J. Musayev [1]
N. Metilli [2]
R. Sholan [3]
A. Hasanov [1]
A. Damirli [4]
K. Bakhshaliyeva [4]

[1] Department of Pathology, Azerbaijan Medical University, Baku, Azerbaijan
[2] Faculty of Medicine, Canakkale Onsekiz Mart University, Canakkale, Turkey
[3] Department of Kidney Diseases and Transplantology, Republican Treatment and Diagnostic Center, Baku, Azerbaijan
[4] Bureau of Pathological Anatomy, Unification of Forensic Medical Expertise and Pathological Anatomy, Baku, Azerbaijan

Надійшла: 09.10.2020
Прийнята: 27.11.2020

DOI: https://doi.org/10.26641/1997-9665.2020.4.101-107

UDC: 616.361-007.272

THE IMPORTANCE OF MORPHOMETRIC PARAMETERS IN DIFFERENTIATING BENIGN/REACTIVE UROTHELIAL CELLS FROM LOW-GRADE UROTHELIAL CARCINOMA: COMPUTER-ASSISTED STUDY ON URINE SPECIMENS

Musayev J. ✉, Metilli N., Sholan R., Hasanov A., Damirli A., Bakhshaliyeva K. The importance of morphometric parameters in differentiating benign/reactive urothelial cells from low-grade urothelial carcinoma: computer-assisted study on urine specimens.
Azerbaijan Medical University, Republican Treatment and Diagnostic Center, Bureau of Pathological Anatomy, Unification of Forensic Medical Expertise and Pathological Anatomy, Baku, Azerbaijan, Canakkale Onsekiz Mart University, Canakkale, Turkey.

ABSTRACT. Background. Urine cytology is deemed a sensitive method in detection of high-grade urothelial carcinoma. In contrast, detection of low-grade urothelial carcinoma (LGUC) and its differentiation from reactive lesions is difficult with urinary cytology. **Objective.** Our study aims to determine the effectiveness of morphometric parameters in differentiating reactive urothelial cells from LGUC by cytological examination of urine specimens. **Methods.** Voided urine samples were used for the study, while the cases were randomized into two groups: those diagnosed with LGUC (first group; N=10) and those which were not diagnosed with LGUC (second group; N=10). The morphometric parameters of major nuclear diameter (MaND), minor nuclear diameter (MiND), mean nuclear area (MNA), cell diameter (CD), mean cell area (MCA), as well as MaND/CD, MiND/CD, MiND/MaND and MNA/MCA ratios were measured on 100 urothelial cells for each case through ScopeImage® 9.0 software. **Results.** A statistically significant difference was found between the mean values of MiND/CD (p=0.017) and MNA/MCA (p=0.002) ratios of groups. The mean value of both parameters in the first group constituted 0.2 and higher, and below 0.2 in the second group. **Conclusion.** The ratios of MiND/CD and MNA/MCA in urothelial cells proved significantly higher in patients with LGUC than benign/reactive cases. The reliability of these findings in differentiating LGUC from benign/reactive lesions needs to be verified through studies examining a large number of cases. These parameters can be assessed much faster through a special software enabling an automatic measurement and thus can be used in routine cytological examination.
Key words: morphometry, urothelial carcinoma, urine, cytology.

Citation:
Musayev J, Metilli N, Sholan R, Hasanov A, Damirli A, Bakhshaliyeva K. The importance of morphometric parameters in differentiating benign/reactive urothelial cells from low-grade urothelial carcinoma: computer-assisted study on urine specimens. Morphologia. 2020;14(4):101-7.
DOI: https://doi.org/10.26641/1997-9665.2020.4.101-107

Musayev J. 0000-0002-9202-6990; Metilli N. 0000-0003-3332-8312
Sholan R. 0000-0002-1047-167X; Hasanov A. 0000-0002-1156-056X
Damirli A. 0000-0001-8440-2645; Bakhshaliyeva K. 0000-0002-9284-175X
✉ patolog.jamalmusaev@gmail.com

Introduction

Urinary cytology constitutes a significant percentage of non-gynecological cases in routine cytopathology practice, and it continues to be one of the difficult specimens for (cyto)pathologists. The inadequate cellularities of samples, cellular degeneration prior to fixation, as well as unrealistic expectations for diagnosing low-grade urothelial carcinoma (LGUC) are the main challenges encountered in urinary cytology practice (1). The ability to consistently diagnose LGUC in urine specimens remains controversial, as the reported sensitivity of urinary cytology in detection of LGUC is as low as 10% (2). Some cytological diagnostic criteria were attempted to be determined for LGUC, while McCroskey et al. reported that most of the features described previously as diagnosticwere observed almost equally in cases negative for LGUC (2).

These features of urine cytology were also reflected in the reporting system elaborated in 2015. Accordingly, The Paris System for Reporting Urinary Cytology (TPS) focused primarily on detection of high grade urothelial carcinoma (HGUC) while minimizing the detection of LGUC, since cytology has a high sensitivity of detecting the former with a poor sensitivity for the latter (1).

While the presence of three-dimensional papillary structures with fibrovascular cores is a unique diagnostic clue of LGUC in cytology, however, it is only seen in about 2% of cases. Nevertheless, this type of papillary structures can be observed in any low-grade papillary lesion, including papillomas, papillary urothelial neoplasia of low malignant potential, and LGUC. To this end, "low-grade urothelial neoplasm (LGUN)" was recommended as a diagnostic category for similar cases in TPS (1, 2).

Aim

The main purpose is to determine the effectiveness of morphometric parameters in differentiating benign/reactive urothelial cells from LGUC by cytological examination of voided urine specimens.

Material and methods

Case selection: Ten urine cytology specimens of cases with histologically confirmed diagnosis of LGUC (1st group) and the urine cytology specimens of 10 benign/reactive cases (2nd group) were selected for the current study. All specimens were Papanicolaou stained conventional smears prepared from voided urine specimens through centrifugation, and each case had two slides. Cases with LGUC diagnosis were confirmed histologically within one month after collecting the urine sample. Other 10 benign/reactive cases were patients who underwent poliomavirus screening following renal transplantation, or who were diagnosed with cystitis without any history of urothelial carcinoma before and within six months after the urine sample has been collected.

Morphometric examination: A morphometry was performed on randomly selected 100 urothelial cells for each case through ScopeImage® 9.0 software. Morphometric parameters of major nuclear diameter (MaND), minor nuclear diameter (MiND), mean nuclear area (MNA), cell diameter (CD), mean cell area (MCA), as well as ratios of MaND/CD, MiND/CD, MiND/MaND and MNA/MCA were measured for each cell (Figure 1).

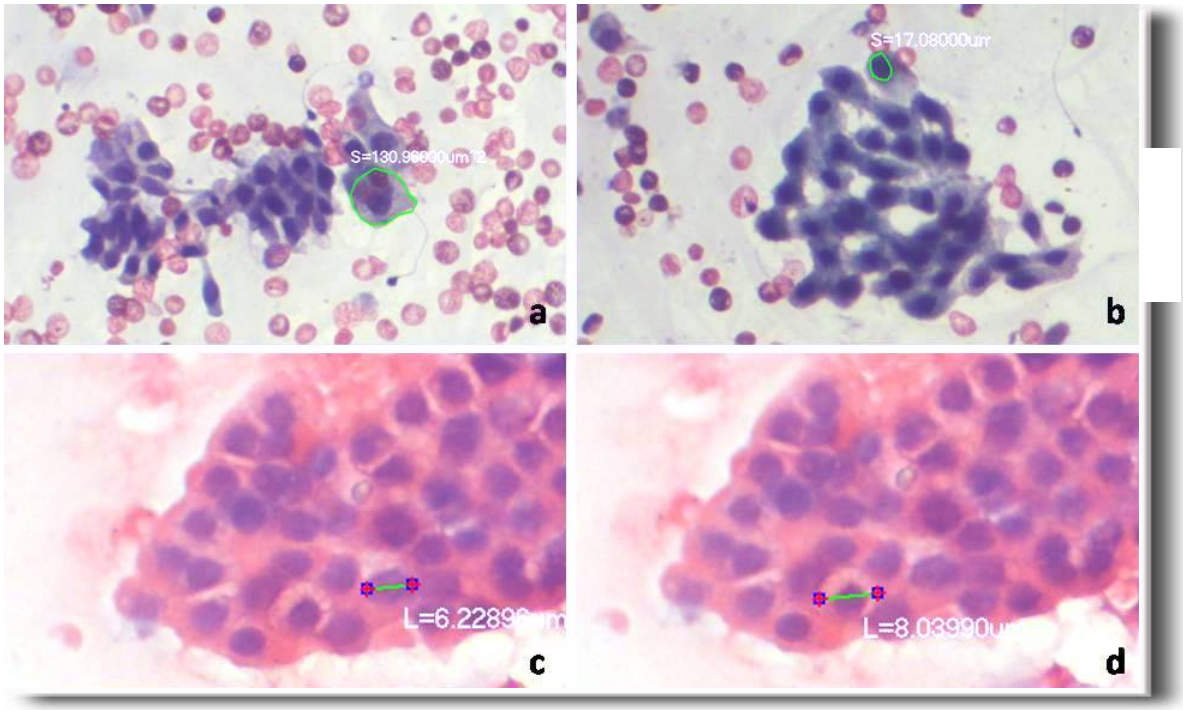

Figure 1. Measurement of Mean Cytoplasmic Area (a), Mean Nuclear Area (b), Major Nuclear Diameter (c) and Cytoplasmic Diameter (d).

Only non-overlapping isolated cells with well-preserved cytoplasm and individual cells with clear cytoplasmic and nuclear borders in some clustered groups were selected for measurement. Three-dimensional cell clusters, degenerative and swollen cells with vacuolar cytoplasm, as well as cells thoroughly or partially covered with inflammatory and red blood cells were excluded from the study.

Statistics: The mean value of morphometric parameters for each case, as well as the mean value and standard deviation of these parameters in each group were calculated. Independent sample t test was used for determination of the p value and p value ≤ 0.05 was considered significant.

Results

The mean value of morphometric parameters for each case, the mean value and standard deviation of these parameters for each group were shown in tables 1 and 2.

Table 1

Mean value of morphometric parameters in the first group (LGUC cases)

No	MaND (μm)	MiND (μm)	MNA ($μm^2$)	MCA ($μm^2$)	CD (μm)	MaND/ CD	MiND/ CD	MiND/ MaND	MNA/ MCA
1	7.597	5.500	38.417	176.209	18.780	0.446	0.320	0.734	0.339
2	8.003	5.082	38.844	154.045	16.541	0.505	0.323	0.649	0.280
3	8.393	6.186	50.084	168.096	19.782	0.444	0.326	0.747	0.327
4	6.211	3.797	24.372	90.664	15.122	0.441	0.270	0.626	0.328
5	4.895	2.684	14.950	77.883	14.586	0.357	0.207	0.588	0.227
6	6.653	4.212	32.112	107.277	14.212	0.478	0.310	0.660	0.322
7	7.378	4.911	40.863	222.444	19.609	0.418	0.281	0.675	0.250
8	10.362	7.942	83.287	457.578	29.537	0.367	0.279	0.769	0.201
9	8.680	6.227	57.410	231.051	20.732	0.443	0.319	0.729	0.276
10	6.650	4.547	35.023	130.997	15.353	0.464	0.316	0.692	0.293
Mean value	7.482± 1.51	5.109± 1.466	41.536± 18.909	181.624± 109.726	18.425± 4.576	0.436± 0.045	0.295± 0.037	0.687± 0.057	0.284± 0.046

Table 2

Mean value of morphometric parameters in the 2nd group (benign/reactive cases)

No	MaND (μm)	MiND (μm)	MNA ($μm^2$)	MCA ($μm^2$)	CD (μm)	MaND/ CD	MiND/ CD	MiND/ MaND	MNA/ MCA
1	6.905	4.974	38.361	973.317	41.158	0.173	0.124	0.725	0.046
2	5.696	3.483	22.328	541.598	30.277	0.209	0.127	0.620	0.060
3	5.975	3.977	27.079	458.728	30.294	0.221	0.145	0.677	0.079
4	5.574	3.709	24.471	452.541	30.214	0.205	0.137	0.670	0.068
5	4.466	2.747	16.564	203.434	19.972	0.274	0.169	0.625	0.132
6	5.383	3.259	21.410	262.397	22.142	0.273	0.164	0.622	0.115
7	5.231	3.491	21.448	320.629	24.179	0.235	0.158	0.684	0.089
8	4.849	3.401	20.698	398.162	28.133	0.187	0.134	0.716	0.068
9	4.693	2.703	15.737	176.052	19.577	0.248	0.146	0.602	0.096
10	4.987	3.451	21.206	207.675	19.285	0.288	0.198	0.700	0.132
Mean value	5.376± 0.713	3.520± 0.642	22.93± 6.349	399.453± 237.104	26.523± 6.887	0.231± 0.039	0.150± 0.022	0.664± 0.044	0,089± 0,029

The mean values of parameters such as MaND, MiND and MNA, as well as MaND/CD, MiND/CD and MNA/MCA ratios were higher in urothelial cells of LGUC cases. However, the mean values of MCA and CD were higher in benign/reactive cases. The MiND/MaND ratio presented almost a similar value in both groups.

A statistically significant difference was revealed only between the mean values of MiND/CD (p=0.017) and MNA/MCA (p=0.002) ratios of two groups. The mean value of both parameters comprised 0.2 and higher in all cases of the first group, and below 0.2 in all cases of the second group.

Discussion

Some attempts have been made to detect LGUC with urinary cytology. Barkan et al. showed that the UroVysion FISH test can increase the sensitivity of cytology for detection of LGUC from 25 to 60 to 75%. However, they consider that the FISH result will not impact the clinical management as low-grade neoplasms are usually clearly visible by cystoscopy (1). Jackson et al. detected a relation between the size of LGUC and positivity in urine

cytology. Namely, tumors with a size of 2 cm and more were associated with the initial positive or suspicious cytology result in their study (3). In another study Önal et al. argued that the NMP22 value of urine is more sensitive than urinary cytology to capture LGUCs by offering an alternative to cytology (4).

The morphometric features of urothelial carcinoma were mostly studied on paraffin-embedded tissue samples, especially in the 90s. These studies, which started with the measurement of diagnostic value of morphometry in determination of urothelial carcinoma, later suggested morphometry as the determinant of tumor grade and prognosis (5-18). MNA value of urothelial carcinoma higher than 95 μm² was associated with poor prognosis in the studies of Blomjous et al (6, 12). Lipponen, who has conducted a number of studies on this subject, stated that morphometric parameters are better than the histopathological grade in predicting progress at nodal or metastatic stage of urothelial carcinoma (15). However, the morphometry has been presented as an alternative to grading urothelial carcinoma (8, 11, 13). Pich et al. found concrete MNA values for various grades of urothelial carcinoma; these were 35.53 μm2 for G1, 38.65 μm2 for G2 and 83.62 μm2 for G3 cases (16). Some authors consider that morphometric parameters can be critical in detecting the proliferative activity of urothelial carcinoma (5, 10, 14).

The first morphometric study on urine samples was carried out by Kern and MNA value was reported as 36 μm^2 for normal cells, 52 μm^2 for benign atypical cells, 54 μm^2 for cells from papillary carcinoma Grade I, 78 μm^2 for papillary carcinoma Grade II, and 90 μm^2 for transitional cell carcinoma Grades III and IV (19). In the study of Bishop et al. MNA value was showed as 29-55 μm^2 for benign cells and 78 μm^2 for malignant cells (20). In another similar study MNA value constituted 30.3 μm^2 for normal urothelial cells, 60 μm^2 for suspicious of malignancy cases, 79.2 μm^2 for LGUC, and 116 μm^2 for HGUC cases (21). In the meantime, the attention was directed towards the nucleocytoplasmic (N/C) ratio in other morphometric studies conducted on urine samples. Murphy et al. showed the N/C ratio <0.5 for benign conditions, Boon et al. had found N/C ratio >0.6 for high-grade neoplasms, and Manna et al. reported N/C ratio as 0.55 for LGUC, 0.75 for HGUC, 0.31 for suspicious cases, and 0.15 for inflammatory cases (21-23). In our study, MNA value was 22,9 μm^2 and 41,5 μm^2, major diameter-based N/C ratio was 0,23 and 0,43, minor diameter-based N/C ratio was 0,15 and 0,29, area-based N/C ratio was 0.08 and 0.28 in benign/reactive and LGUC cases respectively.

Prior studies on urine samples had concurred with the fact, that cytomorphometric analysis is superior to conventional urine cytology in detecting malignant cells (20, 24, 25). These studies stated that especially the MNA and N/C ratio are generally successful in differentiating malignant cells from benign cells (20, 25). In the first studies aiming to determine LGUC in urine samples, increased N/C ratio was presented as a key cytologic criterion (26). For the first time, Shin et al. reported that the MNA/MCA ratio is efficient with good sensitivity and specificity for differentiating malignant urothelial cells, both high- and low-grade, from the benign ones, since the value of parameter in cases of LGUC was significantly higher than that of the benign urothelial cells (27). In another study where morphometry and immunocytochemical markers were used together, a similar result was reached (21). However, according to Ohsaki et al. only a linear factor is statistically significant as a nuclear parameter in differentiating reactive renal tubular cells in renal disease from LGUC (28). Similarly, in our study, the MNA/MCA ratio was efficient in differentiation of LGUC and benign/reactive cases and the cut-off value was determined as 0.2 for the parameter. In addition, the more accessible voided urine and conventional smear method were used in our study, as it was infeasible to demonstrate the definite superiority of liquid-based cytology for discriminating malignant urothelial cells from benign cells through cytomorphometric analysis in previous studies (27).

Conclusion

In our study, MiND/CD and MNA/MCA ratios of urothelial cells derived from voided urine was significantly higher in cases with LGUC than benign/reactive cases. The reliability of these findings in differentiating LGUC from benign/reactive lesions needs to be verified through studies examining a large number of cases. The most remarkable limitation of this study lies in the high number of working hours allotted for the measurement of morphometric parameters, as the measurement of all parameters on 100 cells for each case by one person encompasses a full working day. This is our humble opinion that these parameters can be assessed much faster with a special software enabling automatic measurement, which thus can be used in a routine diagnosis process.

Prospects for further development is to determine the effectiveness of morphometric parameters in differentiating cells from LGUC by cytological examination.

Information about conflicts of interest

Potential or obvious conflicts of interest, related to this manuscript, at the time of publication does not exist and is not expected.

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Мусаєв Дж.С., Метіллі Н.Ф., Шола Р.Ф., Гасанов А.Б., Дамірлі А.Н., Бахшалієва Х.А. Важливість морфометричних параметрів в диференціації доброякісних/реактивних уротеліальних клітин від уротеліальної карциноми низького ступеня злоякісності: комп'ютерне дослідження зразків сечі.

РЕФЕРАТ. Актуальність. Цитологічне дослідження сечі вважається чутливим методом виявлення уротеліальної карциноми високого ступеня злоякісності. На відміну від цього, виявлення уротеліальної карциноми низького ступеня злоякісності (УКНС) і її диференціація від реактивних уражень утруднено за допомогою цитологічного дослідження сечі. **Мета**. Наше дослідження спрямоване на визначення ефективності морфометричних параметрів у диференціюванні реактивних уротеліальних клітин від УКНС шляхом цитологічного дослідження зразків сечі. **Методи**. Для дослідження використовувалися зразки сечі з сечовипусканням, а пацієнти були рандомізовані на дві групи: ті, у яких був діагностований УКНС (перша група), і ті, яким не був діагностований УКНС (друга група). Морфометричні параметри: великий діаметр ядра, малий діаметр ядра, середня площа ядра, діаметр клітини, середня площа клітини, а також їх співвідношення вимірювали на 100 уротеліальних клітинах для кожного випадку за допомогою програмного забезпечення ScopeImage® 9.0. **Результати**. Статистично значуща різниця була виявлена між середніми значеннями відносин малий діаметр ядра / діаметр клітини (p = 0,017) і середня площа ядра / середня площа клітини (p = 0,002) для груп. Середнє значення обох показників в першій групі склало 0,2 і вище, у другій - нижче 0,2. **Підсумок**. Співвідношення малий діаметр ядра / діаметр клітини і середня площа ядра / середня площа клітини в уротеліальних клітинах виявилися значно вище у пацієнтів з УКНС, ніж у доброякісних/реактивних випадків. Надійність цих результатів в диференціації УКНС від доброякісних/реактивних уражень повинна бути підтверджена дослідженнями, що вивчають велику кількість випадків. Ці параметри можуть бути оцінені набагато швидше за допомогою спеціального програмного забезпечення, що забезпечує автоматичне вимірювання, і, таким чином, можуть використовуватися при рутинному цитологічному дослідженні.

Ключові слова: морфометрія, уротеліальная карцинома, сеча, цитологія.

Мусаев Дж.С., Метилли Н.Ф., Шолан Р.Ф., Гасанов А.Б., Дамирли А.Н., Бахшалиева Х.А. Важность морфометрических параметров в дифференциации доброкачественных/реактивных уротелиальных клеток от уротелиальной карциномы низкой степени злокачественности:

компьютерное исследование образцов мочи.

РЕФЕРАТ. Актуальность. Цитологическое исследование мочи считается чувствительным методом выявления уротелиальной карциномы высокой степени злокачественности. В отличие от этого, выявление уротелиальной карциномы низкой степени злокачественности (УКНС) и ее дифференциация от реактивных поражений затруднено с помощью цитологического исследования мочи. **Цель.** Наше исследование направлено на определение эффективности морфометрических параметров в дифференцировке реактивных уротелиальных клеток от УКНС путем цитологического исследования образцов мочи. **Методы.** Для исследования использовались образцы мочи с мочеиспусканием, а пациенты были рандомизированы на две группы: те, у которых был диагностирован УКНС (первая группа), и те, которым не был диагностирован УКНС (вторая группа). Морфометрические параметры: большой диаметр ядра, малый диаметр ядра, средняя площадь ядра, диаметр клетки, средняя площадь клетки, а также их соотношения измеряли на 100 уротелиальных клетках для каждого случая с помощью программного обеспечения ScopeImage® 9.0. **Результаты.** Статистически значимая разница была обнаружена между средними значениями отношений малый диаметр ядра / диаметр клетки (p=0,017) и средняя площадь ядра / средняя площадь клетки (p=0,002) для групп. Среднее значение обоих показателей в первой группе составило 0,2 и выше, во второй - ниже 0,2. **Заключение**. Соотношения малый диаметр ядра / диаметр клетки и средняя площадь ядра / средняя площадь клетки в уротелиальных клетках оказались значительно выше у пациентов с УКНС, чем у доброкачественных/реактивных случаев. Надежность этих результатов в дифференциации УКНС от доброкачественных/реактивных поражений должна быть подтверждена исследованиями, изучающими большое количество случаев. Эти параметры могут быть оценены намного быстрее с помощью специального программного обеспечения, обеспечивающего автоматическое измерение, и, таким образом, могут использоваться при рутинном цитологическом исследовании.

Ключевые слова: морфометрия, уротелиальная карцинома, моча, цитология.