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Histological Classification of Thymoma: Evaluation by Computer-Assisted Morphometry

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Abstract:

Background: Many thymoma classifications have been followed and have been updated by newer or alternative schemes. Many classifications were based on the morphology and histogenesis of normal thymus as the backbone, while other classifications have followed a more simplified scheme, whereby thymomas were grouped based on biological behavior. The WHO classification is currently the advocated one, which is based on "organotypical" features (i.e. histological characteristics mimicking those observed in the normal thymus) including cytoarchitecture (encapsulation and a "lobular architecture") and the cellular composition, mostly the nuclear morphology is generally appreciated.

Objectives: This study aims to re-classify thymomas by establishing certain morphometric parameters to evaluate the epithelial cells nuclei. An appraisal of thymoma classification as cortical/ lymphocytic/ type B1 and B2 or medullary/ spindle cells/ type A will be attempted as objective re-evaluation of thymoma.

Patients: This study is a retrospective evaluation of 50 cases of thymoma, 20 cases of thymic hyperplasia and 10 cases of normal thymus (control group). Using a 5 µm formalin-fixed paraffin embeded tissue sections, stained with hematoxylin-eosin stain, these cases were previously classified histologically into lymphocytic (6 cases), lymphoepithelial (mixed) (28 cases) and epithelial (16 cases), including 2 cases of spindle cell thymoma.

Methods: Computer-assisted morphometry was performed for 80 cases. This involves digitization of the histopathological features and application of morphometric analysis through software. The morphometric parameters used are nuclear area, maximum nuclear diameter and Form factor of epithelial cells nuclei. Ten normal thymus glands from the archived cases were also evaluated as a control groups.

Results: The results showed that epithelial thymomas possess significantly different nuclear areas from that of a normal thymus, the maximum nuclear diameter (D-Max) follows the same pattern and adds no further outcomes. The numerical morphometric analysis showed no significant differences between lymphocytic predominant thymoma and those classified as cortical thymoma (Type B2). Thus it does not support such a re-classification. Form factor is an indication of pleomorphism, but it should be cautiously used when spindle cells are present since it may give a false indication of pleomorphism.

Conclusion: Computer-Assisted morphometric analysis provides an objective, reproducible and comparable results for thymoma histological classification.

Keywords: Thymoma, Histological classification, Grading, Morphometry, Computer-assisted morphometry

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Introduction:

Thymic epithelial tumors were classified in several histological classifications based on lymphocytes to epithelial cells ratio and / or shapes of the epithelial cells. In the latest WHO classification of thymus tumors, the five main histologic subtypes are designated by letters or letters and numbers and distinguished from other rare thymic tumors. The five main subtype are: type A (spindle cell; medullary), type AB (mixed), type B1 (lymphocyte-rich, lymphocytic predominant, cortical), type B2 (cortical), and type B3 (Epithelial, well differentiated thymic carcinoma). Further subdivision depends on the content of neoplastic epithelial cells and non-neoplastic immature T-cells. In type A and B3 thymomas there is a paucity or even lack of immature T-cells throughout the respective tumors. Type A and AB) show closely packed spindle cells or sheets of polygonal epithelial cells (type B3), whereas there is a variable and reciprocal abundance of immature T-cells and epithelial cells in type AB, B1, and B2 thymomas (1, 2). The controversy regarding the relationship between those histologic classifications and the clinical features of thymoma was recognised. This controversy is due to lack of objective data to assess the histological classification (Fig.1). Furthemore, the subjectivity of histological grading makes it a less reproducible. Many studies showed the importance of quantitative analysis in the grading of urinary bladder transitional cell carcinoma and mammary carcinoma as an important method in assessing the risk of tumor recurrence. Some other

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studies showed the value of nuclear morphology measurement as a prognostic tool for bladder carcinoma (3, 4, and 5). Marino and Muller –Hermelink (1985) have reported that histological differences in the epithelial cells present in normal cortical and medullary zones of the thymus may constitute a basis to distinguish thymoma with cortical or medullary differentiation and that cortical thymomas tend to be frequently invasive and associated with myasthenia gravis than the medullary and mixed types (6). In this study, we classified thymoma histologically into lymphocytic, mixed and epithelial types according to the ratio of epithelial cells to lymphocytes and compared the malignant potential of these subtypes by morphometric analysis of epithelial cells nuclei in thymic tissue and thymoma (7).

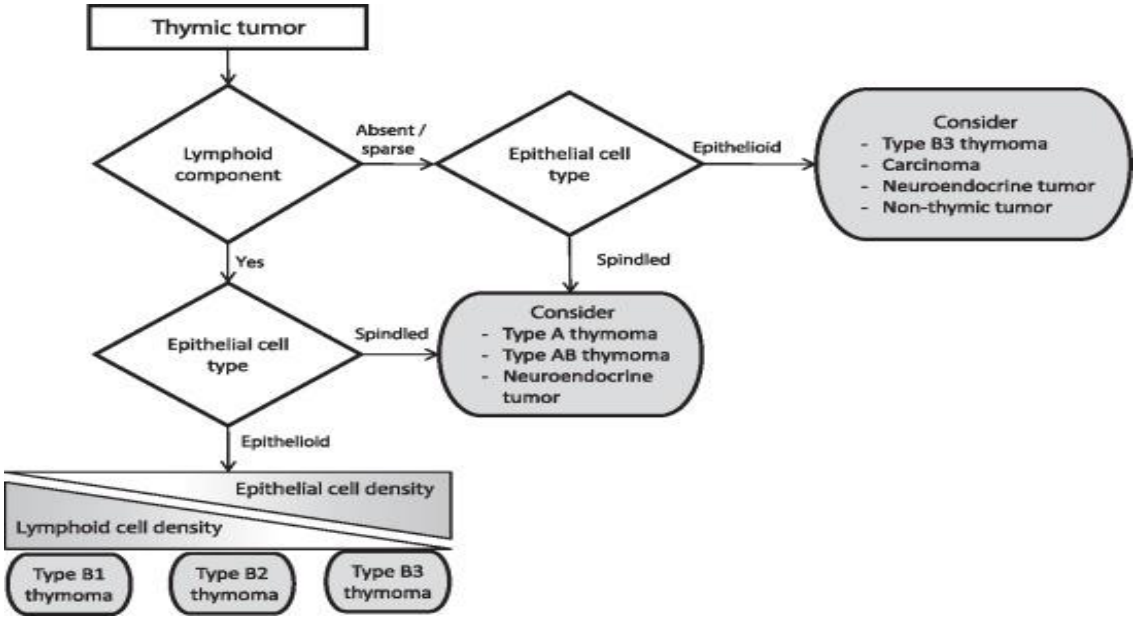

Figure 1: Algorithm chart for initial H&E-based subtyping of thymoma.

Although undoubtedly, immunohistochemistry has its role in the diagnosis of difficult cases, to date; there are no specific markers that can distinguish thymic epithelial tumors from other neoplasms and the interpretation of immunohistochemistry should only be made in correlation with objective morphological assessment in correlation with careful clinical evaluation (8). Computer-assisted morphometry is a semiautomatic machine which incorporates a "graphic tablet" and a "digitizer" linked to a microcomputer. The image is projected onto the tablet. A cursor connected to the electronics of the tablet is moved by the operator around the periphery of the object of interest. The movements of the cursor are translated electronically into a stream of coordinates, which are parameters required by the microscopist. The possibility of an inherent manual error may be elicited, but studies have shown that intra- and inter- observer reproducibility was excellent or good.

Methods:

Eighty cases of thymic lesions seen during the period 1985 - 1996 were included in this study. There were 50 cases of thymoma and 20 cases of thymic hyperplasia with or without myasthenia gravis. In addition, 10 cases of normal thymus were considered as a control group. These cases were diagnosed at the Central Public Health Laboratory and the slides were retrieved from the lab archives. The specimens included mediastinal biopsies and thymectomy specimens. The use of polyvar microscope and the macro-dual zoom, in the Anatomy department of Al Nahrain Medical College, allows computations to be performed directly on tissue sections visualized in the microscope without the necessity to draw or photograph them. The basic units of the image analysis system are: control computer, monitor, keyboard, printer, digitizer tablet and cursor .In H&E stained sections, random selection of two microscopic fields from each case and measurement of epithelial cells nuclear area was done. Each field was viewed under X100 Oil –immersion lens and displayed on the screen of the system (9).The image of 25 epithelial cells nuclei per field was outlined with the drawing software and the data were processed by the

computer , which calculated the nuclear area. The morphometric parameters used were selected from a menu program. These are nuclear area, maximum diameter (D- Max) and Form factor (Form PE) (6, 7). Form PE is calculated from the formula:

Form PE = $4\frac{\pi}{(perimeter)2} x\ area$

Form factor will produce a value of (1) in perfectly circular structures. Irregular structures will be less than (1). Form factor is a measure of the degree of "pleomorphism". (10)

Results:

Three-dimensional frequency distribution was used to get an insight of the relation between different pathological conditions. Values of thymic hyperplasia and benign thymoma were grouped together, while the three types of malignant thymoma (lymphocytic, mixed and epithelial thymoma) formed another group. Then composite three-dimensional frequency distribution of nuclear area, maximum diameter and (form PE) were made. Nuclear area of epithelial cells in our work show a uniform distribution in normal control compared to that in benign thymoma (Fig.2). There is a varying distribution of nuclear area in the three subtypes of thymomas, compared to the normal controls especially in epithelial thymoma which shows skewing of the graph to the right, (Table.1, Fig.3)

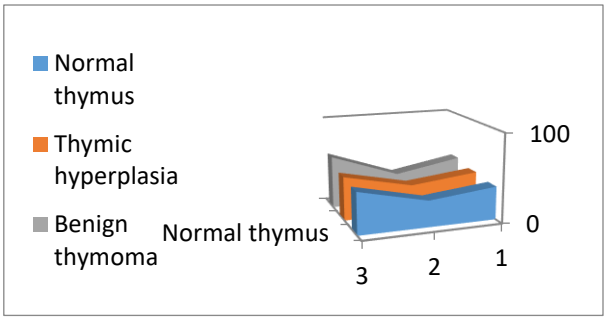

Figure2: Composite 3-dimensional frequency distribution of the nuclear area in normal, hyperplastic and benign thymoma.

The maximum diameter (D-Max) was homogenously distributed in the range of (5.5-14.5 µ) for the three histologic subtypes of thymoma compared to normal control (Table 2, Fig 4, 5).

Table 2: Mean ± SD for D-Max of nuclei in different types of thymoma compared to normal

Thymus tissue type	Mean ± S.D	Range ± S.D
Normal Thymus	7.3 ± 1.02	6.31 - 8.33
Thymic hyperplasia	7.9 ± 1.05	6.87 - 8.97
Benign thymoma	8.0 ± 1.05	6.97 - 9.07
Epithelial thymoma	9. 8 ± 1.28	7.96 - 11.06
Mixed thymoma	8.8 ± 1.11	7.68 - 9.90
Lymphocytic thymoma	7.6 ± 1.11	6.46 - 8.68

Table 1: Mean ± SD for the nuclear area measurements in different types of thymomas

Diagnostic category	Mean ± SD	Range ±1 SD
Normal thymus	37.4 ± 8.4	29.60 - 47.0
Thymic hyperplasia	40.9 ± 8.3	32.58 - 49.18
Benign thymoma	46.2 ± 13.4	32.84 - 59.64
Epithelial thymoma	63.7 ± 17.5	46.16 - 81.16
Mixed thymoma	51.0 ± 11.2	39.84 - 62.24
Lymphocytic thymoma	37.9 ± 7.5	30.37 - 45.37

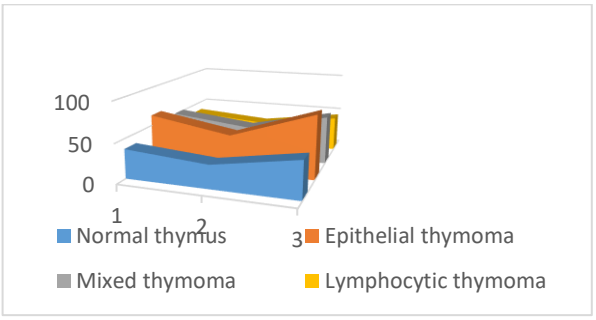

Figure 3: Composite 3- dimensional frequency distribution of the nuclear area in thymomas.

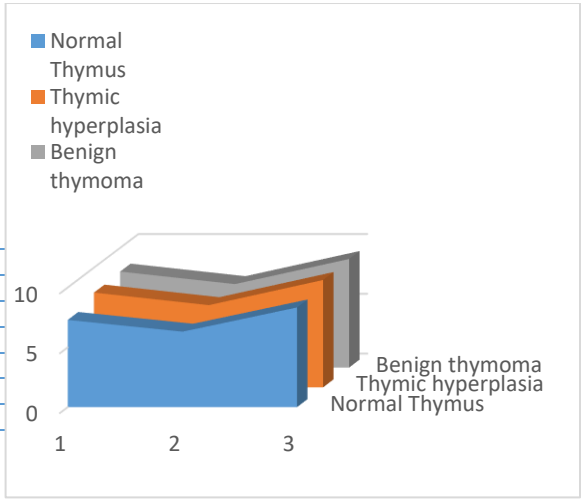

Fig.4: Composite 3-Dimensional frequency distribution of nuclear maximum diameters in normal, hyperplastic and benign thymoma

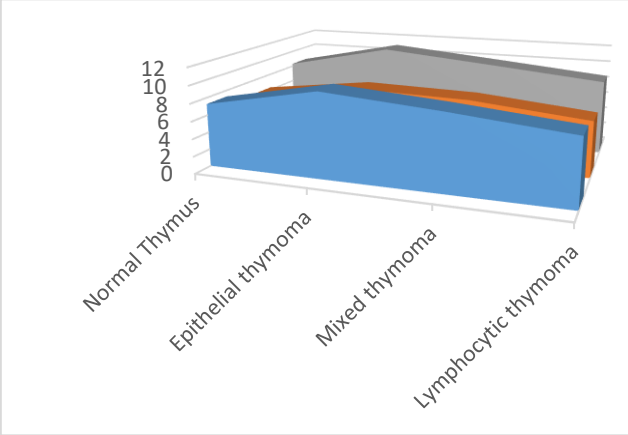

Fig.5: Composite 3-dimensional frequency distribution of nuclear D-Max in thymomas

Normal, hyperplastic thymus, and benign thymoma have a uniform (Form PE) in the range of (0.8 - 1) as can be seen in (Fig.6), while the three histological subtypes of thymomas show a heterogeneous (form PE) that deviates more from these values (Table 3, Fig.7).

Table 3: Mean ± SD for the form factor (PE) of nuclei in different types of thymoma compared to normal

Thymus tissue type	Mean ± 1S.D	Range
Normal Thymus	0.89 ± 0.052	0.835 - 0.941
Thymic hyperplasia	0.88 ± 0.049	0.831 - 0.929
Benign thymoma	0.89 ± 0.046	0.846 - 0.938
Epithelial thymoma	0.87 ± 0.057	0.813 - 0.927
Mixed thymoma	0.89 ± 0.056	0.834 - 0.946
Lymphocytic thymoma	0.49 ± 0.056	0.387 - 0.599

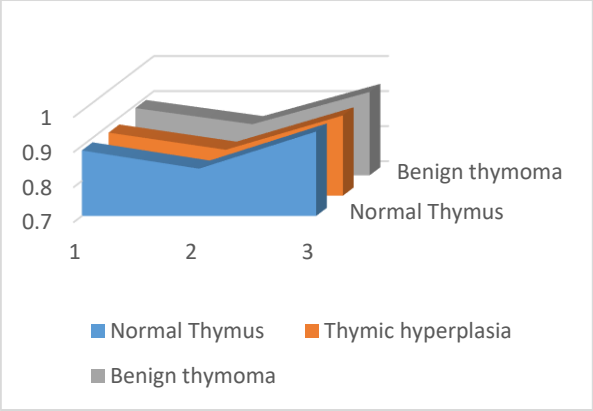

Figure 6: Composite 3-Dimentional frequency distribution of Form factor PE in normal, hyperplastic and benign thymoma.

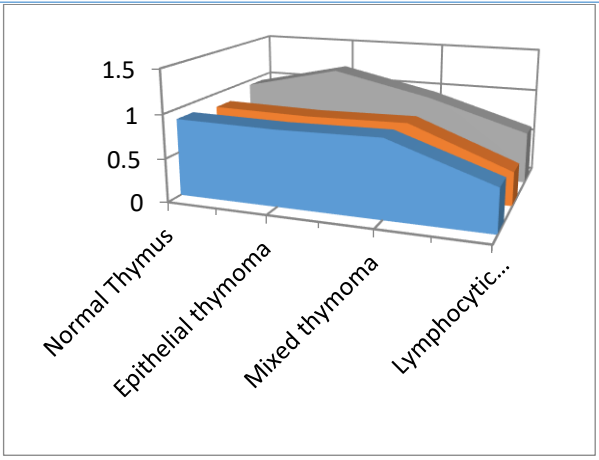

Fig.7: Composite 3-Dimensional frequency distribution of Form factor PE in thymoma

Applying T-Test showed a statistically significant difference between epithelial, mixed and lymphocytic thymoma compared to the normal thymus, P-value < 0.001 in case of epithelial and mixed thymoma, for the nuclear areas of epithelial cells (EC) in epithelial and mixed thymoma. In case of lymphocytic thymoma, the T-test shows a statistically significant difference with a P-value of < 0.05, which means that we accept the hypothesis (Ha), which means there is no significant difference between nuclear areas of EC in lymphocytic thymoma compared to normal thymus. When comparing the three histological subtypes of thymoma using ANOVA test, the calculated F value was much less than tabulated, indicating no significant difference between the nuclear areas in three histological types of thymomas.

Discussion:

According to the most recent classification proposed by the WHO and the previous classification proposed by Marino and Muller-Hermelink in 1985, thymomas are histologically classified to cortical, predominantly cortical, mixed (composite) thymoma, medullary thymoma and thymic carcinoma (11). This classification is based on the morphological features of the EC component in thymoma, and it is consistent with the anatomic architecture of the normal thymus. Cortical thymomas were mainly formed by medium sized to large epithelial cells and round to oval nuclei, prominent nucleoli, the lymphocytes are numerous, designated as type AB, B1 and B2 in the recent WHO classification. Characteristic features of cortical thymoma are the presence of "starry sky" pattern, areas of medullary differentiation and perivascular epithelial cells palisading (12). Medullary thymoma consists of small to medium sized epithelial cells with irregular and sometimes spindle shaped nuclei, usually lacking nucleoli; designated as type A, AB and B3 in the WHO classification. Typical features of medullary thymoma are the presence of epithelial cysts and presence of a storiform–like pattern. In mixed (composite) thymoma,

both features of cortical and medullary thymomas are identified, intermingled with a variable amount of small lymphocytes (13). It seems evident from the previous description that cell morphology is the hallmark of such classification and particularly the nucleus, such classification admittedly, is still a subjective matter. Nomori et al. (1989) applied the method of computer-assisted morphometry and concluded that invasive thymomas are morphometrically malignant tumors according to their nuclear sizes and shapes (14). In the present work, we aimed to evaluate cases that were already graded / classified as lymphocytic predominant, mixed lymphoepithelial and epithelial thymoma according to nuclear size and shape. Nuclear areas in our work showed a uniform distribution in normal controls; however, in epithelial thymomas, the distribution of nuclear area was very variable with skewing of the graph to the right. This indicates that higher proportion of cells with large nuclei. Statistical tests confirmed the presence of a significant difference between the nuclear areas of EC in epithelial thymoma compared to that of normal thymus. Our finding thus confirmed the work of Nomori et al. (1988) (15). Computer-assisted measurements of nuclear areas, based on our suggested readings (63.7 ±17.5µm) for epithelial thymoma compared to that of normal thymic epithelium (38.3 ±8.7µm) can be readily used for objective segregation of epithelial thymoma. If we compare nuclear areas of cortical thymomas (according to the classification of cortical vs. medullary thymoma), it can be concluded that the range of cortical thymoma (45.6=± 7.1µm) as defined by (Nomori et al. (1989) (16) will be overlapping with the lymphocytic thymomas in our study. Histopathologically, the morphometric data collaborate with the histopathological features (17). Despite the fact that lymphocytic and cortical thymomas, microscopically showed large sheets of EC with round to oval nuclei, vesicular chromatin and prominent central nucleoli, these features are similar to those of EC in the outer cortex of the normal thymus. However, the cells are usually much larger and their cytoplasm is more abundant and sometimes vacuolated or clear. Single or multiple, sometimes densely packed immature lymphoid cells are found within the cytoplasm. Many lymphoid cells are seen between the EC processes as densely packed lymphoid cells of small to medium sizes. Lymphoid follicles with germinal centers are not infrequent. Cortical thymomas have a lobular architecture with conspicuous fibrous septae surrounding each lobule (18). Despite the fact that lymphocytic predominant thymoma (type B1) has distinctive histopathological features, such features seem not to include the nuclear area, and has no significant difference from that of nuclear areas in the cortex of normal thymus (Table 3). Such findings will rule out the possibility of morphometric segregation of cortical (in one classification) or lymphocytic thymoma (in another classification) from that of normal thymus. (19) Nuclear areas in epithelial thymoma showed very variable distributions with skewing of the graph to the right. This indicates a higher proportion of cells with large nuclei. Statistical tests confirmed the presence of a significant difference between the nuclear areas of epithelial cells in epithelial thymoma compared to that of a normal thymus. If we compare nuclear areas of cortical thymoma, it can be concluded that the mean for cortical thymoma (45.6 ± 7.1 µm) as defined by Nomori et al (1989) will be overlapping with the lymphocytic thymoma in our study. In the case of mixed (lymphoepithelial) thymoma, the cell population seems heterogeneous; the frequency distribution shows wider dispersion of nuclear areas compared to normal but less pronounced than that of epithelial thymoma. There is a statistically significant difference between mixed thymoma and normal thymus. However, because of the pathological nature of this tumor which is actually a mixed tumor of EC, having both cortical and medullary EC components, with no defined proportions, this makes it unsuitable for comparison. (20, 21) In pathological terms, changes in the (shape) of the nuclei is a significant finding used for typing of tumors (30,31 ,32). In thymoma, spindle shaped nuclei and irregular nuclei can be seen in both benign and malignant thymoma, and usually found classically in medullary thymomas which are found to be benign in most cases. (22, 23, 33) In this study, the form factor (PE) is used to judge the shape of the nuclei (34, 35). It seems that normal thymus, hyperplastic thymus and benign thymomas have a uniform form factor, mostly in the range of (0.8-1). Different types of thymomas show a heterogeneous form factor that deviates more from these values, indicating irregular or spindle shaped nuclei. This in fact, is a morphometric translation to the pathological term "Pleomorphism"(36, 37). Because of the great variation in the shape of the nuclei and the sensitivity of the form factor used, direct measurement of the form factor can be used to document the presence of pleomorphism but cannot be used for discrimination purposes. (24, 25, 38, 39) D-Max is a morphometric parameter used in this study primarily to detect enlargement in the nuclear size. It did not yield much information, based on the fact that Form factor shows a great variation. The basic configuration or shape of the nuclei is thus changing, which makes it difficult to judge the size of the nuclei as a function of D-Max. (26, 27, 28, 40, 41)

Conclusions:

The morphometric evaluation of EC in thymoma was important for the typing of thymomas and found to increase with increasing invasiveness under the clinical context. The (Nuclear area) parameter can be used for objective segregation of epithelial thymoma based on the nuclear areas of EC that shows a significant difference from that of normal thymus. Morphometric

data and histopathological features of lymphocytic thymomas are overlapping with cortical thymoma, but the morphometric evaluation showed no significant difference from that of normal thymus, this rules out the possibility of morphometric segregation of cortical thymoma from normal thymus. There is a statistical significant difference between mixed thymoma and normal thymus. However, because of pathological heterogeneity of this tumor, makes it unsuitable for comparison with other subtypes of thymoma. Nuclear pleomorphism is often taken as a measure of the malignant grade of many neoplasms and is presented morphometrically as the (Form factor), which is calculated from the (nuclear area/ perimeter). Accordingly, spindle cells in thymoma, possessing higher pleomorphism of the nuclei than round or polygonal cells, because of its variation in nuclear perimeter, often mistakenly reported as benign. Therefore; the (Form factor) is not a proper index of nuclear pleomorphism in thymoma. Objective histologic typing of thymoma, using morphometric analysis is a valuable tool to be correlated with the clinical staging and histological grading of malignancy.

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التصنيف النسيجي لاورام الغدة التوتية: تقويم بالمقايسة الشكلية المسندة بالحاسوب

د. إبتسام حسين العبيدي*
*** المركز الوطني للمختبرات التعليمية- مدينة الطب**

الخلاصة:
خلفية البحث: اعتمادا على التصنيف الحديث لاورام الغدة التوتية باستخدام تصنيف منظمة الصحة العالمية للعام 2015, الطبعة الرابعة والذي يصنف الأورام إلى نوع **A, AB, B1** و**B**2 اعتمادا على انواع الخلايا النسجية المكونة للغدة التوتية، وبالرغم من ذلك لازالت هناك حاجة ماسة لإيجاد مؤشرات شكلية لهذه الأورام تتعلق بالسلوك البايولوجي ودرجة السرطانية لأنواع الورم المختلفة. أظهرت مراجعة المقالات البحثية عن تطبيق طريقة المقايسة الشكلية باستخدام الحاسوب في دراسة أورام الثدي والبروستات وغيرها نتائج واعدة لفحوص اكثر دقة وبالامكان تطبيقها على أورام الغدة التوتية.
الاهداف: تشمل هذه الدراسة خمسين (50) حالة من اورام الغدة التوتية وقد تم تصنيف هذه الاورام نسيجيا باستخدام شرائح زجاجية لمقاطع نسيجية من الأورام وبصبغة هيماتوكسيلين- ايوسين، تم تصنيفها الى لمفاوية (6 حالات) , لمفاوية طلائية او خليطة (19 حالة) , طلائية (16حالة) , حالتين لاورام توتية مغزلية الخلايا و (9 حالات) غير مصنفة نسيجيا.
طريقة البحث : جرت مقايسة شكلية لجميع الحالات وشمل ذلك تقويم الصفات النسيجية المرضية ومن ثم تحليلها باستخدام برنامج حاسوب خاص بقياس الاشكال .كانت المؤشرات الشكلية المستخدمة في المقايسة هي مساحة النواة ,القطر الاكبر للنواة ومعامل الشكل لنوى الخلايا الطلائية. استخدمت عشرة (10 حالات) لغدة توتية سليمة وعشرون (20 حالة) لفرط التنسج للغدة التوتية
نتائج البحث : اشارت النتائج الى ان الاورام الطلائية التوتية تمتلك مساحة نواة مختلفة عن مثيلاتها في الغدد السليمة, ولم يضف قياس القطر الاكبر للنواة معلومات مفيدة الى تلك التي قدمها قياس مساحة النواة في الخلايا الطلائية. لم يظهر التقويم والتحليل الرقمي لاورام الغدة التوتية اللمفاوية النوع او نوع **(B 2)**اختلافا عن ذلك المتعلق بصنف الورم التوتي القشري وذلك لايقدم دعما لمثل هذا التصنيف.
مناقشة النتائج: ان معامل الشكل للنواة كان مؤشرا لتعدد اشكال النوى في الخلايا الطلائية الورمية ولكن ينبغي ان يستخدم بحذر عند وجود خلايا مغزلية في مقطع النسيج الورمي حيث ان الخلايا المغزلية وجدت النوع الغالب من الخلايا في الاورام التوتية الحميدة برغم تنوع اشكال الخلايا وقد تعطي انطباعا كاذبا عن درجة سرطانية الورم من الناحيةالسريرية
الاستنتاج: ان المقايسة الشكلية المسندة باستخدام الكومبيوتر تقدم طريقة رقمية , قابلة للتكرار وللمقارنة مع التصنيف الغير رقمية المعتمد على التقييم الشخصي للمقاطع النسيجية في مختلف اورام الغدة التوتية وبالامكان استخدامها وتحليلها كمياً لتواكب وتدعم التصنيف السريري لدرجة سرطانية الورم وبالتالي صفاته الجائحة

كلمات البحث: ورم الغدة التوتية، المقايسة الشكلية، المقايسة الشكلية باستخدام الحاسوب، التصنيف النسيجي لاورام الغدة التوتية .