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Impact of Implementing the Paris System for Reporting Urinary Cytology: A Single-institutional Experience With Emphasis on Diagnostic Yield of High-grade Urothelial Carcinoma and Low-grade Urothelial Neoplasm

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Abstract. *Background/Aim: The Paris System (TPS) has recently been proposed as a method to standardize urinary cytology reporting. In this study, we evaluated the impact of implementing TPS compared to the traditional reporting system. Patients and Methods: In total, 299 urine samples were reclassified according to TPS. We examined correlations between cytological and histological diagnoses, and calculated probabilities for detecting high-grade urothelial carcinoma (HGUC). Results: TPS resulted in a decrease in the proportion of cases diagnosed as atypical urothelial cell (AUC) (43% to 31%). Among the AUC cases, the proportion of histologically confirmed HGUC cases rose (75% to 80%), as did the proportion of low-grade urothelial neoplasms (57% to 71%). All probabilities for detecting HGUC significantly increased using TPS. Conclusion: TPS improved the diagnostic yield of urinary cytology. The implementation of TPS is expected to be a major step towards standardizing urinary cytology reporting and providing clear information to clinicians.*

Along with the development of quality medical treatment, non-invasive diagnostic tools have become essential for diagnosis, management, and surveillance. Urinary cytology is a noninvasive, low-cost, and accessible diagnostic tool. Along with cystoscopy, the ultimate goal of urinary cytology is the detection of high-grade urothelial carcinoma (HGUC), and urinary cytology has excellent sensitivity for detecting this disease (1). Because HGUC cells are shed into urine specimens, a positive cytological diagnosis is a meaningful result even in the absence of histological confirmation. Thus, patients with positive cytological results but negative cystoscopic or histological results should be closely monitored (2). However, there are some limitations to using urinary cytology for UC screening. For example, diagnoses of HGUC have been confused with degenerative atypia due to high osmolality or the influence of interventions, and architectural atypia is sometimes misinterpreted as low-grade urothelial neoplasm (LGUN) (3, 4). As a result of these limitations, it has been hard to define the ambiguous 'atypical cells' category. It is also difficult to reliably discriminate technical artifacts or reactive changes from malignant cells and many of these urine samples are categorized as atypical cells (5), such that the atypical cells category has become something of a 'wastebasket' for urine samples for which diagnoses are uncertain, whether benign or malignant. It is therefore clear that a more definitive reporting system would improve communication between cytopathologists and clinicians.

Over the years, various reporting systems for urinary cytology have been proposed to enable more accurate and standardized diagnoses, including classification systems described by Papanicolaou (6), Koss *et al.* (7), and Layfield *et al.* (8). The Paris system (TPS) emerged from the 2013 International Congress of Cytology, as a method to standardize the reporting of urinary cytology, reduce interobserver variability, and increase reproducibility (9). TPS utilizes seven diagnostic categories: i) Inadequate; ii) negative for HGUC (NHGUC); iii) atypical urothelial cell (AUC); iv) SHGUC; v) HGUC; vi) LGUN; and vii) other primary and metastatic malignancies (9). In particular, TPS provides

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specific cytomorphological criteria for distinguishing each category, with an emphasis on identifying HGUC as the main objective (4, 9).

The poor definition of the AUC category in urinary cytology has made it difficult for pathologists to diagnose specimens effectively and for clinicians to manage patients appropriately. The percentage of samples that fall into the AUC category varies (2% to 23%) among institutions. Furthermore, the risk of malignancy associated with AUC varies widely (8% to 38%), underscoring the poor definition of this category (5, 10-12). Much effort has gone into refining the description of atypical cells and minimizing the reporting rate of this category (13). In TPS, this is achieved through cytomorphological criteria which include high nuclear-to-cytoplasmic ratio, nuclear hyperchromasia, irregular nuclear membrane, and coarse chromatin pattern, which are expected to improve the certainty of categorization. The adoption of more unified and definitive criteria by diagnostic laboratories will standardize reporting for urinary cytological samples and render clinically relevant diagnoses similar to those achieved for cervical and thyroid cytology using the Bethesda system (14, 15). In this study, we aimed to objectively assess TPS compared to the current reporting system by retrospectively reviewing urine samples.

Patients and Methods

Case selection. This study (2020-03-211) was reviewed and approved by the Institutional Review Board of Samsung Medical Center (Seoul, Republic of Korea), with a waiver of informed consent. A total of 304 consecutive lower urinary tract cytological preparations diagnosed from 2017 to 2018 at Samsung Medical Center (Seoul, Republic of Korea) were re-assessed. The corresponding transurethral resection of bladder (TURB) specimens obtained up to 6 months before and after cytological diagnosis were also assessed. Five urine samples categorized as inadequate specimens or nonurothelial malignancies were excluded. Consequently, 299 urine preparations were retrieved for this study. The sex distribution of the patients sampled was 252 men and 47 women (ratio of 5.3:1) and they ranged in age from 28 to 88 years (median=70 years). All cytological specimens were voided and processed using the ThinPrep method (Hologic, Marlborough, MA, USA). Previous cytological/histological diagnoses were extracted from the electronic medical records.

Cytological examination and cytohistological correlation. The original cytological diagnosis was established according to the traditional reporting system, including i) Negative for UC (NFUC); ii) AUC; iii) suspicious for UC (SFUC); and iv) positive for UC (PFUC). All cases were reclassified according to TPS by a Board-certified cytopathologist (reviewer 1) and two experienced cytotechnologists (reviewers 2 and 3), who were blinded to clinicopathological information and patient identity. For each sample, histological diagnosis of the associated TURB specimen was made based on the World Health Organization Classifications. For the purpose of this study, histological diagnoses were separated into the following categories: i) Benign; ii) LGUN (encompassing urothelial hyperplasia, papilloma, papillary urothelial neoplasia of low malignant potential, and low-grade papillary UC); and iii) HGUC (16). When the same patient had one histological sample but multiple cytological diagnoses, the cytological diagnosis was determined based on the worst diagnosis. Moreover, histologically confirmed HGUC cases were further classified by the presence or absence of infiltrating features. Cases showing invasion of the subepithelial connective tissue were considered to have infiltration.

Statistical analysis. The original cytological diagnoses were compared to those based on TPS, and both were compared with the corresponding histological diagnoses. The probabilities for detecting histologically confirmed HGUC, including the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for AUC and higher degrees of diagnostic categories to evaluate the diagnostic performance of reporting systems. The PPV for detecting HGUC of each category (*i.e.*, AUC, SHGUC, and HGUC) was also calculated. McNemar's and Bennett's tests were used to compare the above probabilities for diagnosis between TPS and the traditional system. In addition, Cohen's κ coefficient was calculated to evaluate the correlation among the reviewers, and the degree of agreement was interpreted according to the guidelines proposed by Landis and Koch (17) as follows: less than 0.20, poor; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and 0.81-1.0, almost perfect. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corporation, Armonk, NY, USA).

Results

Cytological examination and cytohistological correlation. Table I summarizes the distribution of cytological diagnoses compared with histological diagnoses. The frequencies of TPS-based diagnostic categories were as follows: NHGUC, 31% (93/299); AUC, 31% (94/299); SHGUC, 16% (49/299); HGUC, 18% (54/299); and LGUN, 3% (9/299). The frequencies of the original diagnoses were as follows: NFUC, 36% (107/299); AUC, 43% (127/299); SFUC, 17% (52/299); and PFUC, 4% (13/299). The histological diagnoses obtained from TURB specimens consisted of 13% benign (39/299), 12% LGUN (35/299), and 75% HGUC (225/299).

We observed that the proportion of the samples diagnosed as AUC according to TPS (31%) was lower than that of the traditional system (43%). Furthermore, histologically confirmed HGUC cases were more frequently identified among AUC cases diagnosed by TPS (80%) compared with the traditional system (75%). Representative photomicrographs of AUC cases reclassified by TPS as either NHGUC, HGUC, or LGUN are shown in Figure 1. In addition, implementing TPS resulted in 25 out of 35 (71%) cases with histologically confirmed LGUN being reallocated to the NHGUC (19/25) and LGUN (6/25) categories, respectively. In contrast, using the traditional system, 20 (57%) cases were diagnosed as NFUC.

Table I. *Distribution of cytological diagnoses under the Paris System and traditional system according to histological diagnoses.*

Histological diagnosis	Paris System, n					Traditional system, n			
	NHGUC	AUC	SHGUC	HGUC	LGUN	NFUC	AUC	SFUC	PFUC
Benign	20	11	1	6	1	14	19	5	1
LGUN	19	8	1	1	6	20	13	1	1
HGUC	54	75	47	47	2	73	95	46	11

AUC: Atypical urothelial cell; HGUC: high-grade urothelial carcinoma; LGUN: low-grade urothelial neoplasm; NFUC: negative for urothelial carcinoma; NHGUC: negative for high-grade urothelial carcinoma; PFUC: positive for urothelial carcinoma; SFUC: suspicious for urothelial carcinoma; SHGUC: suspicious for high-grade urothelial carcinoma.

In 22 histologically confirmed LGUN cases, the original and TPS-based diagnoses showed concordant results. Sixteen cases were diagnosed as NHGUC (TPS-based)/NFUC (original), five as AUC/AUC, and one as HGUC/PFUC, respectively. Of the remaining 13 LGUN cases showing discrepancies between the two systems, eight cases originally diagnosed as AUC were reclassified by TPS as LGUN in four, NHGUC in three, and SHGUC in one.

Of the 225 histologically confirmed HGUC cases, the number of cases diagnosed as SHGUC (47) and HGUC (47) increased using TPS compared to the traditional system (46 and 11 cases, respectively). Moreover, their ratio was lower using TPS compared with the traditional system (1.0 vs. 4.2, respectively).

Diagnostic yield. The probability values regarding the ability of TPS and the traditional system to detect HGUC are shown in Table II. The diagnostic yield from TPS for AUC or higher categories showed a significant improvement in all parameters. Implementation of TPS increased sensitivity from 68% to 75% (p=0.005), specificity from 46% to 62% (p=0.014), PPV from 79% to 86% (p=0.002), and NPV from 32% to 45% (p=0.001). In addition, we calculated the PPVs for detecting HGUC in each diagnostic category. The PPVs of AUC and HGUC (80% and 87%, respectively) diagnosed using TPS were higher than those using the traditional system (75% and 85%, respectively). Moreover, the PPV of SHGUC showed a conspicuous increase from 89% (traditional system) to 96% (TPS). It was not possible to evaluate the differences between individual diagnostic categories for statistical significance because the number of samples was different.

The distribution of cytological diagnoses according to the presence of infiltrating features in histologically confirmed HGUC cases are shown in Table III. The sensitivity, specificity, PPV, and NPV for detecting infiltrating features are shown in Table IV. The sensitivity for detecting HGUC with infiltrating features was significantly higher using TPS (84%) compared with the traditional system (74%; p=0.016).

Interobserver agreement. Three independent reviewers re-assessed all cases according to TPS guidelines. The distribution of cytological diagnoses is demonstrated in Table V. The frequencies of NHGUC and SHGUC diagnoses were similar among all three reviewers but those of AUC and HGUC were somewhat different. The frequency of AUC diagnoses was higher for reviewer 2 (44%) than for reviewers 1 (31%) and 3 (21%). Reviewer 3 diagnosed HGUC more frequently (33%) than reviewers 1 (18%) and 2 (6%). Cohen's κ coefficient analysis revealed a moderate degree of agreement between reviewers 1 and 2 (κ=0.52) and between reviewers 1 and 3 (κ=0.45), while the agreement between reviewers 2 and 3 (κ=0.28) was interpreted as fair.

Discussion

Urinary cytology is an easily accessible tool for UC screening (18). TPS was designed to standardize urinary cytology reporting by clarifying each category and reducing interobserver variability. In this study, 299 urinary cytological preparations were reclassified according to TPS and the resulting cytological diagnoses were compared with those from the traditional system, as well as with the corresponding histological diagnoses. We observed that the proportion of cases that were assigned to the AUC category decreased when TPS was implemented (from 43% to 31%). The rate of AUC cases that were histologically confirmed as HGUC increased from 75% (traditional system) to 80% (TPS). These results are comparable to those of recent studies (2, 4, 12), which suggest that when TPS is employed, more samples that are possibly HGUC are categorized as AUC.

In this study, the frequency of TPS-based AUC was 31%, which may seem high in comparison to the 12% and 26% rates reported by Zare *et al*. (4) and Hassan *et al*. (2), respectively. However, Brimo and Auger have argued that even when the categorization of AUC is well defined, its incidence and association with a subsequent diagnosis of HGUC varies due to differences in study design, patient population, and laboratory conditions (11). The higher AUC

rate observed in this study may be attributable to the method by which the patient population was selected. We extracted HGUC cases based on the TURB diagnosis. Since patients are referred from local clinics and smaller hospitals to a tertiary hospital for major operations, the proportion of histologically confirmed HGUC among the sampled population is likely to be high. Seventy-five percent of the patients who underwent TURB were diagnosed as having HGUC, which probably influenced the rate of AUC.

TPS includes a distinct new category called LGUN, which does not exist in the traditional system. This category encompasses low-grade papillary lesions, including papilloma, papillary urothelial neoplasia of low malignant potential, and low-grade UC (9). LGUN is very prevalent and is readily encountered in cystoscopy analyses. Many articles have described the cytomorphological features of LGUN, including three-dimensional papillary structures, fibrovascular cores, cellular uniformity, and nuclear crowding and overlapping (19, 20). However, the reliable diagnosis of LGUN remains controversial, and the reported sensitivity of detecting it ranges widely, from 10% to 70% (19, 21-23). A recent study by McCroskey *et al*. suggested that the morphological features of LGUN are subtle and even expert cytopathologists cannot reliably apply them for diagnosis (24). In our study, the rates of TPS-based LGUN and NHGUC diagnoses with subsequent histologically confirmed LGUN was 71%. In contrast, the rate of NFUC categorization in the traditional system was 57% of histologically confirmed LGUN cases. Of 35 histologically diagnosed LGUN cases, eight were originally diagnosed as AUC but reclassified as three NHGUC, one SHGUC, and four LGUN under TPS. These findings indicate that the LGUN category of TPS contributes to improved diagnostic yield.

We calculated the sensitivity, specificity, PPV, and NPV for detecting HGUC, and examined the differences in these probabilities between the two reporting systems. All assessments of TPS efficacy showed a significant improvement compared to those of the traditional system. The PPV for HGUC detection of the individual categories (including AUC, SHGUC, and HGUC) using TPS also appeared to increase compared to the matched traditional category, even though it was not possible to perform statistical analysis due to the different numbers of samples. It should be noted that previous studies have described controversial results regarding the impact of the individual TPS categories on HGUC detection. Zare *et al*. showed that the PPV for detecting HGUC significantly increased in SHGUC (from 50% to 72%) but decreased in AUC (from 23% to 17%). They hypothesized that a subset of cases showing severe cytological atypia might be upgraded from AUC to SHGUC (4). Hassan *et al*. also demonstrated an increased PPV of TPS-based AUC for detecting HGUC (from 33% to 53%) but decreased PPV for the SHGUC category (from 91% to 83%) (2).

Invasiveness is one of the most important histological features of HGUC. In this study, histologically confirmed HGUC cases were also classified according to the presence of infiltrating features. TPS-based cytological diagnosis exhibited a significantly higher sensitivity (84%) for detecting HGUC with infiltrating features compared with the original diagnosis (74%). To the best of our knowledge, there has been no study examining the correlation between TPS-based cytological diagnosis and the presence of infiltrating features in HGUC. Further studies with larger numbers of samples are necessary to clarify the diagnostic value of TPS for detecting infiltrating HGUC.

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Figure 1. *Cytohistological correlation of four cases originally diagnosed as 'atypical urothelial cells'. Such cases are reclassified as negative for high-grade urothelial carcinoma (NHGUC), HGUC, or low-grade urothelial neoplasm (LGUN) under the Paris System (TPS). NHGUC: A: Cytologically, a few scattered urothelial cells exhibit slightly enlarged nuclear-to-cytoplasmic ratio (<0.5). The presence of neutrophils in the background suggests active inflammation. B: The nuclei of urothelial cells display smooth nuclear membrane and fine chromatin pattern, compatible with NHGUC under TPS. C: Histologically, the urothelium shows reactive nuclear atypia associated with mixed inflammatory infiltrates, without evidence of HGUC. HGUC: D: Cytologically, atypical urothelial cells show hyperchromatic nuclei with increased nuclear-to-cytoplasmic ratio (>0.7). E: The atypical cells form a small cluster displaying severe nuclear pleomorphism and hyperchromasia, indicating HGUC under TPS. F: Histologically, HGUC consists of neoplastic urothelial cells showing high-grade nuclear atypia. The papillae are frequently fused and anastomosed, forming cords, trabeculae, or small nests. G: Cytologically, a small, hyperchromatic cellular cluster (green arrow) of neoplastic urothelial cells showing increased nuclear-to-cytoplasmic ratio (>0.7), nuclear membrane irregularity, clumped chromatin, and hyperchromasia are visible, diagnostic of HGUC under TPS. Some urothelial cells show degenerative-appearing chromatin pattern (yellow arrows), including irregular clumping, clearing with prominent nuclear membrane (ground-glass appearance), pyknosis, and karyorrhexis. These features might interfere with a cytopathologist's judgment in deciding malignancy. H: Histologically, HGUC consists of haphazardly arranged neoplastic urothelial cells and a fibrovascular core covered with a thickened urothelial layer, forming solid, sheet-like architecture. LGUN: I: A three-dimensional papillary structure with a fibrovascular core consists of monotonous cells, which are mildly crowded and overlapped each other but maintain polarity. These urothelial cells exhibit minimal nuclear atypia, compatible with LGUN under TPS. J: At low-power magnification, variable-sized nests and trabeculae of urothelial cells invaginate into the underlying lamina propria, producing endophytic mass covered by normal urothelium. K: A high-power view of inverted urothelial papilloma reveals inversion of papillary fronds surrounded by fibrovascular stroma. Microcysts containing eosinophilic material are evident. A, B, D, E, G, and I: Papanicolaou stain; C, F, H, J, and K: hematoxylin and eosin stain. Original magnification, A, B, C, F, H, and I: ×200; D, E, and G: ×400; J, ×40; K, ×100.*

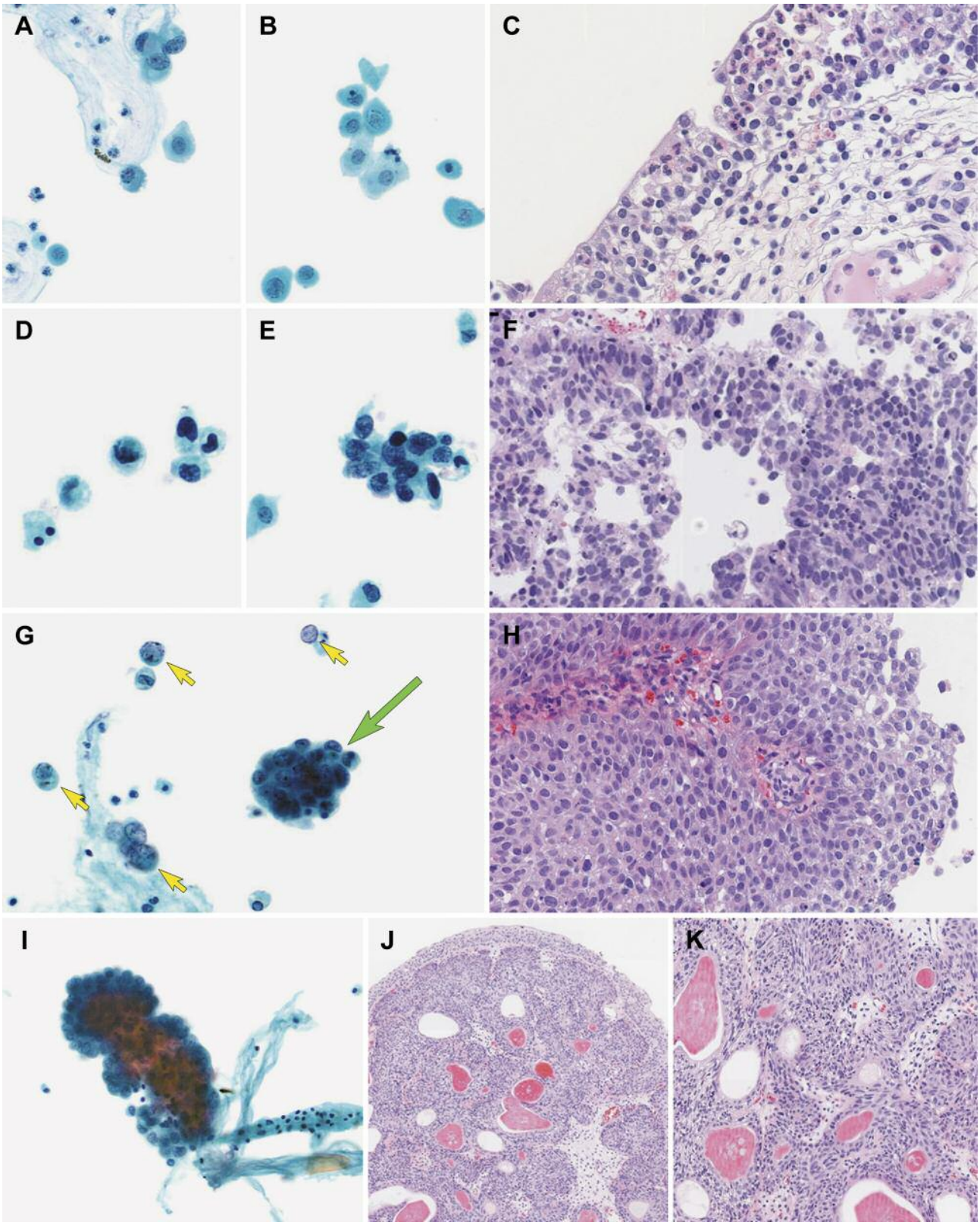
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Table II. *Diagnostic yield of the Paris System and the traditional system for histologically confirmed high-grade urothelial carcinoma.*

Paris System (95% confidence interval)			Traditional system (95% confidence interval)			*p*-Value
AUC or higher	Sensitivity	75% (69-81)	AUC or higher	Sensitivity	68% (61-74)	**0.005**
	Specificity	62% (50-73)		Specificity	46% (34-58)	**0.014**
	PPV	86% (80-90)		PPV	79% (73-85)	**0.002**
	NPV	45% (35-55)		NPV	32% (23-41)	**0.001**
AUC	PPV	80%	AUC	PPV	75%	NA
SHGUC	PPV	96%	SFUC	PPV	89%	NA
HGUC	PPV	87%	PFUC	PPV	85%	NA

AUC: Atypical urothelial cell; HGUC: high-grade urothelial carcinoma; PFUC: positive for urothelial carcinoma; PPV: positive predictive value; NA: not applicable; NPV: negative predictive value; SFUC: suspicious for urothelial carcinoma; SHGUC: suspicious for high-grade urothelial carcinoma. Bold values indicate statistical significance.

Table III. *Distribution of cytological diagnoses according to the presence of infiltrating feature in histologically confirmed high-grade urothelial carcinoma.*

Infiltrating feature	Paris System, n					Traditional system, n			
	NHGUC	AUC	SHGUC	HGUC	LGUN	NFUC	AUC	SFUC	PFUC
Present	16	24	26	34	0	26	36	32	6
Absent	38	51	21	13	2	47	59	14	5

AUC: Atypical urothelial cell; HGUC: high-grade urothelial carcinoma; LGUN: low-grade urothelial neoplasm; NFUC: negative for urothelial carcinoma; NHGUC: negative for high-grade urothelial carcinoma; PFUC: positive for urothelial carcinoma; SFUC: suspicious for urothelial carcinoma; SHGUC: suspicious for high-grade urothelial carcinoma.

Table IV. *Diagnostic yield of the Paris System and the traditional system for histologically confirmed high-grade urothelial carcinoma with infiltrating feature*

	Paris System (95% confidence interval)	Traditional system (95% confidence interval)	*p*-Value
Sensitivity	84% (75-91)	74% (64-82)	**0.016**
Specificity	32% (24-41)	38% (29-47)	0.169
PPV	50% (42-57)	49% (41-57)	0.569
NPV	71% (58-83)	64% (52-75)	0.124

PPV: positive predictive value; NPV: negative predictive value. Bold values indicate statistical significance.

Table V. *Frequency of cytological diagnoses under the Paris System among three reviewers.*

Paris System	Reviewer 1	Reviewer 2	Reviewer 3
NHGUC	31%	28%	23%
AUC	31%	44%	21%
SHGUC	16%	21%	18%
HGUC	18%	6%	33%
LGUN	3%	1%	3%

AUC: Atypical urothelial cell; HGUC: high-grade urothelial carcinoma; LGUN: low-grade urothelial neoplasm; NHGUC: negative for high-grade urothelial carcinoma; SHGUC: suspicious for high-grade urothelial carcinoma.

The diagnostic consistency of TPS was assessed by analyzing the distribution of the diagnostic categories and determining Cohen's κ coefficient between the reviewers. The distribution of NHGUC and SHGUC diagnoses was similar, and the level of agreement was fair to moderate (κ=0.28, 0.45, and 0.52, respectively). Our findings are similar to those of Glass *et al*. (12) which showed only fair to moderate agreement for each category and for morphological features. Likewise, in the Paris Interobserver Reproducibility Study (PIRST) (25) and a study by Long *et al*. (26), the highest agreement was shown in the diagnosis of urine samples for NHGUC.

Our results may have been affected by some limitations. Firstly, this study was based on retrospective review. This allows the opportunity to identify more atypical features that were not found at the time of the original diagnosis. TPS-based

diagnoses were rendered by a single Board-certified pathologist who was specialized in cytopathology and had over 10 years of experience, whereas the original diagnoses were established by pathologists with various specialties other than cytopathology. In addition, because urinary cytological preparation often shows degenerative atypia due to high osmolality or interventional procedures, several of our samples may have deteriorated over time such that they became insufficient for definitive diagnosis. Further studies are necessary to confirm our observations about the impact of TPS.

In conclusion, we demonstrate promising results that the use of TPS increases the diagnostic yield of urinary cytology screening. TPS reduced the proportion of AUC diagnoses and, among AUC cases, the proportion of histologically confirmed HGUC cases increased. The proportion of histologically confirmed LGUN also increased using TPS. All probabilities for HGUC detection significantly increased when TPS was employed. In addition, TPS-based cytological diagnosis exhibited a significantly higher sensitivity for detecting HGUC with infiltrating features. Our results suggest that TPS provides more standardized criteria for stratifying malignancy risk and enables cytopathologists to make more definitive diagnoses. The implementation of TPS for reporting urinary cytology is expected to be a major step toward standardizing urinary cytology diagnoses and providing clear information to guide clinicians in the decision-making process.

Conflicts of Interest

None of the Authors have any conflicts of interest to declare.

Authors' Contributions

All Authors made substantial contributions to the conception and design of the study; the acquisition, analysis, and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; and the final approval of the version to be published.

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References

1 Bastacky S, Ibrahim S, Wilczynski SP and Murphy WM: The accuracy of urinary cytology in daily practice. Cancer *87*: 118-128, 1999. PMID: 10385442. DOI: 10.1002/(sici)1097-0142(19990625)87:3<118::aid-cncr4>3.0.co;2-n

2 Hassan M, Solanki S, Kassouf W, Kanber Y, Caglar D, Auger M and Brimo F: Impact of implementing the Paris System for reporting urine cytology in the performance of urine cytology: A correlative study of 124 cases. Am J Clin Pathol *146*: 384-390, 2016. PMID: 27543983. DOI: 10.1093/ajcp/aqw127

3 Owens CL, Vandenbussche CJ, Burroughs FH and Rosenthal DL: A review of reporting systems and terminology for urine cytology. Cancer Cytopathol *121*: 9-14, 2013. PMID: 23192885. DOI: 10.1002/cncy.21253

4 Zare S, Mirsadraei L, Reisian N, Liao X, Roma A, Shabaik A and Hasteh F: A single institutional experience with the Paris System for reporting urinary cytology: correlation of cytology and histology in 194 cases. Am J Clin Pathol *150*: 162-167, 2018. PMID: 29878037. DOI: 10.1093/ajcp/aqy043

5 Kapur U, Venkataraman G and Wojcik EM: Diagnostic significance of 'atypia' in instrumented *versus* voided urine specimens. Cancer *114*: 270-274, 2008. PMID: 18548527. DOI: 10.1002/cncr.23656

6 Papanicolaou GN: Cytology of the urine sediment in neoplasms of the urinary tract. J Urol *57*: 375-379, 1947. PMID: 20283486. DOI: 10.1016/s0022-5347(17)69643-5

7 Koss LG, Bartels PH, Sychra JJ and Wied GL: Diagnostic cytologic sample profiles in patients with bladder cancer using TICAS system. Acta Cytol *22*: 392-397, 1978. PMID: 364909.

8 Layfield LJ, Elsheikh TM, Fili A, Nayar R and Shidham V: Review of the state of the art and recommendations of the Papanicolaou Society of Cytopathology for urinary cytology procedures and reporting: The Papanicolaou Society of Cytopathology Practice Guidelines Task Force. Diagn Cytopathol *30*: 24-30, 2004. PMID: 14696141. DOI: 10.1002/dc.10401

9 Rosenthal DL, Wojcik EM and Kurtycz DFI: The Paris System for Reporting Urinary Cytology. Springer: Cham, Switzerland, 2016.

10 Brimo F, Vollmer RT, Case B, Aprikian A, Kassouf W and Auger M: Accuracy of urine cytology and the significance of an atypical category. Am J Clin Pathol *132*: 785-793, 2009. PMID: 19846822. DOI: 10.1309/ajcpprzlg9kt9axl

11 Brimo F and Auger M: The atypical urothelial cell category in the Paris System: strengthening the Achilles' heel. Cancer Cytopathol *124*: 305-306, 2016. PMID: 26692545. DOI: 10.1002/cncy.21668

12 Glass R, Rosca O, Raab S, Szabelska J, Chau K, Sheikh-Fayyaz S and Cocker R: Applying the Paris System for reporting urine cytology to challenging cytology cases. Diagn Cytopathol *47*: 675-681, 2019. PMID: 31017746. DOI: 10.1002/dc.24166

13 Renshaw AA: Subclassifying atypical urinary cytology specimens. Cancer *90*: 222-229, 2000. PMID: 10966562.

14 Nayar R and Wilbur DC: The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria and Explanatory Notes. Third Edition Springer: Cham, Switzerland, 2015.

15 Ali SZ and Cibas ES: The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria and Explanatory Notes. Second Edition. Springer: Cham, Switzerland, 2010.

16 Moch H, Humphrey PA, Ulbright TM and Reuter VE: WHO Classification of Tumours of the Urinary System and Male Genital Organs. Fourth Edition IARC: Lyon, France, 2016.

17 Landis JR and Koch GG: The measurement of observer agreement for categorical data. Biometrics *33*: 159-174, 1977. PMID: 843571.

18 Kiyoshima K, Akitake M, Shiota M, Takeuchi A, Takahashi R, Inokuchi J, Tatsugami K, Yokomizo A and Eto M: Prognostic

significance of preoperative urine cytology in low-grade non-muscle-invasive bladder cancer. Anticancer Res *36*: 799-802, 2016. PMID: 26851042.

19 Hughes JH, Raab SS and Cohen MB: The cytologic diagnosis of low-grade transitional cell carcinoma. Am J Clin Pathol *114 Suppl*: S59-67, 2000. PMID: 11996171. DOI: 10.1093/ppr/114.1.s59

20 Murphy WM, Soloway MS, Jukkola AF, Crabtree WN and Ford KS: Urinary cytology and bladder cancer. The cellular features of transitional cell neoplasms. Cancer *53*: 1555-1565, 1984. PMID: 6697294. DOI: 10.1002/1097-0142(19840401)53:7<1555::aid-cncr2820530723>3.0.co;2-g

21 Xin W, Raab SS and Michael CW: Low-grade urothelial carcinoma: reappraisal of the cytologic criteria on ThinPrep. Diagn Cytopathol *29*: 125-129, 2003. PMID: 12951678. DOI: 10.1002/dc.10311

22 Yafi FA, Brimo F, Auger M, Aprikian A, Tanguay S and Kassouf W: Is the performance of urinary cytology as high as reported historically? A contemporary analysis in the detection and surveillance of bladder cancer. Urol Oncol *32*: 27.e21-26, 2014. PMID: 23410943. DOI: 10.1016/j.urolonc.2012.09.011

23 Renshaw AA, Nappi D and Weinberg DS: Cytology of grade 1 papillary transitional cell carcinoma. A comparison of cytologic, architectural and morphometric criteria in cystoscopically obtained urine. Acta Cytol *40*: 676-682, 1996. PMID: 8693885. DOI: 10.1159/000333938

24 McCroskey Z, Pambuccian SE, Kleitherms S, Antic T, Cohen MB, Barkan GA and Wojcik EM: Accuracy and interobserver variability of the cytologic diagnosis of low-grade urothelial carcinoma in instrumented urinary tract cytology specimens. Am J Clin Pathol *144*: 902-908, 2015. PMID: 26572997. DOI: 10.1309/ajcpe1o9ykmrsqkg

25 Kurtycz DFI, Barkan GA, Pavelec DM, Rosenthal DL, Wojcik EM, VandenBussche CJ, Mangiulli K and Olson MT: Paris Interobserver Reproducibility Study (PIRST). J Am Soc Cytopathol *7*: 174-184, 2018. PMID: 31043274. DOI: 10.1016/j.jasc.2018.02.005

26 Long T, Layfield LJ, Esebua M, Frazier SR, Giorgadze DT and Schmidt RL: Interobserver reproducibility of the Paris System for reporting urinary cytology. Cytojournal *14*: 17, 2017. PMID: 28828030. DOI: 10.4103/cytojournal.cytojournal_12_17

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