Cytological diagnosis of thyroid lesions by Bethesda system and correlation with sonography and biochemical profile

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Abstract

Thyroid gland is unique among endocrine glands. The most common thyroid lesion is colloid goiter. A careful physical examination and relevant investigations like thyroid function tests, fine needle aspiration cytology and ultrasonography may be required for their accurate diagnosis. FNAC is considered as the method of choice for primary diagnosis of thyroid lesions. Ultrasound is a sensitive and specific modality in assessment of thyroid nodule with good overall accuracy. However, histopathology is the gold standard for confirmation of the diagnosis. Patients coming for thyroid FNA in the department of pathology were selected as study sample. Thyroid FNA was reported using Bethesda system of reporting. They were correlated with biochemical and sonographic findings. Histopathologic correlation was done for the specimens available for biopsy and the diagnostic accuracy of ultrasonography and FNAC was calculated for the subgroup whose biopsy is available. Pearson Chi-square test and Fisher's Exact test were used for comparing categorical variables between groups. A p value of <0.05 was considered statistically significant.

The diagnostic accuracy of both USG and FNAC were calculated with histopathology as gold standard. The accuracy of USG is 80.6% and the accuracy of FNAC is 91% according to this study. TFT has only a supportive role in the diagnosis of thyroid disorders.

Keywords: Bethesda system, TIRADS, Thyroid FNA, Thyroid USG

Introduction

Thyroid gland is largest of all endocrine glands and it is unique among endocrine organs. It is the first to develop in fetal life. It is easily approachable for direct physical

and cytological examination as it is superficial in location. Thyroid lesions are four times more common in females than in males.[1] The incidence of clinically apparent thyroid nodules is 4-5%.[2] About 90 % of the thyroid lesions are benign and malignant lesions constitute only 10%.[1] Some studies showed an overall prevalence of hypothyroidism to be 5.4% and hyperthyroidism to be 1.9% in goitres .

Colloid goitre is the most common thyroid lesion followed by Hashimoto thyroiditis.[2] Those clinically presenting as thyroid nodule may not be solitary nodule, it might be a dominant nodule of multinodular goitre (MNG). It may be impossible to differentiate malignancy of thyroid clinically especially in cases of thyroiditis. Previously benign adenoma or MNG can have malignant transformation. Therefore, the accurate diagnosis and appropriate management of thyroid lesions become very important. So, a careful physical examination, relevant investigations like thyroid function tests (TFT), fine needle aspiration cytology (FNAC)and ultrasonography (USG) may be required for accurate diagnosis and to plan the management accordingly.[3]

Thyroid function tests are done routinely in all thyroid lesions as a primary investigation. TFT includes T3, T4 and TSH. It helps to rule out certain conditions like Grave's disease, Hashimoto thyroiditis, toxic adenoma and toxic MNG. TFT is to be done before performing FNAC, as it can cause a transient increase in the thyroid hormone levels. Autoimmune thyroid diseases are usually accompanied by the presence of anti-thyroid peroxidase (TPO), anti-thyroglobulin (Tg) and anti-thyroid stimulating hormone receptor (TSHR).

Fine Needle Aspiration Cytology is considered as the method of choice for primary diagnosis of thyroid lesions. Every lesion is classified according to Bethesda system of reporting thyroid cytopathology. It includes six categories(I-VI). The main advantages are that it has excellent patient compliance, simple and quick to perform on OP basis, time saving and is cost effective and has high degree of sensitivity and specificity.[4]FNAC evaluation of the thyroid can also decrease the load of unnecessary surgeries for benign lesions and open the way for timely surgical intervention when there is risk of malignancy. A negative diagnosis should always be followed up with repeat ultrasound and FNA should be repeated in suspicious cases.

Ultrasound is a sensitive and specific modality in assessment of thyroid nodule with good overall accuracy. It is very much sensitive in detecting hypo echogenicity of the nodule that gives the suspicion of malignancy.[5] Also it gives good knowledge of internal anatomy of thyroid and its relation to adjacent organs. It tells about internal composition (solid and cystic), presence of nodularity, invasion of nearby structures, antero-transverse diameter assessment of blood flow pattern in and around the lesion, calcification and presence of peripheral halo to differentiate between benign and malignant nodules. Ultrasound features are extremely useful in selecting the site within a nodule for FNAC in order to improve diagnostic yield. Thyroid lesions are classified according to TIRADS (Thyroid Imaging Reporting and Data System) which was proposed by American college of radiology. It classifies thyroid lesions into five categories. Ultrasound examination is safe, non-radioactive and a non- invasive method. USG- guided FNA is widely accepted as primary tool for evaluating thyroid lesions. However, histopathology is the gold standard for confirmation of the diagnosis.[1]

This study is done to classify thyroid lesions cytologically and evaluate correlation with biochemical parameters and ultrasonographic findings.

Materials and Methods

Study setting

Department of Pathology, Govt. Medical college, Thrissur.

Study design

Cross sectional study.

Study subjects

Cases of thyroid swellings coming to the Department of Pathology for FNAC with their biochemical and sonographic work up done and those that satisfy the inclusion and exclusion criteria.

Inclusion criteria

Patients of both sex with thyroid swelling, with ultrasonography and thyroid function tests done.

Exclusion criteria

Patients less than 18 and above 80 years.

Sample size calculation

Calculated using the formula,

$$N = \frac{z^2 \times specificity\ (1\text{-}specificity)}{W^2\ (1\text{-}p)}$$

Z=1.96

As per study of Sudhir V. Bhise.et.al,

Specificity = 91.6%

W = 0.05   p = 30%

Thus, the calculated sample size is 169.

Study procedure

Patients who came for thyroid FNA in the department of pathology whose TFT and USG reports are done are selected and consent taken. FNA was done using 25 G needle. Dry and wet smears were made. Wet smears were fixed in ethanol and stained using Papanicolaou stain. Dry smears were stained with Leishman stain.

Thyroid FNA was reported using Bethesda system of reporting. They were correlated with biochemical and sonographic findings. Histopathologic correlation was done for the specimens available for biopsy and the diagnostic accuracy of USG and FNAC was calculated for the sub group whose biopsy is available.

Statistical analysis

All he data collected were coded and entered in Microsoft Excel sheet and analyzed using SPSS statistical software version 22. Quantitative variables were summarized using mean and standard deviation (SD). Diagnostic characteristics of USG and FNAC were found out by comparing it with biopsy. Pearson Chi-square test and Fisher's Exact test were used for comparing categorical variables between groups. A p value of <0.05 was considered statistically significant.

Study duration: Maximum of 12 months

Results and Discussion

Age distribution

The sample size was 169. The age range was 18- 80 years with a mean of 46.11 and a standard deviation of 13.02. The most frequent age group in this study is 41-50 years with 33.1 % of the sample size. It is only 3.6% in the age group of ≤20 years.

Table 1: Age Distribution

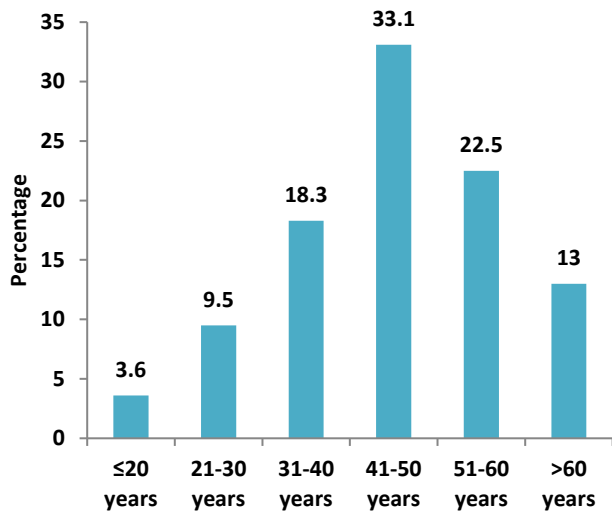| Age	Number	Percent
≤20 years	6	3.6
21-30 years	16	9.5
31-40 years	31	18.3
41-50 years	56	33.1
51-60 years	38	22.5
>60 years	22	13

Figure 1: Age distribution

Gender distribution

Out of 169 cases, 152 were females (89.9%).

Table 2: Gender Distribution

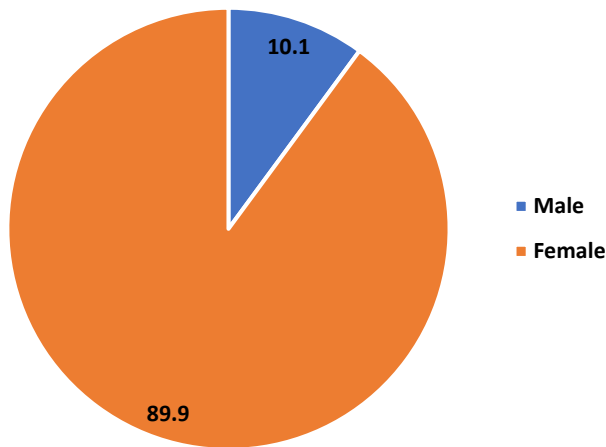| Gender	Number	Percent
Male	17	10.1
Female	152	89.9

Figure 2: Gender distribution

Serum T3 level

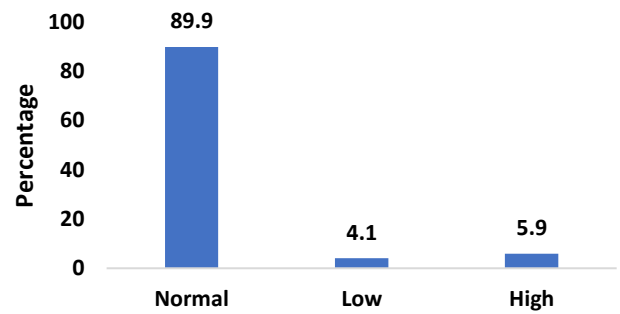T3 levels were normal in 152 cases (89.9%).

Figure 3 : T_3

SERUM T4 LEVELS

Serum T4 levels were normal in 152 samples (89.9%)
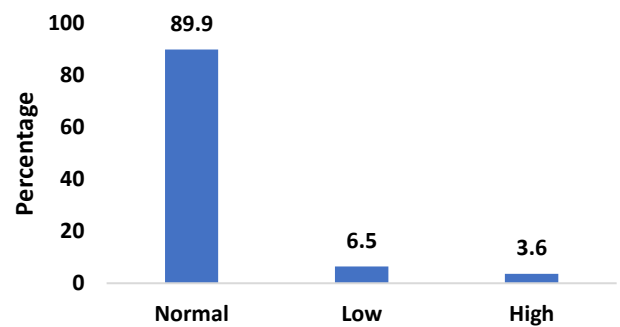

Figure 4: T_4

SERUM TSH LEVEL

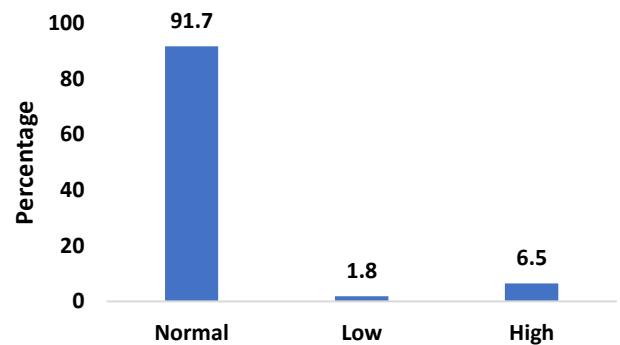Serum TSH levels were normal in 155 samples (91.7%).

Figure 5: TSH

TFT does not play a major role and it has only a supportive role in the diagnosis of thyroid disorders.

USG Findings

According to the study conducted by Periakaruppan et.al., the most common thyroid lesions belong to TIRADS category 2.[6] Most of the thyroid pathologies in

this study also belong to TIRADS 2 USG classification (55%) that include benign conditions with 0% risk of malignancy. The second most common is TIRADS 3 which are probably malignant with <5% risk of malignancy.

Table 3: USG Findings

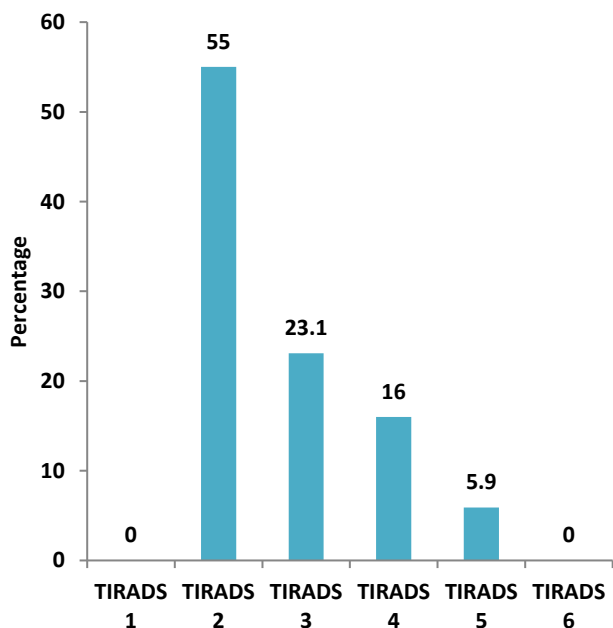| USG findings	Number	Percent
TIRADS 1	0	0
TIRADS 2	93	55
TIRADS 3	39	23.1
TIRADS 4	27	16
TIRADS 5	10	5.9
TIRADS 6	0	0

Figure 6: USG findings

FNAC diagnosis

In this study, 26% of the cases were cytologically diagnosed as nodular colloid Goitre followed by nodular colloid goitre with cystic degeneration (20.7).

Table 4: FNAC Diagnosis

| Cytological diagnosis	Number	Percent
Nodular colloid goitre	44	26
Nodular colloid goitre with cystic degeneration	35	20.7
Lymphocytic /Hashimoto thyroiditis	27	16
Nodular colloid goitre with lymphocytic thyroiditis	29	17.2
Benign follicular nodule	11	6.5
Atypia of undetermined significance	3	1.8
Suspicious of follicular neoplasm	6	3.6
Follicular neoplasm	3	1.8
Suspicious of malignancy	3	1.8
Papillary carcinoma	8	4.7
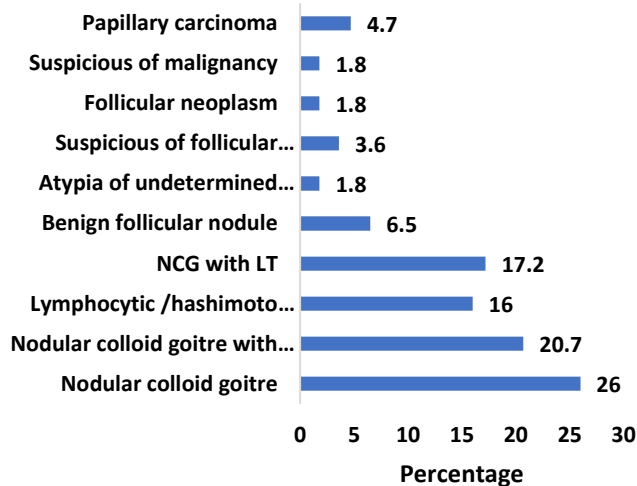
Figure 7: FNAC Findings

Nature of lesion- FNAC

Out of the 169 samples, 146(86.4%) cases were benign.

Only 11 cases (6.5%) were found to be malignant.

Table 5: Nature of Lesion- FNAC

According to the study conducted by Reuter et.al., 59.6% thyroid lesions were benign. [7]But in our study, 86.4% were found to be benign.

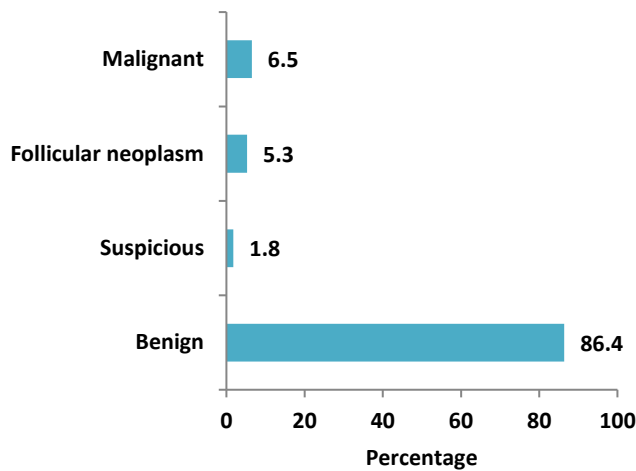| Nature of lesion- FNAC	Number	Percent
Benign	146	86.4
Suspicious	3	1.8
Follicular	9	5.3
Malignant	11	6.5

Figure 8: FNAC

Histopathological Diagnosis

Out of the 169 cases, only 67 were available for biopsy. Majority of them were diagnosed as multinodular goitre (22.4%). According to study conducted by Magdalene et.al., most common non- neoplastic lesion is colloid goitre as in our study.[8] Least common were hyperplastic nodule with LT and hurthle cell carcinoma. Follicular adenoma, follicular carcinoma and papillary carcinoma constitutes 6%, 7.5% and 14.9% respectively.

Table 6: Histopathological Diagnosis

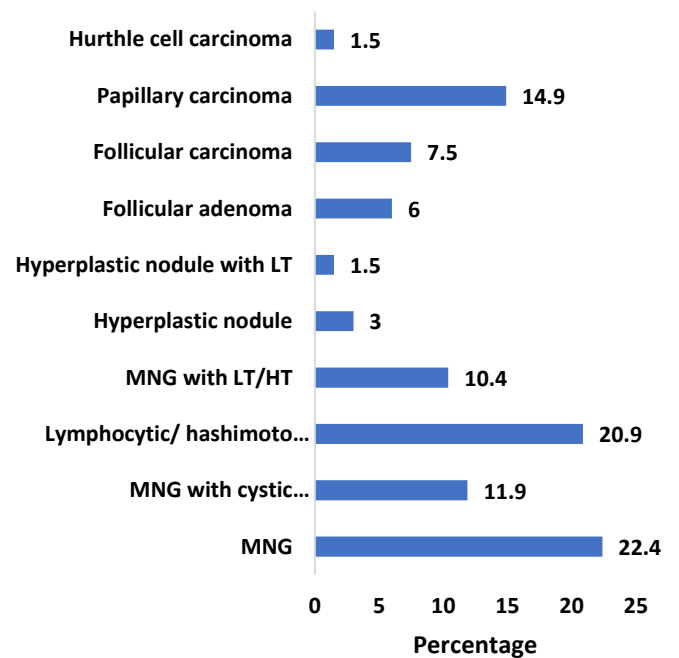| Histopathological diagnosis	Number	Percent
MNG	15	22.4
MNG with cystic degeneration	8	11.9
Lymphocytic/ Hashimoto thyroiditis	14	20.9
MNG with lymphocytic /Hashimoto thyroiditis	7	10.4
Hyperplastic nodule	2	3
Hyperplastic nodule with lymphocytic thyroiditis	1	1.5
Follicular adenoma	4	6
Follicular carcinoma	5	7.5
Papillary carcinoma	10	14.9
Hurthle cell carcinoma	1	1.5

Figure 9: Histopathological diagnosis

Nature of lesion- Histopathology

Most of the lesions available for the biopsy were found to be benign (76.1%). Out of the available cases, 23.9% turned out to be malignant.

Table 7: Nature of lesion- Histopathology

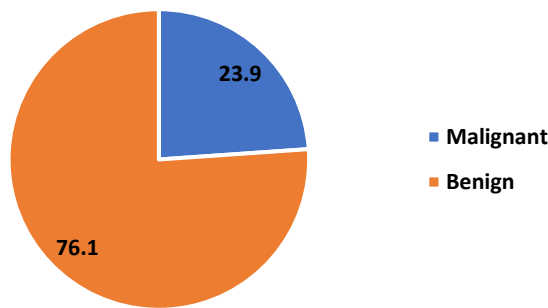| Nature of lesion- biopsy	Number	Percent
Benign	51	76.1
Malignant	16	23.9

Figure 10: Nature of lesion-Biopsy

Diagnostic accuracy of USG and FNAC

According to the study of ayub et.al., sensitivity rate of FNAC was 96.39% and specificity was 76.47%. Positive predictive value was 95.24% and negative predictive value was 81.25%. [9] according to the study conducted by Chaudhary et.al., the sensitivity and npv of USG are 91% and 94.7% respectively.[10]

In our study, the sensitivity of FNAC is 62.5% and specificity is 100%. The specificity of USG is 37.5% and specificity is 94.1%. The accuracy of FNAC is 91% and that of USG is 80.6%. The positive predictive values of USG and FNAC are 66.7% and 100% respectively. The negative predictive values of USG and FNAC are 82.8% and 89.5% respectively.

Table 8: diagnostic accuracy of USG and FNAC

	Biopsy	
	Malignant	Benign
FNAC		
Malignant	10	0
Benign	6	51
USG		
Malignant	6	3
Benign	10	48

	Sensitivity	Specificity	PPV	NPV	Accuracy
FNAC	62.5	100	100	89.5	91
USG	37.5	94.1	66.7	82.8	80.6

Table 9: biopsy v/s USG Findings

USG findings	Biopsy- no. (%)									
	MNG	MNG with cystic degeneration	LT/HT	MNG with LT/HT	Hyper plastic nodule	Hyperplastic nodule with LT	Follicular adenoma	Follicular carcinoma	Papillary carcinoma	Hurthle cell ca
TIRADS 2	10(32.3)	4(12.9)	9(29)	5(16.1)	1(3.2)	0	0	1(3.2)	1(3.2)	0
TIRADS 3	3(20)	2(13.3)	2(13.3)	2(13.3)	0	1(6.7)	2(13.3)	3(20)	0	0
TIRADS 4	1(8.3)	2(16.7)	2(16.7)	0	1(8.3)	0	1(8.3)	1(8.3)	3(25)	1(8.3)
TIRADS 5	1(11.1)	0	1(11.1)	0	0	0	1(11.1)	0	6(66.7)	0

Biopsy v/s USG findings

Multinodular goitre, MNG with cystic degeneration, lymphocytic thyroiditis and MNG with lt, which are benign conditions that belongs to tirade 2 were even grouped under tirades 3, 4 and 5 that has an increase in risk of malignancy.66.7% of papillary thyroid carcinoma cases were grouped in tirade 5 category. Rest of the cases in tirade 2 and 4. Follicular neoplasms were in tirade 2-5 categories. Hurthle cell carcinoma was included in tirade 4.

Biopsy v/s FNAC Findings

Most of the cases diagnosed as nodular colloid goitre, nodular colloid goitre with cystic degeneration, lymphocytic thyroiditis and nodular colloid goitre with lymphocytic thyroiditis were turned out to be MNG in biopsy. Only cases of nodular colloid goitre with cystic degeneration were diagnosed same in both FNAC and biopsy. FNAC diagnosis of suspicious of follicular neoplasm came out as follicular adenoma (40%),

follicular carcinoma (40%) and hyperplastic nodule (20%). Those diagnosed as follicular neoplasm in FNAC came as either follicular adenoma or follicular carcinoma in biopsy. FNAC suspicious of malignancy were follicular or papillary carcinoma in histopathological examination. Papillary carcinoma cases (8 cases) in FNAC were confirmed by biopsy. Hurthle cell carcinoma was previously diagnosed as atypia of undetermined significance in FNAC.

Biopsy v/s FNAC findings

Table 10: biopsy v/s FNAC findings

FNAC	Biopsy- no. (%)									
	MNG	MNG with cystic degeneration	LT/HT	MNG with LT/HT	Hyperplastic nodule	Hyperplastic nodule with LT	Follicular adenoma	Follicular carcinoma	Papillary carcinoma	Hurthle cell carcinoma
NCG	6(75)	0	0	0	0	1(12.5)	0	0	1(12.5)	0
NCG with cystic degeneration	5(38.5)	8(61.5)	0	0	0	0	0	0	0	0
LT/HT	2(14.3)	0	12(85.7)	0	0	0	0	0	0	0
NCG with LT	2(15.4)	0	2(15.4)	7(53.8)	1(7.7)	0	1(7.7)	0	0	0
AUS	0	0	0	0	0	0	0	0	0	1(100)
Suspicious of follicular neoplasm	0	0	0	0	1(20)	0	2(40)	2(40)	0	0
Follicular neoplasm	0	0	0	0	0	0	1(33.3)	2(66.7)	0	0
Suspicious of malignancy	0	0	0	0	0	0	0	1(50)	1(50)	0
Papillary carcinoma	0	0	0	0	0	0	0	0	8(100)	0

Statistical Significance

P- value was calculated for each factors including age, gender, t3, t4 and TSH. The calculated p- value were 0.113, 0.345, 0.645, 0.327 and 0.501 for age, gender, t3, t4 and TSH respectively. A p value of <0.05 is considered statistically significant. Thus, in our study no statistical significance is found between thyroid lesions and age, gender, t3, t4 and TSH.

Conclusion

In our study, 169 cases were studied. The age range considered was 18-80 years. Most of the patients were in the age group of 41- 50 years. Most of the patients were females. A majority of the cases had normal TFT values. Majority of the thyroid lesions were categorized as TIRADS 2 which are benign. Cytological diagnosis was based on Bethesda system of reporting thyroid cytopathology. In FNAC, 86.4% were found to be benign, 1.8% suspicious of malignancy, 5.3% follicular neoplasms and 6.5% malignant. Most common lesion was nodular colloid goitre. In biopsy also, most common lesion was multinodular goitre, 76.1% benign and 23.9 cases were proven to be malignant. The diagnostic accuracy of both USG and FNAC were calculated with histopathology as gold standard. The accuracy of USG is 80.6% and the accuracy of FNAC is 91% according to this study. TFT has only a supportive role in the diagnosis of thyroid disorders. In our study, no statistical significance is found between thyroid lesions and age, gender, T3, T4 and TSH.

Abbreviations

TFT- Thyroid function tests

FNAC- Fine needle aspiration cytology

USG- Ultrasonography

SD- Standard deviation

TIRADS- Thyroid Imaging Reporting and Data System

MNG- multinodular goiter

TPO- Thyroid peroxidase

TG- thyroglobulin

TSH- Thyroid stimulating hormone

TSHR- Thyroid stimulating hormone receptor

Rt3- Reverse T3

TBG- Thyroid binding globulin

TBPA- Thyroid binding pre albumin

MIT- Mono iodothyronine

DIT- Di iodothyronine

HT- Hashimoto thyroiditis

RIA- Radio immune assay

GD- Graves' disease.

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