Review of Literature
REVIEW OF LITERATURE

The thyroid gland is affected by a wide spectrum of pathologic entities including benign and malignant lesions and thus causes complex diagnostic problems. The main objective in imaging the thyroid is to identify lesions that are likely to be malignant and once the diagnosis of malignant disease is confirmed by pathologic examination, imaging is further useful to delineate the extent of tumor or metastatic disease.

**Hyperplasia** is the most commonly observed thyroid pathology. It may be familial due to iodine deficiency, or compensatory to hypoplasia of one lobe or partial thyroidectomy. Hyperplasia may be diffuse or nodular. Because the follicles are filled with colloid, the term colloid goiter has been applied to this condition [19].

**Adenomas** are benign thyroid tumors that present clinically as solitary nodules. They are characterized histologically by complete fibrous encapsulation, compression of thyroid parenchyma around them and lack of multinodularity in rest of the gland. Follicular adenoma cannot be reliably differentiated from follicular carcinoma on fine needle aspiration cytology[4].

**Malignancy:** The commonest primary thyroid malignancy is papillary carcinoma. It is often multifocal in nature and metastasizes primarily by lymphatic route. Histologically papillary structures, psammoma bodies and ground glass appearance of nuclei characterize it.
Follicular carcinoma has a peak incidence in the 5th and 6th decades. It metastasizes usually by hematogenous route and multiple foci are seldom seen. They may appear encapsulated macroscopically, but there is evidence of invasion of capsule and vascular spaces microscopically.

Medullary carcinoma arises from parafollicular cells of thyroid. It is characterized by amyloid stroma, elaboration of calcitonin and other peptides. It may occur as part of multiple endocrine neoplasia [1].

Anaplastic carcinoma usually occurs in the elderly and presents as large necrotic tumor with local invasion [19].

Thyroid primary lymphoma is rare (4% of all thyroid malignancies), mostly of non-Hodgkin’s type and usually affects elderly females. The typical sign is a rapidly growing mass, which may cause symptoms of obstruction such as dyspnoea and dysphagia. In 70-80% of cases, thyroid lymphoma arises from a pre-existing chronic thyroiditis with subclinical or overt hypothyroidism [1].

Metastasis to thyroid is rare and usually occurs from primary carcinoma of breast, colon, kidney and melanoma. More commonly thyroid is involved by adjacent malignancy of trachea or esophagus.

GRAY SCALE ULTRASONOGRAPHY

The first diagnostic application of ultrasonography for the living tissue was reported in 1947 by Dussik et al [24].
In 1951, Wild and Neal [25] concluded that information obtained by ultrasonography could be of value in medicine as they observed that tissues of abnormal texture could be detected and no harmful effect was seen in tissues subjected to ultrasonic waves.

The superficial soft tissue structures were examined for the first time in 1954 by Howry et al [26] and they predicted an important role of sonography in visualizing benign and malignant tumors of neck, liver and extremities.

Yamakawa and Naito [27] employed ultrasonic scans for the assessment of thyroid gland size in 1965.

Fujimoto et al [28] described basic patterns of ultrasonic tomogram of thyroid gland using a two dimensional display system in 1967.

Using a combination of A scan and B scan, Rasmussen and Holm [29] differentiated solid from cystic thyroid masses in 1969.

Blum et al [30] sonographically demonstrated areas of cystic degeneration in solid thyroid masses. They found a variable sonographic pattern in multinodular goiter comprising solid, cystic and mixed echogenic patterns.

Thijs [31] emphasized a distinct supplemental role of sonography in evaluation of thyroid disorders and found that the most important information obtained was the ability to distinguish solid thyroid tumors from cystic lesions. This was based on the belief that thyroid carcinoma was uncommon in cystic lesions. However, it was not possible to distinguish between solid malignant
and benign tumors. He also described the sonographic features of multinodular goiter as coarse and irregular echoes with calcification appearing as strong echoes in it.

Miskin, Rosen and Walfish [32] found ultrasonography to be helpful in assessment of the thyroid gland particularly the solitary hypofunctioning thyroid nodules. They could differentiate between solid and cystic lesions in 94% of cases which was important to the clinician in deciding the course of management.

Chilcote [33] evaluated 33 patients of thyroid disorders sonographically and described the appearances of thyroid cysts, adenomas, goiters and carcinomas. However, the benign lesions could not be differentiated from malignant lesions based on the solid or cystic nature.

Walfish et al [34] carried out a prospective study of combined sonography and fine needle aspiration biopsy in hundred cases of solitary hypofunctioning thyroid nodules. They were able to accurately detect 95% of solid lesions and 88% of cystic and mixed lesions. They found three of fifteen malignancies to be cystic in part or full.

Spencer et al [35] evaluated 87 cases of clinically solitary thyroid nodules by ultrasonography and scintiscan and observed higher accuracy of ultrasonography (92%) compared to scinti-scan (52%) in the diagnosis of solitary and multinodular goiter. By sonography they could identify cystic areas with hundred percent accuracy.
Lees et al [36] showed that sonography could distinguish normal from abnormal thyroid. In addition they documented local and generalized thyroid disease with 94% accuracy. They also diagnosed multinodular colloid goiter with 78% accuracy.

It was in 1979 when high-resolution real time sonography was used for the first time by Schieble et al [37] for detection and characterization of solid thyroid masses. They described three most rational applications of high resolution ultrasonography. Firstly to identify patients who have multinodular goiter, secondly to assess the response of suppressive hormonal therapy in a nodule and finally guiding the needle for aspiration cytology in proper direction. They also described the sonographic appearances of various nodular lesions of thyroid. Most nodules were isoechoic to normal thyroid parenchyma. Adenomas and adenomatous nodules were found to have a variable echogenicity and nearly all of them had a sonolucent halo around them. Adenomatous nodules, which represented nodular elements of multinodular goiter, had many sonographic features common with true adenomas. These nodules had variable degree of cystic degenerations with calcification in few cases.

Combination of physical examination, sonography and needle aspiration was advocated for assurance of benignity to avoid unnecessary surgical interventions by Allen et al [38]. They reported a case of pedunculated carcinoma within the lumen of an otherwise benign appearing cyst.
Leopald [39] described the ‘halo sign’ as the most helpful feature in diagnosing adenoma. Peripheral rim calcification was found to be specific for it. He described carcinoma as a focus of decreased echogenicity, devoid of any halo and having few areas of calcification and cystic degeneration. However extensive cystic degeneration was found in some of the involved lymph nodes.

Soon after its description, the non-specificity of ‘halo sign’ was documented by Propper et al [40]. They evaluated 28 patients with solitary thyroid nodules and reported two cases of proven carcinoma with peripheral halo around them. They suggested that pericapsular inflammatory infiltrate could produce ‘halo sign’.

Sonographic features of various thyroid disorders were described by Simeone et al [41]. Adenomas were characterized by variable echogenicity and a halo around most of the lesions. Of the seventeen patients with thyroid malignancy, sixteen lesions were hypoechoic relative to normal thyroid parenchyma while one papillary carcinoma was hyperechoic with perinodular halo around it. They also evaluated the sonographic features of nodular goiter. Out of 21 patients, 11 showed a diffuse inhomogeneous gland with no recognizable normal tissue. In other 10 patients, multiple discrete nodules were seen throughout an otherwise normal appearing gland. Sonographic differentiation could not be made between follicular adenoma and adenomatous nodules.

These findings were endorsed in a study by Austin [42] in the same
year. He documented the ability of sonography in detecting thyroid lesions that
were not demonstrated by other means. Malignant thyroid lesions were nearly
always heterogeneously hypoechoic with characteristic irregular margins.

Halo sign was found to be reliable sign for diagnosing benign adenoma
and adenomatous nodules in the study conducted by Herle et al [43].

Beuglet et al [44] described punctate calcification in papillary
carcinoma. Calcification in benign lesions was characterized as coarse,
centrally located bright curvilinear echoes with discrete acoustic shadowing.

Katz et al [45] examined twenty-eight patients with thyroid gland
abnormality using a high-resolution real time sonographic scanner. They
correlated sonographic findings with gross and microscopic examination in
detail and found sonography to be very accurate in detecting architectural
variation, adenomatous goiter and solitary nodules. They attained a sensitivity
of 89% and specificity of 84% in diagnosing adenomatous goiter. They
concluded that ultrasound could be used to measure changes in nodule size but
could not distinguish benign from malignant nodules.

In a series of 48 cases of thyroid abnormalities, Radecki et al [11]
evaluated the role of ultrasonography and computed tomography. They found
that the computed tomography required higher doses of radiation and took
longer time for evaluation while ability of high-resolution sonography to detect
smaller nodules made it the procedure of choice in the evaluation of thyroid
disease.
James et al [46] inferred from their study that egg shell like calcification
was the most reliable feature in distinguishing benign from malignant nodule.

Solbiati et al [9] performed sonographic examination in 401 patients
having isotopically cold solitary lesions of the thyroid gland. They gathered
useful information on analyzing and correlating various sonographic
echopatterns with the pathologic diagnosis. The incidence of malignancy was
found to be extremely low in hyperechoic and anechoic lesions. Majority
(59%) of colloid goiters were iso-hyperechogenic. They concluded that
calcification and cystic changes occurred in both benign and malignant nodules
at the same rate. Appearance of margins were not helpful in differentiating the
lesions. The perinodular echo free halo was seen in 36% of the lesions and was
found to be present more frequently in benign than malignant lesions (86% vs.
14%). The average size of the nodule was 2.9 cm with most lesions between
2.5 cm and 3.5 cm.

In a study of 200 cases of clinically solitary thyroid nodule, Walker et al
[47] diagnosed 49 solid lesions, 47 mixed lesions, 67 cystic lesions, 39
multinodular goiters, 20 diffuse thyroid enlargements and 4 extrathyroid
lesions with an overall accuracy of 95% on ultrasonography. They considered
ultrasonography to be quick, safe and non-invasive technique providing
accurate assessment of thyroid and extrathyroid lesions.

Hayashi et al [18] concluded from their study that the only reliable
indicator of malignancy was local invasion of surrounding structures. They
found cystic components in 46% of adenomatous goiters compared to 21% of malignant lesions. Hypoechogenicity was seen in 23% of adenomatous goiters and 32% of malignant nodules.

Simeone et al [48] suggested sonography to be the investigation of choice for the earliest detection and localization of recurrent thyroid carcinoma.

High reliability of sonography in detecting recurrence of medullary carcinoma of thyroid was shown by Gorman et al [20]. They noticed punctate bright echogenic foci in the main thyroid tumor (83%) and in the metastatic nodes (75%) in cases of medullary carcinoma of thyroid. They recommended sonography as a first line investigation method for detection of recurrence after thyroidectomy.

Sonography was found extremely useful in detecting recurrent thyroid carcinoma by Sutton et al [49].

Sonographic feature of thyroid lymphoma were described by Takashima et al [50] and Kasagi et al [51]. Lymphoma appeared as extremely hypoechoic lesion intermingled with echogenic structures, clearly distinguishable from residual normal thyroid parenchyma.

Hatabu et al [52] demonstrated high accuracy of ultrasound compared with fine needle aspiration cytology in detecting cystic papillary carcinoma of thyroid. They described the 'calcified nodule in cyst' sign specific for cystic papillary carcinoma.
Solbiati et al [19] reported thyroid hyperplasia as the commonest pathologic entity of thyroid gland. It presented both as diffuse and nodular enlargement. Diffuse form manifested sonographically as inhomogeneity of parenchymal texture. Nodular form manifested as single or multiple nodules of various sizes separated by normal parenchyma. Most of these nodules were isoechoic with a peripheral halo around them. 25% to 40% of nodules had cystic changes which represented colloid collections or central hemorrhages. In differentiating benign from malignant lesions, the presence of microcalcification had low sensitivity (59.3%) but extremely high specificity (95.2%) with total diagnostic accuracy of 83.8%.

One hundred twenty patients undergoing surgery for thyroid nodules were examined by preoperative ultrasound and fine needle aspiration cytology. Different thyroid pathologies showed different sonographic features and no single feature was pathognomic. Malignant lesions tended to be solid and hypoechoic without a halo, but there was a cystic element in 26% of the lesions and calcification was seen in 37% of cases [6].

Zhu [53] compared benign and malignant nodules based on internal echogenicity, cystic components, margins and extrathyroidal extension and concluded that difference was statistically significant.

Gimondo et al [54] studied thyroid nodules in terms of their echopattern and found that 60-70% of neoplastic nodules possessed hypoechogenic echopattern with hyperechogenicity in only 2-4% of neoplastic nodules.
Brkljacic et al [55] studied 165 patients with multinodular goiter and found that certain sonographic signs increased the likelihood of given lesion being benign or malignant but there was no absolute specific feature for confirmation. They suggested that carcinomas were more often hypoechoic and contained nodular calcification while benign lesions were more often iso-hyperechogenic with intranodular cystic degenerations and perinodular hypoechoic rim. They also found that relative proportion of malignant nodules was highest in upper halves of thyroid lobes. The mean diameter of benign nodules was 2.29 cm and of malignant nodules was 1.93 cm.

Garetti et al [56] reported their results in 160 patients affected with thyroid nodules after examining with sonography and fine needle aspiration cytology. They found 69.2% of the malignant lesions were hypoechoic and 46.1% exhibited microcalcification.

Mehta et al [57] evaluated sonographic features to suggest benign or malignant nature of thyroid nodule. They found that no sonographic feature could reliably differentiate a malignant lesion from benign lesion. However, they suggested that a cystic, predominantly cystic or solid hyperechoic nodule was unlikely to be malignant. 52% of colloid nodules were iso-hyperechoic and 50% of malignant lesions were showing cystic component.

Takashima et al [58] documented that microcalcification had the highest accuracy (76%), specificity (93%) and positive predictive value (70%) for detecting malignancy as a single sonographic sign, but its sensitivity (36%)
Ahuja et al [59] emphasized the significance of comet-tail artifact in thyroid sonography. They suggested the presence of comet-tail artifact as an indicator of benignity with a sensitivity and specificity of 100% in complex cystic nodules. They suggested that artifact could be related to the presence of colloid.

Kakkos et al [60] evaluated the significance of sonographically detected thyroid calcification in the diagnosis of thyroid malignancy. They found that detection of calcification in solitary nodules showed significantly higher specificity (82%) and positive predictive value (55%) than did the detection of calcification in multiple nodules (60% and 17% respectively). More than half of the calcified solitary nodules were malignant, while the incidence of cancer in the calcified multiple nodules was relatively low.

Ahuja et al [61] evaluated sonographic features of metastatic nodes from papillary carcinoma to the thyroid. 52% of metastatic nodes showed punctate calcification and 71% were hyperechoic compared to adjacent muscle.

**COLOR DOPPLER**

No color flow was detected within thyroid parenchyma in any of the 15 normal volunteers evaluated by Ralls et al [62] using Color Doppler sonography in 1988.

Fobbe et al [23] in 1989 found that 24 out of 28 patients with an autonomous adenoma and all patients with thyroid carcinoma in their study
had increased vascularity on Color Doppler sonography.

Anguissola [63] endorsed the finding of no detectable color flow in thyroid gland of normal subjects.

Hubsch et al [64] inferred from their study that the hypothesis of hypervascularisation of malignant nodules could not be used unconditionally for detection of carcinoma due to high percentage of false positive and false negative diagnosis associated with it.

Solbiati et al [19] in 1992 described Color Doppler findings in various thyroid disorders. Hyperplastic nodules did not show internal flow signals. In a minor percentage low velocity (15-20 cm/s) flow was detected in the peripheral halo. Toxic adenoma had intense peripheral and internal flow signal with peak systolic velocity of upto 160-220 cm/s. Thyroid malignancies had intramural arterial flow signals with peak velocity less than 40 cm/s.

Forty seven patients with thyroid nodules (13 papillary carcinomas, 14 adenomas and 20 adenomatous goitres) were evaluated by Shimamoto et al [65] using Color Doppler sonography. Perinodular or intranodular color flow signals were depicted in 10 of 13 papillary carcinomas, in 10 of 14 follicular adenomas, and in 14 of 20 adenomatous goitres. No correlation was found between the presence of color signals and pathology, whereas the detection rate of color signals had a dependence on the size of the lesions. No specific flow pattern for malignancy could be detected.

Role of spectral analysis to improve the predictive value of Color
Doppler sonography was studied by Lagalla et al [66]. They concluded that flowmetry (peak systolic and diastolic frequency shift) did not provide more useful diagnostic information than Color Doppler sonography in nodular thyroid disease.

Stern et al [67] in 1994 in their study found peripheral vascular halo on Color Doppler in adenomas and adenomatous nodules which had a diagnostic sensitivity of 96% and specificity of 93%. Malignant nodules showed marked internal arterial vascularity.

Li et al [68] in 1994 discussed the clinical significance of high velocity Doppler signals in the tumors and the pathologic basis of various sonographic features of benign and malignant thyroid tumors. Malignant tumors usually had hypoechoes, indistinct and irregular margins, microcalcification and arterial flow signals as compared with benign tumors.

Clark et al [69] evaluated patients with thyroid pathology by scintigraphy and Color Doppler and correlated the findings with pathology. They found that majority of ‘cold’ nodules demonstrated peripheral flow. A large percentage of hot nodules demonstrated internal vascularity. According to them, Color Doppler could not reliably distinguish between benign and malignant lesions.

Fifty patients with solitary or dominant thyroid nodules were studied by Holden [70] with Color Doppler and spectral analysis was performed on vascular lesions. Majority of nodules could be accurately categorized by Color
Doppler appearances. All neoplastic nodules had intranodular signals. Majority of colloid nodules were either avascular or had halo flow signals only, with only a few colloid nodules being vascular. Although Color Doppler lacked absolute specificity in discriminating neoplastic and non-neoplastic nodules, the data suggested that the modality had considerable use in clinical practice. A statistically significant difference between mean RI value in colloid and neoplastic group was noted.

Argalia et al [71] in 1995 studied 83 consecutive patients with solitary thyroid nodules to assess the role and efficacy of Color Doppler ultrasound in the characterization of thyroid nodules. Using Color Doppler, they studied presence and distribution of nodular vascularization, flow velocity, resistance index and Doppler spectrum morphology. They concluded that vascular patterns alone were not helpful, compared with gray scale sonography, in distinguishing among thyroid nodules. They suggested peak velocity and Resistance index may be of great usefulness in the characterization of solid nodules and thus selecting patients to submit to fine needle biopsy.

Messina et al [72] analyzed sonographic echotexture and Color Doppler findings in patients with thyroid carcinoma. Thyroid neoplasms showed hypoechoic pattern in 60-70% of cases while hyperechoic pattern was seen in only 2-4% of cases. 90% of thyroid carcinomas showed type III (significant intranodular and perinodular flow) pattern on Color Doppler study. They suggested routine use of ultrasonography and Color Doppler studies in
conjunction with fine needle aspiration cytology for the diagnostic evaluation of thyroid carcinoma.

Urso et al [73] evaluated the role of Color Doppler sonography in patients with thyroid nodules and demonstrated that Color Doppler sonography was highly sensitive (100%) and specific (82%) method of predicting malignancy in thyroid nodules.

In another study, ninety one patients affected with thyroid diseases (97 lesions) were examined with gray scale and Color Doppler sonography. To verify if Color Doppler could provide additional information in the ultrasonographic diagnosis, two diagnoses were expressed for each lesion: first on conventional ultrasonographic patterns and the second on Color Doppler patterns. These were compared with histologic findings that identified 73 benign lesions and 24 malignant lesions. With conventional gray scale ultrasonography the diagnosis was correctly expressed in 62/73 benign lesions (85%) and in 18/24 malignant lesions (75%) while it was misdiagnosed as positive in 11/73 cases(15%) and as negative in 6/24 cases(25%). With use of Color Doppler patterns along with conventional sonographic diagnosis, the false negative cases were reduced to 4% and false positive to 6.8% [74].

Erdem et al [75] did a prospective study in 26 patients with cold thyroid nodules (five malignant and twenty one benign nodules) to evaluate the diagnostic value of Color Doppler and Tc-99m tetrofosmin scintigraphy in differentiating malignant from benign thyroid nodules. Both the uptake and
vascularity were classified as low, iso or high. Eight (including four malignant tumors) out of twenty-six nodules showed increased vascularity compared with normal thyroid tissue on Color Doppler sonography. The sensitivity, specificity, negative predictive value and positive predictive value of Color Doppler were determined to be 80%, 80%, 50% and 94% respectively. They concluded that Color Doppler sonography had limited role in the detection of malignant thyroid nodules.

Rago et al [76] studied one hundred and four consecutive patients with thyroid nodules who were to undergo surgery using gray scale and Color Doppler sonography. With gray scale ultrasonography they evaluated the presence of halo sign, hypoechogenicity and microcalcification. The vascular pattern of Color Doppler was classified as: Type I (absence of blood flow); Type II (perinodular blood flow); Type III (marked intranodular blood flow). Thirty nodules were diagnosed as malignant and seventy-four as benign nodules on histology. On ultrasound, the echographic pattern most predictive for malignancy was absent halo sign, which was found in twenty of thirty carcinomas and in seventeen of seventy-two benign nodules with specificity of 77% and sensitivity of 66.6% (p = .0001). The most specific combination on ultrasound, absent halo sign/ microcalcification, was found in eight of thirty carcinomas and in five of seventy-four benign nodules with specificity of 93.2% and sensitivity of 26.6%. The type III pattern on Color Doppler was found in twenty of thirty carcinomas and thirty eight of seventy four benign
nODULES (not statistically significant). The combination of absent halo sign/microcalcification on ultrasound with Type III pattern on Color Doppler was the most specific combination of the two techniques with specificity of 97.2% but sensitivity of 16.6% only. They concluded that findings on ultrasound and Color Doppler become highly predictive for malignancy only when multiple signs are simultaneously present in a thyroid nodule. Thus the predictive values of these techniques increase at the expense of their sensitivity. Only in a small proportion of patients with thyroid carcinoma ultrasound and Color Doppler information was highly predictive of malignancy.

Naru et al [77] assessed the usefulness of Color Doppler sonography in the diagnosis of thyroid nodules. They reported that the distribution of tumor vessels on Color Doppler, pulsatility index and resistance index were useful in making the differential diagnosis between benign and malignant nodules.

Sonographic appearance of focal thyroiditis presenting as thyroid nodule was evaluated by Langer et al [78] using gray scale and Color Doppler sonography. They most commonly appeared as solid hyperechoic nodules with ill-defined margins. On Color Doppler, vascularity of these nodules varied widely without a distinguishing pattern.