cancer risk twofold, compared with predominantly solid nodules without any calcifications. Which is consistent to our study.

In this study, the overall accuracy of thyroid ultrasound for depicting a malignant nodule was 76.92%. With the presence of one of the ultrasound findings suggesting a malignant nodule,

Table 9: Stratification of ultrasound with respect to gender, exposure to ionizing radiation and family history

			Histopathology		Sen, Spec. PPV, NPV	Accuracy
			Yes	No		
Gender	Male	Ultra-sound-Yes	14	6	77.78%	80.77%
			70.0%	30.0%	82.35%	
		No	4	28	70%	
			12.5%	87.5%	87.5%	
	Female	Ultra-sound-Yes	28	31	68.29%	75.82%
			47.5%	52.5%	78.01%	
		No	13	110	47.46%	
			10.6%	89.4%	89.43%	
Exposure to Ionizing Radiation	Yes	Ultra-sound-Yes	11	8	78.57%	80.7%
			57.9%	42.1%	81.4%	
		No	3	35	57.89%	
			7.9%	92.1%	92.11%	
	No	Ultra-sound-Yes	31	29	68.89%	75.71%
			51.7%	48.3%	78.03%	
		No	14	103	51.67%	
			12.0%	88.0%	88.03%	
Family History	Yes	Ultra-sound-Yes	4	5	66.67%	69.57%
			44.4%	55.6%	70.59%	
		No	2	12	44.44%	
			14.3%	85.7%	85.71%	
	No	Ultra-sound-Yes	38	32	71.7%	77.73%
			54.3%	45.7%	79.75%	
		No	15	126	54.29%	
			10.6%	89.4%	89.36%	

the overall sensitivity was about 71.19% in nodules 1 cm or larger. A false-negative rate of 89.03 is not trivial, even if the diagnosed cancer is low risk.

In the literature the diagnostic yield of FNAC has different values ranging from 50% to 95%. Kumar S[3] revealed sensitivity and specificity of 77% and 100% respectively. In Moosa FA[16] study the yield of FNAC was that sensitivity was calculated 77.7%, specificity 98.9%, and with a positive and negative predictive value of 87.5% and 97.8% respectively. Similarly, Abu salem,[15] studied specificity of 99% and a sensitivity of 93% while Tariq M,[17] reported sensitivity of 75% and specificity 97.6% PPV, NPV 85.71%, 95.34% respectively. As the diagnostic yield of FNAC has great variation my results are comparable to the results of studies conducted nationally and internationally. Saddique M,[1] showed in his study sensitivity of 75%, specificity of 95.83%, positive predictive value of 81.81% and negative predictive value of 93.81%. Likewise, Alam M,[18] reported sensitivity of 100% and specificity of 95.12%. Our results are lesser than the study of Korah T,[14] who reported 88%, 98%, 100% and 100%, for sensitivity, negative predictive value (NPV), specificity and positive predictive value (PPV) respectively. The outcome of FNAC in Mehmood Q,[13] study was sensitivity 79.17% and specificity 91.40%.

Our results indicate that besides size, other ultrasonographic parameters should be considered. In particular, the proportion of accuracy was significantly greater for nodules with well-defined margins than for nodules with blurred margins. The echo structure, the presence of calcifications, and the echogenicity features were not associated with accuracy of ultrasound.

Conclusion:
In conclusion, ultrasound criteria for the discrimination of malignant from benign nodules are taller-than-wide shape, spiculated margins, marked hypo-echogenicity, and the presence of micro- or macro-calcifications. Radiologists must be familiar with the various signs on ultrasound that help to distinguish benign from malignant thyroid nodules and the typical appearance of common thyroid cancer. On other hand, FNAC is a primary diagnostic tool for solitary thyroid nodule because it is simple, safe, quick, reliable, minimally invasive, and cost effective. The combination of FNAC and ultrasound give much better results as compared to individual.

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Role and contribution of authors:
Tayyaba Ayaz, collected the data, references and

did the initial write up.

Muhammad Naeem, critically review the article and made final changes.

Qaviullah Mian, collected the data and helped in introduction writing.

Amir Hamza Khan, collected the references and helped in discussion writing.

Rashid Waheed, collected the data, references and helped in interpretation of data.

Mushtaq Ahmad, went through the article and did the useful changes.

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