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ROLE OF ULTRASOUND IN EVALUATION OF THYROID DISEASES.

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INTRODUCTION

Ultrasonography is the most common and most useful way to image the thyroid gland and its pathology, as recognized in guidelines for managing thyroid disorders published by the American thyroid Association.[1] Thyroid nodule is a common clinical problem. Epidemiologic studies have shown that the prevalence of palpable thyroid nodules is found in approximately 5% of women and in 1% of men living in iodine - sufficient parts of the world.[2]

On the other hand, ultrasound (US) studies could detect thyroid nodules in 19-67% of selected individuals with higher frequencies mainly in women and elderly people.[3] The majority of patients with thyroid nodule can be managed conservatively and it justifies the effort to select better candidates for thyroidectomy. A number of clinical, US, and cytological parameters have been previously studied; however, none of them have shown significant impact on clinical practice.[10] Molecular markers are promising but they have not yet been sufficiently validated to be used in clinical practice.[4] The role of clinical evaluation of patients who have thyroid nodule is to minimize the risk of overlooking thyroid cancer.

KEYWORDS: Thyroid gland masses, High Resolution Ultrasound, Fine Needle Aspiratopn, Cytohistopathology.

AIMS AND OBJECTIVE

1. To diagnose a thyroid disease as accurately as possible by high resolution sonography.
2. To do ultrasound guided FNAC for microscopic examination and final diagnosis.

MATERIAL AND METHODS

Selection Criteria

All patients of any age group presenting with a thyroid condition were taken up for study. The study comprised of 21 patients referred from various departments, O.P.D's/ wards, of Tata Main Hospital.

Exclusion Criteria

a) Patients lost to follow up.
b) Ultrasound guided FNAC was not done in patients with deranged coagulation profile.
c) Known cases of thyroid disorders on treatment.

Machine Specification

Ultrasound machines

1. LOGIQ PRO 5 [GE] with 10-12 MHz probe.
2. SSD DYNAVIEW-II [Aloka, Tokyo] with 7.5 MHz probe

Doppler examination: Following sonography, color flow imaging and spectral waveform analysis were performed. The color and pulsed Doppler parameters including wall filter, gate width, gain and velocity scale were optimized for detection of flow and calculation of impedance indices. Each tumor was imaged in multiple planes and evaluated with respect to the number and origin of vessels supplying the tumor, and the pattern of vascular branching within the tumor, the presence and degree of intratumoral blood flow. Intratumoral vascularity was graded on a four point scale:
Grade 0 = no intratumoral flow is detectable or vascular rim identified.
Grade 1 = occasional pixels of color was transiently present within the tumor parenchyma.
Grade 2 = vascular rim or a large feeder vessels in the periphery of the mass only; little or no blood flow is detectable in the central portions of the tumor.
Grade 3 = well-defined vascular rim surrounds the tumor; large feeder vessels are visible; flow is easily detectable throughout the tumor parenchyma.

Pattern of vascular branching within the tumor as seen on color Doppler imaging were characterized as either peripheral (basket-like) or central (branching) or mixed.

Angle-corrected frequency spectra were obtained from intratumoral vessels and evaluated for the presence of disturbed or turbulent blood flow. Peak systolic and end-diastolic velocities were measured the intratumoral vessels and the vascular impedance was estimated by calculating a resistive index (RI) & pulsatility index (PI).

Ultrasonographic and Doppler findings were correlated with clinical findings, cytohistopathology & surgical findings or follow up as in TB patients.

FNAC (USG FNAC): With the free-hand method, the needle is inserted parallel to, or at an angle to the ultrasound beam and at a distance from the transducer, aiming at the lesion/nodule. Oblique to a perpendicular approach is simple and lacks complications. The needle shaft is not imaged with this technique but its tip is seen as a very bright spot when it crosses the plane of the scan. The tip of the needle must be within the lesion during aspiration. Employing Doppler technique to identify and avoid puncturing blood vessels in the region of a nodule provides a distinct advantage to reduce the amount of blood in the aspirate and facilitates interpretation of the cytology.

OBSERVATIONS

Table 1: Distribution of benign and malignant thyroid lesions.

	Benign	Malignant
	19	2
Percentage	90%	10%

Table 2: Age and sex distribution of cases-final diagnosis.

	0-10	11-20	21-30	31-40	41-50	51-60	>60	total	M:F
colloid goiter		1	3	6	2	2		14	5:9
Diffuse enlargement			1	2				3	0:3
Follicular lesion				2				2	0:2
Thyroid malignancy			1				1	2	0:2

Thyroid disorders were more in females in age group 21-40 years (15 cases) accounting for 71% of thyroid masses.

Table 3: Final diagnosis vs. HRUSG.

USG diagnosis	No. of cases (US)	Same on FNAC	Different (was diagnosed on US)	Final diag.
Colloid goiter	13	12	1 (Papillary ca.)	14
Diffuse enlargement	3	3		3
Follicular lesion	4	2	2(colloid goiter)	2
Thyroid malignancy	1	1		2

The ultrasonographic diagnosis was in agreement with the final diagnosis in 18 out of 21 cases (85%).

Colloid Goiter: 14 Cases

Out of 21 thyroid cases (5 males and 16 females), 14 cases had uninodular or multinodular colloid goiter. This group comprised 66.6% of all thyroid masses. Age distribution of cases was as, 6 cases in the age group of 31-40 years, 3 patients in the age group of 21-30 years, 2 cases were in each age group of 41-50 & 51-60 years and 1 case was seen in the age group of 11-20 years. All patients presented with clinical symptom of swelling of neck and 1 patient complained of dysphagia and difficulty in breathing due to pressure effect on trachea. None of the patients had signs or symptoms of hypo or hyperthyroidism. Laboratory investigation revealed anemia in 7 cases. Thyroid function test were normal in all the 14 patients. Soft tissue X-ray of neck, AP and lateral views were positive in 3 cases in the form of soft tissue swelling, calcification and/or lateral displacement of trachea. FNAC revealed all the cases to be colloid goiter.

Table 4, HRUSG Features of colloid goiter (14cases).

USG Features	No. of cases	Percentage
Echogenicity		
Isoechoic	3	21%
Hypoechoic		
Hyperechoic	2	14%
Mixed	9	65%
Nodularity		
Solitary	9	64%
Multiple	5	36%
Calcification		
Coarse Punctate	5	36%
Halo		
Well defined complete	8	57%
Ill-defined incomplete	6	43%
Margins		

Well defined	10	71%
Ill defined	4	29%

The most common finding on grey scale examination was that of mixed echogenicity containing areas of degeneration and sponge like honey comb pattern. Purely anechoic areas of serous or colloid degeneration were seen in 7 of 9 cases containing bright echogenic foci with comet tail artifacts. Coarse calcifications were seen in 5 (36%) cases with characteristic egg shell calcifications seen in 2 cases. Hypoechoic halo of 2-3mm was seen in all cases but it was well defined and complete only in 57% of cases including 3 cases with isoechoic nodules. Hypoechoic halo and well defined margins were mostly associated with nodules of size < 3cm. Multiple nodules (2 or above) were present in 5 (36 %) cases, seen in both lobes, which were **not appreciated** on clinical examination.

Table 5: Doppler features of colloid goiters; - 14cases.

Doppler features	No. of cases	Percentage
Grading of vascularity Gr 0 Gr 1 Gr 2 Gr 3	 10 4	 72% 28%
Pattern of vascularity Central Peripheral Mixed	 2 2	 14% 14%

Most of the nodules were avascular, 4 cases showed low vascularity mostly peripheral with RI>0.5.

Diffuse Thyroid Enlargement: - 3 Cases

A 32 years old female patient presented with swelling in the neck of 3 mth duration. No other symptoms were related to the swelling. Thyroid functions were found to be normal. USG revealed diffuse homogenous enlargement of both lobes of thyroid gland. The volume of right lobe thyroid was 37.5 ml and that of left lobe of thyroid was 30ml. There was no evidence of any calcification within the gland or cervical lymphadenopathy. On Doppler evaluation the lesion was mildly vascular with grade 1 vascularity with central pattern of vascularity. Two other cases also had similar features one 28 years and other 35 years old females. One of them had small areas of degeneration and calcification. The cut off limit for normal thyroid size and volume was taken as 25 ml in males and 20 ml in females.

Goitrous enlargement (diffuse and nodular) of thyroid gland formed about 81% (17/21) of thyroid masses.

Follicular Adenoma: - 2 Cases

Follicular adenoma comprised 9.5% of thyroid masses in my study. Two cases were seen both females 33 and 36 years old. Both had a long standing history of mild asymmetrical thyroid enlargement (7years and 1 year). Nodules were palpable moving with deglutition, firm but not tender on palpation. Grey scale US showed enlarged thyroid lobes containing well marginated haloed hyper echoic nodules of sizes 4x2 cms and 3.5x3 cms. Nodule of size 4x2 cm had a small anechoic cystic area. Both had intrasubstance chaotic vascularity (grade II) with RI of 0.5-0.6. Internal calcific foci and cervical adenopathy was not seen. Both cases under went US guided FNA which revealed follicular adenoma which were latter operated. Biopsy specimen showed the benign nature as capsule was not infiltrated. Two other cases were also diagnosed on HRUSG as follicular adenoma which on FNAC were found to be colloid nodules. Table 6 below summarizes the US features of 4 cases diagnosed follicular lesions on US.

Table 6: US feature in follicular lesions of thyroid.

F. lesion on US	US features	FNAC diag.
Case 1	Well defined, hyperechoic, halo, grade II vascularity, no cyst or calcification.	Follicular lesion
Case 2	Well defined, hyperechoic, halo, grade II vascularity, small cyst, no calcification seen.	Follicular lesion
Case 3	Well defined, hyperechoic, incomplete halo, grade II vascularity, cyst seen, calcification outside the nodule.	Colloid nodule
Case 4	Well defined, hyperechoic, halo, grade I vascularity, no cyst or calcification	Colloid nodule

Early colloid changes may show increased vascularity and appear hyperechoic.

Papillary Carcinoma Thyroid: - 1 Case
A 24 years old unmarried female patient studying in college presented with well defined firm nodule in the right lobe of thyroid gland with associated loss of appetite and loss of weight for 7mth duration.

USG finding: - Well defined iso to hypoechoic nodule of size 1.5x0.8 cm in right lobe of thyroid. Nodule had a well-defined hypoechoic halo with internal cystic area. Doppler study showed grade I vascularity. A diagnosis of colloid goiter was made on the basis of US features though it was considered suspicious. No enlarged lymph nodes were seen in neck. US guided FNA was done which latter revealed papillary carcinoma. So it was an atypical papillary carcinoma with no features of a typical one except for hypoechogenicity.

Anaplastic Carcinoma:- 1 Case
A 60 yr. old female patient presented with large neck mass for over a year which had rapidly increased in size for last 4 weeks causing dysphagia with difficult breathing and hoarse voice. Early FNAC was in favour of goitrous enlargement of thyroid.

USG:-10 cm mass on left side having heterogenous echopattern with areas of degeneration and amorphous calcifications. Doppler showed grade II vascularity with low resistance (RI 0.12).

Right lobe was normal in size and had calcific foci. A 3cm hypoechoic lymph node was seen at level 4. There was retrosternal extention of the mass so lower limit could not be found. FNAC was repeated and MRI advised. FNAC was now suggestive of anaplastic thyroid carcinoma. MRI showed the hetregenous mass with its retrosternal extension. Patient died within few days in the hospital.

Table 8: [2X2 table], US in detecting neoplastic thyroid lesions [2 Follicular, 1 Papillary, 1 Anaplastic] in 21 thyroid cases.

Test Result	Diseased	Non-diseased	Total
Positive	a (3)	b(2)	5
Negative	c(1)	d(15)	16
Total	4	17	21

Sensitivity (True positive) = $\frac{a}{a+c} \times 100 = 75\%$

Specificity (True negative) = $\frac{d}{b+d} \times 100 = 88\%$

Positive Predictive Value = $\frac{a}{a+b} \times 100 = 60\%$

Negative Predictive Value = $\frac{d}{c+d} \times 100 = 94\%$

Accuracy = $\frac{a+d}{a+b+c+d} \times 100 = 86\%$

Horvath E et al correlated Thyroid Imaging Reporting and Data System (TIRADS) with needle-biopsy results. In a sample of 1097 nodules (benign: 703; follicular lesions: 238; and carcinoma: 156), the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 88, 49, 49, 88, and 94%, respectively.[5]

Ito Y, Amino N et al studied 1244 nodules identified by ultrasonography in 900 patients, stratified these nodules into classes 1 to 5. They found the positive predictive value of ultrasonographic evaluation of malignancy was 97.2%.[6]

DISCUSSION

Thyroid diseases
There was a high female preponderance in lesions of thyroid gland (76%). Adenomatous or colloid MNG is the most common cause of asymptomatic thyroid enlargement with an incidence of about 3% to 5% of the general population in developed countries (there is a higher incidence in endemic goiter regions in the world).[7] It is universally acknowledged that nodular goiter of thyroid has a striking female preponderance with a ratio of 8:1 (Anderson's - 10th). Malignant lesions of thyroid also tend to occur more commonly in

Females.[8] The most common symptoms observed in this study were swelling in the neck (100%), pain (14%). fever (4%), loss of appetite and loss of weight. The most common clinical signs were palpable mass (100%) which was causing difficulty in swallowing in upto 20% of cases.

Laboratory investigations revealed presence of anemia in 20%. Thyroid function tests were found to be normal in all cases. It has been reported that most patients with benign and malignant tumors of thyroid are euthyroid; a goiter may be euthyroid, hypothyroid, or hyperthyroid.[9]

Colloid goiter
Present study included 14 (36%) patients of colloid goiter, 9 females and 5 male with an age range of 18-56 years. The most common presentation was swelling in the neck with 1 case complaining of dysphagia and difficulty in breathing due to pressure effects of the enlarged thyroid gland, all had multinodular goiter. Patients of MNG usually are older women, present with pressure effects due to enlarged thyroid gland.[10]

Sonography revealed all solitary nodules to be iso-hyperechoic (mostly mixed) in echo texture showing nodular cystic changes with perinodular hypoechoic halo

which was found to be thin & well defined. Halo was complete in 8 cases.

In view of the sonographic findings a diagnosis of colloid goiter was suggested in 10 cases with solitary thyroid nodule. Nine cases were same on FNAC but1 case was shown to be **papillary carcinoma** which was relatively hypoechoic on sonography. So this also proves that hypoechoic nodules should not be left alone.

Iso to hyperechoic echo-texture, intranodular cystic changes with perinodular hypoechoic halo have been described as features of benign nodules.[11] This corresponded with the findings in my study. A hypoechoic rim is thought mainly to represent the nodular capsule and is a feature of benign nature.[12] This was also seen in my study.

In one study, the highest incidence of calcification was found in thyroid cancer (54%), followed by multinodular goiter (40%), solitary nodular goiter (14%), and follicular adenomas (12%). The authors reported that calcifications in a "solitary" nodule in a person younger than 40 years person should raise a strong suspicion of malignancy because of a relative cancer risk of 3.8 versus 2.5 in patients older than 40 years with calcified nodules.[13]

In a study conducted by Solbiati et al,[14] perinodular halo was far more frequent in benign than in malignant lesions (86% vs. 14%). They noticed a significant difference between incomplete and complete halo, the latter being more frequently although not exclusively, encountered in benign lesions. This was also seen in the present study. They concluded that sonographic diagnosis of solitary thyroid nodules should be mostly based upon the echo pattern compared with normal parenchyma. Hyperechoic and especially liquid nodules can be safely regarded as benign and therefore further diagnostic procedures and surgery is spared.

On Doppler a total of 4 cases were vascular out of the 14 cases and the entire vascular colloid goiters showed grade 1vascularity except for 2 cases which showed slightly raised vascularity and were erroneously diagnosed as follicular lesions. The peripheral halo showed vascular signals in all cases. All the cases of colloid goiter showed a high resistance flow (RI>0.5).

Recently various flow related parameters using color Doppler have suggested a possible role for these techniques. But overlap between values in benign and malignant nodules is extensive and further studies are needed.[15]

Diffuse thyroid enlargement

Three cases of diffuse thyroid enlargement evaluated by sonography revealed the volume of individual thyroid gland lobes to be 25ml to 34ml in both lobes; the thyroid gland showed diffuse homogenous enlargement one showing few calcific foci. All cases were females in the age group of 21- 40 years. In view of the normal thyroid function tests and USG findings a diagnosis of diffuse thyroid enlargement (Diffuse goiter) were made.

Solbiati et al have shown that the volume of thyroid lobes up to 25 ml in men and 18 ml in women is considered as normal.[16] Diffuse enlargement of the thyroid gland is secondary to goiter in 80% to 85% of cases with a female to male ratio of 3:1. Sonographically, a diffuse goiter is more echogenic than the normal gland, displaying intrinsic coarse structures with rounded poles.

As published in journal of ultrasound in medicine, 2004, Palpation revealed poor discrimination of smaller thyroid sizes as determined by ultrasonography. Stepwise linear regression (backward selection) revealed that of the 3 thyroid dimensions, only the latero-medial dimension of the thyroid lobe had a significant correlation to lobe volume, accounting for 82.5% of the variability in lobe volume. The lobe volume (in milliliters) is given by the lobe latero-medial dimension (in centimeters) multiplied by 13 minus a constant of 15.[17]

Follicular lesions of thyroid: Follicular adenoma comprised 9.5% of thyroid masses in my study. Two cases were seen both females 33 and 36 years old. Both had a long standing history of mild asymmetrical thyroid enlargement (7years and 1 year). Grey scale US showed enlarged thyroid lobes containing well marginated haloed hyper echoic nodules. Both had intrasubstance chaotic vascularity (grade II) with RI of 0.5-0.6. Both were found to be benign on post-operative histopathological examination of biopsy specimen. Follicular adenomas are most commonly solitary and cytological differentiation from a follicular carcinoma is not possible on aspirates obtained from FNAB. The Scandinavian cytopathologists recommended that all thyroid aspirates containing abundant follicular cells be grouped into one category called "follicular neoplasms," indicating that the cytological differentiation between benign and malignant follicular neoplasms is not possible.[18]

On Doppler imaging, the majority (80-90%) of benign follicular lesions show perinodular blood flow signals (type II vascularity) where as 90% of malignant follicular lesions have a type III vascularity in over 90% of cases, as was also seen in our cases.

Two other cases were also diagnosed on HRUSG as follicular adenoma which on FNAC were found to be goiter nodules. Both of them were hyperechoic with increased vascularity but had incomplete halos.

Thyroid Carcinoma

Two cases were detected both were females one young lady who had papillary carcinoma and other elderly who had anaplastic carcinoma.

Papillary carcinoma: A 24 year old female patient presented with swelling in the neck with loss of appetite and weight. Thyroid function test was normal. Soft tissue x-ray neck AP and lateral view was done and no abnormality was detected. On sonography well defined iso to hypoechoic nodule was detected. Nodule had a well-defined hypoechoic halo with few small internal cystic areas. Doppler study showed grade I peripheral vascularity. No associated adenopathy was detected in the neck. A diagnosis of colloid goiter was made on the basis of US features though it was considered suspicious. US guided FNA was done which latter revealed papillary carcinoma. So it was an atypical papillary carcinoma with only feature in favor of malignancy being reduced echo pattern.

In a study done by Solbiati et al most malignancies were found among hypoechoic nodules (63%); moreover 95% of hypoechoic lesions were found to be adenomas or malignancies at surgery. In our case the thyroid malignancies were heterogeneous or hypoechoic.

Papillary carcinoma is the most common malignancy of thyroid, accounting for 60-70% of all thyroid malignancies.[19] The majority of patients are females, and it is the most frequent cancer in young individuals. The 20 year survival rate is reported to be as high as 90%.[20]

Sonographically papillary carcinomas are hypoechoic lesions, rarely of mixed or isoechogenic character. It has been analyzed that papillary carcinoma is more common in upper pole of the lobes whereas medullary carcinoma is situated in upper and middle part of the lobes.[21] Small punctate calcifications are considered characteristic of papillary or medullary carcinomas.[22]

Anaplastic carcinoma: -A 60 yr. old female patient with a long standing neck mass which has rapidly increased in size for last 4 weeks causing dysphagia with difficult breathing and hoarse voice. Early FNAC was in favour of goiter. Sonography this time showed a large mass on left side having heterogeneous echopattern with areas of degeneration and amorphous calcifications; it was involving the whole left lobe. Doppler showed grade II vascularity with low resistance (RI 0.12). There was associated cervical adenopathy; nodes were hypoechoic with similar vascularity as seen in thyroid mass. FNAC confirmed our diagnosis of anaplastic carcinoma. MRI showed the heterogenous mass with retrosternal extension pushing the trachea towards right side. In 47% of cases the anaplastic ca. develops within the substrate of goiters and may arise from papillary and follicular thyroid cancers,[23] as was our case with previous long standing goiter.

Anaplastic carcinoma is one of the most aggressive head and neck cancers and has a grave prognosis. It accounts for 15%–20% of all thyroid cancers. The diagnosis is suspected clinically with rapid growth in a long-standing thyroid nodule. Patients frequently present with signs and symptoms of airway compression. Sonographically they are hypoechoic diffusely involving the entire lobe or gland with ill-defined margin, areas of necrosis and nodal or distant metastases. Extracapsular spread and vascular invasion is seen in about one third of patients.[24]

CONCLUSION

Ultrasound was useful in demonstrating the origin of masses, their size, shape, internal composition, nature and extent of the lesion in most of the cases. USG appearance was virtually diagnostic in cases of colloid goiter, thyroid neoplasms,

RECOMMENDATION

It is recommended that ultrasonography should be the preliminary imaging modality in evaluation of a patient with thyroid mass as it provides real time high resolution imaging.

Ultrasonographic appearance alone is reliably diagnostic in most cases of colloid goiter. Combination of HRUSG and ultrasound guided FNAC is confirmatory in most cases.

Colour Doppler Imaging (CDI) by demonstrating the vascularity and pattern of vascularity can add to the diagnostic capability, hence its use is strongly recommended to further narrow the differential diagnosis.

BIBLIOGRAPHY

1. Cooper DS, Doherty GM, Haugen BR, et al: Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid, 2009; 19: 1167-1214.
2. Tunbridge WMG, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community.
3. The Whickham Survey. Clin Endocrinol (Oxf), 1977; 7: 481-493.
4. Tan GH, Gharib H. Thyroid Incidentalomas. Management approaches to non palpable nodules discovered incidentally on thyroid imaging. Ann Intern Med., 1997; 126: 226-231.
5. 4. Nikiforov YE, Steward DL, Robinson- Smith TM, et al. Molecular Testing for Mutations in Improving the Fine-Needle Aspiration Diagnosis of Thyroid Nodules. J Clin Endocrinol Metab, 2009; 94: 2092-2098.
6. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, Dominguez M. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinal Metab, 2009; 94: 1748-51.
7. Ito Y, Amino N, Yokozawa T, Ota H, Ohshita M, Murata N, Morita S, Kobayashi K, Miyauchi A:Ultrasonographic evaluation of thyroid nodules in 900 patients: comparison among ultrasonographic,

cytological, and histological findings. Thyroid17, 2007; 12: 1269-76.
8. VandenBrekel MW, Castelijns JA, Snow GB: Imaging of cervical lymphadenopathy. Neuroimaging clin North AM, 1996; 6: 417-34.
9. Weber AL, Siciliano A. CT and MR imaging evaluation of neck infections with clinical correlations. RCNA, 2000; 38(5): 941-68.
10. Ross DS: Evaluation of the thyroid nodule. J Nucl Med, 1991; 32: 2181-92.
11. Binder RE, Pugatch RD, Failing LJ, et al. Diagnosis of posterior mediastinal goiter by computed tomography. J CAT, 1980; 4: 550-552.
12. BrKljacic B, ViseslavCuk, Tomic H ,Zac B, Zigman ZB, Delic D ,Kljacic B, Drinkovic I, Ultrasonic evaluation of Benign and Malignant Nodules in Echo graphically multinodular thyroids. J. Clin Ultrasound, 1994; 22: 71-76.
13. Hassani SN, Bard RL. Evaluation of solid thyroid neoplasms by grayscale and real time ultrasonography: The "halo" sign. Ultrasound Med, 1977; 4: 323.
14. Kakkos SK, Scopa CD, Chalmoukis AK, Karachalios DA, Spiliotis JD, Harkoftakis JG, Karavias DD, Androulakis JA, Vagenakis, AG .Relative risk of cancer in sonographically detected thyroid nodules with calcifications. J Clin Ultrasound, 2000; 28: 347.
15. Solbiati L, Volterrani L, Rizzalto G, et al: The thyroid gland with low uptake lesions: Evaluation by ultrasound. Radiology, 1985; 155: 87.
16. Cerbone G, Spiezia S, Colao A, et al. Power doppler improves the diagnostic accuracy of color doppler sonography in cold thyroid nodules: follow up results. Horm Res., 1999; 52: 19.
17. Solbiati L, Livraghi T, Ballaratti G, et al. Thyroid gland. In: Solbiati L, Rizatto G, editors. Ultrasound of superficial structures. Churchill Livingstone, 1995; 49-55.
18. Sheikh M, Suhail A, Doi R, Sinan T, Kamal AS, Shoumer A: Technical Observations on the Assessment of Thyroid Volume by Palpation and Ultrasonography: JUM, 2004; 23: 261-266.
19. Whagen T, Spencer E. Cytologic presentation of thyroid tumors in aspiration biopsy smears. Acta Cytol, 1974; 18: 192-197.
20. Bruneton JN, Normand F. thyroid gland. In: Bruneton JN, editor. Ultrasonography of the neck. Springer-Verlag, 1987; 22-50.
21. Yousen DM, Scheff AM. Thyroid and Parathyroid. In: Som PM, Curtin HD, editors. Head and Neck Imaging, (3rd ed.). St Louis: Mosby, 1996; 952-975.
22. Melliere D, Marsin JP, Calmettes C, et al: Lepsque de malignik des nodules broidsthyroidiea La Presse Medicole, 1970; 78: 311.
23. Gritzmann N, Koischwitz D, Rettenbacher T. Sonography of the thyroid and Parathyroid glands. RCNA, 2000; 38(5): 1131-45.
24. Aldringer KA, Samaan NA, Haney M, et al: Anaplastic carcinoma of the thyroid: A review of 84 cases of spindle and giant cell carcinoma of thyroid. Cancer, 1978; 41: 2267-2275.
25. Wong KT and Ahuja AT. Cancer Imaging, 2005; 5: 157–166.