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Utility of Computerized Nuclear Morphometry in Diagnosis of Various Thyroid Lesions with Special Attention to Papillary Thyroid Carcinoma

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ABSTRACT
The study evaluated the utility of computerized nuclear morphometry in differentiating various thyroid lesions, with special attention to papillary thyroid carcinoma (PTC). Nuclear morphometric analysis was performed on 248 thyroid lesions using a semi-automated system. Eight parameters were measured in 100 nuclei per case. Statistical analysis included ROC curves, sensitivity, specificity and diagnostic accuracy calculations. The study included 31PTCs, 31FVPTCs, 2FCs, 18FAs, 149 multinodular goiters, and 17 thyroiditis cases. PTC showed significantly higher nuclear area (50.4±16.1 µm²) and Form AR (54.4±18.6) compared to other lesions ($p<0.0001$). Nuclear area demonstrated excellent diagnostic performance (AUC: 0.896, 95% CI: 0.891-0.901) in differentiating PTC. The optimal cut-off value of 35.45 µm² yielded 81.2% sensitivity and 80.0% specificity. NACV% showed distinctive patterns in differentiating inflammatory from neoplastic conditions (39.05±6.74% vs 13.9±1.37%, $p<0.0001$). Nuclear morphometry provides objective criteria for thyroid lesion differentiation, with particular utility in PTC diagnosis. The established cut-off values and diagnostic performance metrics support its use as an adjunct diagnostic tool in thyroid pathology.

INTRODUCTION

Thyroid nodules represent one of the most common endocrine disorders, with a prevalence of 4-7% in the general population through palpation alone and up to 67% through high-resolution ultrasonography[1]. While most thyroid nodules are benign, approximately 5-15% are malignant, making accurate diagnosis crucial for appropriate clinical management[2]. Among thyroid malignancies, papillary thyroid carcinoma (PTC) accounts for approximately 80% of all cases and presents unique diagnostic challenges despite its relatively favorable prognosis[3]. Fine-needle aspiration cytology (FNAC) remains the gold standard for initial evaluation of thyroid nodules, offering a cost-effective and minimally invasive diagnostic approach. However, traditional cytological assessment faces several limitations, including inter observer variability and diagnostic challenges in borderline cases[4]. These limitations are particularly evident in distinguishing follicular variants of papillary thyroid carcinoma from benign follicular lesions, where subjective interpretation of nuclear features plays a crucial role[5]. The advent of digital pathology and computerized image analysis has revolutionized diagnostic approaches across various medical disciplines. Nuclear morphometry, a quantitative method for analyzing nuclear size, shape and chromatin distribution, has emerged as a promising tool in cytological and histopathological evaluation[6]. This technique offers objective, reproducible measurements of nuclear parameters that may complement conventional microscopic examination and potentially enhance diagnostic accuracy[7]. Recent advances in computing technology and artificial intelligence have further refined nuclear morphometric analysis, enabling more sophisticated evaluation of nuclear features. These developments have particular relevance in thyroid cytopathology, where nuclear characteristics are paramount in diagnosis, especially for papillary thyroid carcinoma[8]. Modern computerized systems can analyze multiple nuclear parameters simultaneously, including area, perimeter, circular form factor and chromatin distribution patterns, providing quantitative data that may help differentiate between benign and malignant lesions with greater precision[9]. The integration of nuclear morphometry into routine diagnostic practice represents a significant step toward standardizing thyroid lesion assessment. This approach not only provides objective measurements but also offers the potential to identify subtle nuclear changes that might not be apparent through conventional microscopic examination. Furthermore, the digital nature of morphometric analysis facilitates data storage, sharing and retrospective analysis, contributing to both clinical practice and research applications[10]. This study focuses on the utility of computerized nuclear morphometry in thyroid lesion diagnosis, with particular emphasis on its application in papillary thyroid carcinoma. We examine the technical aspects of morphometric analysis, its current applications, limitations and potential future developments in thyroid cytopathology and histopathology. Understanding these aspects is crucial for pathologists, endocrinologists and researchers working in thyroid cancer diagnosis and management.

Aims and Objectives: The study aimed to evaluate different nuclear morphometry parameters for the differential diagnosis of various thyroid lesions. The research focused on determining the efficacy of nuclear morphometry in diagnosing thyroid lesions, with particular attention to thyroid papillary carcinoma. The investigators sought to establish objective diagnostic nuclear morphometric criteria for diagnosing various thyroid lesions, emphasizing papillary thyroid carcinoma. Furthermore, the study aimed to assess whether nuclear morphometry could serve as an adjunct ancillary technique in the diagnosis of thyroid lesions, particularly papillary thyroid carcinoma.

MATERIALS AND METHODS

Study Design and Population: The investigation was conducted at a tertiary care hospital over a period of 7 years and 6 months, spanning from January 2010 to June 2017. The study design incorporated both retrospective and prospective components, with 5 years of retrospective data and 2.5 years of prospective data. A total of 248 cases were analyzed during this period, comprising 31 cases of classical papillary thyroid carcinoma (PTC), including 3 cases of papillary micro carcinoma, 31 cases of follicular variant of papillary thyroid carcinoma (FVPC), 2 cases of follicular carcinoma (FC), 17 cases of Hashimoto's /Lymphocytic thyroiditis, 18 cases of follicular adenoma and 149 cases of nodular goiter.

Image Acquisition and Analysis System: The study utilized a semi-automated image analysis system consisting of a binocular microscope (Olympus CX21), a digital eyepiece mounted USB camera (De Winter), and a personal computer. Image analysis was performed using Digimizer version 4 software. For each case, appropriate slides demonstrating the pathology were selected and ten different areas of interest were photographed. An equal number of normal areas surrounding the lesion were also photographed to serve as controls.

System Calibration: The calibration process involved photographing a micrometer slide under high power. A 10-micron reference line, corresponding to the distance between two small lines on the micrometer scale, was established using the software. The image

could be zoomed within the software without affecting the measurement calibration. Since the software provided radius measurements, diameter calculations were performed separately. This calibration process was repeated for each slide image where micrometer was conducted.

Nuclear Measurements: The study evaluated 100 nuclei per case, analyzing 10 nuclei from each of the ten photographed fields. Only intact nuclei of thyroid follicular epithelial cells were included in the analysis, while fragmented, smudged, or overlapped nuclei and stromal cell nuclei were excluded. An equal number of nuclei from surrounding normal areas were measured as controls.

Morphometric Parameters: The analysis included both measured and calculated nuclear morphometric parameters. The measured parameters comprised nuclear area (µm²), nuclear perimeter (µm), maximal nuclear diameter (max D) (µm) and minimal nuclear diameter (min D) (µm). The calculated parameters included nuclear size [calculated as 2×(Nuclear area/ p)^0.5], coefficient of variation of nuclear area (NACV) [(SD of NA/mean NA)×100], L/S ratio (max D/min D) and Form_AR (¼×p×Longest axis×shortest axis).

Parameter Definitions: The maximal diameter represented the longest diameter of any object, while the minimal diameter represented the shortest diameter. For shape analysis, axis measurements were crucial, defined as lines joining two points on the perimeter passing through the center of the object. In elliptical shapes, the L/S ratio exceeded 1, while circular shapes had an L/S ratio of 1. Nuclear area was measured in square micrometers and nuclear perimeter, representing the outline of the nucleus, was expressed in micrometers. Shape factors, including L/S ratio and Form_AR, were utilized as dimension less quantities to numerically describe nuclear shape independent of size.

RESULTS AND DISCUSSIONS

The study analyzed 248 thyroid lesions with a mean age of 37.63±12.18 years (range: 13-80 years) and a male-to-female ratio of 1:8. The distribution of cases included 149 (60.1%) multinodular goiter, 31 (12.5%) classical papillary thyroid carcinoma (PTC), 31 (12.5%) follicular variant of papillary thyroid carcinoma (FVPTC), 18 (7.3%) follicular adenoma (FA), 17 (6.8%) Hashimoto's/lymphocytic thyroiditis and 2 (0.8%) follicular carcinoma (FC) cases. Nuclear morphometric analysis revealed significant differences across all lesion types ($p<0.0001$). PTC demonstrated the highest mean values for maximum diameter (9.1±1.4 µm), minimum diameter (7.0±1.2 µm) and nuclear area (50.4±16.1 µm²). The Form AR parameter showed marked elevation in PTC (54.4±18.6) compared to other lesions, while NACV% was notably lower in PTC (13.9±1.37) compared to other pathologies. In differentiating PTC from other thyroid lesions, nuclear area demonstrated excellent diagnostic performance with an AUC of 0.896 (95% CI: 0.891-0.901, $p<0.0001$). The optimal cut-off value for nuclear area (35.45 µm²) yielded a sensitivity of 81.2% and specificity of 80.0%. Minimum nuclear diameter showed the highest positive predictive value (0.91) with a cut-off of 5.66 µm, achieving 90.1% sensitivity and 74.4% specificity. For FVPTC, morphometric parameters showed moderate diagnostic utility, with nuclear perimeter demonstrating an AUC of 0.418 (95% CI: 0.408-0.429, $p<0.0001$). Hashimoto's/lymphocytic thyroiditis exhibited distinctive features, particularly in NACV% (AUC: 0.936, 95% CI: 0.929-0.942, $p<0.0001$). In distinguishing neoplastic from non-neoplastic lesions, both nuclear area and Form AR achieved identical AUC values of 0.728 (95% CI: 0.721-0.735, $p<0.0001$). The analysis of follicular carcinoma was limited by the small sample size (n=2), though it showed distinctive NACV% patterns (41.59±0.64%). Multinodular goiter, representing the largest subgroup (60.1%), consistently showed lower values across most parameters compared to neoplastic lesions. The nuclear area for goiter (26.4±7.7 µm²) was significantly lower than all neoplastic entities ($p<0.0001$). All morphometric parameters demonstrated statistically significant differences between groups ($p<0.0001$) through one-way ANOVA analysis, with Form AR and nuclear area showing the most consistent diagnostic utility across different lesion types. The findings suggest that nuclear morphometry provides objective criteria for differentiating various thyroid lesions, with particular utility in identifying PTC.

Nuclear morphometry has emerged as a valuable tool in thyroid cytopathology, offering quantitative parameters that complement traditional histopathological assessment. The present study demonstrates significant differences in nuclear morphometric parameters across various thyroid lesions, particularly in distinguishing papillary thyroid carcinoma (PTC) from other thyroid pathologies. The predominance of female patients (89.1%) and mean age of 37.63±12.18 years in our study aligns with the demographic patterns reported by Kumar[11], who found 88.5% female predominance in their analysis of 245 thyroid lesions. The higher nuclear area (50.4±16.1 µm²) and Form AR (54.4±18.6) in PTC cases corresponds with findings by Priya[12], who reported mean nuclear areas of 48.9±14.8 µm² in PTC cases ($p<0.001$). Our study found that nuclear area demonstrated excellent diagnostic performance in differentiating PTC from other lesions (AUC: 0.896, $p<0.0001$). This finding is supported by Wang[13], who reported similar diagnostic accuracy (AUC: 0.882) using

Table 1: Demographic Distribution of Thyroid Lesions (N=248)

Diagnosis	Female	Male	Total	Percentage
Papillary thyroid carcinoma	24	7	31	12.5%
Follicular variant of papillary carcinoma	27	4	31	12.5%
Follicular carcinoma	1	1	2	0.8%
Follicular adenoma	16	2	18	7.3%
Multi nodular goiter	136	13	149	60.1%
Lymphocytic thyroiditis	16	1	17	6.8%
Total	221	28	248	100%

Table 2: Nuclear Morphometric Parameters in Different Thyroid Lesions (Mean±SD)

Parameters	PTC	FVPTC	FA	FC	H-L Thyroiditis	Goiter	p-value
Max. D(µm)	9.1±1.4	7.1±1.2	8.2±0.9	7.4±1.3	7.9±1.5	7.0±0.9	<0.0001
Min D(µm)	7.0±1.2	5.1±1.1	5.9±1.0	5.0±1.4	5.8±1.3	4.8±1.0	<0.0001
NA(µm²)	50.4±16.1	28.6±10.8	37.9±9.6	30.0±12.5	36.4±15.1	26.4±7.7	<0.0001
Form AR	54.4±18.6	30.8±11.4	40.9±10.6	32.4±13.2	39.0±15.6	28.5±8.1	<0.0001
NACV(%)	13.9±1.37	25.8±4.45	25.26±1.76	41.59±0.64	39.05±6.74	28.14±3.12	<0.0001

Table 3: Diagnostic Performance of Nuclear Morphometry for PTC vs Other Lesions

Parameter	Cut-off Value	Sensitivity	Specificity	PPV	NPV	Accuracy
Max D(µm)	7.69	82.0%	71.2%	0.82	0.15	0.73
Min D(µm)	5.66	90.1%	74.4%	0.91	0.08	0.75
NA(µm²)	35.45	81.2%	80.0%	0.81	0.16	0.80
Form AR	38.11	80.5%	80.0%	0.80	0.16	0.80
NACV(%)	10.58	100.0%	0.0%	0.10	1.00	0.10

Table 4: ROC Analysis for Differentiation of Thyroid Lesions

Lesion Type	Parameter	AUC	95% CI	p-value
PTC vs Others	NA(µm²)	0.896	0.891-0.901	<0.0001
FVPTC vs Others	Form AR	0.428	0.417-0.438	<0.0001
FA vs Others	NP(µm)	0.736	0.727-0.745	<0.0001
H-L Thyroiditis vs Others	NACV(%)	0.936	0.929-0.942	<0.0001
FC vs Others*	NACV(%)	0.972	0.423-0.510	0.104

*Limited by small sample size (n=2)

Table 5: Neoplastic vs Non-Neoplastic Lesions-ROC Analysis

Parameter	AUC	95% CI	p-value
NA(µm²)	0.728	0.721-0.735	<0.0001
Form AR	0.728	0.721-0.735	<0.0001
NACV(%)	0.185	0.179-0.191	<0.0001
Min D(µm)	0.723	0.717-0.730	<0.0001
NP(µm)	0.724	0.717-0.731	<0.0001

nuclear morphometry. However, Deligeorgi[14] found slightly lower diagnostic accuracy (AUC: 0.801) in their series of 180 cases, possibly due to differences in measurement techniques. The challenges in distinguishing FVPTC from follicular lesions were evident in our moderate diagnostic utility findings (AUC: 0.428). This aligns with observations by Thompson[15], who reported similar difficulties in morphometric differentiation of FVPTC (AUC: 0.452, p<0.001). The integration of nuclear morphometry with other diagnostic modalities may enhance diagnostic accuracy in such cases. Our finding of significantly different NACV% patterns in Hashimoto's thyroiditis (39.05±6.74%) compared to neoplastic lesions corresponds with research by Rodriguez[16], who reported NACV% values of 37.8±5.9% in autoimmune thyroiditis. This suggests that nuclear variation patterns may serve as useful markers in distinguishing inflammatory from neoplastic conditions. The establishment of specific cut-off values for various parameters represents a significant contribution to standardized assessment. Our cut-off value for nuclear area (35.45 µm²) in PTC diagnosis showed higher sensitivity (81.2%) compared to the findings of Chen[17], who reported 76.5% sensitivity using a similar cut-off. The limited sample size for follicular carcinoma (n=2) represents a study limitation, similar to challenges faced by Kimat[18] in their morphometric analysis. However, the consistent statistical significance across other categories supports the reliability of our findings for major thyroid pathologies.

CONCLUSION

Nuclear morphometry provides objective, quantifiable parameters for differentiating thyroid lesions, with particular utility in identifying papillary thyroid carcinoma. The study established specific cut-off values for various nuclear parameters, demonstrating high diagnostic accuracy (AUC: 0.896) for PTC diagnosis. Nuclear area and Form AR emerged as the most reliable discriminatory parameters across different thyroid pathologies. The technique showed particular strength in distinguishing neoplastic from non-neoplastic lesions, with significant differences observed across all measured parameters (p<0.0001). While the method shows promise as an adjunct diagnostic tool, integration with conventional histopathological assessment remains essential for comprehensive evaluation. Future studies with larger sample sizes, particularly for follicular carcinoma, would further validate these findings.

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