

## Comparison between patients with thyroid follicular tumors in the histological pattern and size of follicular lesion

Ban Jumaah Qasim\*, Wijdan Basheer Abid\*\*, Buthainah Ibraheem Hameed Al-Ezzi\*\*\*, Zahraa Ahmed Okhti\*\*\*.

\* College of Medicine, Al-Nahrain University, Baghdad, Iraq, Department of Pathology,

\*\*College of Education for Pure Sciences (Ibn Al-Haitham), University of Baghdad, Baghdad, Iraq, Biology department

\*\*\*Department of Laboratory and Clinical Sciences, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq

BanQasim@yahoo.com

Wijanabed18@gmail.com

forever.1964@yahoo.com

Zehraa.ahmed@uomustansiriyah.edu.iq

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### Abstract:

The main problem encountered in thyroid nodule is difficult to differentiate between a benign and malignant lesion. Differential between follicular thyroid cancer (FTC) and benign follicular thyroid adenoma (FTA) is a great challenge for even an experienced pathologist and requires special effort.

A total of 120 paraffin block were included in the study, 30 blocks were (FC), 30 blocks were (FVPC). 30 blocks were (FA), 30 blocks were blocks thyroid follicular hyperplasia. 20 blocks endocervical epithelium. 20 paraffin blocks of colonic epithelium as control. From each paraffin block, 4 slides, each of thickened were taken, stained with Hematoxylin and Eosin (H&E) for revision of histopathological diagnosis.

The histological arrangement in follicular carcinoma and follicular adenoma was significant ( $P=0.001$ ) in trabecular pattern and the difference was significant ( $P=0.016$ ) in mixed pattern while no significance with microfollicular, macrofollicular and normofollicular pattern in both follicular carcinoma and adenoma. There was no significant difference in size follicular lesion among FA, FVPC and follicular hyperplasia ( $P>0.05$ ) while, the size follicular lesion in of (FC) was significantly higher from all other groups ( $P<0.05$ ).

**Key words:** Follicular adenoma, Follicular carcinoma, Thyroid lesions.

المقارنة بين المرضى الذين يعانون من أورام الغدة الدرقية الجريبية في النمط النسيجي وحجم الآفة الجريبية

بان جمعة قاسم\*، وجدان بشير عبد\*\*، بثينة إبراهيم حميد العزي\*\*\*، زهراء احمد اوختي\*\*\*

\*\*قسم علم الامراض، كلية الطب، جامعة النهرين

\*\*\*قسم علوم الحياة، كلية التربية للعلوم الصرفة (ابن الهيثم)، جامعة بغداد

\*\*\*فرع العلوم المختبرية السريرية / كلية الصيدلة، الجامعة المستنصرية

### الخلاصة:

أن المشكلة الرئيسية التي تظهر عند اكتشاف انتفاخ الغدة الدرقية هو في التمييز بين الآفة الحميد والآفة الخبيثة. وان التشخيص التفريقي بين سرطان الغدة الدرقية الجريبية (FTC) والورم الحميد الدرقية الجريبية (FTA) يمثل تحدياً كبيراً حتى لطبيب الامراض ذو الخبرة وهذا يتطلب جهداً خاصاً.

تضمنت الدراسة (120) قالب شمعي وكان (30) قالب بارافين من السرطان الجريبية FC، (30) قالب بارافين من التنوع الجريبية للسرطان الحليمي، (30) قالب بارافين من الورم الحميد الجريبية، (30) قالب بارافين من التضخم الجريبية ومجموعه السيطره (20) عينه من انسجه القولون الطبيعي و(20) عينه من باطن عنق الرحم الطبيعي.

تم اخذ اربع شرائح نسيجية، الشريحة الاولى تم صبغها بصبغه الهيماتوكسيلين والايوسين لغرض التشخيص النسيجي المرضى كان الترتيب النسيجي في السرطان الجريبية والورم الحميد الجريبية معنوياً في كل من النمط التريبيقي

والنمط المختلط  $P=0.016$  وبينما كان غير معنويًا في كل من النمط الجريبي الصغير والجريبي الكبير والجريبي السوي. لم يظهر حجم الآفة الجريبية فرق معنوي في السرطان الجريبي والتنوع الجريبي للسرطان الحليمي ( $P>0.05$ ) والتضخم الجريبي في حين ظهر حجم الآفة الجريبية فرق معنوي كبير في السرطان الجريبي مقارنة بالمجاميع الأخرى ( $P<0.05$ ).

**الكلمات المفتاحية:** الورم الحميد الجريبي، سرطان الجريبي، آفات الدرقية.

## Introduction:

Thyroid gland reaching posteriorly the esophagus and carotid sheath. It starts cranially at the oblique line on the thyroid cartilage (just below the laryngeal prominence, or Adam's Apple), and extends inferiorly to approximately the fifth or sixth tracheal ring<sup>[1, 2]</sup>. It is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves position in relation to these during swallowing<sup>[3]</sup>. The thyroid gland is covered by a thin fibrous sheath, the capsula glandula ethyroidea, composed of an external and internal layer<sup>[4]</sup>.

The thyroid gland is made out of numerous circular empty sacs, called thyroid follicles. Each follicle appears as an irregular circle of cells. The follicular cells, which surround the follicles are simple cuboidal epithelium. The parafollicular Calcitonin cells (C-cells) are usually embedded in the wall of the follicles (intra follicular cells), inside the basal lamina surrounding the follicles. Parafollicular cells arise from the neural crest and enter thyroid gland through the ultimobranchial body<sup>[5]</sup>. The parafollicular cells produce and secrete the calcitonin hormone also known as thyrocalcitonin(CT).

Histopathologically, follicular adenomas can be classified according to their cellular architecture and relative amounts of cellularity and colloid into the following types:

- 1- Fetal (microfollicular), have the potential for microinvasion.
- 2- Colloid (macrofollicular), don't have any potential for microinvasion.
- 3- Embryonal (atypical), have the potential for microinvasion.
- 4- Hürthle cell adenoma (oxyphil or oncocyctic tumor), have the potential for

microinvasion. Hurthle cell tumor made up of microfollicles lined by large acidophilic cells, the cytoplasm of which is granular and filled with mitochondria.

Unlike the differentiated forms of thyroid cancer, which originate in the follicular cells of the thyroid gland. Medullary thyroid cancer (MTC) originates in the parafollicular cells (C cells) of the thyroid gland<sup>[6]</sup>.

Follicular thyroid carcinoma (FTC) is Cancer of the thyroid is the most widely recognized endocrine malignancy. Thyroid neoplasms emerging from follicular cells (adenoma, carcinoma, and follicular/papillary carcinoma) demonstrated broad range of overlapping clinical and cytologic features. Anaplastic thyroid cancer (ATC) is a very rare form of thyroid cancer. It is about 1.5% of cases. Although sharing some characteristics with papillary thyroid carcinoma (PTC) but this cancer have a high mitotic rate and lymphatic vessels invasion.

## Materials and Methods

The study was done in the period between (2015-2017) in the department of Biology/ College of Education for Pure Science /Ibn-Haitham /Baghdad University and in the department of Pathology college of medicine / Al-Nahrain University. Paraffin blocks of thyroid tissues samples used in this study were collected from laboratories of Baghdad Teaching Hospital, Al-Khadhmiya Teaching Hospital, Al-Yarmouk Teaching Hospital, Al-Kindi Teaching Hospital, Al-Karama Teaching Hospital, Ghazi Al-Hariri Hospital for surgical specialist in Baghdad, Al-Hussein Hospital (Kerbala Health Office) in

Karbala, Al-Sadder Medical City in Al-Najaf , Al-Sadder Teaching Hospital (Al-Ashraf/pathology unit) in Basra, Rizgary Teaching Hospital in Erbil, KalarEducational Hospital in Al-Sulaymaniyah and private laboratories, for the years(2006-2016).The clinicopathological parameters were obtained from patients' admission case sheets and pathology reports, including age, gender. The total number of the thyroid samples used in this study was 120 paraffin blocks, these include 30 thyroid follicular carcinoma,30 follicular variant of papillary carcinoma, 30 follicular adenoma and 30 follicular hyperplasia.

Patients were classified based on the presence or absence of tumor size, histopathological evaluation.

Sections 5µm obtained from formalin fixed paraffin embedded blocks of thyroid tissues specimen were stained with Harris hematoxylin and alcoholic eosin stain<sup>[7]</sup>.

Aim of the study: relationship between size and the follicle an type of follicular tumor as well as the follicular were examined grouped as macrofollicular normofollicular and microfollicular by histopathological specialist.

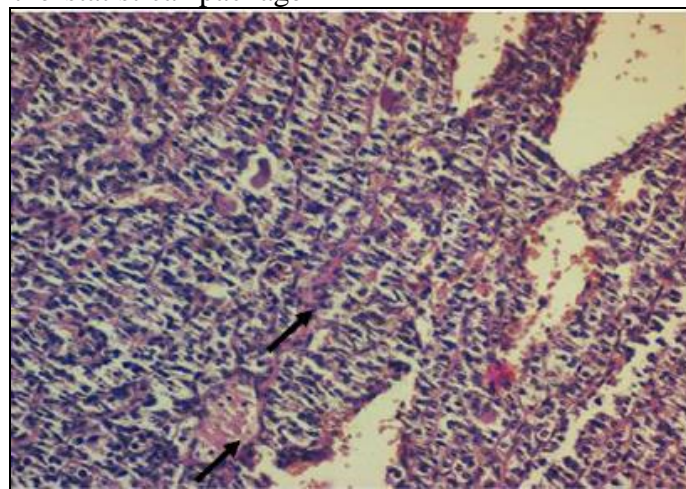
### Statistical analysis

Data were collected, summarized, analyzed and presented using three statistical software programs: the statistical package

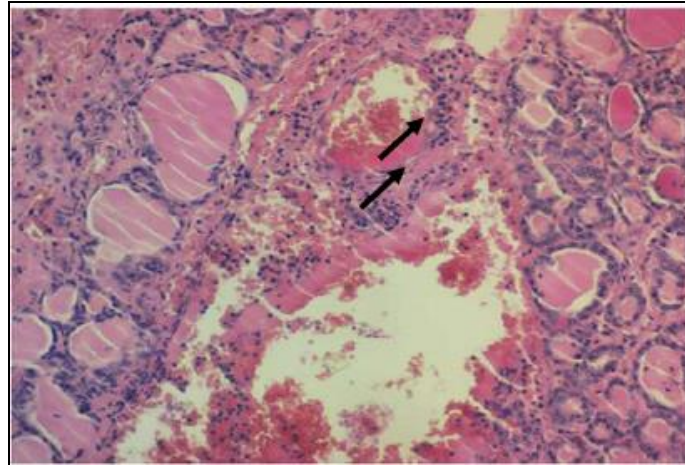
for social science (SPSS version 22). Categorical variables were presented as number and percentage whereas numeric variables were presented either as mean and standard deviation (SD) or median and interquartile range (IQR), according to the results of Kolmogrov Smirnov test of normality distribution for numeric variables. The association between categorical variables was assessed using Chi-square test and correction was done as needed. Comparison of mean values between two groups was carried out using either independent samples-t test or Mann Whitney U test, while comparison of mean values among more than two groups was carried out using either one-way analysis of variance (ANOVA) test or Kruskal Wallis tests. Correlation was evaluated using Spearman correlation test.

### Results

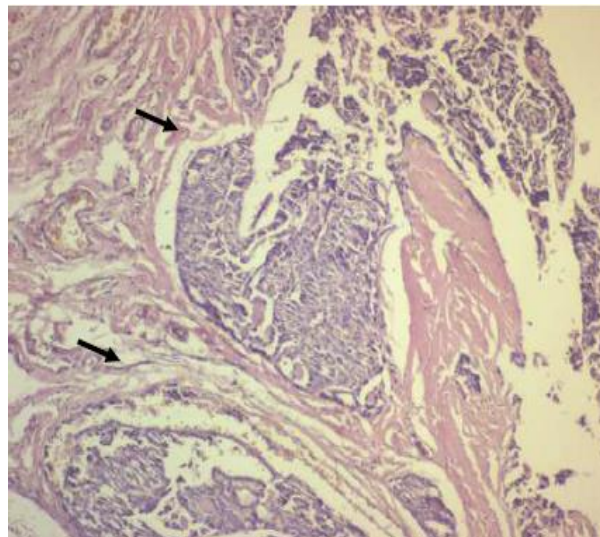
Hematoxylin and Eosin stained slides were used for review and classification of the tumors. Included follicular carcinoma, follicular adenomas showing infiltration of the capsule, without evidence of entire thickness capsular invasion and minimally invasive follicular carcinoma consisted Hürthle cell carcinoma, well differentiated follicular carcinoma, trabecular cancer, follicular variant of papillary carcinoma, and follicular hyperplasia (Figure 1-12).



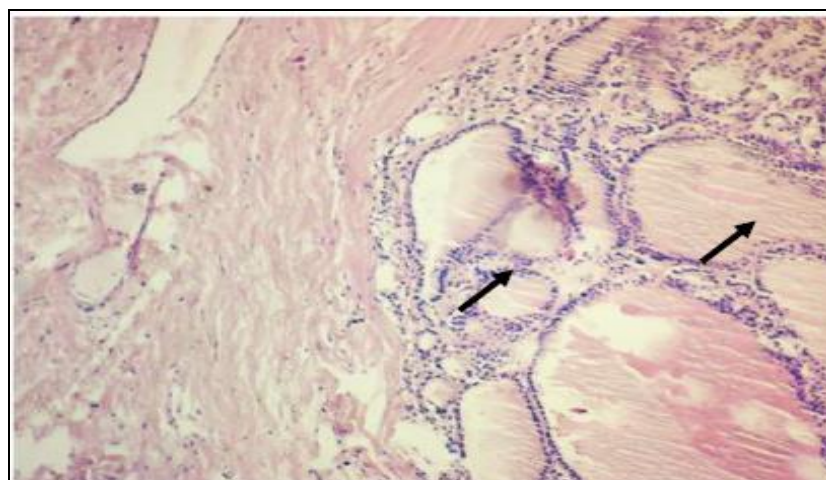
**Figure-1: Tissue Section of thyroid follicular carcinoma, microfollicular variant with predominantly small size follicles (Black arrow)(H&E, 10x).**



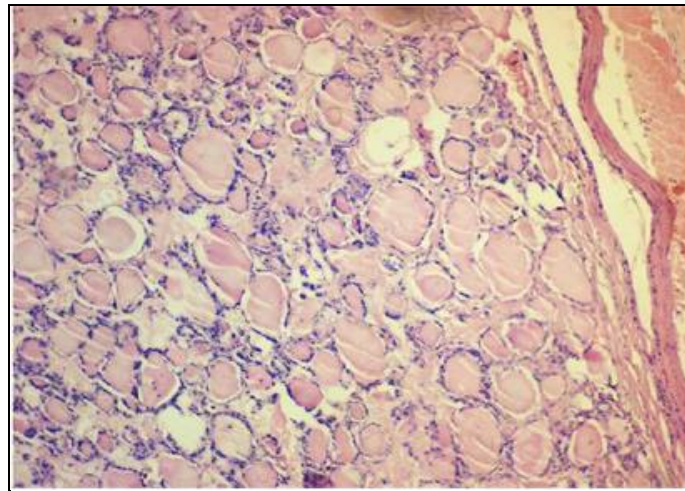
**Figure-2: Tissue section of thyroid follicular carcinoma ,vascular invasion (Black arrow)(H&E, 10x).**



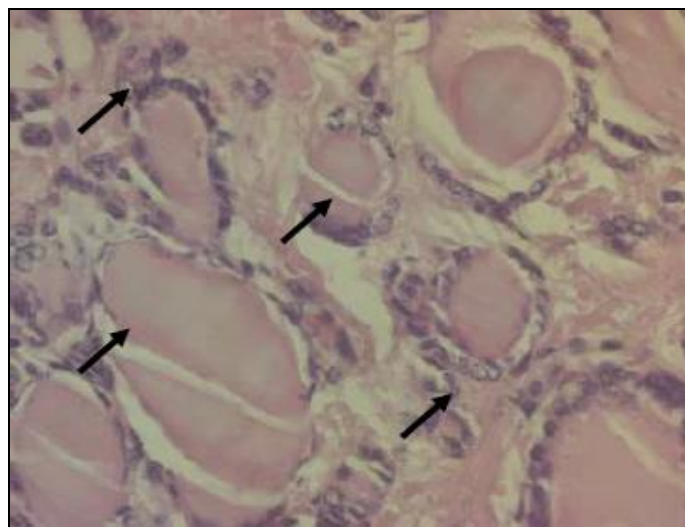
**Figure-3: Tissue section thyroid follicular carcinoma, microfollicular capsular invasion (Black arrow) (H&E, 4x).**



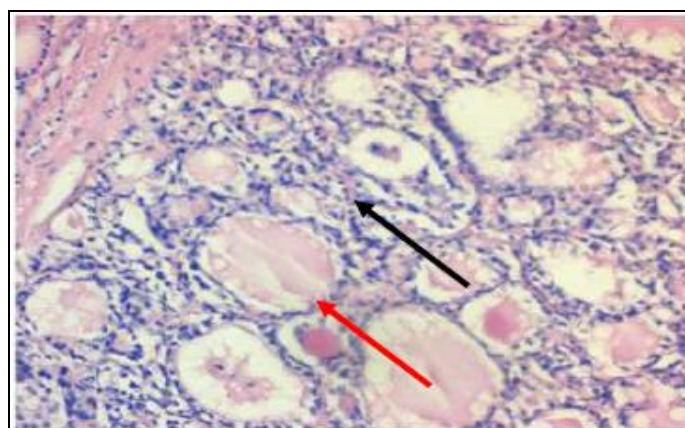
**Figure -4: Tissue section of thyroid follicular carcinoma, macrofollicular (Black arrow) (H&E,4x).**



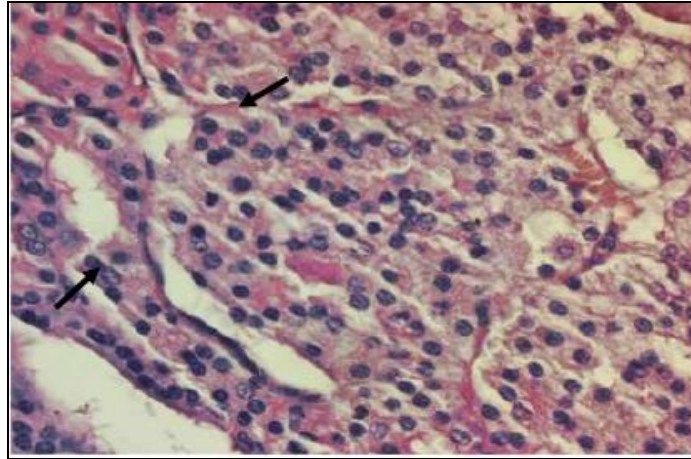
**Figure-5: Tissue section of follicular variant of papillary carcinoma showing follicular arrangement (Black arrow) (H&E,10x).**



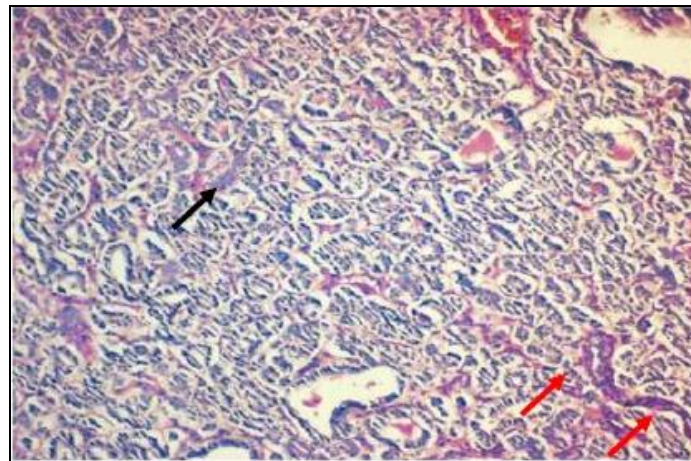
**Figure-6: Tissue section of follicular variant of papillary carcinoma showing follicular arrangement (Black arrow) (H&E, 40x).**



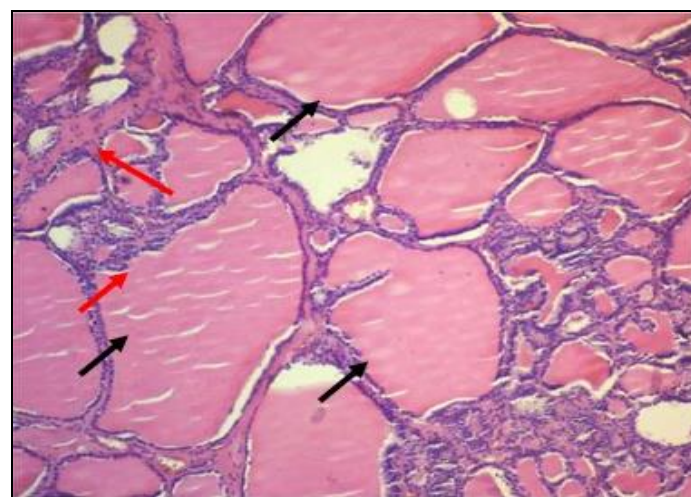
**Figure-7: Thyroid section of thyroid macrofollicular adenoma showing predominantly large size follicular pattern (red arrow) with compression of the surrounding normal tissue defined capsular (black arrow)(H&E,20x).**



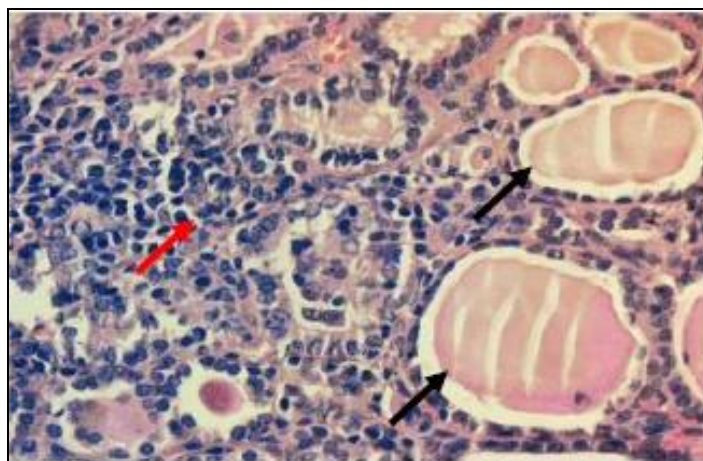
**Figure-8: Tissue section of thyroid normofollicular adenoma showing predominantly normal size follicular pattern (black arrow) (H&E, 40x).**



**Figure-9: Tissue section of thyroid microfollicular adenoma showing predominantly small follicular (black arrow) and hyalinization (red arrow) (H&E, 10x).**



**Figure-10: Tissue section of thyroid follicular hyperplasia in which there are variable sized follicles some are large (black arrow) and there is neither distinction from nor compression of the surrounding tissue (red arrow)(H&E, 4x).**



**Figure-11: Tissue section of follicular hyperplasia in which there are variable sized follicles some are large (Black arrow) and some are small (Red arrow) and there is neither distinction from nor compression of surrounding tissue (H&E, 40x)**

From histological point of view, follicular adenoma and carcinoma cases showed various forms of microscopical arrangements. These arrangements and their comparable proportions are shown in table (1). Microfollicular pattern was observed in 14 adenoma cases (46.67%) and in 16 carcinoma cases (53.33 %), and the difference was not significant ( $P=0.606$ ). Macrofollicular pattern was observed in 6 adenoma cases (20.00 %) and in a single carcinoma case (3.33%),

and the difference was not significant ( $P=0.101$ ). Normofollicular pattern was observed in 7 adenoma cases (23.33%), and in 13 carcinoma cases (43.33%), and the difference was not significant ( $P=0.100$ ). Trabecular pattern was limited to 10 adenoma cases (33.33%) and the difference was significant ( $P=0.001$ ). Mixed pattern was limited to 7 adenoma cases (23.33%), and the difference was significant ( $P=0.016$ ).

**Table-1: Number and proportion of cases according to histological types in follicular adenoma and follicular carcinoma cases**

Histological Pattern	Cases of Study Groups			
	Follicular Adenoma n (%)	Follicular Carcinoma n (%)	P-value	Significance
Microfollicular	14 (46.67)	16 (53.33)	0.606*	NS
Macrofollicular	6 (20.00)	1 (3.33)	0.101*	NS
Normofollicular	7 (23.33)	13 (43.33)	0.100†	NS
Trabecular	10 (33.33)	0 (0.00)	0.001*	S
Mixed	7 (23.33)	0 (0.00)	0.016†	S

\*Chi-square test; †: Corrected chi-square test; n= number of cases; NS: not significant; S: significant

The solid evidence of malignancy in a follicular thyroid neoplasm is represented by capsular and or vascular invasion. Capsular invasion was seen in 8 follicular carcinoma cases (26.67%) while vascular invasion was seen in 6 cases (20.00%). Minimally invasive lesions were identified in 14 cases (46.67%). Nevertheless, 8 cases showed uncertain malignant potential.

diameter, mean size and size range of thyroid follicle nodules are shown in table (2) classified with respect to histological diagnosis. Mean size of follicular lesion in follicular carcinoma was 6.36 ±3.42 cm with a range of 1.50 - 12.00 cm. Mean size of follicular lesion in Papillary carcinoma was 5.86 ±2.81 cm, with a range of 0.50 -12.00 cm.

Mean size of follicular lesion in of follicular adenoma was 4.86 ±2.56 cm, with a range of 0.90 -10.20 cm. Mean size of follicular lesion in follicular hyperplasia was 3.90 ±1.66 cm, with a range of 0.50 -8.00cm. Overall comparison using Kruskal Wallis test revealed highly significant difference (P<0.001) in size of follicular lesion among all four groups however, individual comparisons using Mann Whitney U test showed no significant difference(P> 0.05) in size follicular lesion among follicular adenoma, papillary carcinoma and follicular hyperplasia while, the size follicular lesion in follicular carcinoma was significantly higher (P< 0.05) from all other groups

**Table-2: Size of follicular lesion (mean ± standard deviation) in the cases of study groups.**

Cases of Study Groups (cm)	Size of Follicular Lesion (cm)		P-value*
	Mean ± SD	Range	
<b>Follicular Carcinoma</b>	6.36 ±3.42	1.50 -12.00	<0.001 HS
<b>Follicular variant of Papillary Carcinoma.</b>	5.86 ±2.81	0.50 -12.00	
<b>Follicular Adenoma</b>	4.86 ±2.56	0.90 -10.20	
<b>Follicular Hyperplasia</b>	3.90 ±1.66	0.50 -8.00	

\* Kruskal Wallis test; HS: Highly significant.



## Discussion

The results of the present study showed that microfollicular, macrofollicular and normofollicular patterns can be seen with equal frequency in both follicular adenoma and follicular carcinoma, and that this histological feature by its own is not helpful in suggestion of or ruling out of malignancy when follicular proliferation is detected in a solitary thyroid nodule; however, mixed pattern and trabecular pattern were mainly seen in follicular adenoma. These findings are in agreement with majority of published literatures that considered the patterns of follicular arrangement (macrofollicular, normofollicular, microfollicular, fetal, embryonic and trabecular) insignificant factors in establishing clinical behavior and that they are of no value in distinguishing malignant from benign lesion<sup>[8, 9, 10]</sup>.

The detection of malignancy in a follicular growth, in thyroid lesions, mainly resides on finding of capsular and or vascular invasion<sup>[11, 12, 13, 14, 15]</sup>. Moreover, no histological criteria, other than these two, can be used to predict malignancy, for example severe dysplastic changes can be seen in benign as well as malignant lesions<sup>[16, 17, 18, 19]</sup>. One of the objectives of the present study was to study marker expression, aiming at solving the problem of malignancy detection in follicular growths. Follicular carcinoma has microscopic features that are similar to a follicular adenoma. However, a follicular carcinoma tends to be more cellular with a thick irregular capsule, and often with areas of necrosis and more frequent mitoses. A follicular carcinoma cannot be distinguished from a follicular adenoma based on cytologic features alone. It is distinguished from a follicular adenoma on the basis of capsular invasion, vascular invasion, extrathyroidal tumor extension, lymph node metastases, or systemic metastases. Capsular invasion is defined as tumor extension through the entire capsule. Vascular invasion is defined as tumor penetration into a large caliber vessel

within or outside the capsule. Tumor invasion of a large vessel with an identifiable wall and an endothelial lining is definitive morphologic evidence of vascular invasion. Vascular invasion is the most reliable sign of malignancy<sup>[16, 20, 21, 22, 23, 24]</sup>.

The current study showed that trabecular pattern was significantly associated with benign follicular nodule rather than malignant. Actually, this finding is supported by the finding of<sup>[25]</sup> in 2016 who stated that hyalinizing trabecular tumor is generally accepted to be a benign tumor.

Hyalinizing trabecular tumor (HTT) of the thyroid gland is a rare neoplasm of follicular cell origin that was initially described by<sup>[26]</sup>. This rare form of tumor is commonly circumscribed or encapsulated, consisting of polygonal and spindle cells arranged in a trabecular pattern and separated by hyalinized stroma<sup>[25]</sup>. Microscopically, this neoplasm shows hyaline contents and nuclei with frequent grooves and intranuclear inclusions, mimicking the presence of amyloid in medullary thyroid carcinoma (MTC) or the nuclear features of papillary thyroid carcinoma (PTC), potentially leading to misdiagnosis of this benign tumor as malignant based on preoperative fine needle aspiration (FNA) cytology<sup>[27]</sup>. In this tumor the majority do not present with aggressive behavior such as capsular/vascular invasion, local recurrences, or distant metastases<sup>[25]</sup>. Nevertheless, finding of hyalinizing trabecular tumor does not rule out malignancy and that although being, malignant neoplasms with this pattern of morphology have described in published literatures<sup>[28]</sup>.

In the present study, overall comparison revealed highly significant difference in size of follicular carcinoma among all four groups ( $P < 0.001$ ); however, individual comparisons showed no significant difference in size of follicular lesion among follicular adenoma, follicular variant of papillary carcinoma and

follicular hyperplasia ( $P > 0.05$ ); meanwhile, mean size of follicular carcinoma was significantly higher from all other groups ( $P < 0.05$ ). Specialists recommend thyroidectomy for nodules  $\geq 4$  cm even in the setting of benign FNAC, because of expanded risk of malignancy and increased false negative rates in large thyroid nodules [29, 30, 31]. Even more aggressive surgeons use a threshold of 3 cm [32]. This opinion suggests, in accordance with the results of the current work, that the larger size of the nodule the more is the risk of malignancy. Within this concept, it has been stated by several authors that larger size (more than 4 cm) correlates with higher incidence of malignancy [33]. For instance, [34] concluded, after reviewing 4955 cases of thyroid nodules, that when size of tumor increases the risk of cancer becomes higher, particularly for follicular carcinomas and other rare thyroid malignancies [35].

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