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DIAGNOSTIC ACCURACY OF ULTRASONOGRAPHY IN DIAGNOSIS OF PAPILLARY CARCINOMA IN PATIENTS WITH THYROID NODULES

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Abstract:
Papillary thyroid carcinoma (PTC), the most common malignancy of the thyroid, accounts for more than 75% of thyroid malignant tumor. Differentiating PTC from more frequently occurring benign thyroid nodules has proved challenging as there may be a significant overlap in their clinical presentation and sonographic manifestation. The high-resolution ultrasound is an accurate, noninvasive and low-cost imaging technique in detecting thyroid malignant tumor. However, certain cases with false-negative or false positive PTCs from sonography have been reported. Therefore, it is necessary to further investigate sonographic features of PTC and display the characteristic even more. The aim of our study was to investigate specific characteristics of color duplex sonography (CDUS) that can improve the differentiation of malignant thyroid nodules from benign ones by analyzing manifestations of 115 thyroid nodules with papillary carcinoma confirmed with pathology.
Objective:*The objective of this study was to determine the diagnostic accuracy of ultrasonography in the diagnosis of papillary carcinoma in patients with thyroid nodule, keeping histopathology as gold standard.*
Study Design: *Cross Sectional Study*
Material and Methods: *The study conducted in the Department of Otorhinolaryngology / Head & Neck Surgery and those referred from OPD or other units of Khyber Teaching Hospital, Peshawar in the duration of one year from1st January 2011 to 1ˢᵗ January 2012.*
Sample Size: *Sample size was 153, using 59% sensitivity. 69.77% specificity, 95% confidence level, 75% proportion of thyroid nodule, 2.3 and 9% margin of error.*
Results: *In this study mean age was 49 years with standard deviation ± 2.13. Most of the patients 83% were female and 17% patients were male. Seventy-four percent patients had multinodules and 26% patients had solitary nodules. Correlation of Ultrasonic versus histopathological findings was analyzed as in 55 diagnosed cases of ultrasound, histopathological report has shown 48 cases in which papillary carcinoma was present and in 7 cases the papillary carcinoma not found. Similarly, in 98 undiagnosed cases of ultrasound, histopathological report has shown 82 cases in which papillary carcinoma was present and in 16 cases the papillary carcinoma was not found. Sensitivity was found to be 75%, specificity was 92%, positive predictive value was 87% and negative predicative value was 83%.*
Conclusion:*In conclusion, CDUS, with the advantages of being noninvasive, radiation free and lower cost, may be employed as the first-line study in screening for PTC. Characteristics of CDUS on thyroid imaging are useful in differentiation of the malignant nodules from the benign ones. However, ultrasound- guided fine needle aspiration of the thyroid nodules should be considered as the standard in diagnosing PTC.*
Key words: *Thyroidectomy, Papillary carcinoma, Hypoparathyroidism, Recurrent Laryngeal Nerve Paralysis.*

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INTRODUCTION:

In the early phase of goitrogenesis, it is diffuse and with time. Tends not only to grow but also to become nodular. These nodules may be solitary or multinodular and may palpable thyroid nodules, thought to be solitary, are actually part of a multinodular thyroid gland. these nodule accur in 4-7% of the adult population, and with high resolution ultrasonography, these have been detected in up to 50% of people over 40 year of age. the indigence of these nodules increase with age, iodine deficiency, history of radiation exposure, and diet containing goitrogenic material. exposure to radiation in childhood results in changes in thyroid endocrine function and increases the risk of both benign and malignant thyroid nodules [1]. Thyroid nodules are more common in females (6.4%) as compared to males (1.5%) and this predisposition exists throughout all age groups, while these nodules in males is much more likely to be malignant then in females thee nodules are very common between 30 to 60 years. but the chances of malignancy are more in patients younger then 30 year or older than 60 years. Thyroid cancer is the most common endocrine malignancy, in which the incidence of papillary thyroid carcinoma, the most common malignancy of the thyroid, accounts for more than 75% of thyroid malignant tumore.[2] Thyroid ultrasonography is use as fist time diagnostic procedure for detecting and characterizing nodular thyroid disease [9]. Micro calcification is the most important indicator of papillary thyroid carcinoma on ultrasonography. With a sensitivity of 59% and specificity of 69.77%. This appears only 0.74% in giter. [3]. The aim of this study is to find out the importance of ultrasonography in the diagnosis of papillary thyroid carcinoma because there is no facility of fine needle aspiration eytology in our hospital and routinely we do ultrasonography for every patient having thyroid nodule but there is no study conducted on it in our institution in the past. If in our study the sensitivity and specificity of ultrasonography in detecting papillary thyroid carcinoma is found to be significant. Then we will recommend ultrasonography as a screening tool for the detecting of papillary carcinoma of thyroid nodules because it is cost effective, less time consuming, non invasive and the expertise are easily available in our hospital.

ANATOMY OF THYROID GLAND
Embryology of thyroid gland:

The thyroid gland appears as an epithelial proliferation in the floor of the pharynx between the tuberculum impar and the copula, at a point latter indicated by the foramen cecum. Subsequently, thyroid descends in front of the pharyngeal gut as a bi-lobed diverticulum. During this migration the gland remains connected to the tongue by a narrow canal, the thyroglossal duct. This latter becomes solid and finally disappears [4,5]. With further development, the thyroid gland descends in front of the hyoid bone and the laryngeal cartilages. It reaches its final position in front of the trachea in the seventh week. By then it has acquired a small median isthmus and two lateral lobes. These lateral lobes are thought to be the source of the 'para follicular C cells' that secrete calcitonin. However, there is histochemical evidence that these C cells may well be derived from the neural crest and are part of the neuroendocrine system [5]. The thyroid gland begins to function at approximately the end of the third month, at which time the first follicles containing colloid becomes visible [6-8].

Gross Anatomy of Thyroid gland;

It consists of right and left lobes connected by a narrow isthmus. It is a very vascular organ, surrounded by a sheath derived from the pretracheal layer of deep cervical fascia. The sheath attaches the gland to the larynx and the trachea [9]. Each lobe is pear shaped, with its apex directed upwards as far as the oblique line on the lamina of the thyroid cartilage; its base lies below at the level of the fourth or fifth tracheal rings. The isthmus extends across the midline in front of the second, third and fourth tracheal rings [10,11]. A pyramidal lobe is often present, usually to the left of the midline. A fibrous or muscular band frequently connects the pyramidal lobe the hyoid bone: if it is muscular, it is referred to as the 'levetor glandulae thyroideae [12,13].

RELATIONS OF THE LOBES [13]:
Anterolaterally:
The sternothyroid, superior belly of the omohyoid, sternohyoid, and anterior border sternocleidomastoid.
Posterolaterally:
The carotid sheath with the common carotid artey, internal jugular vein, and the vagus nerve.
Medially;
The larynx, trachea, inferior constrictor of the pharynx, and esophagus. Associated with these structures are the cricothyroidmuscle and its nerve supply, the external laryngeal nerve. In the groove between the esophagus and the trachea is the recurrent laryngeal nerve.

RELATIONS OF THE ISTHMUS:
Anteriorly;
The sternothyroid, sternohyoid, anterior jugular veins, fascia and the skin.

Posteriorly;
The second, third and fourth rings of the trachea. The terminal branches of the superior thyroid arteries anastomose along its upper border.

BLOOD SUPPLY
The arteries to the thyroid gland are;
The superior thyroid artery, a branch of the external carotid artery, descends to the upper pole of each lobe, accompanied by the external laryngeal nerve.
The inferior thyroid artery, a branch of the thyrocervical trunk, ascends behind the gland to the level of the cricoid cartilage. It then turns medially and downwards, to reach the posterior border of the gland. The recurrent laryngael nerve crosses either in front of or behind the artery or may pass between its branches.

The veins from the gland are;
- **The superior thyroid vein**, which drains into the internal jugular vein.
- **The middle thyroid vein**, drains into the internal jugular vein.
- **The inferior thyroid vein**, which receives its tributaries from the isthmus and the lower pole of the gland. The inferior thyroid veins of the two sides anastomose with one another as they descend in front of the trachea. They drain into the left brachiocephalic vein in the thorax. (Blood supply of thyroid gland is shown in figure No 1).[16,17]
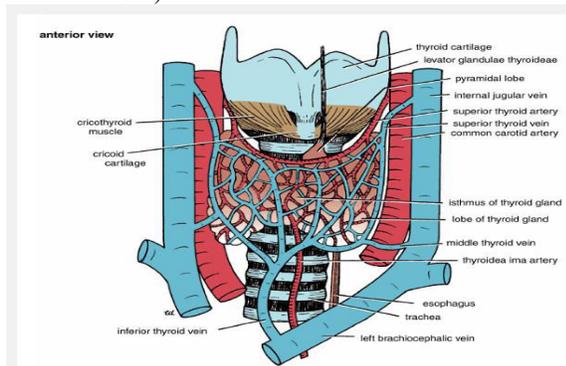

Figure 1: Blood Supply of thyroid gland (Ref. clinical anatomy by regions: Snell Anatomy)

Nerve Supply
The bulk of the sympathetic (vasoconstrictor) supply is derived from the middle cervical ganglion and enters the gland on the inferior thyroid artery; some fibers from the superior cervical ganglion travel with the superior thyroid artery. Vagus nerve fibers are traceable to the gland; their purpose is unknown [18].

Lymph Drainage;
The lymph from the thyroid gland drains mainly into the deep cervical lymph nodes. A few cervical lymph vessels descend to the partracheal nodes. (Anatomy of thyroid gland is shown in figure No 2) [19,20].
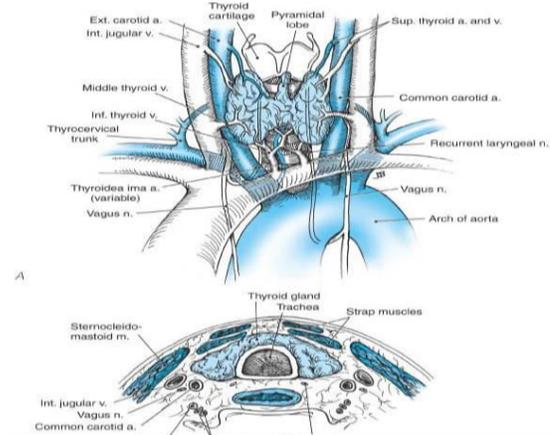

Figure No 2. Anatomy of thyroid gland; From Schwartz's Principles of Surgery

Histology
Microscopically, the thyroid is divided into lobules that contain 20-40 follicles. There are roughly 3 into 10 (raised to the power 6) follicles in the adult male thyroid gland. The follicles are spherical and average 30 um in diameter. Each follicle is lined by cuboidal epithelial cells and contains a central store of colloid secreted from the epithelial cells under the influence of the pituitary hormone, thyroid stimulating hormone (TSH). The second groups of thyroid secretory cells are the C cells or parafollicular cells, which contain and secrete the hormone, Calcitonin. They are found as individual cells or clumped in small groups in the interfollicular stroma, abutting between follicular cells [21]. They are located in the upper poles of the thyroid lobes, reflecting their origin as neuroectodermal cells derived from the ultimo branchial bodies, and are part of the amine containing precursor uptake decarboxylase (APUD) series described by Pearse. (Figure No 3 shows histology of thyroid gland) [22].
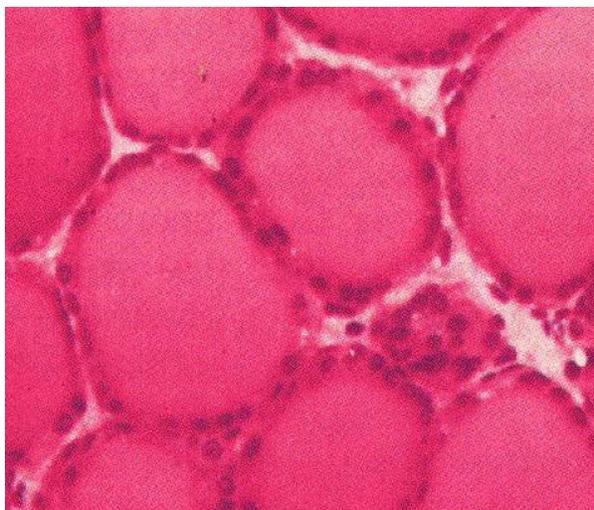
Figure No 3. Histology of thyroid gland; from eMedicine

Thyroid Hormones;

The principal hormones secreted by the thyroid gland are thyroxin (T4) and triiodothyronin (T3). T3 is also formed in the peripheral tissues by deiodination of T4. Both hormones are iodine containing amino acids. Small amounts of reverse triiodotyronine (3,3',5'-triiodotyronine, RT3) are also formed. In the thyroid gland, iodide is oxidized to iodine and bound in a matter of seconds to the tyrosine molecule attached to thyroglobulin, the enzyme responsible for the oxidation and binding of iodide is 'thyroid peroxidase'. Monoiodotyrosine is then iodinated to form di-iodotyrosine. Two DIT molecules then undergo oxidative condensation to form T4. This is called coupling reaction [24,25].

Secretion and regulation;

The human thyroid normally secretes about 80 ugm (103 nmol) of T4, 4 ugm (7 nmol) of T3, and 2 ugm (3.5 nmol) of RT3 per day. The details of the thyroid hormone regulation are beyond the scope of the present study [26].

Effects of thyroid hormones;

Many of the widespread effects of thyroid in the body are secondary to stimulation of O2 consumption (calorigenic action), although the hormones also affect growth, and development in mammals, help regulate lipid metabolism, and increase the absorption of carbohydrates from the intestines. They also increase the dissociation of oxygen from hemoglobin by increasing red cells 2,3 diphosphoglycerate (DGP). T4 is a prohormone for T3, before it can produce its effects. T3 acts more rapidly and is 3-5 times more potent than T4 [27,28].

T4 and T3 increase the oxygen (O2) consumption of almost all metabolically active cells. The exceptions are the adult brain, testes, uterus, lymph nodes, spleen, and anterior pituitary. Thyroid hormones increase the activity of the membrane bound Na-K ATPase and increase the energy consumption for the increased metabolic rate. When the metabolic rate is increased, nitrogen excretion is increased, endogenous proteins and fat stores catabolized and weight is lost. Large doses of thyroid hormones cause enough extra heat production to lead to a slight rise in body temperature. Thyroid hormones are necessary for hepatic conversion of carotene to vitamin A. Milk secretion is decreased in hypothyroidism and stimulated by thyroid hormones.[29]

The effects of thyroid hormmomes on the nervous system are to help in the development and maturation of the brain and the peripheral nervous system. In hypothyroid infants, synapses develop abnormally, mentation is slow, and myelination is defective. Some of the effects of the thyroid hormones on the brain are probably secondary to increased responsiveness to catecholamines. Thyroid hormones increase the number and affinity of B-adrenergic receptors in the heart and consequently increase its sentivity to ionotropic and chronotropic hormones.[30] Muscle weakness occurs in most patients with hyperthyroidism (thyrotoxic myopathy). The muscle weakness may be due in part to increased protein catabolism. Hypothyroidism is also associate with muscle weakness, cramps, and stiffness.[31,32]

Effects on metabolism;

Thyroid hormones increase the rate of absorption of carbohydrate from the gastrointestinal tract. In hyperthyroidism, therefore, the plasma glucose level rises rapidly after a carbohydrate meal, sometimes exceeding the renal threshold. Thyroid hormones lower circulating levels of cholesterol. The plasma level drops before the metabolic rate rises, which indicates that this action is independent of the stimulation of O2 consumption [33].

Effects on growth and development

Thyroid hormones are essential for normal growth and development. In hypothyroid children, bone growth is slowed and epiphyseal closure delayed. In absence of thyroid hormones, growth hormone secretion is also depressed, and thyroid hormones potentiate the effects of growth hormone on the tissues [34].

Regulation of Thyroid Secretion;

Thyroid function is regulated primarily by variations in the circulating levels of pituitary thyroid stimulating hormone (TSH). TSH secretion is increased by the, hypophysiotropic hormone, thyrotrotropic releasing hormone (TRH) and inhibited in a negative feedback fashion by circulating free T4 and T3. TSH secretion is also

inhibited by stress, and in experimental it is increased by cold and decreased by warmth [34].

Effects of TSH on thyroid

Under the effect of TSH, there is an increase in iodide binding; synthesis of T3 and T4, and iodotyrosins, and secretion of thyroglobulin into colloid, and endocytosis of colloid. Whenever TSH stimulation is prolonged, the thyroid gland becomes detectably enlarged. Enlargement of the thyroid is called Goiter [35].

PAPILLARY THYROID CARCINOMA

Papillary thyroid carcinoma (PTC) is the most common malignant tumor of the thyroid.[36,37] Its pathologic diagnosis is based on classic nuclear features, ie, elongated nuclei with inconspicuous eccentric nucleoli and crinkled nuclear membranes, chromatin clearing, and intranuclear grooves and holes. [38,39] When a diagnosis of PTC is established, the tumor can be classified further on the basis of tumor size, architecture and growth pattern, cell size, cytoplasmic features, and tumor stroma: ie, microcarcinoma, classic or conventional PTC, follicular variant, tall cell variant, oncocytic variant, and PTC with nodular fasciitis–like stroma.[40] Although a majority of papillary cancers can be diagnosed and classified on the basis of set pathologic criteria, there exists a group of cases in which benign thyroid tissue or lesions can mimic nuclear cytologic features or the architecture and growth pattern of PTC, posing diagnostic problems [41].

Specimen Fixation and Processing Artifacts

It is well known that the correct morphologic interpretation of any specimen is dependent largely on well-fixed and well-prepared cytologic or histologic slides [42].

Air-Drying Artifact

Air-drying artifact of thyroid fine-needle aspiration (FNA) specimens (seen especially in smears) can lead to enlargement and marked hypochromasia of the follicular cells. This chromatin change in some cases may assume a circumferential shape with sharp borders and mimic intranuclear inclusions of papillary carcinoma [43].In our experience, this pseudoclearing of the thyroid follicular cells is more pronounced in specimens containing large amounts of peripher blood, which hinders proper fixation of smears. This can be avoided by using a thinner gauge needle (preferably, a 25- gauge needle), limiting the number of passes, and using the concentration technique to make smears [43,44]. It is suggested that monolayer preparatory techniques can get rid of peripheral blood and allow proper fixation [44,45].

Calcification

Calcification within the thyroid gland is common. It can occur in benign and malignant thyroid lesions. The reported incidence of calcification is 26% to 54% in malignant lesions and 8% to 32% in benign lesions.16-20 histopathologically. Thyroid calcifications are divided into psammomatous and dystrophic calcifications. [46] The latter are further divided into "egg-shell" or rim-like peripheral calcifications and coarse dense nodular calcifications. In some cases, the calcifications may be extensive and require decalcification of the thyroid tissue before sectioning. The decalcification process can lead to extensive hypochromasia of follicular cells, which can be mistaken for the optically clear nuclei of papillary carcinoma. However, this change is global, ie, clearing of all follicular cell nuclei (lesional and non-lesional), and will be limited to the decalcified tissue sections [47,48].

Frozen Section

It is well-known that the value of frozen section in the diagnosis of PTC is limited because of loss of nuclear detail owing to freezing artifact [49]. However, in some cases, freezing of the thyroid tissue can lead to artifactual nuclear clearing, which can be mistaken for PTC, leading to a false-positive intraoperative diagnosis. In our experience, if one needs to diagnose PTC on frozen section (especially in cases that have been diagnosed as "suggestive of papillary carcinoma" in preoperative FNA), an adjunct intraoperative cytologic preparation is useful for avoiding a false-positive diagnosis of PTC [50].

Improper Fixation

In our experience, marked nuclear chromatin clearing can also be seen in thyroid specimens owing to improper fixation. This can occur because of delay in placing the specimen in fixative or in inadequate amounts of fixative or if the entire thyroid or lobe is placed in the fixative without "bread loafing" or sectioning.

Thyroid Lesions Mimicking PTC Chronic Lymphocytic Thyroiditis

Chronic lymphocytic thyroiditis (CLT) is a common disorder of thyroid gland with an incidence in females 20 times that in males. Most patients are hypothyroid at initial examination and/or have elevated serum thyrotropin concentrations.[51] The histologic presentation of CLT can range from focal involvement of the gland usually seen in surgically resected glands for benign or neoplastic disease to that of diffuse involvement leading to follicular atrophy, Hürthle cell metaplasia, brisk lymphocytic

infiltration, lymphoid germinal center formation, and variable sclerosis known as Hashimoto thyroiditis [52]. It has been suggested that incidence of PTC is higher in patients with lymphocytic thyroiditis than in the general population. This varies from 18% to 23%. Long-term prospective studies have failed to confirm this relationship between CLT and PTC. Therefore, most experts believe that this association is merely coincidental. Molecular analyses have engendered this controversy. Studies of loss of heterozygosity indicate that follicular epithelium in some cases of CLT shows genetic changes similar to PTC [53,54]. Rearrangements of the *ret* gene and somatic mutations in the epithelium of the thyroid gland affected by CLT have been described [55].

Tall Cell Variant of PTC and Oncocytic PTC

The tall cell variant of PTC and oncocytic PTC arising in a background of CLT can be mistaken for Hürthle cell lesions; however, the nuclear cytologic features are always helpful for differentiating these lesions.[62] It has been shown that an immunostain panel comprising cytokeratin, HBME-1, and galectin-3 can be helpful in the diagnosis of PTC in cytologic and histologic specimens. In our experience, which is shared by others, all of the aforementioned stains can display positive immunostaining of the reactive follicular and Hürthle cells in CLT. Therefore, in our practice, we do not use immunostains in CLT cases to aid in the diagnosis of PTC [63].

Hyperplastic Ultimo Branchial Body Rests/Solid Cell Nests

These developmental rests often are located in the lateral lobes and appear as round to oval structures composed of a monotonous population of small cells, which can demonstrate nuclear chromatin clearing and/or grooves.[64] Some of these lesions also can show central cystification, the presence of mucin, and predominant lymphocytic infiltration. Solid cell nests stain positively for cytokeratin and p63 and are negative for thyroglobulin and thyroid transcription factor-1.[65].

Benign Papillary Proliferations

Papillary formations can occur as a focal change or in the form of a dominant nodule in multinodular goiter, Hashimoto thyroiditis, and Graves disease. These papillary patterned lesions can be partly or totally composed of oncocytic cells and show complex papillae with well-formed vascular cores or stroma-poor edematous papillae with subfollicles [66].

Solitary Papillary Hyperplastic Nodules

Solitary papillary hyperplastic nodules occur frequently in children and teenagers. A radionuclide scan might show these nodules as hyperfunctioning [63]. Grossly, the lesions are encapsulated and often

demonstrate central cystification, with the tips of the papillae pointing to the center of the cyst.3 although most of these nodules lack the nuclear features of papillary carcinoma, some cases, especially those with oncocytic cells, reveal intranuclear grooves and poorly formed nuclear holes. However, the cells are round with prominent nucleoli and an even chromatin pattern. Despite these changes, these lesions can be diagnosed as benign on the basis of the structure of papillae and nuclear cytologic features. Immunostains for cytokeratin, HBME-1, and galectin-3 are helpful for differentiating between benign and malignant papillary lesions of the thyroid [67,68].

Papillary Hyperplasia in Graves Disease

Papillary hyperplasia in Graves' disease usually occurs in a diffuse manner; however, in long-standing and treated (with methimazole or radioactive iodine) cases, partially encapsulated nodules with papillary hyperplasia and varying degrees of sclerosis can occur [70]. Nuclear clearing can be seen in the cells lining the papillae, but it is not as pronounced as that seen in papillary carcinoma. In addition, the cells lining the papillae are columnar with basally located, round nuclei lacking other nuclear features of papillary carcinoma [71]. FNA specimens from nodules arising in the background of Graves's disease can demonstrate varying degrees of nuclear atypia, especially in treated cases. This nuclear atypia can occur as nuclear enlargement with hyperchromasia or nuclear chromatin clearing. Therefore, it is prudent to make a diagnosis of PTC in a gland affected by Graves disease only when all features of papillary carcinoma are seen [72].

Dyshormonogenetic Goiter

Dyshormonogenetic goiters result from complete or partial blockage of the biochemical steps required for the normal production and use of thyroid hormone. The severity of hypothyroidism is dependent on the type and degree of derangement of the enzymatic pathways within the thyroid gland [73]. Grossly, the thyroid gland is enlarged and multinodular.

Microscopically, the most common alteration

Consists of markedly cellular nodules exhibiting follicular and/or papillary growth patterns [74]. Random nuclear atypia can occur in the form of enlarged pleomorphic nuclei with or without nuclear chromatin. These cellular changes can be mistaken for follicular, papillary, medullary, or undifferentiated thyroid carcinoma in cytologic and surgical pathology specimens. Awareness of the clinical situation is, of course, extremely helpful. Absence or marked depletion of colloid in the background, a nonnodular gland, and the presence of

diffuse hyperplasia with random nuclear atypia are the best clues to the presence of a dyshormonogenetic goiter [75].

Hyalinizing Trabecular Neoplasm

In 1987, Carney et al82 described a distinct tumor of thyroid that they termed hyalinizing trabecular adenoma. This tumor showed a peculiar growth pattern of elongated tumor cells arranged in trabeculae interspersed with dense hyaline material and calcification resembling psammoma bodies. The tumor cells contained the well-formed nuclear cytologic features of papillary carcinoma [76]. Therefore, most often this tumor is misdiagnosed as PTC in cytologic preparations [77]. The clinical follow-up on all tumors described to date that fit the initial morphologic description has been benign [78]. Some authors believe that this tumor represents a peculiar form of PTC based on its nuclear features, immune histochemical profile, and *ret/PTC* arrangements [79]. However, no *BRAF* mutations, which are specific for PTC, have been reported in these tumors.[80] The question arises, "How should these tumors be classified?" Because of the controversy about the nature of this tumor, the preferred term is hyalinizing trabecular neoplasm [80].

Post-FNA Histologic Alterations

It is well recognized that the trauma induced by the FNA needle can lead to tissue alterations of varying severity and occasionally could lead to problems in histologic assessment of thyroid nodules. LiVolsi and Merino divided post-FNA changes into acute and chronic types. The acute changes include hemorrhage, granulation tissue formation, and nuclear atypia; chronic changes include capsular distortion, pseudo invasion into the tumor capsule and vessels, and papillary endothelial hyperplasia.[81] The term reactive cellular or nuclear atypia often is used in the context of reparative and/or inflammatory processes in various organs; in some cases, these changes are difficult to distinguish from neoplastic processes. They are characterized by nuclear enlargement, chromatin clearing, and prominent nucleoli. These changes can occur in gastric ulcers, inflammatory colon polyps, inverted papilloma of the bladder, and endometrial and endocervical polyps. As mentioned, similar cellular or nuclear changes are encountered in CLT and can be mistaken for PTC.[82]

DATA COLLECTION PROCEDURE

Approval of the ethical committee of the hospital was sought. Patients having thyroid nodule & fulfilling the inclusion criteria was selected. The selection of patients having thyroid nodule were physically examined, selected from out patient department (OPD) of otorhinolaryngology /Head & Neck surgery, those referred from OPD or from other units of the Khyber Teaching Hospital Peshawar. All the included patients were explained the purpose of procedure. Use of data and publication of the study informed written consent was taken from the patients. The demographic information like name, age sex and address were recorded. Through history was taken and detail physical examination was preformed.

The base line investigation as will specific investigation like thyroid function test was done. The ultrasound was done from an ultrasound specialist having more than seven years' experience. Its characteristics having solid echo structure, hypo echogenicity, fine or micro clarification, and ill-defined margin, were recorded as the papillary carcinoma. After surgical excision of the thyroid nodule by an expert ENT, Head & Nick surgeon, the specimen was sent in formation for histopathological examination to histopatholigist having more then seven-year experience to detect papillary thyroid carcinoma. The type of treatment was performed according to medical ethics, beneficial and non harmful to the patients. The exclusion criteria were strictly followed to control confounders and exclude bias in study result. All the result was followed by me and all the above mentioned information's were recorded in pre-diagnosed proforma.

DATA ANALYSIS:

The collected data was entered in SPSS version 10. Mean and standard deviation was calculated for numeric variables like age, while the frequency and percentage was calculated categorical variables like sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) was determined by taking histopathology as gold standard 2X2 table.

		HISTOPATHOLOGY	
		+	-
ULTRASOUND	+	48	7
	_	16	82

RESULTS:

This study was conducted at Otorhinolarynogology department, Khyber Teaching Hospital, Peshawar. In which a total of 153 patients of papillary carcinoma in thyroid nodular were study. Age distribution among 153 patients were analyzed as most of the patients n=54(35%) were in age group 51-60 years followed by n=46(30%) patients were in age group 41-50 years, n=31(20%) patients were in age group 31-40 years, n=13(9%) patients were above 60 years, n=7(5%) patients were in age group 21-30 years and only two patients were below 20 years of age. Mean age was 49 years with standard deviation ± 2.13. (as shown in Table no 1). Gender distribution among 153 patients were analyzed as most of the patients n=127(83%) were female while n=26(17%) patients were male. (as shown in Table no 2). Type of thyroid nodules among 153 patients were analyzed as most of the patients n=113(74%) had multinodules while n=40(26%) patients had solitary nodules. (as shown in Table no 3). Ultrasonic findings among 153 patients were analyzed as papillary carcinoma was found in n=55(36%) patients while papillary carcinoma not found in n=98(64%) patients. (as shown in Table no 4).

Histopathological findings among 153 patients were analyzed as papillary carcinoma was found in n=130(85%) patients while papillary carcinoma not found in n=23(15%) patients. (as shown in Table no 5). Correlation of Ultrasonic versus histopathological findings was analyzed as in 55 diagnosed cases of ultrasound, histpathological report has shown 48 cases in which papillary carcinoma was present and in 7 cases the papillary carcinoma not found. Similarly, in 98 undiagnosed cases of ultrasound, histpathological report has shown 82 cases in which papillary carcinoma was present and in 16 cases the papillary carcinoma not found. (as shown in Table no 6). Sensitivity and specificity of papillary carcinoma was analyzed as sensitivity was 75%, specificity was 92%, Positive predictive value was 87% and Negative predicative value was 83%. (as shown in Table no 7).

TABLE NO 1. AGE DISTRIBUTION
(n=153)

AGE DISTRIBUTION	FREQUENCY	PERCENTAGE
< 20 YEARS	2	1%
21-30 YEARS	7	5%
31-40 YEARS	31	20%
41-50 YEARS	46	30%
51-60 YEARS	54	35%

ABOVE 60 YEARS	**13**	**9%**
TOTAL	**153**	**100%**

Mean age was 49 years with SD± 2.13.

TABLE NO 2. GENDER DISTRIBUTION

(n=153)

GENDER DISTRIBUTION	FREQUENCY	PERCENTAGE
MALE	**26**	**17%**
FEMALE	**127**	**83%**
TOTAL	**153**	**100%**

TABLE NO 3. TYPE OF THYROID NODULES

(n=153)

TYPE OF THYROID NODULES	FREQUENCY	PERCENTAGE
SOLITARY NODULE	**40**	**26%**
MULTINODULES	**113**	**74%**
TOTAL	**153**	**100%**

TABLE NO 4. PAPILLARY CARCINOMA ON ULTRASOUND

(n=153)

PAPILLARY CARCINOMA ON ULTRASOUND	FREQUENCY	PERCENTAGE
YES	**55**	**36%**
NO	**98**	**64%**
TOTAL	**153**	**100%**

TABLE NO 5. PAPILLARY CARCINOMA ON HISTOPATHOLOGY

(n=153)

PAPILLARY CARCINOMA ON HISTOPATHOLOGY	FREQUENCY	PERCENTAGE
YES	130	85%
NO	23	15%
TOTAL	153	100%

TABLE NO 6. CORELATIONS OF ULTRASOUND VS HISTOPATHOLOGICAL FINDINGS

(n=153)

		HISTOPATHOGICAL		TOTAL
		YES	NO	
ULTRA	YES	48	7	55
SOUND	NO	82	16	98
TOTAL		130	23	153

TABLE NO 7. SENSIVITY AND SPECIFICITY OF PAPILLARY CARCINOMA

(n=153)

		HISTOPATHOLOGY	
		+	-
	+	48	7
ULTRA SOUND	_	16	82

Sensitivity was 75%
Specificity was 92%
Positive Predictive value (PPV) was 87%
Negative Predictive Value (NPV) was 83%

DISCUSSION:

The morbidity of PTC has been increasing in China in recent years. Thyroid carcinoma, especially PTC, has high prevalence in women at young age. In our study, 40% patients with PTC were women at age between 25 and 35 years, which was four times as many as that in men (10%) with PTC. CDUS with high-resolution images has been considered the imaging of first choice in screening for thyroid diseases, especially in detecting PTC at early stage. In our study the incidence of multinodular was more 74% as compare to solitary nodules 26%. Moreover, ultrasonic had detected 36% cases of papillary carcinoma while according to Histopathological reports a total of 85% cases were recorded in which papillary carcinoma was diagnoses. Similar results were observed in study done by Chan BK et al [107], in which the incidence of multinodular was 76% and solitary nodules were 24%. Forty percent cases of papillary carcinoma were deleted by ultrasound while sixty percent cases were recorded by histopathological reports.

In our study the correlation of ultrasonic findings versus histopathological findings was analyzed and

had been concluded that although the ultrasound findings in diagnosis of papillary carcinoma are not accurate as compare to histopathological results but it can help to predict the papillary carcinoma in some extant. In these study 55 diagnosed cases of ultrasound, histopathological report has shown 48 cases in which papillary carcinoma was present and in 7 cases the papillary carcinoma not found. Similarly, in 98 undiagnosed cases of ultrasound, histopathological report has shown 82 cases in which papillary carcinoma was present and in 16 cases the papillary carcinoma not found. Similar observation was recorded in other studies done by Chan BK et al, Wienke JR et al [107,108].

How to distinguish malignant nodules from benign ones is still challenging. Certain characteristics on CDUS images would be helpful in the differential diagnosis of PTC and benign nodules [106]. The types of the calcification in the thyroid nodule with PTC can be classified into microcalcification, coarse calcification, peripheral calcification and "eggshell" calcification. Microcalcification is the most important indicator of PTC, with a sensitivity of 29% to 59% and specificity of 96.77%, which appears only 0.74% in goiter. Microcalcification could be detected in 29% to 59% of the primary thyroid carcinomas, especially in PTC. It can also be visualized in follicular thyroid carcinomas. Furthermore, microcalcification may appear not only in the primary thyroid carcinoma, but also in metastatic thyroid carcinoma. Therefore, the appearance of microcalcification in the thyroid nodule could be considered as an indicator of high risk for malignancy. However, microcalcification must be distinguished from the condensed colloid and dense fibrosis in benign thyroid nodules. The comet-tail or ringdown artifact is commonly observed in the thyroid nodule with condensed colloid and dense fibrosis. Coarse calcification, presenting as irregular hyperechoic foci with acoustic shadowing, can be seen in benign nodules of the thyroid. Malignant thyroid nodule is highly suggested when there is a single solid nodule with internal abundant blood supply and high resistance index in a young patient. Peripheral and "eggshell" calcifications are more commonly seen in benign nodule, which is rarely observed in PTC.

Thyroid nodule is a very common condition, which is about 4% to 7% in the adults (this probability increases with age). Most of the thyroid nodules are benign, and only less than 7% are malignant; it is highly concerned which one is malignant among numerous nodules. In our study, 51 cases (50%, 51/104) of PTC had coexistence of goiter and papillary carcinoma, which is the same as what KIM EK et al [109] had reported that among numerous solitary nodules, the risk of benign nodules was equal to malignant. The number of the thyroid nodule, as a single factor in detecting PTC, is not related with either benign or malignant. More important factors that need to be observed carefully are echotexture, vascularity, capsule and microcalcification. The maximum diameter of PTC in this study was 19.4 mm. The size of the nodules that reaches up to a significant diameter can demonstrate more manifestations and symptoms of local infiltration or metastasis. There were 29 nodules of PTC with smaller than 10 mm in diameter detected in our study. There were 63.5% cases with ill-defined border and 36.5% with well-defined border in the patients with PTC. We noticed that the smaller PTC had clearer border than that in larger ones. Being larger, PTC may infiltrate into thyroid parenchyma, which forms irregular boundary. Therefore, the border of the thyroid nodule alone is not helpful in determining benign or malignant of the thyroid nodule. Ill-defined border is seen in some nodules with PTC on CDUS, in which the capsule of the nodule is found on histological review. As reported, about 15% to 59% of benign nodules had ill-defined border and appeared as macrolobulations or microlobulations.

Majority of PTC typically appears solid and hypoechoic compared with healthy thyroid parenchyma. Using the strap muscles as the reference, the hypoechoic rises up to 94% for the specificity of malignant nodule, but sensitivity is lowered down to 12%. Markedly hypoechogenic nodule is suspicious for malignancy. Although single or multiple thyroid nodules with cystic component suggest benignity, the cystic nodule with papilla solid component should be carefully distinguished from cystic PTC. Manifestations of cystic PTC on CDUS are no-capsule cystic lesion containing solid papillary component, abundant blood flow in papilla and microcalcification in the nodule. Our study shows that sensitivity and specificity of papillary carcinoma was analyzed as sensitivity was 75%, specificity was 92%, Positive predictive value was 87% and Negative predicative value was 83%. Similar results were found in study done by Wienke JR et al [108], in which sensitivity of papillary carcinoma was 76%, specificity was 91%, Positive predictive value was 85% and Negative predicative value was 84%. Similary results were also observed in another study conducted by Frates MC et al [110] in which sensitivity of papillary carcinoma was recorded as

74%, specificity was recorded as 93%, Positive predictive value was 82% and Negative predicative value was 81%.

The pattern of blood flow in the thyroid nodule on color Doppler or power Doppler is very useful in the diagnosis of PTC. Intrinsic or intranodular flow is more common than peripheral flow in PTC. The resistance index of the artery in the nodules is generally not used in assessing the degree of malignancy in PTC. It is very common to see cervical lymph nodes while performing CDUS of the thyroid and carotid artery. Enlarged cervical lymph nodes may result from malignant metastases, such as thyroid carcinoma, lymphoma and lung cancer. It can also be a benign condition, for instance, in Hashimoto thyroiditis. An enlarged cervical lymph node with hypervascularity was the first clinical finding in 4 of 104 cases in our study. Lymph node metastasis from PTC would be suspected if the lymph node appears microcalcification, hypervascular and the same characteristics as the nodule in the thyroid.

CONCLUSION:
In conclusion, CDUS, with the advantages of being noninvasive, radiation free and lower cost, may be employed as the first-line study in screening for PTC. Characteristics of CDUS on thyroid imaging are useful in differentiation of the malignant nodules from the benign ones. However, ultrasound- guided fine needle aspiration of the thyroid nodules should be considered as the standard in diagnosing PTC.

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