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RESEARCH ARTICLE

THYROID NODULE ULTRASOUND AND SCINTIGRAPHY

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T3:tri-Iodothyronine , T4: Thyroxin, TSH: Thyroid Stimulating Hormone , US: Ultrasound , CT: Computerized Tomography ,MRI; Magnetic Resonance imaging ,Tc-99m:Technetium-99m, I -123 :Iodine-123, I -131:Iodine-131 ,TL-201:Thallium-201, Ga-67:Galium 67, MHZ :Megahertz, CCA: Common Carotid Artery , IJV: Internal Jugular Vein, A:artery,V:vein, PEI: Percutaneous ethanol injection, H thyroiditis: Hashimoto,s Thyroiditis, FNAB: fine Needle Aspiration Biopsy, USA: united state America.

ABSTRACT

Purpose: to evaluate the efficacy of scintigraphy, ultrasound and fine needle aspiration in thyroid nodule detection and determination whether it is benign or malignant , in order for malignant to get timely diagnosis and be adequately treated in early stages of the disease, reducing morbidity and mortality and avoiding unnecessary procedures, including unnecessary surgical treatments of benign ones .

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INTRODUCTION

Anatomy: the thyroid gland is a gland situated in the anterior part of the neck, immediately in front of the trachea and below the thyroid cartilage (1). The thyroid gland consist of right and left lobes connected in the midline by an isthmus. Each lobe is lateral to the trachea and is bounded posterolaterally by the carotid artery and internal jugular vein. The conical upper pole partly covers the lower portion of the thyroid cartilage, and the rounded lower pole partially covers the third and fourth tracheal rings. The sternocleidomastoid and strap muscles (sternohyoid. sternothyroid and omohyoid) are situated anterolateral to the thyroid. The two lobes of the gland are of similar size and shape in most persons, although the right lobe is often slightly larger. The isthmus which lies anterior to the trachea is variable in size. A triangular cephalad extension of the isthmus, the pyramidal present in 15% to 30% of the thyroid glands (2).

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Physiology: The role of the thyroid, an endocrine gland is to maintain normal body metabolism, growth and development by the synthesis, storage and secretion of thyroid hormones. The mechanism for production of thyroid hormones is iodine metabolism, it produces tri-iodothyronine (T3) and thyroxin ('I'4) which are released when needed by the action of thyrotropin or thyroid stimulating hormone (TSH) produced by pituitary gland. The secretion of TSH is regulated by thyrotropin releasing factor which is produced by hypothalamus.

Thyroid Nodule: The clinically solitary nodule may be defined as a goiter which, on clinical examination, appears to be a single nodule in an otherwise normal gland (3). The term nodule is nonspecific and embraces a variety of pathologic processes, including adenomas, carcinomas, cysts, or merely ill defined lumps resulting from a process of cyclical hyper plastic and involutional processes (1). Thyroid nodule is extremely common. its prevalence has been estimated to be more than 5% in the adult population (19).

Nodular thyroid diseases are common. They are present in around 4-7% of the general population. Out of the total number cancer is diagnosed in 5-20% cases (4). Clinically solitary nodules fall into two categories. In the first category there is a certainly or a grave suspicion of malignancy in which exploration is essential . In the second and far larger category, there is smooth, firm, mobile nodule which is probably benign but carries a small but significant risk of being carcinoma. In this category about 50% prove to be simple multinodular goiters when explored (20). The primary goal in examination of the thyroid is to determine whether it has benign or malignant nodules, in order for patients with cancer to get timely diagnosis and be adequately treated in early stages of the disease, reducing morbidity and mortality and avoiding unnecessary procedures, including unnecessary surgical treatments of benign changes (14). The thyroid status of these patients must be established by clinical examination, laboratory investigations including radio immunoassay of T3, T4 and TSH, in addition to the following radiological investigations:

- Conventional soft tissue radiography.
- Xero radiography.
- Isotope scintigraphy.
- Ultrasound examination (US), with needle biopsy,
- Computarized tomography; (CT)
- Magnatic resonance imaging (MRI).
- Florescent scanning (3)

Conventional soft tissue radiography of the thyroid gland region (neck), is helpful in detecting calcification in the thyroid gland lesions. Xero radiography was found to be superior to the conventional soft tissue radiography in detecting calcification in thyroid lesions because of edge enhancement using a modified oblique projections. Conventional radiography of the thoracic inlet is also helpful in detecting any tracheal deviation and retrosternal extension (20). Nuclear medicine, US, CT and MRI are imaging methods that can be used to evaluate the thyroid gland. All these techniques give structural informations about the gland and show the location and size of thyroid nodule. Nuclear medicine scanning also adds functional information about nodules (21). C.T has a role in detection of thyroid nodules, but not the small ones, which its identification needs using thinner sections and increments than 6mm. This would have required a significantly higher level of ionizing radiations and also unduly prolonged the examination (22). Yoslhiko and Iris associates; evaluate thyroid nodules by I-123 thyroid scintigraphy and histogram of C.T values in the nodules. Radio-iodine accumulation and the histograms on C.T of the thyroid nodules were correlated with the histopathology. Results showed on definite correlation between radio-iodine accumulation in the thyroid nodule and the pattern on C.T reflecting iodine concentration in the nodule. Benign thyroid nodules tended to have lower iodine concentration than malignant nodules. It was concluded that the function and/or differentiation of tumor cells in the thyroid nodule must be evaluated not only by radio-iodine accumulation in the nodule but also by iodine concentration in the nodule and that thyroid nodules with only minimal iodine concentration are most likely benign (23). Reading, C.C. and Corman C.A.: stated that CT is an imaging method that can be used to evaluate the thyroid gland, and it is very useful in identifying distant metastases in the chest and abdomen (21). MRI has only a small role to play in the day to day of thyroid disorders (3).

Mountz, J. mid his associates; their study showed that MRI cannot reliably distinguish benign from malignant tumor. However using intensity ratio data there was a statistically significant difference between solid and hemorrhagic cystic disease (24). Corman . C.A.; said that MRI can be used to evaluate the possibility of recurrent thyroid cancer, however because of its relatively high cost, it is used less frequently than other imaging methods (21). The clinically solitary thyroid nodule presents a diagnostic problem, when the nodule is firm and mobile in an euthyroid patient. Scanning, needle biopsy and IJ.S may increase or decrease the suspicion of malignancy, but there is only one certain diagnostic procedure and that is excisional biopsy (3)

The following schematic diagram outlying the diagnostic approach to thyroid nodules; Figure-1-

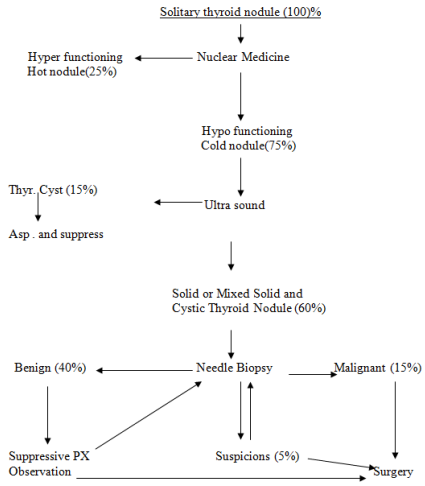

Figure 1. Schematic diagram outlying the diagnostic approach to thyroid nodules

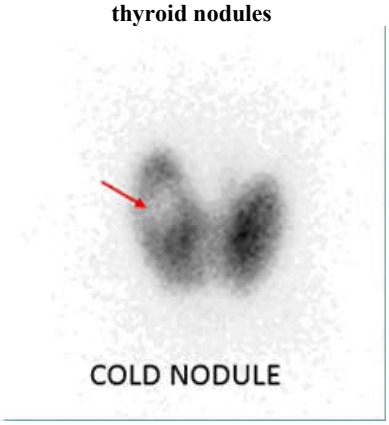

Figure 3. Cold nodule in the rt. lobe of thyroid glan

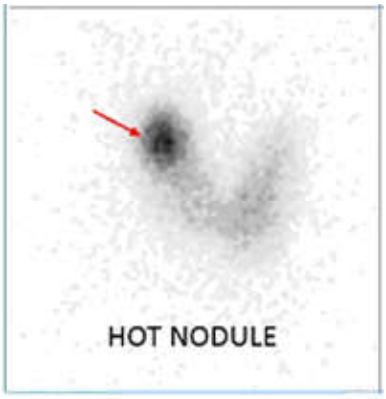

Figure 4. Hot nodule in the right lobe of thyroid gland

Thyroid Scintigraphy

Radiopharmaceuticals: the most commonly used radiopharmaceuticals used in thyroid studies include

- Iodine-131: It has several disadvantages mostly of increase radiation dose to the thyroid.
- Iodine-123: Its main advantage is low energy gamma ray.
- Technetium-99m pertechnetate**:** It is the radiopharmaceutical of choice for thyroid scanning in most cases, generally little background interference occur with repeated studies.
- Other radiopharmaceuticals**:** Iodine-132, Iodine-125, Galiium-67 citrate, Thallium-201 Chloride, Sezium-75 and selomethionine (l).

Geatti, O. (1994) stated that thyroid scans are usually performed with Tc-99m for its favorable physical properties, availability, low cost and good correlation with I-123.(27) **Normal Scan;** Fig-2: The thyroid gland has a homogeneous appearance with sharply defined borders . The lateral margins are either straight or convex, left and right anterior oblique views are taken at angles of 30 to 40 degree in addition to the anterior view (1).

Indications of thyroid scintigraphy: The following are the most frequent indications:

- Goiter.
- Palpable nodule in the neck.
- Clinical hypothyroidisim or hyperthyroidism.
- Evaluation of the process of thyroiditis.
- History of prior neck irradiation.
- Evaluation of substernal mass.
- Post operative search for functioning metastases.
- Suspicion of occult malignancy.
- Evaluation of the effects of thyroid stimulating and suppressing medications (1).

The important indication here is thyroid nodule. The thyroid nodule by scintigraphy either:

- **Cold nodule:** Fig.3. Which concentrate less isotopes than the surrounding thyroid tissue. Approximately 20% of cold thyroid nodules are malignant and about 20% are cystic. While most of the remainder are benign adenomas.
- **Hot nodules:** Fig..4. Represent increase thyroid activity, or concentrate more radio nuclide than the remaining thyroid, they are never malignant if hot by I-131 scan.
- **Worm nodules:** Because of overlapping or underlying functional, tissue has masked their true nature. In general they are best deled as if they are cold nodules (1)
- Radionuclide studies provide important functional but limited anatomic information (28)

The hyper functioning nodules may be multiple or solitary . The literature does contain occasional reports of both benign and malignant nodules that trap pertechnetate. Therefore any palpable nodule that appears to be functioning with pertechnetate should also be studied using radio iodine. The following diagram illustrate a practical approach to the management of hyperfnnctioning nodule |Fig-5-] (1). The discovery of a solitary thyroid nodule is a common clinical problem 25% of these nodules are hyper functioning (hot) on scintiscan. These are rarely malignant when normal functioning thyroid tissue is also present. Of the remaining 75% which are hypo functioning (cold) by scintigraphy, approximately 20% are cystic and 80% are solid (29).

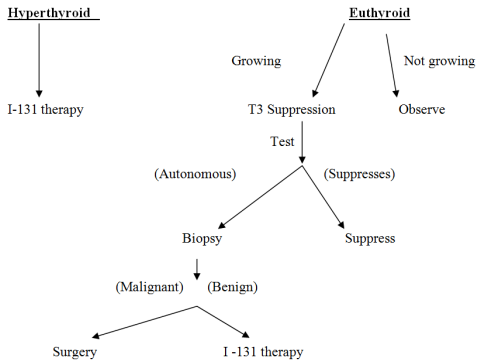

Figure 5. Disposition of solitary hyper functioning thyroid nodules

Role et. al. believed that it can stated quite confidently that hot nodules are benign. Since approximately 20- 30 % of nodules studied, were hot. This percentage of patients can be eliminated from consideration for surgery or other regimens designed for diagnosis: and treatment of malignant disease (25). Scheible and Leopold; stated that the solitary hypo-functioning nodule is the lesion of most concern, since approximately 20% of these are malignant. Another 20 % prove to be cysts, and most authorities advocate a conservative approach, since the incidence of malignancy is low. The remaining 60 % of isotopicallv cold nodules are benign but solid tumors. Most frequently, these are true adenomas or adenomatous nodules (28).

Autonomous Thyroid Nodule: Is that hot nodule which does not suppress with T3, but it does suppress the normal surrounding thyroid tissue. This nodule can be demonstrated by TSH stimulation test. About half of all autonomous functioning nodules occur in association with hyperthyroidism (1) Ramsay and Meire ; in their study on 47 patients with suspected thyroid disease, found 5 patients who had hyper functioning nodules with lack of isotope uptake in the contralateral lobe, there was either no detectable contralateral lobe on U.S (in 3 patients) or a lobe with small anteroposterior diameter (30). Khan O. in his study of 280 of autonomous thyroid functioning nodules found that there were 10 cases had carcinoma of thyroid. In most cases the carcinoma involved area of the gland beside the nodule .He pointed out the coexistence of thyroid carcinoma with functioning autonomous nodule was extremely rare (31). Corstens and his associates ; reported that Thallium-201 scintigraphy of the thyroid gland suppressed by autonomous nodule was compared with I-123 scintigraphy after TSH stimulation. In all patients .similar images were obtained by both methods. This study suggests that TL-201 scintigraphy is a reliable alternative for scanning after TSH. It is a relatively simple method, not inducing any TSH related allergic reactions. Iodine uptake in extra-nodular tissue is not stimulated and therefore TL- 201 scintigraphy and radioiodine therapy can be combined on one day (32). Michigishi and Mizakami: staled that autonomously functioning thyroid carcinoma is thought to be extremely rare, they found in their study 3 of I7 cases reported, the patients were euthyroid and non had ophthalmopathy typical of Grave's disease. Also a patient with carcinoma associated with euothyroid Grave's disease was treated (33).

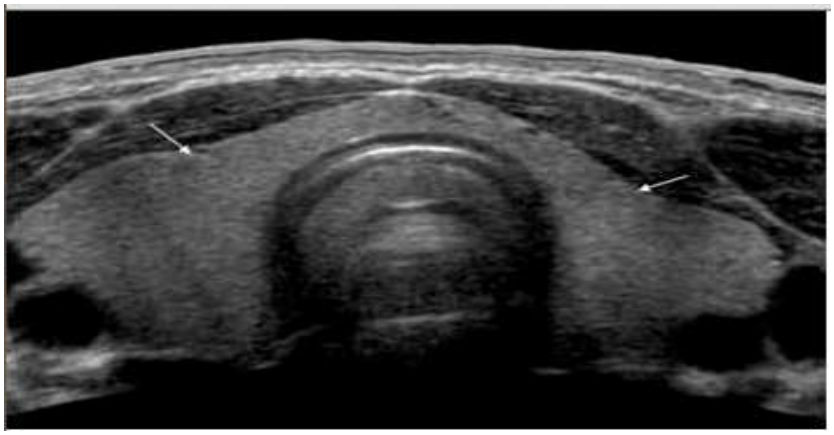

Figure 6. Transverse scan of the normal thyroid gland. SCM= sternocledomastoid CCA= common carotid artery, IJV= internal jugular vein A and V lateral to the gland

Table l. Prevalence of thyroid abnormalities discovered by U.S in a clinically normal thyroid

Author	'Total No.	Normal U.S	Abnormal U.S	Pattern of abnormal U.S findings
Wocsten	300	223 74.3%	77	67(19%); echoic Nodules 20(6%); Unechoic Nodules
Brander	101	6.5 64. 3%	36 55.3%	10 (9.9%); Unechoic Nodules 16(15.8%);hypoechoic Nodules 4(3..9%); Mixed echoic Nodules 6(5.9%); hyperechoic nodules

Table 2. P.E.I Comparison between different studies

Author	No, of patients	Isotope results	Clinical Results After PEI
Papini	6	Toxic nodule	all hot nodules become smaller clinically and by U.S
Parachii	28	Autonomous Nodules 22 6 toxic non toxic	12 patients complete cure 10 = partial cure 1 = delay cure
Goletti	31	cold nodules	all nodules shrank 85.5% repeated treatment needed in 4 patients

Table 3. Incidence of benign and malignant thyroid lesions in different US studies

Author	No. of Patients	Malignant lesions	Benign lesions
Ramsy	47	2(4.5%)	5(10.6%)
Miskin,s	174	29(16.6%)	145(83.3%)
Scheble	98	2(2%)	96(97.9%)
Prepper	28	2(7.1%)	26(92.9%)
Josef	133	17(12.8%)	116(87.2%)
Walker	101	8(7.9%)	93(92.1%)

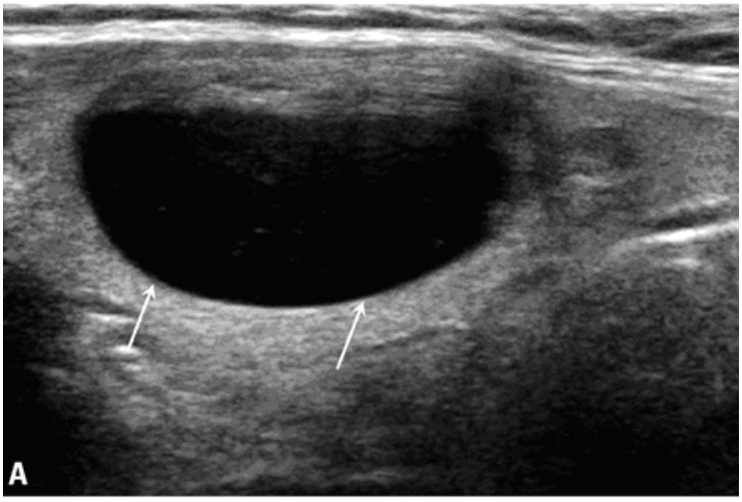

Figure 7. Simple thyroid cyst (US appearance absence of internal echoes ,well defined back wall and some through transmission)

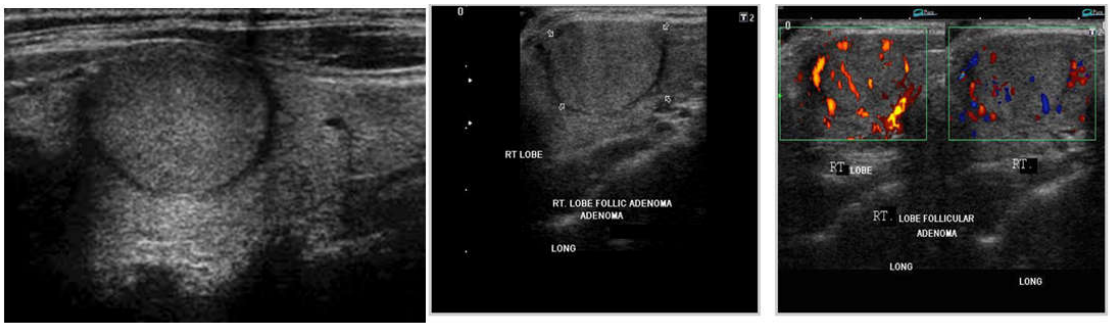

Figure 8. US, power and color doppler, of follicular adenoma in the rt. Lobe ,note the peripheral sonolucent "halo"

Tab 4 demonstrate the results of this study. (55)

Table 4. Pathological Interpretation of 28 Solid Thyroid Masses, in Proppers study

	Halo			
	Cases	Defined	Equivocal	No Halo
Benign				
_Follicular adenoma	14	4	2	8
_Benign nodule in nodular thyroid	11	1	1	9
_Hashimotos thyroiditis	0	0	1	
Total	26	5(19.2%)	3(11.5%)	18(69.2%)
Malignant				
_Follicular carcinoma	1	1	0	
_Papillary carcinoma	1	1	0	
Total	2	2(100%)	0(0%)	

Table 5. Ultrasound pattern of malignant thyroid lesions

Ultrasound Pattern: Author	No. of Malignant	Solid	cystic	Mixed	Lesions
Ramsay	2	1(50%)			1(50%)
Miskin	29	26(89.6%)		1(3.4%)	2(6.8%)
Scheible	2	2(100%)			
Propper	2	2(100%)			
Josef	17	15(88.2%)			2(11.8%)
Walker	8	8(100%)			

Florescent Scanning: In florescent imaging of thyroid was performed, with incidence of low energy photons generated by an X. ray tube .The images were comparable on quality and information content to these obtained with I-123 or Tc-99m pertechnetate. The estimated absorbed radiation dose to the gland is much less than scintigraphy using long lived radio-nuclides. Florescent imaging is a clinically useful means of evaluating the thyroid (34). Tadros, T. G. et, al.; in their study iodine concentration was measured by X-ray florescent in normal and pathological specimens which were generally lower with lowest values found in thyroid cancers, either undetectable or just detectable iodine concentration. The detection of iodine in a thyroid nodule by X-ray florescent preoperatively would significantly decrease the probability of malignancy. The main advantage of this technique lies in the very low radiation dose to the patient's neck without any exposure to the rest of the body, and investigates the thyroid gland without introducing any radionuclides in the body (35). Baily and Love's; stated that florescent scanning is a comparatively new technique which permits an in vivo demonstration of thyroid iodine concentration. This technique is still being evaluated and it may be used to distinguish benign from malignant lesions (3).

Thyroid Ultrasound

Historical Aspects: The first reference to ultrasonic investigation of the thyroid gland appeared in 1965 Yamkawa and Naitio described a method for calculating the size of the thyroid gland. In Fujimoto et. al. presented a series of 300 patients were examined with a moving transducer in a water bath placed on the patients neck, and then followed serially by other studies (29). To start with U.S examination of thyroid gland was performed using A-scan and B-scan for e.g the study done by Ramsey and Meire in using A-scan and a machine of frequency 2.25 MHz (3). Miskin,s study was done using a combination of A and B scans with transducer of 2.5 MHz (29). Wayne, S. ', his study was performed using ultrasonography, with a transducer frequency 5 MHz (36). In Croker, E. used gray-scale U.S with a frequency of 7.5 MHz (37). Walker, J. in used B-scan U.S with frequency *7-5* MHz transducer (38). Later on the more advanced and recent studies all of them were done using a high frequency real time US e.g Simeone et. al. Corman et. al., Sutton et al Brander et. al. Takashima.et. al. and others.

Scanning Technique: The patient is placed in supine position, with a cushion or pillow placed under the neck to facilitate its extension. This moves the mandible out of the field of the interest. Ordinary vegetable oil has proven to be the most effective and economical couplant (29). Because of the limited field of the high resolution scanner, it is not possible to image entire thyroid gland in each scan. Transverse scanning begins at the lower pole of one lobe and continues up through the entire gland . The carotid artery and jugular vein are used as lateral land markers, and the trachea as medial reference . Longitudinal scans are then performed from medial aspect of the gland to the lateral surface through the lower, middle and upper poles. After each lobe is evaluated the isthmus must be scanned. A number of systems has been designed that utilize frequencies in the 7 to 10 MHz range and incorporate water or oil path high class results in high class scans (2).

Normal Ultrasound Appearance of Thyroid Gland: The normal thyroid gland has a smooth homogeneous texture of medium level echoes. Lateral to the gland the carotid artery and internal jugular vein are identified in transverse plane. The vein which is usually partly collapsed is lateral and slightly superficial. to the artery. The strap muscles are anterolateral to the gland. The trachea is in the mid line posterior lo the isthmus (Fig-6-). On longitudinal scan the strap muscles and longus colli border the gland anteriorly and posteriorly respectively. The upper and lower poles appear as conical projections (2). Miskin, M.; stated that diagnostic U.S provides a simple, painless, rapid and readily reproducible method of differentiation between solid and cystic thyroid nodules and accurately measuring thyroid gland and nodule size . especially in those nodules which extend deep into the neck or behind an adjacent sternomastoid muscle, these nodules are often found to be larger on U.S than on palpation (29). Ramsay, I. found measurement of individual nodules or cysts was accurate to within 5mm when compared with the tissue removed at operation. U.S examination was able to differentiate other lumps in the neck from those arising in the thyroid gland, by showing lack of continuity between the lump and the normal thyroid tissue (30). Role, P.; believed that U.S of thyroid permits assessment of a lesion while patients are maintained on suppressive therapy, unlike thyroid scintigraphy (25). Croker, E.; discovered a large parathyroid adenoma and a smaller follicular thyroid adenoma were visualized with a combination of gray-scale U.S and radionuclide imaging in a patient with primary hyper - parathyroidism (37). Simoenc, J.; concluded that primary uses of U.S study of the thyroid include the detection of a multinodular gland when only one nodule is suspected clinically and by radionuclide study. Other use is the detection of occult thyroid malignancy when evidence of metastatic disease is present elsewhere in the body. A third potential use is for screening purposes in patients with histories of head and neck irradiation, in addition to the traditional use of U.S to separate cystic from solid lesions(40). Harberts ; concluded that the use of high resolution real time U.S has greatly increased the ability to define thyroid morphology and to detect nodules too small to be imaged by radionuclide scanning (1).

Walker and his associates; reported that U.S is a quick, noninvasive technique which allows accurate assessment of the solid and cystic nature of thyroid lesion . It has no morbidity or mortality (38). Woesten; and Barnder; performed two studies on normal persons who had no any previous thyroid disease. The U.S examination was done, the results and abnormalities are shown in [Table-1-]. No thyroid malignancy were found in both (41) (44). Blum, M. ;believed that the informations which are achieved by US non invasive, without exposing the patient to ionizing radiation and at low cost. A major breakthrough has been the demonstration of non palpable disease, a capability that is particularly important in people with a history of exposure to therapeutic X-ray in youth (42). Sutton, R.. Stated that high frequency US be sensitive in the detection of recurrent thyroid cancer in patients who have undergone surgery for thyroid malignancy (43). Tramalloni and Leenhardt, said that although modern high resolution real time U.S equipment permits excellent visualization of the thyroid nodules, their ultrasonic appearance and characteristics do not accurately predict the histological results (45)

Multinodularity of thyroid gland U.S: Scheible et. al. believed that one of the most rational application of high resolution U.S is to identify multinodular gland rather than solitary lesion superior to isotope methods or physical

examination. Multinodularity is much less likely to indicate malignancy than a solitary lesion. Non the less multicentric cancers do exist (28). Simeone et. al.; said that from the primary uses of U S is the detection of multinodular gland when only one nodule is suspected clinically and by radionuclide study . It is importance lies in the fact that solitary cold nodule carries a probability of malignancy between 15 to 25% and the multinodular goiter is considered a benign disease (40). Walker et. al-, suggested that U.S examination cannot differentiate between benign and malignant disease, but by diagnosing multinodular goiters, it enables a conservative approach and, reassessment can be made, and treated safely by observation (38). Blum, M.; (1986) concluded that the U.S finding of non palpable multinodularity is common, its finding in the presence of a solitary nodule may make the cancer in the nodule less likely than in the absence of multinodularity (42). Gareine and Doneman; found that although multinodular disease of the thyroid is considered rare in children and adolescents, but some of them have high incidence of associated clinical findings, which should alert the clinician to examine for these associated clinical findings (46).

Ultrasound Guided Biopsy of thyroid Nodule: It is known that ultrasound guided FNAB, due to high sensitivity and specificity, is the best individual diagnostic procedure for diagnosing malignant nodules. However, taking into consideration a large percentage of nodule occurrences, it is necessary to make a selection of nodules to be diagnosed through the aforementioned method (7). Needle aspiration biopsy is a diagnostic procedure which is simple, safe and inexpensive, when combined with isotope and U.S examinations, it is of significant value in obviating unnecessary surgery on thyroid nodules. Roke, P. ;in his study concluded that the chance of missing malignant lesion is negligible (approximately 2%), complications of this procedure are extremely rare (25). Fine needle aspiration under U.S guidance is of value in the preoperative diagnosis of thyroid nodules (1). Blum, M.; believed that most nodules over 2.5 cm in diameter have cystic degenerated zones or hemorrhage which make the biopsy result more false negative. Aspiration of the solid material offers a far better diagnostic yield than necrotic debris from the cystic element.

US can provide a map showing the location of the solid component as a guide for insertion of the needle (42) Percutaneous biopsy with U.S guidance was performed by Sutton et.at; on 52 patients who had a cervical mass or lymphadenopathy or both from 300 patients who had undergone surgery for thyroid cancer. 44 of these 52 nodules were non palpable clinically and can give results of positive or negative for malignancy (43). Priollet el, al; tried to assess the diagnostic value of fine needle aspiration biopsy performed under U.S guidance in a series of patients with a cold nodule and a systematic surgical control. A very high of adequate material was obtained (96.2%). Sensitivity, specificity, and global accuracy were 95 %, 87.7 % and 89'% respectively. (47) Boigon and Moyer; said that although features found on history taking, physical examination, thyroid function test and imaging studies help to categorize solitary' thyroid nodules as benign or malignant, U.S guided biopsy is the diagnostic test of choice.(67)

Percutaneous Treatment Under U.S Guidance: Papini et. al.; treated 6 patients who had toxic thyroid nodules by percutaneous injection of 2-4 ml of 95% sterile ethyl, alcohol through a spinal needle, this induce clinical improvement and hormonal control by the end of the treatment and no complications took place (48). Another study on percutaneous treatment by ethanol injection was performed by parachii et. al.;Their data suggest that this form of treatment could constitute an alternative to surgery' and radioiodine for the ablation of autonomous thyroid nodules (49). Percutaneous ethanol injection (PEl) has been recently used with excellent results to treat toxic and pretoxic thyroid adenomas. Here a new study was done by Goletti et. al. investigated PEI efficiency in the treatment of cold thyroid nodules, in which there was no clinical or cytological suspicion of cancer (50).

The following 'Table -2- demonstrates comparison between different studies about PEl

Color Doppler U.S and Thyroid Gland: 'I'orng, K.; reported that the efficacy of color doppler U.S in the detection of the thyroid functional state was investigated, the conclusion is that cases of hyperthyroidism have a higher valium of blood flow of both the common carotid arteries and thyroid arteries than the euthyroid cases (51): Gooding. G.; described other use of color doppler U.S in the distinction between thyroid and parathyroid lesions, Thyroid lesions tend to be vascular after they reach size greater than 5 cm, where as parathyroid lesions tend to be avascular until they are nearly *2* cm in size. However because of overlap exists the distinction cannot be made on the bases of vascularity alone (52): Argalia and his associates; in their study aimed to investigate the role and efficacy of color doppler U.S in the characterization of thyroid nodules. Conclusions seem to confirm that vascular pattern alone are not particularly helpful, compared with B-mode U.S results in distinguishing among thyroid nodules (53).

Benign Thyroid Lesions

These include: cyst, adenoma, diffuse non toxic colloid goiter, adenomatous hyperplasia (multinodular goiter) and, thyroiditis, Tab -3- shows the incidence of benign and malignant thyroid lesions in different US studies

Thyroid Cyst: U.S (Fig-7-)

US (Fig.-7-); Miskin; stated that differentiation between solid and cystic thyroid nodules by -A- and/or -B- scans. B mode scan of simple cyst characterized by persistent sonolucency up to high gain setting. Cytological examination for the aspirate was negative for malignant cells (29). Scheible et. al.; found that U.S was used to differentiate cystic from solid thyroid nodules using the familiar acoustic criteria (28). Joseph et. al.; using a high resolution real time U.S found that a true simple thyroid cyst is rare, and most of these cystic lesions are not pure cyst but contain some solid tissue or blood, that produce a complex echo pattern which are pathologically follicular adenomas with cystic degeneration (64). Walker; in his study of a clinically solitary thyroid nodule of 200 patients undergone U.S examination, 13 were correctly diagnosed as simple cysts (38). Blum, M.; believed that true thyroid cyst is quite rare, and that almost all large solid nodules undergo cystic or hemorrhagic degeneration. Therefore a cystic space with a solid nodule must be carefully differentiated from a true cyst by performing the study from several angles (42).

Lensick: in his prospective study on patients with a clinically isolated thyroid swellings, 37% of the swellings were cystic,

and aspiration biopsy under U.S guidance found 14% of these cystic lesions were malignant (54). Sandra; stated that 20 % of solitary thyroid nodules are cysts. Many thought that the cysts represent cystic degeneration of follicular adenoma. Simple cyst has a well demarcated smooth margins, and lack of internal echoes (2).

Thyroid Cyst: Scintigraphy: Ramsay; in his study found that a large cyst was identified on isotope scan as cold area.(30) Harbert, staled that thyroid cysts on scintigraphy appear as soft cold nodule with smooth borders (1).

Thyroid Adenoma: Miskin; staled that a benign follicular adenoma has an U.S appearance very similar to that of follicular carcinoma, so we are unable to differentiate between solid benign and solid malignant thyroid lesions (29). Rolf; agreed with Miskin that it can be extra ordinarily difficult to differentiate hyper cellular follicular adenomas from follicular carcinoma (25). Ramsay; and Wayne suggested that thyroid adenomas is the commonest solid tumor, and on U.S showed as solid, homogeneous with fine echo pattern, it may undergo degeneration leading to development of small echo free discontinuities (30) (36). Scheible reported that U.S in nearly all cases of adenomas include a well defined sonolucent rim or halo and varying degrees of internal cystic changes Fig -8- (28)

Hassni and Bord; reported that solid thyroid lesions showing the halo sign, non of which proved to be carcinoma. This raised to possibility and the hope that the halo sign might be a significantly reliable criterion for a benign lesion. So Propper el. al.; did a series of studies on patients with solitary thyroid nodules on U.S . some of them had halo sign which could surround benign or malignant lesion. Tab -4- demonstrate the results of this study (55).

Pathological Interpretation of 28 Solid Thyroid Masses, in Proppers study: Blum; agreed with Propper in that the halo sign may signify a boundary, perhaps a capsule around any kind of lesion wither benign or malignant (42).

Thyroid Adenoma: Scintigraphy: Ramsay; stated that thyroid adenomas showed by scintiscan as nodules which did not take up radioactive iodine (30). Harbert; stated that benign thyroid adenomas appeared as nonfunctioning nodules on Iodine or Tc 99m scans (1).

Thyroiditis U.S: Thyroiditis can be a result of infection or autoimmune causes. The disease may be chronic (lymphocytic and Hashimoto's disease), or sub acute (De Quervian's), or acute. Thyroiditis usually appears as an enlarged gland with generalized low echogenicity than normal parenchyma. Areas of relative sonolucency and or high reflectivity may be seen as well as discrete solid nodules (2). Blum and Anthony; studied 10 patients;, with sub acute thyroiditis with gray scale technique revealed a decrease echo pattern. Remission resulted in a normal echogram. Sub acute thyroiditis should not be confused with true cyst or hemorrhagic degeneration of goiter (56). Joseph; reported cases of Hashimoto's thyroiditis with surgical and pathological proof. In all cases the echo pattern was always diffusely abnormal with decrease in overall echogenicity. Some cases had discrete nodules. It is always difficult Io differentiate H. thyroiditis from multinodular goiter by U S, however clinical and laboratory criteria helpful. (64) Hayashi et. al. did an U.S study on patients confirmed to had H. thyroiditis, combined with hormonal and histological studies. Histologic analysis indicates that hypoechoic thyroid had sever degeneration and disappearance of follicles, with these changes thyroid function would deteriorate. So this article describes how the echogenicity of H. thyroiditis is related to thyroid function and histopathological findings (57). Mailloucx, G.; in his study: U.S B-scan images of normal thyroid and patients with H. thyroiditis, these images were digitized and processed by a computer method of image analysis, which revealed that their gray level histogram were very different from that of normal thyroid (58)

Panilckar; reported a case of H. thyroiditis and malignant lymphoma, however such association has been reported previously, but this case had hypoechoic anechoic confluent nodular appearance which has not been described in H. thyroiditis (59). Brichall, l.;reported 2 cases with De Querv'ian's thyroiditis, one had typical hypoechogenic areas, the other had multiple small areas giving a spotty appearance not previously reported (60). Takashima: found that a high frequency of coexistent nodules in the thyroid has been documented in H. thyroidits, particularly in association with malignant lymphoma, so making a histologic diagnosis of thyroid nodules associated with H. thyroiditis by U.S guided biopsy very useful method (61).

Thyroiditis: Scintigraphy: Harbert; stated that thyroid scan pattern in H. thyroiditis highly variable . The gland may be completely non visualized or may have only faint outline of an enlarged gland, or more commonly may show patchy irregularity . In acute sub acute thyroiditis the uptake is usually low (1)

Bartles, P. reported a case of subacute thyroiditis which presented in early phase as solitary painless cold nodule (62) Sjoberg; staled that although thyroid uptake of Gall-ium 67 is not commonly used, but it has been reported to occur with subacute thyroiditis, anaplastic carcinoma and occasionally with H. thyroiditis, He reported a case with progressive systemic sclerosis incidentally found to have abnormal Ga-67 uptake only in thyroid gland, biopsy revealed H. thyroiditis (63).

Malignant Thyroid Lesions: Thyroid carcinoma is relatively rare. Evidence suggests an increased risk of thyroid cancer in adults with childhood history of face, neck or upper mediastinal irradiation. Primary cancers of thyroid can be catigorized in 4 types; papillary, follicular, medullary and anapalstic. Malignant Lymphoma and metastatic tumors also occur (2)

Thyroid Carcinoma: US:

There is a statistically significant difference in average values of nodule size according to cytological exam results. In this study, for cancers diagnosed using the cytological method the size of nodules was above 3 cm. However, the literature review showed different results. According to Rosario et al, the size of nodules above 2 cm is a significant predicator of malignancy (7). Shico et al in their research results stated that the size of nodules did not influence malignant lesions (8). Kovacevic et al stated that in course of their study the average value of nodules with cancer was 28±12 mm, in correlation to benign lesion that were 8±10mm (9). Greek authors Polzos and Kita stated that cancer is more likely found amongst men and solitary nodules larger than 4.5mm (10) Miskin:, Roles; and Scheible; indicated their inability to differentiate by US alone

between benign and malignant solid nodules. Propper; reported 2 cases of thyroid carcinoma presented sonographically as solid nodules surrounded by halo.(55) Joseph, F .; concluded that malignant thyroid lesions mostly were hypoechoic relative to the normal thyroid, rarely echogenic or surrounded by a halo (64). Aforementioned data are in line with the similar research results. Papiri et al showed that hypoechoic nodules showing additional ultrasound characteristic (irregular margins, micro calcification), in 87% have confirmed cancer using FNAB method (12). Lee et al in their cystic nodule research showed that eccentric position of solid part and presence of micro calcification were extensively associated with a malignant characteristic (13). Frederico FR Maia et al in their study stated that ultrasound was proven very effective against differentiation of malignant nodules on the basis of their ultrasound characteristics – irregular margins, hypoechoic, and presence of micro calcification in 82% of cases (11). Kovacevic et al in their research showed that ultrasound characteristics related to malignancy are hypoechoic, irregular margins, calcification, absence of hypoechoic margin. The difference in echoic of malignant and benign lesions was not statistically significant (9). Authors from the USA Iannuccilli et al stated that comparison of ultrasound characteristics of benign and malignant nodules resulted in defining of micro calcification as the only statistically significant indicator of malignancy (35.3% sensitivity, 94.4%, p>0.005) (14). Hong et al stated that ultrasound haracteristics for cancer are considered positive when the presene of micro calcification, absence of halo sign and hypoechoic lesions were recognized. Sensitivity and specificity of ultrasound in their research is 81% and 70%, and FNAB 87.62% (15). Gul et al in Turkey stated that ultrasound characteristic – hypoechoic, micro calcification and irregular margins were the most important in determining malignancy (16). Kim et al stated that sensitivity, specificity, positive predictive value, negative predictive value of ultrasound were as follows: 93%, 66%, 56%, 95.9% (17). Tramalloni et al stated the importance of ultrasound in estimation of outspread to regional lymph nodes on the basis of ultrasound characteristics of malignancy, being round lymph nodes, loss of normal echogenicity, loss of normal hilar vascularization, micro calcification, cystic component and hyperechogenicity of lymph nodes (18). Table-5- demonstrates the U.S pattern of malignant thyroid nodules done by different authors. Schneider in his study on patients who received childhood head and neck irradiation for benign conditions, there is 36% cumulative prevalence of thyroid nodule and among these who have had surgery 36% have had thyroid cancers (65). During the study, scintigraphy showed that 92.5% of nodules were cold, while 5.3% were warm, while 2.3% were not clearly shown on scintigraphy. Analyzing the gathered results the study proved that there were no statistically significant connection between scintigraphy exam results and cytology exam results with cold nodules. However, a statistically significant connection has been found amongst warm nodules (all showed thyroid follicular cell proliferations in goiter). Frederico et al in their research stated that 62% of cold nodule cases were malignant and76.9% benign. Warm cases were not showing presence of cancer. Furthermore, they proved no statistically significant difference (p=0.33) in scintigraphy exam results between benign and malignant nodules (11)

Papillary carcinoma: U.S: Papillary carcinoma is the most common thyroid malignancy, incidence greater among young females. least aggressive, grow slowly and spread to cervical lymph nodes (2). Ramsay; reported a cases of papillary carcinoma, presented with a mass which had a solid pattern with numerous cystic areas (30). Wayne. reported 2 cases of papillary carcinoma, one with homogeneous cyst filled region having markedly increased echoes through out, and another with irregular coarse echoes (36). Joseph: reported 9 cases of papillary carcinoma, 7 of them were solid, while 2 were almost completely cystic, with a small bit of solid tissue within, one case was echogenic and surrounded by a halo (64).

Follicular Carcinoma: U.S.

Follicular carcinoma accounts for about 15% of thyroid cancer. It affects older females. Metastases travel through the blood to lungs and bone. Lymph node involvement is uncommon (2). Scheible; reported a case of follicular carcinoma, as a well demarcated mass lesion from the normal gland, it is slightly echogenic than normal thyroid tissue (28) Joseph; reported 2 cases of follicular carcinoma. both presented with metastatic lymphadenopathy (64).

Scintigraphy of well Differentiated thyroid Carcinoma (Follicular and Papillary): The decision to useTc-99m. I 123 or I 131 in thyroid scanning depends largely upon individual experience and availability . In general the best resolved image and lowest absorbed radiation dose are achieved with Tc-99m, one disadvantage of it is that its concentration does not reflect thyroid follicular cell organification function. Some well differentiated carcinoma can trap iodine (and Tc-99in) but cannot organify iodine, such nodule appear functional by Tc-99m scanning, but are cold by radioiodine scanning. 'I'he opposite is also true, such discrepancies occur in less than 2% of cold nodules (1).

Medullar Carcinoma: U.S:

Medullary carcinoma arises from parafollicular C-cells of thyroid which produce calcitonine, in 20% of cases it is familial and has a feature of multiple endocrine neoplasm .it may spread to cervical lymph nodes and other distant sites. It has been reported that radiographically detectable calcification may be found in both primary and metastatic medullary carcinomas, which appear sonographically as bright echogenic foci often associated with acoustic shadow . So medullary carcinoma has characteristic (if nonspecific) appearance with hypoechoic solid masses containing central echogenic foci within the thyroid and within the metastases (66). Sutton; in his study on patients who had undergone surgery for thyroid carcinoma found 3 patients with one or more punctate bright echogenic foci with or without acoustic shadowing, were identified with in lymph nodes, biopsies were positive for medullary carcinoma (43).

Medullary Carcinoma: Scintigraphy: Parthasarathy, L. reported that medullary carcinoma of thyroid appears as cold on radioactive iodine scanning (68). Gorman, B.: also stated that the tumor does not accumulate iodine (66). Clarke: did a study on patients with proved medullary carcinoma using I-131 metaiodo benzyl guanidine, the results are variable and give a higher false negative results (69). Udelsman. R.; did a study on patients with medullary carcinoma operated on, but had persistent and serial elevation of calcitonine using Tc-99m DMSA which is proved to be a sensitive localizing agent in the evaluation of asymptomatic medullary carcinoma patients with hypercalcitonaemia (70).

Rivas reported a case with medullary carcinoma inside an autonomously functioning nodules, this is the first of case medullary carcinoma which was presented as hot nodule (71)

Anablastic (Undifferentiated) Carcinoma of thyroid US and Scintigraphy: Anaplastic carcinoma of thyroid is one of the most malignant carcinomas in human, usually occur after fifties (2) Joseph: reported 2 cases of anaplastic carcinoma, one presented with cervical lymphadenopathy and other with multinodular goiter, there were no remarkable difference between the tumor and the shrunken multinodular gland by U.S. (64) Higashi. T; stated that Ga-67 uptake is highly variable, its uptake is predictably high in anaplastic carcinoma, however because of its high positive rate in chronic thyroiditis, Ga-67 offers little help (72)

Lymphoma: Primary lymphoma of thyroid arise in old age patients with somewhat greater incidence in females (2) Parulkar, concluded that the association of Hashimoto's thyroiditis and malignant lymphoma has been reported, he reported such a case which on scintigraphy revealed diminished or absent iodine uptake and a Ga-67 uptake revealed considerably increased up take the tumor area. (59)

Metastatic Tumors to the Thyroid Gland: Cancers from various organs of' the body can metastasize to the thyroid gland, breast cancer is the most common . but metastases from lungs, kidney and colon also reported (2). Joseph; reported 2 cases of metastases to the thyroid, one from the colon and the other from the breast (64). Vone and Jarvi: during 10 years period did a study on 60 thyroid malignancies and imaged with Tc-99m, 3 of them were metastases 2 from carcinomas elsewhere detected as cold nodules. *2.* from hypernephroma and one from gall bladder carcinoma (73)

Role of U.S in Postoperative Patients with Thyroid Cancer: High frequency US can demonstrate clinically occult thyroid bed tumor recurrence and lymph node metastases. U.S guided biopsy is an accurate and safe technique to confirm or exclude malignancies in patients at high risk. The post operative thyroid bed should have a uniform echogenic texture. Any hypoechoic mass detected by U.S is suggestive of recurrence and biopsy should be performed. Lymph node shape rather than over all size may be a more helpful indicator of its pathologic nature . The normal lymph node typically has an oblong and oval shape . even when they are enlarged. While malignant ones more often have rounded or bulging shape.(43)

Conclusion

Thyroid nodule extremely common. Its prevalence has been estimated to be more than 5% in the adult population. The clinically solitary thyroid nodule presents a diagnostic problem and embaraces a variety of pathologic processes including adenomas, carcinomas . cysts or merely ill defined lumps. So identifying those nodules which are likely to be malignant is very important. Nuclear medicine, .U.S. C.T and MRI are imaging methods that can be used to evaluate the thyroid gland. All these techniques give structured informations about the gland and show the location and size of thyroid nodule. Nuclear medicine scanning also add a functional information about nodules. Scanning with I-131 and Tc-99 m which are the most common test in the clinical evaluation of thyroid nodules used in identify hot and cold lesions . Hot or worm nodules about to 20% are seldom malignant, where as cold or hypo functional have a 10 % to 25% chances of being malignant. 'The hot nodules can be stated quite confidently benign, so eliminated from consideration for surgery .Modern high resolution real time US permits excellent visualization of thyroid nodules their ultrasonic appearance and characteristics do not accurately predict the histologic results. US allows the whole thyroid and the adjacent lymph nodes to be examined .It is regarded as valuable in differentiation between solid and cystic lesions, and single or multiple lesions. US provided a non invasive and relatively inexpensive means of following the size of nodule after medical therapy. But predictive positive values of U.S in suggesting malignant diagnosis is somewhat doubtful. A hypoechoic lesion is more suspicions to be malignant and it can be a criterion among many which can help clinician to select patients who must undergo surgery. U.S guided fine needle aspiration biopsy (FNAB) is useful in these cases. U.S has high accuracy rate in differentiating cystic from solid thyroid nodules. It may reach more than '90 % in some studies, but its role in differentiating benign from malignant nodules is doubtful. while if it is combined with FNAR its accuracy rate may reach up to 89% in differentiating benign from malignant lesions. Scintigraphy has high accuracy rate in differentiating hot from cold nodules (may rent h up to 95%), but can't differentiate.; benign from malignant nodules. U.S is more sensitive in detecting even small nodule (.3-4 mm in diameter) than scintigraphy which can't detect nodules less than 1 cm in diameter . So both U.S & scintigraphy arc used to select these nodules which are more suspicious to be malignant and need surgical treatment.

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