Original Article

Ultrasound-guided Fine-needle Aspiration Cytology along with Clinical and Radiological Features in Predicting Thyroid Malignancy in Nodules ≥1 cm

N. Siddhartha Chakravarthy*, Anuradha Chandramohan[1*], Anne Jennifer Prabhu[2], M. Gowri[3], Pavithra Mannam[1], N. K. Shyamkumar[1], Dukhabandhu Naik[4], A. J. Cherian, Nihal Thomas[4], M. J. Paul, Deepak Abraham

Departments of Endocrine Surgery, [1]Radiology, [2]Pathology, [3]Biostatistics and [4]Endocrinology, Christian Medical College (CMC), Vellore, Tamil Nadu, India

*These authors have contributed equally to this work

Abstract

Aims and Objectives: The aim of the study is to examine the adequacy and accuracy of ultrasound-guided fine-needle aspiration cytology (US-FNAC) in thyroid nodules ≥1 cm and to analyze the clinical, sonological, and cytological features in predicting thyroid malignancy. **Materials and Methods:** US-FNAC was done on 290 patients from December 2013 to December 2014 by the radiologist. The Thyroid Imaging Reporting and Data System (TIRADS) was used to record the sonological features. FNAC samples were reported by a dedicated cytopathologist. Accuracy was calculated by comparing US-FNAC, clinical features and ultrasound (US) features for those who had final histopathology till April 2017. **Results:** The adequacy of US-FNAC in this study was 80.2%. Thyroidectomy was performed in 128/290 (44.1%). The sensitivity and specificity of US-FNAC in this study is 83.9 and 76.3%, respectively, with a positive predictive value of 85.2%, negative predictive value of 74.4%, and an accuracy of 81% in predicting malignancy in thyroid nodules ≥1 cm. The malignancy rate in benign FNAC sample was 25% (10/40), and was 69% (8/13) in those with a follicular lesion of undetermined significance (FLUS). Around 80% of benign and 89% of FLUS had follicular variant of papillary carcinoma of thyroid (FVPTC). US-FNAC, a high TIRADS score, and US features such as marked hypoechogenicity, taller than wide, irregular margins, microcalcification, and clinical features, such as hard in consistency and significant cervical lymph nodes, were important in predicting malignancy ($P < 0.001$). **Conclusions:** The accuracy of US-FNAC in this study is 81%. The US-FNAC, a high TIRADS score, a hard thyroid nodule, and significant cervical lymph nodes are important in predicting malignancy. The accuracy rate in benign and atypia undetermined significance categories needs to improve in this study. Further research to help in decreasing false negative rates of FVPTC will help in increasing the accuracy of US-FNAC in the present study.

Keywords: Adequacy and accuracy of FNAC thyroid, Bethesda system of thyroid cytology reporting, fine-needle aspiration cytology, ultrasound-guided fine-needle aspiration of thyroid tumors, ultrasound of thyroid

Introduction

Thyroid nodules are common in the general population. The prevalence of palpable thyroid nodules in adults is between 4 and 7% with a 10-fold increase on ultrasound (US) screening.[1] Most nonpalpable thyroid nodules are benign and majority do not require thyroidectomy.[2]

Fine-needle aspiration cytology (FNAC) has revolutionized the management of thyroid nodules, providing an extremely safe, simple, quick, and cost-effective method for detecting malignancy.[3] FNAC is commonly done by palpatory method but this approach has various limitations, including difficulty in sampling nodules that are small, indistinct, predominantly cystic, posterior in location, and difficulty in selecting the suspicious nodule within a multinodular goiter. FNAC performed under US guidance helps overcome these

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Address for correspondence: Dr. Deepak Abraham, Department of Endocrine Surgery, Endocrine Surgery Office, 2nd floor Paul Brand Building, Christian Medical College Hospital Campus, Vellore, Tamil Nadu, India.
E-mail: deepakabraham@cmcvellore.ac.in

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limitations. Moreover, even with US guidance, high rates of inadequacy (up to 33.6%) have been reported.[4]

Therefore, we conducted this study to determine the adequacy and accuracy of US-FNAC and to identify the clinical, sonological, and cytological features that predict malignancy in palpable thyroid nodules (≥1 cm).

Materials and Methods

Study design

This was a prospective observational study of 290 adults evaluated for a thyroid nodule (>1 cm in size) between December 2013 and December 2014 after approval from the Institutional Review Board (IRB Number: 8561/13). US-FNAC was done by the radiologist in the presence of a surgeon and an onsite cytotechnician.

Participants

Eligibility criteria

Patients referred for a palpatory FNAC from the outpatient department were included in this study after an informed consent. The US-FNAC was done twice a week and all consecutive patients were included.

Test methods

Clinical and sonological features were recorded before doing the US-FNAC. The presence of compressive symptoms such as dysphagia, dyspnea, throat irritation, and voice change was documented. The nodule was examined for its consistency and mobility and the neck examined for presence of cervical lymph nodes. The surgeon documented these clinical features. This was followed by US of the thyroid gland. US was done with a portable USG SonoSite MicroMAXX (USA); 6-13 MHz by the radiologist.

US features

US features of the thyroid nodule were categorized based on the Thyroid Imaging Reporting and Data System (TIRADS) proposed by Kwak *et al*.[5]

Ultrasound-guided fine-needle aspiration cytology

US-FNAC was done by two dedicated radiologists. FNAC was performed under US guidance from the most suspicious thyroid nodule. US-FNAC was performed using a 24-gauge needle with a 10 ml syringe, either by capillary, aspiration, or mixed sampling technique depending on the nodule and radiologist preference. The samples were prepared on glass slides and immediately fixed in 95% alcohol for Papanicolaou staining. Local anesthesia was occasionally used. The smears were assessed for adequacy by the onsite technician. If the sample was inadequate, the FNAC was repeated. In vascular lesions the cell block was selectively sent. These samples were reported by a single dedicated cytopathologist.

FNAC reports were classified into six groups based on the Bethesda system of cytology reporting inadequate, benign, atypia of undetermined significance (AUS), follicular neoplasm (FN), suspicious for malignancy (SM), and malignant (M).[6]

Reference standard

Accuracy was calculated by comparing US-FNAC, clinical features and US features with final histopathology (taken as the gold standard) for those who underwent thyroidectomy till April 2017.

Statistical analysis

The data were analyzed using STATA 13.1. The whole data set was summarized using the mean along with standard deviation for continuous variables and frequency along with percentage for categorical variables. Percentage of adequate and inadequate US-FNACs was calculated and reported according to the Bethesda system of thyroid cytology. For analysis, malignant FNAC, SM, FN, AUS were taken as positive – indication for surgery to rule out malignancy – and benign lesions were taken as negative. The inadequate and nondiagnostic samples were excluded from the analysis. For patients who had subsequent thyroidectomy/histopathology (128/290, 44.13%), the US-FNAC report was correlated with the histopathological examination (HPE) to calculate the accuracy and determine the sensitivity, specificity, and predictive values of US-FNAC. A Chi-square test was performed to determine the association between clinical variables, thyroid stimulating hormone, sonological features, US-FNAC, and final HPE. Univariate and multivariate logistic regression was performed to assess the strength of association between clinical variables and histopathology.

Sample size

Based on the unpublished data of our previous palpatory-FNAC (P-FNAC), the inadequacy rate of FNAC was 30% and the inadequacy rate of US-FNAC for nonpalpable thyroid nodules was 21%. Hence taking an intermediate value of 24% as the inadequacy of P-FNAC, the sample size was calculated. In order to estimate this with a precision of 5 and a 95% confidence interval (CI), the sample size needed is 290 subjects who need FNAC (4pq/d2, $4 \times 24 \times 76/5 \times 5 = 290$).

Results

Two hundred and ninety patients were evaluated for a thyroid nodule during the study period [Figure 1].

Clinical characteristics

The demographic characteristics, the clinical characteristics, the ultrasound features, and the type of operation done in the cohort of patients are described in Table 1. The correlation of clinical characteristic features and final HPE for those who underwent an operation is shown in Table 2.

Ultrasound characteristics

On ultrasound sonography (USG), the mean size of the nodule was 3.29 cm (range 1.1–12 cm). Majority of the nodules 259/290 (89.3%) were <4 cm in size. Solitary thyroid nodules were seen in 87 (30%) patients.

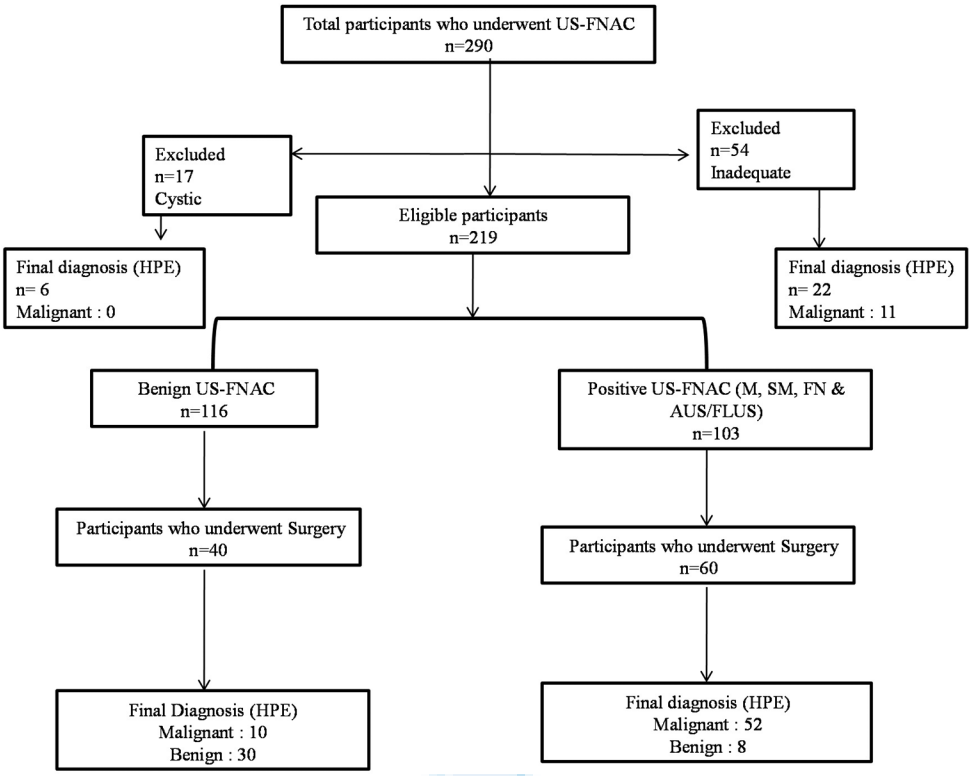

Figure 1: Diagram of the study group

The correlation of USG characteristics and final HPE in those who underwent operation (n = 128) is shown in Table 3. The risk of malignancy in each TIRADS category in shown in Table 4.

Surgery performed

Based on the FNAC result, clinical suspicion of malignancy, US features, compressive symptoms, and patient's wishes, 127 of 290 (43.79%) patients underwent thyroidectomy. One patient had a core biopsy for anaplastic carcinoma of thyroid. Total thyroidectomy was the most common surgical procedure done in 101 (79%) patients. Malignancy was seen in 73/128 (57%) [Table 5].

Adverse events in relation to US-FNAC

One patient had vasovagal syncope after the US-FNAC, which was managed conservatively.

Discussion

Clinical examination along with US examination and FNAC are the pillars of evaluation of a thyroid nodule. FNAC has helped us decrease the number of unnecessary thyroidectomies for benign thyroid swellings.

Clinical features

The role of clinical examination cannot be replaced by technological advances in sonology and other imaging modalities. Historically, the thyroid nodules with restricted mobility and a hard consistency are considered as markers of invasive thyroid cancer.[7] This study has shown that a hard nodule and palpable cervical lymphadenopathy was statistically significant in predicting malignancy ($P < 0.005$). All patients (12/12) with restricted/fixed mobility also had malignancy in the final HPE.

Compressive symptoms such as dysphagia, dyspnea, and a foreign body sensation in the throat are present in both benign and malignant thyroid swellings. Banks *et al.*[8] reported that 53% of patients undergoing thyroidectomy had compressive symptoms and 39% of them were malignant. In the present study, 37% of the patients had compressive symptoms, 60% of them were malignant. There was no association between compressive symptoms and malignancy ($P = 0.594$).

The peak incidence of malignancy is reported in the sixth to seventh decade in males and in the fifth decade in females.[9,10] However, in this study the highest incidence of malignancy was seen between 20 and 40 years (59%). This peak incidence in younger patients is probably due to similar trends seen in other malignancies in the country.[11,12]

Ultrasound characteristics

Kwak *et al.* reported the following US features to be significantly associated with malignancy: solid component, hypoechogenicity, marked hypoechogenicity, microlobulated or irregular margins, microcalcification, and taller-than-wide shape.[5]

In this study, the US features such as marked hypoechogenicity, irregular margins, microcalcification, and taller-than-wide shape were significant in predicting malignancy. As reported

Table 1: Baseline demographic and clinical characteristics of the participants

Demographic characteristics	*n*=290	Total no. of participants who underwent surgery *n*=128* (44%)
Sex		
Female	231 (79.6%)	100 (78%)
Male	59 (20.3%)	28
Side		
Right	160 (55.1%)	77
Left	118 (40.7%)	48
Isthmus	12 (4.1%)	3
Clinical characteristics		
Compressive symptoms	96 (33.1%)	47
Voice change	16 (5.5%)	11 (68.7%)
Consistency (hard)	26 (8.8%)	19
Mobility		
Restricted/fixed	23 (7.9%)	12
Significant lymph nodes	15 (4.1%)	13
Ultrasound findings		
Size of the nodule		
1-4 cm	222 (76.5%)	87
>4 cm	68 (23.5%)	41
Echogenicity		
Hypoechogenicity	59 (20.3%)	25
Marked hypoechogenicity	42 (14.5%)	29
Isoechoic nodule	143 (49.3%)	61
Hyperechoic nodule	30 (10.3%)	9
Calcification		
Microcalcification	97 (33.4%)	57
Macrocalcifications	28 (9.6%)	11
No calcifications	165 (56.9%)	37
Composition		
Solid lesions	171 (59.6%)	88
Mixed lesions	99 (34.5%)	34
Cystic lesions	17 (6%)	6
Margins		
Irregular	48 (16.5%)	35
Microlobulated	18 (6.2%)	6
Well-circumscribed	221 (76.2%)	87
Shape		
Taller-than-wide	41 (14.1%)	26
Wider-than-tall	244 (84.1%)	102
Halo sign		
Present	148 (51%)	55
Absent	137 (48%)	73
Type of operation		
Total thyroidectomy (TT)		101 (79.5%)
TT + CCND + MRND		13 (10.2%)
HT/completion thyroidectomy		6 (4.7%)
TT + CCND		5 (3.9%)
TT + Tracheal resection		2 (1.6%)

*One patient had core biopsy for anaplastic carcinoma of thyroid. TT: Total thyroidectomy, CCND: Central compartment neck dissection, MRND: Modified radical neck dissection, HT: Hemithyroidectomy

in the literature, with the increasing number of suspicious US features, the risk of malignancy also increases.[5]

The specificity of hypoechogenicity, microcalcification, irregular or lobulated margins, and taller-than-wide is greater than 80% and is comparable to Moon *et al*. and other studies in predicting malignancy.[6,13] A predominantly solid criterion alone may not be useful to differentiate malignant from benign nodule. In this study, solid lesions had a sensitivity of 78% and a specificity of 42%.

A TIRADS-3 nodule has a risk of 2–31% malignancy. Similar results were observed in this study, with 34% of TIRADS-3

Table 2: Correlation of clinical characteristics and malignancy rate in patients with final HPE

Clinical characteristics *n*=290	Total no. with HPE *n*=128	Malignant in final HPE (%)	*P*	Sensitivity (95% CI)	Specificity (95% CI)
Compressive symptoms (96)	47	28 (59.6%)	0.582	38.4 (27.2, 50.5)	65.5 (51.4, 77.8)
Voice change (16)	11	7 (63.6%)	0.618	9.59 (3.9, 18.8)	92.7 (82.4, 98)
Consistency (hard) (26)	19	17 (89.5%)	0.003	23.3 (14.2, 34.6)	96.4 (87.5, 99.6)
Significant lymph nodes (12)	11	10 (90.1%)	0.018	13.7 (6.77, 23.8)	98.2 (90.3, 100)
Mobility: Restricted/fixed (23)	12	12 (100%)	-	-	-

Table 3: Association between thyroid malignancy and various ultrasound features

USG characteristics *n*=290	Final HPE *n*=128	Malignant *n*=73 (%)	Univariate analysis		Multivariate analysis		Sensitivity (95% CI)	Specificity (95% CI)
			Odds ratio	*P*	Odds ratio	*P*		
Echogenicity								
Hypoechogenicity (*n*=59)	25	18 (30.5)	9.1 (1.5, 54.3)	**0.017**	7.1 (0.9, 55.03)	0.059	90 (68.3, 98.8)	50 (23, 77)
Marked hypoechogenicity (*n*=42)	29	27 (64.3)	47.2 (5.6, 397.2)	**0.001**	34.3 (2.7, 423.5)	0.006	93.1 (77.2, 99.2)	77.8 (40, 97.2)
Isoechoic nodule (*n*=143)	61	26 (18.6)	2.6 (0.5, 13.5)	0.257	2.5 (0.3, 17.1)	0.347	92.9 (76.5, 99.1)	16.7 (6.9, 31.4)
Hyperechoic nodule (*n*=30)	9	2 (6.4)	1	…	1	…	…	…
Calcification								
Microcalcification (97)	57	46 (47.4)	7.2 (3.1, 16.7)	**0.001**	3.4 (1.1, 10.4)	0.027	67.5 (55.2, 78.5)	77.6 (63.4, 88.2)
Macrocalcifications (27)	10	4 (14.8)	1.4 (0.4, 5.3)	0.582	1.2 (0.2, 5.1)	0.769	18.5 (6.3, 38.1)	86.4 (72.6, 94.8)
No calcification (165)	60	22 (13.3)	1	…	1	…	…	…
Composition								
Solid lesions (171)	88	55 (32.2)	1.5 (0.7, 3.3)	0.335	0.6 (0.2, 1.6)	0.343	75.3 (63.9, 84.7)	32.7 (19.9, 47.5)
Mixed lesions (99)	34	18 (18.1)	1	-	-	-	…	…
Margins								
Irregular (48)	35	28 (58.3)	4.7 (1.8, 11.9)	**0.001**	1.1 (0.2, 4.7)	0.824	41.2 (29.4, 53.8)	87 (75.1, 94.6)
Microlobulated (18)	6	5 (27.8)	5.9 (0.7, 52.4)	0.113	3.1 (0.1, 56.19)	0.435	11.1 (3.7, 24.1)	97.9 (88.9, 99.9)
Well-circumscribed (221)	87	40 (18.1)	1	…	1	…	…	…
Shape								
Taller-than-wide (41)	26	20 (48.8)	3.1 (1.1, 8.3)	**0.026**	0.4 (0.09, 1.8)	0.265	27.4 (17.6, 39.1)	89.1 (77.8, 95.9)
Wider-than-tall (244)	102	53 (21.7)	1	…	1	…	…	…
Halo sign (148)	55	20 (13.5)	4.6 (2.2, 9.8)	**0.001**	1.3 (0.43, 3.87)	0.632	…	…

Table 4: TIRADS classification

TIRADS category	Total number (*n*=290)	Surgery done (*n*=128)	Malignant in final HPE (*n*=73)
1	7 (2.4%)	3	-
2	26 (9%)	7	-
3	103 (35.5%)	35	12 (34.3%)
4a	74 (25.5%)	30	17 (56.7%)
4b	31 (10.7%)	19	14 (73.7%)
4c	30 (10.3%)	16	12 (75%)
5	19 (6.5%)	18	18 (100%)

nodules being malignant.[14-16] Although TIRADS-1, 2 and 3 are associated with benign tumors, 12/73 (16.4%) malignancies were assigned as benign and 67% were follicular variant of papillary carcinomas of thyroid, which are difficult to diagnose both by FNAC or US.[17] Taking TIRADS 4a, 4b, 4c, and 5 as malignant, the sensitivity is 83.6% [73, 91.2 confidence interval (CI)] and specificity of 60% (45.9, 73 CI) in predicting malignancy in the final HPE. TIRADS is a simple and practical method of assessing thyroid nodules.[18]

Adequacy of FNAC

A nondiagnostic FNAC report, even under US guidance, is reported in up to 33.6% in the literature.[4] This study has an inadequacy rate of 19.8%. Richards *et al.* have reported an inadequate US-FNAC rate of 29% in nodules ≥3 cm and Kim *et al.* have reported an inadequacy rate of 9.9% in nodules ≥4 cm.[19,20] In this study, the inadequacy rate is 21.9% in nodules ≥3 cm and 20.8% in nodules ≥4 cm. The inadequacy rate in nodules ≥2 cm to <3 cm is 20.2% and is least in nodules measuring ≥1 cm to < 2 cm, i.e. 11.6%. Factors that can improve the adequacy of thyroid FNACs are use of thinner needles, nonaspiration technique, preparation of cell block, and a dedicated cytopathologist.

Majority of the US-FNAC reports in this study are benign (42%), atypia of undetermined significance and

Table 5: Distribution of US-FNAC and final HPE

US-FNAC report	Total no. *n*=290† (%)	Total no. of patients with final histopathology (*n*=128)	Final histopathology (*n*=128)	
			Benign* (*n*=55*) (43%)	Malignant (*n*=73) (57%)
Malignant	34 (11.7)	28	-	28 (100) PTC-22 PDTC-1 MTC-3 AC-1
Suspicious for malignancy	18 (6.2)	12	1 (8.3) Thyroidits-1	11 (91.7) PTC-9 FVPTC-2
Follicular neoplasm	16 (5.5)	7	3 (43) NH-1 Thyroidits-1 NH-1	4 (57) PTC-2 FVPTC-2
FLUS/AUS	35 (12)	13	4 (30.8) NH-1 AH-1 FA-1 HCA-1	9 (69.2) FVPTC-8 PTC-1
Benign	116 (40)	40	30 (75) NH-18 Thyroiditis-2 CG-1 AH-3 FA-1 HCA-1 IM-4	10 (25) PTC-2 FVPTC-8
Inadequate	54 (18.6)	22	11 (50) NH-4 Thyroiditis-4 DG-1 HCA-2	11 (50) PTC-5 FVPTC-6
Cystic	17 (5.9)	6	6 (66.7) NH-4 IM-2	-

†Includes 17 cystic swellings; *Includes 6 incidental micro carcinomas. PTC: Papillary thyroid carcinoma, PDTC: Poorly differentiated thyroid carcinoma, MTC: Medullary thyroid carcinoma id, AC: Anaplastic carcinoma, FVPTC: Follicular variant of papillary carcinoma of thyroid, NH: Nodular hyperplasia, AH: Adenomatous hyperplasia, FA: Follicular adenoma, HCA: Hurthle cell adenoma, IM: Incidental microcarcinoma, CG: Colloid goiter, DG: Dyshormonogenetic goiter

malignancy rate of 12% each, suspicious for malignancy in 7% and follicular neoplasm 6%. This is comparable with the published literature.[21]

Accuracy of US-FNAC

A total of 127 patients were operated in the study group, out of which 73 (57%) were malignant. This high rate of malignancy >50% is described in the literature and is probably due to increased detection by US-FNAC and a referral bias in a tertiary hospital.[10]

The sensitivity of US-FNAC in predicting malignancy is 83.9% and specificity of 76.3%, with a positive predictive value of 85.2%, negative predictive value of 74.4%, and an accuracy of 81% in predicting malignancy in thyroid nodules ≥1 cm.

Of concern in the current study is an increased rate of malignancy (69%) in AUS/follicular lesion of undetermined significance (FLUS) and 89% of them had FVPTCs. This is probably due to low numbers, selection bias, or difficulty in diagnosing FVPTCs on FNAC. In a study by Ho *et al.*, who analyzed 541 AUS/FLUS lesions, malignancy rate was 26.6–37.8%.[22] They concluded that in some practice settings, AUS/FLUS may have a higher risk of cancer than 10–15% described in Bethesda. However, as recommended in the American Thyroid Association (ATA) guidelines, each institution is advised to validate the Bethesda scoring system.[23] This has been achieved through this study.

Of the 73 malignant histopathology reports, 10 (13.7%) were termed as benign on US-FNAC. However, 8 out of 10 (80%) patients had FVPTC and 2 had classic PTC. Of the 41 classic PTCs in the current study, 2 (4.9%) were reported as benign on US-FNAC and 8 of the 26 FVPTCs (30.8%) were reported benign on US-FNAC. In a study by Didem Ozdemir, 64 out of

306 (20.9%) classic papillary thyroid carcinomas were reported as benign and 18 of 84 (21.4%) FVPTCs were reported benign on FNAC.[17] Fazeli *et al.* reported 15.2% (42/277) and Sheahan *et al.* reported 19% (5/26) of FVPTC as benign on FNAC.[24,25] FVPTCs are known to be difficult to interpret on FNAC and tend to have more benign features, with patchy distribution of nuclear features.[25-27] Sparse cellularity, possible sampling error, and small sample size could also attribute to this high rate. FVPTC needs to be looked at carefully; further research to help in decreasing false negative rates of FVPTC will help in increasing the accuracy of US-FNAC.

Univariate analysis has shown that positive US-FNAC (includes AUS/FN/SM/M), markedly hypoechoic, taller-than-wide, irregular margins, presence of microcalcification, progressive TIRADS (increasing number of suspicious features), and the clinical features such as hard in consistency are significant in predicting malignancy.

Multivariate analysis showed positive US-FNAC (including AUS/FN/SM/M) alone is significant in predicting malignancy.

Limitations

- There was no onsite cytopathologist; however, there was an onsite cytotechnician
- There were six incidental micro carcinomas that were included in the benign category
- Follow-up data for those patients who did not have surgery was not available
- In this study, 44% of the study population underwent thyroidectomy after US-FNAC and 57% of those were malignant on HPE. This could explain the high malignancy rate in each category of the Bethesda classification
- Histopathology reported FVPTC without capsular or vascular invasion in 22 patients. We could not categorize these patients into the recent classification of noninvasive follicular neoplasm with papillary-like nuclear features as the entire gross specimen would need to be re-examined for capsular or vascular invasion.

Conclusions

The adequacy and accuracy of US-FNAC in this study are 80.2 and 81%, respectively. The US-FNAC, a high TIRADS score, and clinical features such as hard in consistency and significant lymph nodes are significant in predicting malignancy in thyroid nodule ≥1 cm. Each institution should validate the Bethesda system of thyroid FNAC reporting, as the rate of malignancy may vary in individual categories. The accuracy rate in benign and AUS categories needs to improve in this study and 84% of them had a FVPTC. FVPTCs are difficult to diagnose, both by ultrasound and FNAC. Further research to help in decreasing false negative rates of FVPTC will help in increasing the accuracy of US-FNAC in the present study.

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Conflicts of interest

There is no conflicts of interest.

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