Original Article

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Contemporary Role of Urine Cytology in Bladder Cancer

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Abstract

Objective: The objective of this study was to assess the efficacy of urine cytology in predicting definitive pathology in patients undergoing transurethral bladder tumor resection.

Materials and Methods: Patients who underwent transurethral bladder tumor resection between January 2019 and April 2022 were included. Urine cytology was performed via the bladder wash of the first urine sample as the initial procedure during cystoscopy. Then, transurethral resection of the bladder tumor was performed. The demographic characteristics of the patients, including age and sex, were recorded. The diagnostic accuracy of urine cytology for bladder tumor detection was calculated using the Paris System for Reporting Urinary Cytology.

Results: A total of 229 patients who underwent endoscopic bladder tumor resection for urothelial carcinoma comprised the study group. Among patients, 193 (84.28%) were male and 36 (15.72%) were female. Urine cytology revealed "negative for high-grade urothelial carcinoma" in 44.11% of the patients, and "low-grade urothelial carcinoma" in 27.31% of the cases as the most common first two findings. The definitive pathological examination after endoscopic surgery revealed benign histology in 23.75% of the patients, whereas the remaining patients had urothelial carcinoma. The overall efficacy of urine cytology in detecting urothelial tumors was 72.89% sensitivity and 90.47% specificity.

Conclusion: Urine cytology can predict the final pathology of bladder urothelial carcinoma with limited sensitivity.

Keywords: Urine cytology, high-grade, bladder cancer, urothelial carcinoma, hematuria

Introduction

Cystoscopy is currently the preferred tool for both diagnosis and follow-up of bladder cancer. However, it is invasive and is associated with significant morbidity. Cytologic examination of urine sediment is an easy-to-obtain test for diagnosing malignant diseases of the urinary tract (1). Urine cytology includes the diagnosis/monitoring of urothelial tumors and evaluation of hematuria (1). It is highly sensitive in high-grade (HG) tumors but is less sensitive in low-grade (LG) tumors. The overall sensitivity of cytology is 48% (1). It was 16% for LG tumors and 84% for HG tumors (1). Furthermore, its low sensitivity ranges from 28% to 100% for different series (2). On the other hand, urine cytology has remarkable specificity, exceeding 90% (3). These findings suggest that urine cytology is largely subjective, and the ability to detect cancer cells is dependent on the experience of cytologists, particularly in detecting LG atypia tumors (4). Consequently, significant variability in cytology results has been reported among the 10 centers and ranges from poor (63%) to excellent (89%) (5). The Paris System (TPS) for Reporting Urinary Cytology, which was proposed in 2016 and updated in 2022, has standardized the diagnostic criteria for HG urothelial carcinoma and provided promising results (6,7). In order to detect the utilization yield of this new TPS, recent clinical trial results are required. The objective of this retrospective study was to document the efficacy of urine cytology in predicting definitive pathology in patients who underwent transurethral bladder tumor resection.

Material and Methods

A total of 240 patients who underwent endoscopic bladder tumor resection between January 2019 and April 2022. The group consisted of patients with either tumor recurrence during follow-up cystoscopy or initial diagnosis of bladder cancer. The exclusion criteria were renal cell carcinoma, prostate cancer, and any other histological subtype that differed from urothelial

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cancer. Two cases of bladder small cell carcinoma and four cases of prostate adenocarcinoma were excluded. Another 3 cases who had different histological characteristics (chronic lymphocytic leukemia/small lymphocytic lymphoma, colon adenocarcinoma, and leiomyosarcoma) were also not included. According to urine cytology results, two cases that were found inadequate in terms of cellularity were also excluded. Finally, 229 patients with urothelial pathology constituted the study group. This retrospective study was approved by the Clinical Research Ethics Committee of Marmara University (protocol number: 09.2024.444, date: 08.12.2023).

Transurethral bladder surgery was performed when the urine culture result was negative in all patients. The demographic characteristics of the patients, including age and sex, were recorded. Urine cytology was performed via the bladder wash of the first urine sample as the initial procedure during cystoscopy. A sterile 0.9% saline solution was used for bladder washing. This fresh sample was sent to the cytopathologist without further procedures. At the pathology laboratory, urine samples were immediately centrifuged at 2,000 rpm for 10 min, and ThinPrep® liquid-based cytology slides were prepared from the sediment. All samples with low cellularity were re-centrifuged at 2,000 rpm for 5 minute. The slides were then stained using the positive airway pressure method. The slides were reported using the TPS. A single dedicated cytopathologist (M.H.T.) evaluated all urine samples. Then, transurethral resection of the bladder tumor was performed. Local pathological staging was performed according to the tumor-node-metastasis (TNM) 2017 by the same pathologist.

The 2017 TNM classification system was used for pathological staging, and the results were divided into Ta, T1, T2, and carcinoma *in situ* (CIS) categories according to T (tumor) stage (8). The 2016 World Health Organization grading system was used for pathological grading, and the results were divided into LG and HG categories (9). According to the transurethral resection-MT pathology results, patients were evaluated in 9 categories: 0) Benign pathologies (inflammation, granulation, edema, etc.) 1) TaLG, 2) TaHG, 3) T1LG, 4) T1HG, 5) T2HG, 6) CIS, 7) Focal dysplasia, 8) Others.

2016 TPS category groups were used for cytological evaluation (10). Cytological findings were evaluated in 7 categories: 1) Adequacy/unsatisfactory, 2) Negative for high-grade urothelial carcinoma (NHGUC), 3) Atypical urothelial cell (AUC), 4) Suspicious for high-grade urothelial carcinoma (SHGUC), 5) Low-grade urothelial carcinoma (LGUC), 6) High-grade urothelial carcinoma (HGUC), 7) Others.

The diagnostic yield of urine cytology based on the TPS for predicting final pathology was assessed using sensitivity and specificity.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for the Social Sciences version 22 (IBM SPSS Statistics for Windows, Chicago, IL, USA). The normality of the distribution of variables was evaluated using the Shapiro-Wilk test. The independent and dependent groups were compared using the Mann-Whitney U test and Wilcoxon signed-rank test, respectively. A p-value <0.05 was set as statistically significant.

Results

Among the included patients, 193 (84.28%) were male and 36 (15.72%) were female. The mean age was 65.88+11.91 and 68.12+10.95 for male and female patients, respectively. Out of the total, 103 patients (45%) presented with hematuria, 23 patients (10%) were incidentally diagnosed, 34 patients (35%) presented with lower urinary tract symptoms (LUTS), and data for 69 were unavailable. A smoking history was noted in 119 patients (52%). Primary bladder cancer was identified in 132 patients (57%), while 97 patients (42%) were diagnosed with secondary bladder cancer.

Out of the total, 50 patients (22%) were classified as low risk, 98 patients (43%) as intermediate risk, and 91 patients (35%) as high risk. Considering the past therapy, 17 patients had a history of intravesical chemotherapy, and 25 patients had a history of intravesical BCG only 7 patients had a history of upper urinary tract urothelial carcinoma with a history of nephroureterectomy.

The investigation of urine cytology revealed NHGUC in 44.11% of the patients, LGUC in 27.31%, HGUC in 13.86%, AUC in 6.72%, and SHGUC in 5.88% of the samples as the first 5 ranks of cytological diagnosis based on TPS criteria. The detailed results are presented in Table 1. Within the excluded patients with different final histologies from urothelial carcinoma, 5 had "others", 3 had NHGUC and 1 had AUC as the cytology result.

The histological evaluation of tissues obtained from endoscopic resection revealed that 23.75% of the patients had benign pathologies, 27.91% had Ta LG, 7.5% had Ta HG, 1.2% had T1 LG, 17.91% had T1 HG, 12.91% had T2 HG, CIS in 2.5% of the cases, and focal dysplasia in 2.5% of the patients. Half of the CIS cases were primary CIS; and the remaining 3 cases had concomitant T1 HG. The findings based on the final pathological findings of the specimens are presented in Table 2.

The efficacy of negative urine cytology in 105 patients in predicting final pathology after transurethral resection was reported as benign in 52 (49.5%) patients, Ta LG in 31 (29.5%) patients, Ta HG in 4 (3.8%) patients, T1 HG in 4 (3.8%) patients, and T2 HG in 6 (5.7%) patients. The corresponding results of

Table 1. Urine cytology findings

Urine cytology results based on the TPS criteria	Number (n)	%
None	1	0.41
Unsatisfactory specimen	1	0.41
Negative for HGUC	105	44.11
Atypical urothelial cells	16	6.72
Suspecious for HGUC	14	5.88
LGUC	65	27.31
HGUC	33	13.86
Others	5	2.1
Total	240	100

TPS: The Paris System for Reporting Urinary Cytology, HGUC: High-grade urothelial carcinoma, LGUC: Low-grade urothelial carcinoma

cytology with definitive pathology are presented in Table 3. The second major subgroup based on the TPS classification was LGUC, which included 65 patients. Final pathological examination revealed a urothelial tumor in all cases (6 patients had LGUC and 59 cases had HGUC or CIS). HGUC was the third most common category according to cytology results, including 33 patients. Final pathological examination revealed LGUC in 24, HGUC in 8, and CIS in 1.

Table 2. Final pathological findings

Local pathological results based on TNM classification (2017)	Number (n)	%
Benign pathologies (inflammation, granulation, edema, etc.)	57	23.75
Ta LGUC	67	27.91
Ta HGUC	18	7.5
T1 LGUC	3	1.2
T1 HGUC	43	17.91
T2 HGUC	31	12.91
Carcinoma *in situ*	3+3*	2.5
Focal dysplasia	6	2.5
Others	9	3.75
Total	240	100

HGUC: High-grade urothelial carcinoma, LGUC: Low-grade urothelial carcinoma, TNM: Tumor-node-metastasis, *: Three patients had primary Carcinoma *in situ*, the remaining 3 had concomitant

The overall efficacy of urine cytology in predicting final pathology based on the presence of urothelial tumor demonstrated 72.89% sensitivity and 90.47% specificity (Table 4). The positive predictive value (PPV) and negative predictive value (NPV) of urine cytology for bladder tumors were calculated as 95.27% and 55.88%, respectively.

Discussion

Urothelial carcinoma is one of the most common organ cancers, with a remarkable incidence rate (11). Most cases present as non-muscle-invasive disease and initially underwent endoscopic tumor resection with remarkably high recurrence rates despite intravesical treatment (12). Therefore, strict surveillance is essential. Current practice in the follow-up of patients with superficial bladder cancer requires regular checkup cystoscopies, and the schedule is maintained when recurrence occurs. Consequently, cystoscopy remains the gold standard follow-up protocol for bladder cancer (12). However, cystoscopy is costly and uncomfortable. In addition, it creates a great burden for busy reference hospitals. On the other hand, some tumors can be missed by cystoscopy. Therefore, there is clearly a need for non-invasive urine markers that can help reduce the number of cystoscopies and increase diagnostic accuracy.

Urine cytology is an important non-invasive technique for the screening, diagnosis, and follow-up of patients with urothelial carcinoma. A standardized evaluation of urine cytology would hypothetically replace cystoscopy, or at least the cystoscopy interval would be prolonged when there is a negative cytology result.

Table 3. Corresponding final pathological results of the cytology subgroups

Cytology	Final pathology									
	Benign	TaLG	TaHG	T1LG	T1 HG	T2 HG	CIS	Dysplasia	Other	Total
Negative for HGUC	52	31	4	0	4	6	0	5	3	105
Atypical urothelial cells	3	7	0	0	2	2	0	1	1	16
Suspecious for HGUC	2	1	2	0	5	1	3	0	0	14
LGUC	0	6	10	0	26	21	2	0	0	65
HGUC	0	21	2	3	5	1	1	0	0	33
Others	0	0	0	0	0	0	0	0	5	5
Total	57	66	18	3	42	31	6	6	9	238

HGUC: High-grade urothelial carcinoma, LGUC: Low-grade urothelial carcinoma, HG: High-grade, LG: Low-grade, CIS: Carcinoma *in situ*

Table 4. Evaluation of cytology parameters for predicting final pathology

Cytology	Final pathology			
	(+) (Ta, T1, T2, CIS)	(-) (benign, dysplasia)	Total	
(+) (atypical urothelial cells) (suspecious for HGUC, LGUC, HGUC)	121	6	127	PPV 95.27%
(-) (negative for HGUC)	45	57	102	NPV 55.88%
Total	166	63	229	
	Sensitivity 72.89%	Specificity 90.47%		

HGUC: High-grade urothelial carcinoma, LGUC: Low-grade urothelial carcinoma, CIS: Carcinoma *in situ*, PPV: Positive predictive value, NPV: Negative predictive value

However, despite advancements in laboratory systems for processing urine specimens, difficulties remain in some cases, and accurate interpretation of certain cells in urine is a major challenge for cytopathologists (7). The evaluation of urine cytology to detect tumor cells is largely subjective, and the ability to detect cancer cells depends on the experience of cytopathologists (13). Therefore, tremendous efforts have been made to standardize urine cytology. Particularly, "atypical cells" are commonly reported and have various diagnostic suggestions (7). TPS was developed to address these problems of variations in cytology evaluation to provide a relatively universal interpretation. TPS was conceived during the International Academy of Cytology Congress held in Paris in May 2013 to ensure uniformity in reporting of urine cytology (10). Recent molecular and genetic studies suggest that these are two separate diseases; first, LGUC with an overall good prognosis and HG cancer with a significant mortality rate (6). Therefore, the conclusion of the first meeting of the TPS working group was that the new reporting system should focus primarily on the detection of HGUC while minimizing LGUC detection. Then, the efforts of this working group proposed an improvement in the reporting system that includes specific diagnostic categories and cytomorphologic criteria for reliable diagnosis of HGUC in 2016 (6).

The new TPS modification in 2016 has been widely accepted and tested by several studies. Rohra et al. (14) reported that the new TPS particularly lowered the rate of atypia based on 486 urine samples with a high rate of HGUC. Another comparison of the evaluation of urine cytology based on pre-TPS and the new TPS classification clearly demonstrated that TPS has an increasing PPV for HGUC (15). It was confirmed that the TPS is an objective template for reporting urine cytology and is particularly useful for identifying HGUC cases (16). The results of the current trial also demonstrated that the new TPS had reasonable specificity for detecting HGUC.

The initial step in optimal urine cytology is proper collection. It has been documented that the sensitivity of instrumented urine cytology is significantly higher than that of the voided cytology (17). Another trial indicated that, in the absence of atypical or malignant cells, an adequate bladder barbotage specimen should have a minimum of 2644 (20 per 10 high-power fields) well-visualized, well-preserved urothelial cells as the cut-off value (18). On the other hand, it was shown that volume was an important component in the evaluation of adequacy for voided urine cytology specimens, and at least 30 mL of urine is required for an adequate test (19). In this study, we preferred bladder wash-out specimens with a volume of 50 mL based on these studies. Only 2 samples were found inadequate in terms of cellularity.

One of the most challenging categories in urine cytology reporting is the "AUC". The AUC category may represent diagnosis that "favor a reactive process" or "is uncertain whether reactive or neoplastic" (20). Strict criteria were proposed by the TPS to define the AUC category and reduce the number of uncertain diagnoses. In four prospective studies, a decrease in AUC category diagnosis rates, ranging from 0.9% to 13%, was observed after the use of the TPS criteria (21,22). In these studies, the overall AUC diagnosis rate after TPS varies between 14.4% and 26%, and the percentage of patients diagnosed with AUC and ultimately diagnosed with HGUC increased (from 33% to 53%). In our study, the AUC category constituted 6.72% of the cytology reports, and according to the surgical pathology results, 25% of these patients were diagnosed with HGUC, which demonstrated similar findings to the literature.

As the main focus of urine cytology is the diagnosis of high-grade urothelial carcinoma and given the great sensitivity of cytology in detecting these tumors, HGUC is the most important category of cytologic interpretation. In a review of the published literature, Pastorello et al. (23) showed that the diagnosis rates of SHGUC and HGUC ranged from 0.2% to 6.6% and 2.2% to 14.1%, respectively. The calculated risk of high-grade malignancy (ROHM) ranged from 33.3 to 100% for SHGUC and 58.8 to 100% for HGUC. Furthermore, the reported sensitivity of TPS ranged from 40% to 84.7%, specificity from 73% to 100%, PPV from 62.3% to 100%, and NPV from 46% to 90% (23). In our study, according to the cytology results, the diagnostic rates for SHGUC and HGUC were 5.88% and 13.86%, respectively. Interestingly, the ROHM rate for HGUC was 27.2%. In fact, all cases in the HG category had a diagnosis of urothelial carcinoma, including LG, HG, and CIS based on the final pathologic results; however, LG urothelial tumors account for the majority of the cases. The overall efficacy of urine cytology for the detection of urothelial tumors demonstrated 72.89% sensitivity, 90.47% specificity, 95.27% PPV, and 55.88% NPV in this study. Our results are similar to those in the literature.

Study Limitations

The main limitation of this trial is that it is a retrospective study. Some data regarding patient characteristics, such as obesity, are missing. Nevertheless, the current trial reflected the current role of cytology in daily practice.

Conclusion

Urine cytology is a non-invasive diagnostic procedure for the primary diagnosis and follow-up of patients with urothelial carcinoma. The results of the current study confirmed that urine cytology has acceptable sensitivity and specificity for detecting HG tumors but is less sensitive for LG tumors. Our findings suggest that although TPS has standardized the diagnostic criteria in particular focusing on detecting HG tumors and improved the quality of reporting and clinical utility of urinary cytology; there is no sufficient data for cytology to replace cystoscopy in the diagnosis and follow-up of patients with bladder cancer.

Footnote

Publication: The results of the study were not published in full or in part in form of abstracts.

Contribution: There is not any contributors who may not be listed as authors.

Conflict of Interest: No conflict of interest was declared by the authors.

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Ethics Committee Approval: This retrospective study was approved by the Clinical Research Ethics Committee of Marmara University (protocol number: 09.2024.444, date: 08.12.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.K., M.Ç., M.H.T., D.F., K.Ç., Concept: K.Ç., Design: M.K., K.Ç., Data Collection or Processing: M.Ç., M.H.T., Analysis or Interpretation: M.K., M.Ç., M.H.T., D.F., Literature Search: M.K., M.Ç., M.H.T., Writing: M.K., K.Ç.

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