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Statistical Measures of Performance of Positivity of Single and Multiple Grey Scale Ultrasound Features Favouring Malignancy, in Sonologically Confirmed Solitary Nodules of The Thyroid

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ABSTRACT

Introduction: *Incidence of malignancy is higher among solitary nodules of thyroid than multinodular disease. There are not many studies quantifying the statistical measures of performance of test criteria of presence of individual gray scale features favouring malignancy in solitary nodules. This study attempts to quantify them and to derive policies to recruit solitary nodules for FNAC.*

Aim of the work: *(1) To estimate the statistical measures of the performance of each of gray scale ultrasound features as a test criterion to identify malignancy in solitary thyroid nodules. (2) To see if a combination of ultrasound features which when present simultaneously will be more 'positively predictive'/ 'specific' than individual features.*

Patients and Methods: *40 cases of sonologically confirmed solitary nodules were selected from cases referred as 'solitary nodule' after palpation. The statistical measures of the performance of each of gray scale ultrasound features namely hypoechogenicity of a non-cystic nodule, microcalcifications, irregular margin and anteroposterior diameter equal to or more than transverse diameter, as a test criterion to identify malignancy in solitary nodules were calculated.*

Results: *When considered in isolation, each of the gray scale ultrasound features suggestive of malignancy has relatively low sensitivity in the setting of sonologically confirmed solitary nodules, though each of them has high specificity. The test criterion of presence of any one of the gray scale ultrasound features has a sensitivity of 100%.*

Conclusions: *All the solitary nodules with any one positive gray scale ultrasound feature should undergo FNAC. Simultaneous presence of any two or moresonologic features gives high levels of specificity and PPV; nodules should be considered highly suspicious.*

Keywords: *Solitary thyroid nodule, recruitment for FNAC, A/T ratio.*

Introduction

It has been observed that incidence of malignancy is higher among solitary nodules of the thyroid than among multinodular disease. The detection of thyroid nodule and differentiation between solitary thyroid nodule and multinodular disease are easy on ultrasonography. Similarly, it is easy to pick up additional nodules, not identified by palpation in cases of clinical diagnosis of solitary nodule and to place such cases in the category of multinodular disease. But differentiation between malignant and benign nodules has not been easy on gray scale ultrasonography. The sonographic features which are more commonly seen in the malignant nodules (microcalcification, hypoechogenicity, irregular margin) have been used as test criteria to diagnose malignancy with variable and low accuracy[1-5]. The low accuracy of ultrasound features for diagnosing malignancy has led to widespread use of FNAC for further evaluation of the nodules. Very often the role of FNAC is considered as a step between clinical examination or ultrasonography and surgical resection. A novel gray scale sonographic feature suggesting malignancy, height more than width was added to the spectrum of candidate test criteria some years ago by Kim et al[1]. The same feature was studied by Frateset al[5] and expressed as 'A/T rato' i.e. Anteroposterior measurement by Transverse measurement ratio ≥1.

There have been many studies on the usefulness of ultrasonography in cases of solitary nodules selected by clinical palpation.[1-8]These studies have highlighted the ability of ultrasound to pick up additional nodules. There have not been many studies on sonologically confirmed solitary thyroid nodules. The present study is an attempt to evaluate the role of ultrasound in '*sonologic solitary nodules'*, which constitute a small subset of the large population of solitary nodules selected by clinical palpation. The study attempts to quantify the statistical measures of performance of the gray scale sonographic features to diagnose malignancy, including the '$A/_T$ ratio ≥1' in the subset of solitary nodules selected sonologically. The present study attempts to evaluate various combinations of individual gray scale ultrasound features, each of which is relatively more specific and less sensitive, to obtain a highly sensitive and highly specific test.

Methodology

Objectives

1. To estimate the statistical measures of the performance of each of gray scale ultrasound features as a test criterion to identify malignancy in solitary thyroid nodules.
2. To see if a combination of gray scale ultrasound features which when present simultaneously will be more 'positively predictive'/ 'specific' than individual ultrasound features to identify malignancy.

Sample size

Total 40 cases of sonologically confirmed solitary nodules selected from patientsreferred as solitary nodule of thyroid on clinical palpation.

Materials and Methods

The study was conducted at Department of Radiodiagnosis, Medical College Hospital, Thiruvananthapuram during the period from Jan 2012 to July 2013.

Inclusion criteria

Presence of both of the palpatory impression of solitary thyroid nodule and the sonological confirmation of solitary nature of the nodule.

Exclusion criteria

1) Unwilling patients
2) Consent not obtained from patients
3) Presence of multiple nodules on ultrasound scanning
4) All the cases in which cytopathological diagnosis was not obtained
5) Patients with history of previous surgery or radiotherapy

Scanning protocol

The patients were reassessed at our department and their history, clinical details and data regarding other imaging studies were noted. Ultrasonography was performed using the

machine GE-Logiq 200 PRO with 7.5 MHz linear probe and if necessary also with 5 MHz sector probe.

The sonographic features of the solitary nodules, particularly echo texture, margin, presence of micro calcifications, three dimensions and presence of lymph nodeswere noted. The statistical measures of performance of each individual ultrasound feature were calculated, taking fine needle aspiration cytology as a confirmatory test and whenever available/possible, histopathology of the resected specimen was used as the confirmatory test.

Data management

Sensitivity, specificity and associated statistical indices were calculated. An attempt was made to evaluate various combinations of gray scale ultrasound features to obtain a test criterion with high'sensitivity' and a test criterion with highpositive predictive value/specificity.

Observations and Results

More than 200 cases of thyroid nodules which were considered to be solitary clinically on palpation underwent ultrasound and a total number of 40 patients confirmed to have solitary nodules on ultrasound scan alone were included in the study.

The age of the patients varied between 16 years 66 years. Majority of patients were (36 out of 40) (90%) females.

Table – 1 Distribution of study population according to age

Age Group	Frequency	Percentage
15-19	3	7.5
20-24	5	12.5
25-29	1	2.5
30-34	5	12.5
35-39	8	20
40-44	3	7.5
45-49	2	5
50-54	5	12.5
55-59	7	17.5
60 and above	1	2.5
Total	**40**	**100**

FNAC+/- histopathology showed benign nodule in 33 patients (82.5%) and malignant disease in 6 patients (15%) and thyroiditis with nodules in one (2.5%), thus making the benign processes 34 in number.

Table – 2 Distribution of study population according to final diagnosis

		Frequency	Percentage
Final diagnosis	Malignant	6	15
	Benign	34	85
Total		**40**	**100**

Sonographically these patients were assessed for size of the nodule, echotexture, margins, peripheral halo, calcification in nodule and lymph node enlargement.

Out of 40 cases studied hypoechoic non-cystic nodules were seen in 17 cases out of which three were malignant and the rest fourteen were benign. Hyperechogenicity was seen in 13 cases all of which were benign. None of the malignant nodules were hyperechoic. Two nodules were isoechoic; one of these was malignant and the other was benign. Mixed echogenicity was seen in four cases of which two were malignant and two were benign. Cystic changes were seen in four cases and they were benign.

Table – 3 (a) Distribution of study population according to echo texture

Echotexture			Total
	Malignant	Benign	
Hyperechoic	0	13	13
Hypoechoic (cystic) nodule	0	4	4
Hypoechoic (non-cystic) nodule	3	14	17
Isoechoic	1	1	2
Mixed echoic	2	2	4
Total	**6**	**34**	**40**

Table - 3 (b)

Echo Texture	Malignant	Benign	Total
Hypoechoic (non-cystic) nodules	3	14	17
Others	3	20	23
Total	**6**	**34**	**40**

Statistical indices of the test criterion of presence of hypoechogenicity (non-cystic nodules) for diagnosing malignancy

Sensitivity: 50%
Specificity : 58.8%
Positive Predictive value: 17.6%
Negative Predictive Value: 86.96%
LR+: 1.21
LR-: 0.85

Ill-defined or irregular margins were seen in 8 nodules out of which5were malignant and 3were benign.The margins of the nodules were a found to be well defined and regular in 32 cases out of which one was malignant and 31 were benign.

Table- 4 Distribution of study population according to presence of ill-defined/ irregular margin

		Malignant	Benign	Total
Margin	Ill-defined/ irregular	5	3	8
	Regular Well-defined	1	31	32
Total		**6**	**34**	**40**

Statistical indices of the test criterion of presence of ill-defined/irregular margin for diagnosing malignancy

Sensitivity: 83.3%
Specificity: 91.17%
Positive predictive value: 62.5%
Negative predictive value: 96.9%
LR+: 9.44
LR-: 0.18

Calcification of thyroid occurs in both benign and malignant nodules. It can be coarse and dense with posterior acoustic shadowing; or fine punctate without shadowing (microcalcification). Sonographically, microcalcificationsare the hallmark of malignancy. Out of the 40 patients with solitary nodule, ultrasound showed microcalcifications in six patients (four benign and two malignant lesions).

Table – 5 Distribution of study population according to presence of microcalcifications

		Malignant	Benign	Total
Microcalcifications	present	4	0	4
	absent	2	34	36
Total		**6**	**34**	**40**

Statistical indices of the test criterion of presence of microcalcifications for diagnosing malignancy

Sensitivity: 66.7%
Specificity: 100%
Positive predictive value: 100%
Negative predictive value: 94.4%
LR+: ∞
LR-: 0.33

Table – 6 Distribution of study population according to presence of an 'AP diameter equal to or more than transverse diameter'

	Malignant	Benign	Total
AP≥ Tr	4	5	9
AP<Tr	2	29	31
Total	**6**	**34**	**40**

Statistical indices of the test criterion ofpresence of an 'AP diameter equal to or more than transverse diameter' for diagnosing malignancy

Sensitivity: 66.67%
Specificity: 85.29%
Positive Predictive value: 44.44%
Negative Predictive Value: 93.55%
LR+: 4.53
LR-: 0.391

A nodule which is'taller than wide' was defined as being greater in its anteroposterior dimension than its transverse dimension (Kim et al)[2] and the feature was considered as a positive indicator of malignancy.

Table – 7 Distribution of Study Population According to Final Diagnosis

Malignant nodule	
Follicular carcinoma	1
Medullary carcinoma	1
Papillary carcinoma	4
	6
Benign nodule	
Follicular Adenoma thyroid	3
Colloid nodule	17
Degenerating colloid nodule	13
	33
Thyroiditis with nodule	
Nodular goitre with lympocytic thyroiditis	1

Table – 8 Distribution of study population according to positivity of the test criterion of presence of any one out of the four ultrasound features*favouring malignancy

		Disease		
		Malignant	**Benign**	**Total**
Any one out of four sonographic features*	(+)	6	20	26
	(-)	0	14	14
Total		**6**	**34**	**40**

Sensitivity: 100%
Specificity: 41.18%
Positive predictive value: 23.08%
Negative predictive value: 100%
LR+: 1.7
LR-: 0.00
*The four ultrasound features are hypoechogenicity of non-cystic nodule, microcalcifications, irregular margins and AP diameter ≥ Transverse diameter.

Table – 9 Distribution of study population according to positivity of the test criterion of simultaneous presence of any two out of the four* sonographic features favouring malignancy

		Disease		
		Malignant	**Benign**	**Total**
Any two out of four sonographic features*	(+)	5	2	7
	(-)	1	32	33
Total		**6**	**34**	**40**

Sensitivity: 83.33%
Specificity: 94.12%
Positive predictive value: 71.43%
Negative predictive value: 96.97%
LR+ : 14.17
LR-: 0.171
*The four ultrasound features are hypoechogenicity of non-cystic nodule, microcalcifications, irregular margins and AP diameter ≥ Transverse diameter.

Table – 10 Distribution of study population according to positivity of the test criterion of presence of any three out of the four ultrasound features* favouring malignancy

		Disease		
		Malignant	**Benign**	**Total**
Any three out of four sonographic features	(+)	4	0	4
	(-)	2	34	36
Total		**6**	**34**	**40**

Sensitivity: 66.67%
Specificity: 100%
Positive predictive value: 100%
Negative predictive value: 94.44%
LR+: ∞
LR-: 0.33
*The four ultrasound features are hypoechogenicity of non-cystic nodule, microcalcifications, irregular margins and AP diameter ≥ Transverse diameter.
Enlarged lymph nodes in deep cervical chain were seen in 3 patients. Among these three, there were two cases of papillary carcinoma which showed microcalcifications and ill-defined border; there was one case of medullary carcinoma, which also showed ill-defined border and calcification.

Table – 11 Distribution of study population according to presence of enlarged lymph nodes

		Malignant	**Benign**	**Total**
Lymph Nodes	present	3	0	3
	absent	3	34	37
Total		**6**	**34**	**40**

Statistical indices of the test criterion of presence of presence of lymph nodes for diagnosing malignancy

Sensitivity: 50.0%
Specificity: 100%
Positive predictive value: 100%
Negative predictive value: 91.89%

An attempt is made to study the test criterion of presence of complete sonolucent halo as marker of benignity and it yielded poor sensitivity; however it had good positive predictive value and specificity. Out of 40 cases studied, peripheral sonolucent halo was seen in 15 cases out of which 14 were benign and one was malignant.

All the malignant lesions with irregular margins had no or incomplete halo;thus, all the malignant lesions with irregular margins formed a subset of the lesions with no or incomplete halo and there was a clear interdependence. So absence of/incomplete halo was not separately assessed as a test criterion to diagnose malignancy.

Final diagnosis of the cases showed malignancy in six cases out of which four were papillary carcinoma, one was follicular carcinoma and one was medullary carcinoma. The benign lesions were follicular adenoma thyroid (3 cases), colloid nodules (17 cases), degenerating colloid nodule (13 cases) and thyroiditis (one). The four follicular neoplasms diagnosed on FNAC were found to be follicular adenoma in three and follicular carcinoma in one on histopathology of surgically resected tissue.

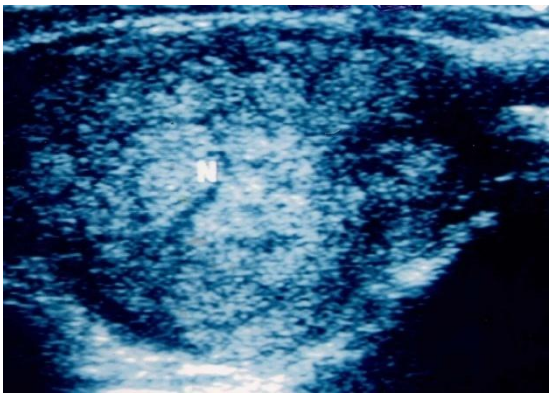

Fig. 1 A case of papillary carcinoma of the thyroid with ill-defined margin and microcalcifications. Its anteroposterior diameter was more than its transverse diameter.

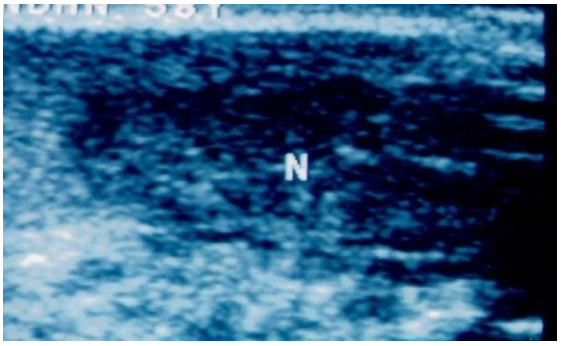

Fig. 2 A case of medullary carcinoma of the thyroid seen as a hypoechoic nodule with microcalcifications and irregular margin.

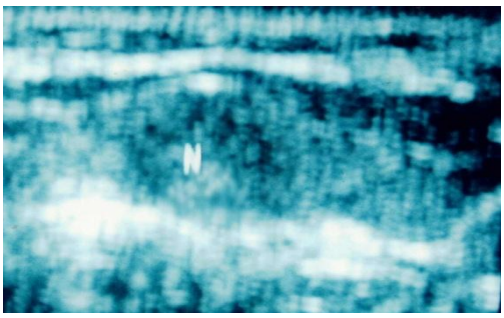

Fig 3. A case of papillary carcinoma of the thyroid with microcalcifications and irregularity in a part of its margin.

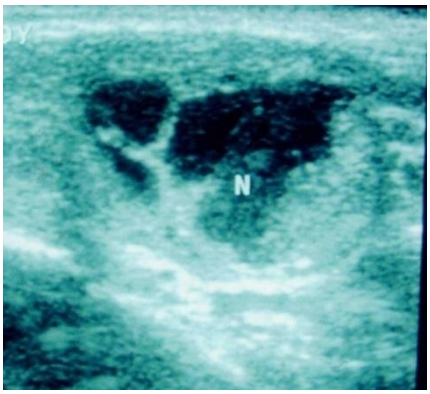

Fig. 4 A case of colloid nodule with well-defined smooth margin and a sonolucent halo.

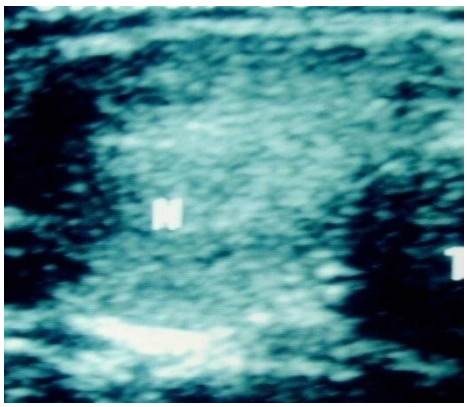

Fig. 5 A nodule with colloid degeneration which is hyperechoic and has well-defined margin

Discussion

Ever since the introduction of the ultrasonography into the imaging of the thyroid diseases, many attempts have been made to identify sonographic characteristics that can potentially diagnose thyroid cancer. To this date not a single criterion has been identified that can differentiate malignant lesions from benign lesions with very high sensitivity and specificity. For this reason, the role of FNAC becomes animportant step between clinical examination or ultrasonography and surgical resection. Due to the poor levels of sensitivity of sonographic criteria for malignancy and due to presence of such features in a significant proportion of benign lesions, FNAC is resorted to, almost always before proceeding to surgery except in frankly malignant masses with infiltration of adjacent structures or metastasis to lymphnodes. The role of ultrasound can be looked upon as a tool to identify the thyroid nodules which can be potentially malignant and to select cases or nodules that should undergo FNAC. The gray scale ultrasonographic characteristics found to be frequently associated with malignant thyroid nodules are irregular or microlobulated margin, marked hypoechogenicity and microcalcification.[1-8]

Most of the studies available in literature focus ultrasound evaluation of cases which gave a clinical impression of solitary nodule on palpation out of which many were subsequently found to be multiple on sonography. The present study is done on sonologically confirmed solitary nodules out of the clinically diagnosed solitary nodules. The stringent criterion of exclusion of cases without FNAC +/- histopathology reduced the number of population in study. Thus the statistical measures of performance of test criteria of presence of gray scale ultrasound features to diagnose malignancy in solitary thyroid nodules, obtained in the present study could be different from those quoted in literature. But the authors feel that the values presented here will be good representatives of those expected in the sonologically confirmed solitary nodules.

Irregular or microlobulated margin was reported to have a sensitivity of 17.4 to 77%, specificity of 38.9 to 85.0%, PPV of 9.3 to 60%, NPV of 38.9 to 97.8%) [1-5]. In the present study this sonographic feature (irregular margin) has the following statistical indices: Sensitivity 83.3%, specificity 91.7%, PPV 62.5%, NPV 96.9%, LR+ 9.44 and LR- 0.18, It can be seen that the values of statistical index is slightly higher than those found in the internationally accepted studies. The probable reason for the same is that the cases included in this study are sonographically confirmed solitary thyroid nodules, whereas the reported studies are on cases which gave a clinical impression of solitary nodule on palpation and were subsequently found to be either solitary or multiple on sonography.

Marked hypoechogenicity is reported to have a sensitivity of 26.5 to 87%, specificity of 43.4 to 94.3%, PPV of 11.4 to 68.4% and NPV of 73.5 to 93.8%.[1-5] In the present study hypoechogenicity present in non-cystic nodules has following statistical indices; sensitivity 50%, specificity 58.8%, PPV 17.6% and NPV 86.96%.

It is reported that microcalcifications had a sensitivity of 26.1 to 59.1%, specificity of 85.8 to 95%, PPV of 24.3 to 70.7% and NPV of 41.8 to 94.2%.[1-5]In the present study, microcalcification, as a tool for diagnosing malignancy has the following statistical indices; sensitivity 67.7%, specificity 100%, PPV 100%, NPV 94.4%, very high LR+ and a very low LR – (0.33).

To the list of the conventionally studied sonographic features, a new criterion, height more than width was added in 2002 by Kim et al[1]. A nodule which is‘taller than wide’ was defined as being greater in the anteroposterior dimension than its transverse dimension. This finding is taken to be positive for malignancy, if any part of the nodule was taller than wide.This feature is reported to have a sensitivity of 32.7%, specificity of 92.5 % and PPV of 66.7% and NPV of 74.8% by Kim et al[1]. The statistical performance indices of thecriterion ‘AP diameter equal to or greater than transverse diameter’was assessed in the

present study and are as follows; sensitivity 66.67%, specificity 85.29%, PPV 44.44%, NPV 93.55%, LR+ 4.53; LR- 0.391.

Though presence of enlarged lymph nodes correlated well with presence of malignancy, lymph node enlargement can be caused by many other pathologies; it can give rise to confusing conclusions if the location of the enlarged node is different from those draining the thyroid gland. Furthermore it is not a feature of the thyroid nodule per se. For these reasons, enlargement of cervical lymph nodes is omitted from further discussion.

On analysis of the distribution of various ultrasonographic characteristics described above, in the benign and malignant groups of solitary thyroid nodules, it can be seen that the incidence of one particular sonographic characteristic favouring malignancy is not strictly related to incidence of another ultrasound characteristic. There is an apparent 'random distribution' of the sonographic characteristics favouring malignancy This corresponds to the observation by Cappelli et al[8] that ultrasound characteristics namely hypoechoic appearance, blurred margin, microcalcification and 'AP diameter equal to or greater than transverse diameter' were relatively independent factors related to malignancy.

It is seen that none of these individual ultrasound features, in isolation, as a test criterionto 'diagnose' malignancy, has sensitivity or specificity near 100%. The present study attempts to evaluate the combinations of ultrasound features to produce a test criterion with high sensitivity.

A test criterion of presence of any one suspicious ultrasound feature out of four (irregular margin, marked hypoechogenicity, microcalficiation and anteroposterior diameter ≥ transverse diameter) in a solitary nodule thyroid is evaluated in the present study. It gives a sensitivity of 100%, specificity of 41.78%, PPV of 23.08%, NPV of 100%, LR+ 1.7, LR- of 0. This test criterion corresponds to a policy in which all solitary nodules of thyroid showing at least one suspicious sonographic feature udergo FNAC. Such a policy allowsfor detection of almost all (100% in this study) malignant solitary nodules; 'negative' or benign FNAC results in atleast 77% of patients can not at all be viewed as a major problem considering that no or negligible number of malignant nodules is missed with this policy and in those 77% of the cases, the clinical suspicion of harbouring a malignant lesion is allayed.

Another test criterion evaluated in this study is the simultaneous presence of any two suspicious ultrasound features in a nodule. This criterion gives a sensitivity of 83.33%, specificity 94.12%, PPV 71.43%, NPV of 96.97%, LR+ of 14.17, LR- of 0.177.

A test criterion of simultaneous presence of any three suspicious ultrasound features in a nodule is also evaluated. With the combination, the sensitivity is found to be 66.67% (less than that of the combination of any two ultrasound criteria); but the specificity and positive predictive valueare 100% (more than those of the previous combination), NPV is 94.44%, LR + is extremely high or ∞ and LR – is 0.33.

Radiologists and surgeons often face the problem of getting an FNAC report with an impression of benign pathology when they expect a malignant pathology. This can happen if the aspirated material cells come from areas superficial or deep to the lesion, if the aspiration site is not accurate or if the lesion is actually benign. There has been no guideline so far, as to what should be the course of action for such patients. From the analysis of data given above, it is clear that when two or more 'suspicious' ultrasound features are present, the positive predictive value and specificity are very high for a malignant lesion. It may be a wise practice to repeat FNAC with accurate ultrasound guidance andundertake follow up ultrasounds at close intervals.

Conclusion

1) When considered in isolation, each of the gray scale ultrasound features suggestive of malignant thyroid nodules, namely

hypoechogenicity of a non-cystic nodule, microcalcifications, irregular margin and anteroposterior diameter equal to or more than transverse diameter, has relatively low sensitivity to diagnose malignancyin the setting of sonologically confirmed solitary nodules, though each of them has high specificity.

2) The test criterion of presence of any one conventional gray scale ultrasound feature in a solitary nodule in thyroid has a sensitivity of 100% in the present study. So the policy of giving a sonologic impression of probable malignancy or a suspicious lesion warranting FNAC when one finding is positive, can ensure that practically no malignant solitary nodules will be 'missed'.
3) A test criterion of simultaneous presence of any two sonologic features in a "sonographically confirmed" solitary nodule of the thyroid gland has high levels of specificity andPPV (specificity 94.12%, PPV 71.43 %,) in the study.
4) A test criterion of simultaneous presence of more than two grey scale features has a very low sensitivity; but very high specificity and positive predictive value. The very high PPV and specificity of such nodules should be given due importance and they should be considered "highly suspicious".

The present authors recommend that all nodules with simultaneous presence of two or more, grey scale ultrasound features should undergo repeat guided FNAC and undertake follow up ultrasounds at close intervals if the first FNAC is negative for malignant cells and surgical resection is not planned for.

Conflict of interest: None

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