The Paris System for Reporting Urinary Cytology: The Quest to Develop a Standardized Terminology

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Abstract: The main purpose of urine cytology is to detect high-grade urothelial carcinoma. With this principle in mind, The Paris System (TPS) Working Group, composed of cytopathologists, surgical pathologists, and urologists, has proposed and published a standardized reporting system that includes specific diagnostic categories and cytomorphologic criteria for the reliable diagnosis of high-grade urothelial carcinoma. This paper outlines the essential elements of TPS and the process that led to the formation and rationale of the reporting system. TPS Working Group, organized at the 2013 International Congress of Cytology, conceived a standardized platform on which to base cytologic interpretation of urine samples. The widespread dissemination of this approach to cytologic examination and reporting of urologic samples and the scheme's universal acceptance by pathologists and urologists is critical for its success. For urologists, understanding the diagnostic criteria, their clinical implications, and limitations of TPS is essential if they are to utilize urine cytology and noninvasive ancillary tests in a thoughtful and practical manner. This is the first international/inclusive attempt at standardizing urinary cytology. The success of TPS will depend on the pathology and urology communities working collectively to improve this seminal paradigm shift, and optimize the impact on patient care.

Key Words: The Paris System, urine, standardized reporting terminology, bladder cancer

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More than 5 decades ago, Dr George Papanicolaou hypothesized that microscopic evaluation of exfoliated cells in the urine was a potentially useful method to detect urinary tract malignancies. Since then, urinary tract cytology has been plagued by less than a stellar literature that showed problems with sensitivity, accuracy, and reproducibility. Particularly troublesome is the low sensitivity in detecting low-grade noninvasive lesions,[1] as well as the lack of standardized diagnostic criteria and wide interobserver variability.

Urine cytology samples comprise a variable, but significant percentage of daily nongynecologic case volume in any cytopathology practice, and continue to be one of the more difficult specimens that pathologists encounter. Problems include inadequate cellularity of samples, cellular degeneration before fixation, as well as unrealistic expectations for diagnosing low-grade urothelial neoplasms (LGUN) by cytology. LGUNs are the most prevalent neoplasms that urologists encounter and are for the most part, readily visualized by cystoscopy. In addition, a standardized/comprehensive reporting system for urinary cytology has been missing that is based on the current understanding of the pathogenesis of urothelial carcinoma (UC), and the clinical significance of various types of urinary tract neoplastic lesions. Over 10 years ago, there was an attempt to create such reporting guidelines.[2] However, the lack of widespread input of the cytopathology community most certainly explains why it has never been generally implemented. In recognition of the need to correct this situation, an international panel of cytopathologists and an urologist with interest in urinary tract cytology convened in Paris in May of 2013 at the 18th International Congress of Cytology organized by the International Academy of Cytology. The goal was to discuss ways to improve the reporting and performance of urinary cytology. The value of ancillary tests in the screening and diagnosis of urinary neoplasms was also included for consideration. The original group that met in Paris included cytopathologists (Drs Dorothy L. Rosenthal, Eva M. Wojcik, Güliz A. Barkan, Lukas Bubendorf, Rana S. Hoda, Ritu Nayar, Stefan E. Pambuccian, Eric Piaton, Momin T. Siddiqui, Margareta Strojan-Fležar, and Philippe Vielh) and a urologist (Dr Marcus L. Quek).

PATHOGENETIC BASES OF THE PARIS SYSTEM FOR REPORTING URINARY CYTOLOGY

According to current scientific data, UC is divided into 2 major groups, low grade and high grade, based on 2 separate pathogenetic pathways and biological behavior.[3–5]

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Approximately 70% of bladder UCs are nonmuscle invasive (TA/T1) papillary tumors that are usually morphologically categorized as low-grade urothelial carcinoma (LGUC). They have a good prognosis, but may be associated with recurrence and "progression" to high-grade urothelial carcinoma (HGUC) in approximately 10% to 15% cases. The remaining 30% are muscle-invasive ($\geq$ T2) tumors, which are histologically categorized as high grade and are associated with worse overall survival than LGUC. The most common molecular alteration in low-grade noninvasive tumors is an activating mutation of FGFR3 (fibroblast growth factor receptor 3). This mutation is associated with overall favorable disease characteristics.[6] In contrast, muscle-invasive tumors show a wide range of genomic alterations, with the most commonly seen deletion or mutation of p53 occurring in about 70% of those tumors. There is a significant body of literature that combines gene expression analysis, whole-genome array, Comparative Genomic Hybridization analysis, and mutational analysis of FGFR3, PIK3CA, KRAS, NRAS, TP53, CDKN2A, and TSC1 with resultant identification of 2 separate neoplastic pathways with 2 intrinsic molecular signatures.[4] This genetic evidence has lead to the provocative question of whether these are 2 separate diseases: one, LGUC, associated with an overall good prognosis, and the other, HGUC, associated with a mortality rate of approximately 60%. Therefore, the conclusion of the first meeting of The Paris System (TPS) Working Group was that the new reporting system would concentrate primarily on the detection of HGUC while minimizing the detection of LGUC, as cytology has a high sensitivity of detecting the former with a poor sensitivity for the latter. This new paradigm became the guiding principle of The Paris System for Reporting Urinary Cytology.

STANDARDIZATION OF THE REPORTING SYSTEM

Anatomic pathologists serve as consultants to their clinical colleagues and patients, and pathology reports officially document this communication. To help clinicians choose the optimal management options for the patient, reports must accurately and clearly communicate the cytopathologic findings and outcome probability.

Pathologists actively use the terms "suspicious," "indeterminate" or "atypical," all too often with resultant failure to provide a clear diagnostic and therapeutic path for clinicians. A survey of pathologists and clinicians, performed by Redman et al,[7] documented the need for a more standardized terminology for reporting cytopathology results [thyroid fine-needle aspiration (FNA)] and for the education of clinicians on that terminology. Although pathologists have paid attention to all elements of the pathology reports (tumor staging summaries, etc.[8]), they have not focused on the issue of report comprehension. In a study looking at surgical pathology reports, surgeons misunderstood pathologists' reports 30% of the time.[9] One of the issues shared by patients and their advocates on websites dedicated to cancer advocacy is that different pathologists and/or different institutions use different highly technical terms to describe the same entities, predictably confusing to both patients and their clinicians.

From a legal perspective, pathologists are advised to issue synoptic reports. Such reporting makes the pathology report clinically relevant, assures that important diagnostic criteria are considered, standardizes information between institutions, and provides essential therapeutic and prognostic details. Litigation experience stresses that medical malpractice claims can be won or lost based on the quality and content of the medical record[10] and patient management based on the pathologic/cytologic report.

In the United States, widespread implementation of Electronic Health Records is central to federal government goals for improving health care quality, safety, and efficiency. The need for a common diagnostic terminology is clearly expressed by the National Committee on Vital and Health Statistics. "If information in multiple locations is to be searched, shared, and synthesized when needed, we will need … common vocabularies for personal, clinical, and public health information."[11] The standardization of the pathology reporting language is a key element to fulfill this mandate.[12,13]

The Bethesda System (TBS) for Reporting Cervical Cytology terminology, initiated in 1988,[14] led the way for standardized reporting in cytopathology. The goals of TBS terminology were to (1) communicate clinically relevant information from the laboratory to the health care provider; (2) be uniform and reasonably reproducible across different pathologists and laboratories, and with enough flexibility to be adopted in a wide variety of laboratory settings and geographic locations; and (3) reflect the most current understanding of cervical neoplasia. TBS also addressed specimen adequacy, correlated morphology with biology of disease process, "lumped" biologically equivalent entities, and recognized the reality and poor reproducibility of "atypia." TBS has seen successful, realizing widespread international implementation leading to the desired standardized terminology, management guidelines,[15–18] and to funding of research.[19] It has become a model for subsequent development of standardized cytopathology and histopathology reporting consensus efforts[20,21] in other body sites.

In 2009, Crothers et al[22] described major elements of quality nongynecologic cytology reporting and encouraged the use of standardization. In urinary cytology, despite 2 well established genetic pathways for the development of bladder cancer, and prognostic implication for LGUC and HGUC, the morphologic terminology for urinary cytology remained disparate and complex.

To be adopted and widely accepted by the pathology community, reporting terminology needs to be based on evidence and consensus. It should be applicable to different practice settings; be practical, flexible, and concise; avoiding redundancy. With this in mind TPS Working group convened to form a reporting system that would allow for evolution/change in our understanding of the disease processes, would correlate patient management with optimal clinical outcomes, and would be understood and accepted by the health care team taking care of the patient.

THE UROLOGIST'S PERSPECTIVE

Urologists depend on cytology to supplement the routine radiographic and endoscopic evaluation of the urinary tract to ensure that a potentially life-threatening urothelial malignancy is reliably detected. Although it may seem contradictory to see a "negative" urine cytology report in the face of a well-defined papillary bladder tumor on direct cystoscopic visualization, this simply reflects the fact that the majority of bladder cancers are of low-grade

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cytomorphology and noninvasive. Most urologists understand the inherent limitations of cytology in diagnosing low grade and noninvasive lesions due to their cellular cohesiveness and lack of nuclear atypia/dysplasia. These tumors have a low risk of progression. Alternatively, there is little controversy when it comes to the ability of cytology to detect HGUC or carcinoma in situ. These lesions clearly have a potential for recurrence, invasion, metastases, and morbidity/mortality; therefore, patients with high-grade cytomorphology represent the high-risk population most likely to benefit from surveillance evaluation with noninvasive urine cytology.

Given the wide differential diagnosis for hematuria (both gross and microscopic), the cost-effectiveness of voided urine cytology as an initial diagnostic study has been questioned.[1] Most often, hematuria is not a symptom of neoplasia.[23] However, in the appropriate clinical setting, urine cytology may play an important adjunctive role, because the test is relatively cheap and collection methods are either minimally invasive or noninvasive. The initial evaluation for patients at higher risk for bladder cancer (older age, male, smoking history, occupational exposures) and those with unexplained irritative urinary symptoms (potentially due to carcinoma in situ) should include urine cytology. Several groups also advocate the use of cytology in the initial diagnosis and surveillance for HGUC.[24–26] This can be performed at the time of cystoscopy during which a bladder washing/barbotage may be obtained, thus increasing the cellular yield available for cytologic interpretation. Even for patients who have undergone radical cystectomy with urinary diversion, urine cytology represents an important means to survey the remnant extravesical urothelial sites (upper tracts, urethra).

Although cystoscopy is considered the "gold standard" diagnostic technique for detection of bladder cancer, it is by no means perfect. Diagnostic accuracy depends on the experience of the urologist, the cytopathologist, and the clinical suspicion. Knowledge of the results of a urinary marker has been shown to influence how subtle urothelial abnormalities may be viewed.[27] The decision to perform a biopsy of an equivocal lesion is justified if the cytologic diagnosis is suspicious for high-grade urothelial carcinoma (SHGUC) or HGUC. A negative urine cytology coupled with a normal cystoscopy is quite specific and reassuring that a potentially lethal high-grade malignancy is most likely absent.[28] A diagnosis of a "positive" or "suspicious" urine cytology should be thoroughly investigated and followed closely, regardless of the cystoscopic findings.[29] The conundrum rests with the "atypical" diagnostic category. Some have advocated the use of adjunctive techniques, such as fluorescence in situ hybridization (FISH) testing, to further characterize this cohort and move interpretation into either a non-neoplastic or neoplastic category. Most critical is an understanding by the clinician of what the cytopathologist considers "atypical" and how that relates to the suspicion for and probability of an underlying malignancy. The smaller the laboratory's frequency of "atypical" interpretations, the more meaningful that category is to the clinician. Clearly, there are limitations to urine cytology. Microscopic morphology is not a perfect reflection of biological behavior. This may be due to disease-related factors (poor sensitivity for low-grade noninvasive tumors), the method of sampling (voided vs. instrumented), and the experience of the cytopathologist. Urologists should understand these limitations when interpreting the reports. To improve the clinical utility of urine cytology, it is important for both urologists and cytopathologists to communicate effectively with each other. The clinical history (symptoms, prior treatments) and cystoscopic findings should be readily available to the cytopathologist to optimize the usefulness of the cytology report.

DIAGNOSTIC CATEGORIES AND MORPHOLOGIC CRITERIA OF THE PARIS SYSTEM

A universally accepted and utilized system for reporting urinary tract cytopathology does not exist. This was eloquently demonstrated and documented by Glatz et al[30] via an international telecytology quiz on urinary cytology where the participants failed to agree even on the proposed categories. The goal of TPS is not only to define morphologic criteria for the various categories in urinary tract cytopathology, but also to standardize the reporting system to be universally acceptable and globally utilized. The published diagnostic categories are shown in Table 1, and Figure 1 shows the algorithmic approach to the TPS.

Adequacy

Unlike surgical pathology, adequacy of the cytopathology specimen is an integral part of the report. For some specimen types, adequacy has been clearly defined, that is, for cervicovaginal cytology,[31,32] and FNA specimens of the thyroid[33–35]; in others, adequacy criteria have been proposed (pancreaticobiliary system cytology,[36] endobronchial ultrasound guided/endoscopic ultrasound-guided FNAs of mediastinal and hilar lymph nodes[37–39]) but are not yet defined or tested; in most other specimen types there are no well-defined, universally accepted adequacy criteria. Adequacy, in general, ensures that the specimen is representative of what is sampled. It is defined according to the type of specimen, which may be truly exfoliated specimens (cerebrospinal fluid, voided urine, serosal cavity fluids), or forced exfoliative cellular samples, for example, Pap test, bladder washing, or FNA specimens. If the sample contains abnormal cells, no matter how few, the specimen is considered "adequate for diagnosis." Otherwise, the definition of adequacy is based on the quantification or at least a semiquantification of the number of cells and/or the volume of voided urine. The adequacy of instrumented urinary tract specimens was recently addressed by an evidence-based study that prospectively and retrospectively evaluated the cellularity of bladder washing specimens. The results supported the conclusion that 2600 cells or 2 well visualized urothelial cells per high-power field in 10 consecutive high-power fields may serve as an objective measure of adequacy in instrumented urine specimens processed using the ThinPrep method.[40] Table 2 shows guidelines for

TABLE 1. Diagnostic Categories for The Paris System for Reporting Urinary Cytology

1. Nondiagnostic/unsatisfactory
2. Negative for high-grade urothelial carcinoma (NHGUC)
3. Atypical urothelial cells (AUC)
4. Suspicious for high-grade urothelial carcinoma (SHGUC)
5. High-grade urothelial carcinoma (HGUC)
6. Low-grade urothelial neoplasm (LGUN)
7. Other: primary and secondary malignancies and miscellaneous lesions

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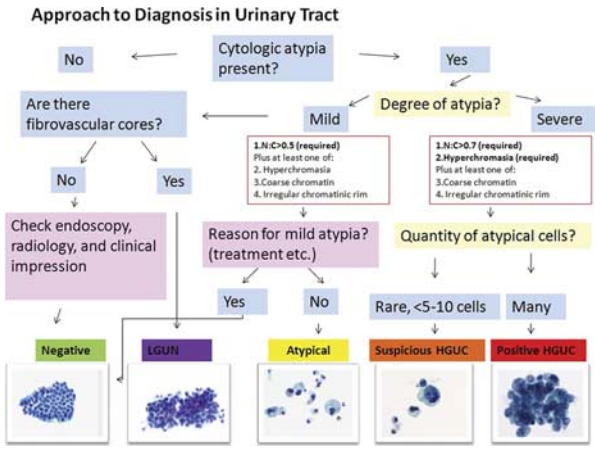

FIGURE 1. Algorithmic approach to diagnosis of urinary cytology in The Paris System. HGUC indicates high-grade urothelial carcinoma; LGUN, low-grade urothelial neoplasms.

estimating cellularity in instrumented urinary tract specimens. Another study evaluated the volume of voided urine, concluding that specimens >30 mL are more likely to be cellular/satisfactory.[42,43]

Regardless of the specimen type (voided urine or instrumented), if the urothelial cells are completely obscured by lubricant, or inflammatory cells, this represents an "unsatisfactory" specimen. Conversely, if there are any atypical cells regardless of the overall cellularity this represents a satisfactory specimen.

Negative for High-grade Urothelial Carcinoma

The majority of urinary tract specimens fall in this category. The most common cellular element is benign superficial urothelial cells, followed by intermediate and basal urothelial cells that are more commonly observed in instrumented specimens. Superficial squamous cells from the female genital tract often out-number urothelial cells. Benign glandular cells (from cystitis glandularis), squamous cells originating in squamous metaplasia of urothelium or external genital tract skin, and rarely benign seminal vesicle cells also fall into this category. Groups or fragments of urothelial cells that may be seen in both instrumented and noninstrumented urine specimens should be classified as negative unless the cytomorphology of the cells forming the group fits the criteria outlined under the atypia category. Similarly, changes associated with urolithiasis, treatment-related changes, and polyomavirus (BK virus) cytopathic changes should all be classified as negative for high-grade urothelial carcinoma (NHGUC).[44]

Figures 2A and B depict benign urothelial cells classified under the NHGUC category.

Atypical Urothelial Cells

A major goal of TPS was to clarify the ill-defined category of "atypia" as much as possible, and minimize the reporting rate of this category. To date, pathologists have not agreed upon the general definition of atypia in urinary tract specimens. Some have defined atypia as "cells that are reminiscent of, but not diagnostic of, HGUC." Others define it as "clusters of urothelial cells, suspicious for LGUC," and yet others believe degenerated urothelial cells should be reported as atypical. As a result, there is a wide interobserver and intraobserver variability, which is the reason why the rates of atypia vary among institutions from 1.9% to 23.2%.[45,46] In a small survey sent to a voluntary group of US laboratories, the reported percentages of their atypia categories range from 0.8% to 22% (mean, 12.9%). A similar survey sent to 20 international groups including France, Canada, and Japan showed similar results of atypia ranging from 1.8% to 23.7% (mean, 13.75%).

A review of the literature[47–49] and surveys sent out to TPS groups responsible for the AUC and SHGUC chapters concurred on the 4 cytomormorphologic features in predicting HGUC: nuclear cytoplasmic ratio, hyperchromasia, irregular nuclear membrane, and coarse chromatin. The criteria for the categories were set using these cytomorphologic features (Fig. 1, Table 3).

Therefore, the criteria for diagnosing atypical urothelial cells include 1 major and 1 minor criterion. The major or required criterion is the presence of nonsuperficial and nondegenerated urothelial cells with an increased nuclear cytoplasmic (N/C) ratio (> 0.5). The minor criteria, of which only 1 is required, include: (1) mild nuclear hyperchromasia, (2) irregular nuclear membranes (chromatinic rim or nuclear contour), and (3) irregular, coarse, clumped chromatin. Figure 3 depicts a bladder washing specimen with cytologic atypia, hence classified under AUC.

In TBS for Reporting Gynecologic Cytology, the category "atypical squamous cells" typically raises the possibility of a low-grade intraepithelial lesion and "atypical squamous cells, a high-grade lesion cannot be excluded" typically raises the possibility of a high-grade squamous intraepithelial lesion. In TPS in both equivocal categories,

TABLE 2. Guidelines for Estimating Cellularity of Instrumented Urine Specimens

		FN20 Eyepiece ×10 Objective		FN20 Eyepiece ×10 Objective		FN20 Eyepiece ×10 Objective		FN20 Eyepiece ×10 Objective	
Prep Diameter (mm)	Area (mm^2)	No. Fields at FN20, ×10	No. Cells/Field for 2644 Cells Total	No. Fields at FN20, ×40	No. Cells/Field for 2644 Cells Total	No. Fields at FN20, ×10	No. Cells/Field for 2644 Cells Total	No. Fields at FN20, ×40	No. Cells/Field for 2644 Cells Total
13	132.7	42.3	62.5	676	3.9	34.9	75.8	559	4.7
20	314.2	100	26.4	1600	1.7	82.6	32	1322	2

Adapted from Solomon and Nayar.[41]

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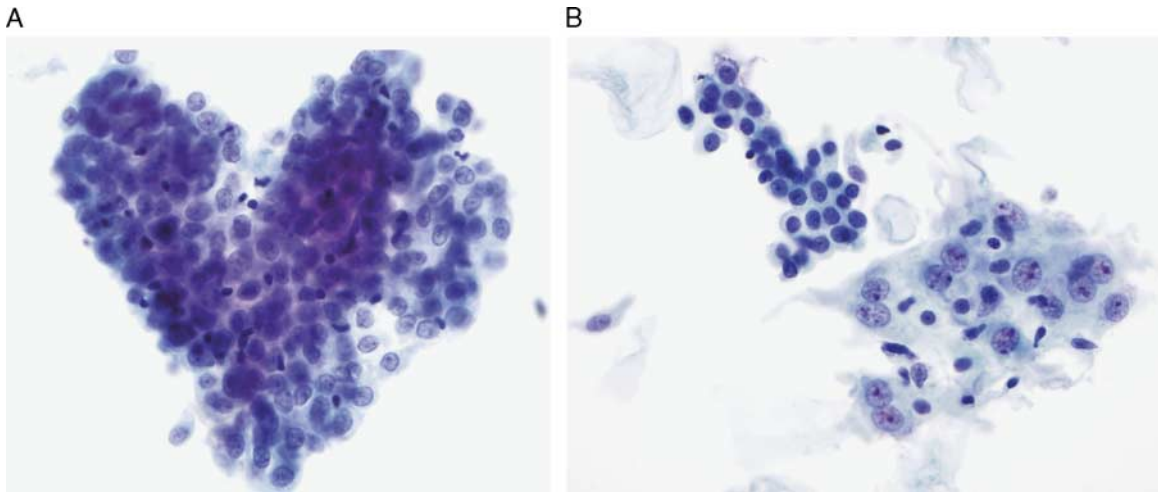

FIGURE 2. Negative for high-grade urothelial carcinoma (bladder washing, ThinPrep, Papanicolaou stain ×600). A, A cluster of benign intermediate and basal type urothelial cells with scant cytoplasm, and normochromatic nuclei. B, A group of reactive superficial urothelial cells with open chromatin and prominent chromocenters juxtaposed to benign basal type small umbrella cells with scant cytoplasm. The nuclear contours of all these benign cells are relatively smooth and regular. Please see this image in color online.

AUC and SHGUC, the atypia refers to the probability of HGUC. Of course, the prediction of HGUC is much lower in AUC compared with SHGUC.

Usually, management of an AUC diagnosis will have routine follow-up akin to the "negative" category. By minimizing the atypia rate we will help guide our urology colleagues toward an appropriate management strategy, and reduce patient anxiety related to an indeterminate diagnosis. According to the open ASC web-based forum on TPS, 97% of the participants agree that there should be a diagnostic category of AUC and similarly, 93% of the participants agree that this category should be kept at the lowest possible rate to maintain clinical significance.

Suspicious for High-grade Urothelial Carcinoma

This category includes cases with severe urothelial atypia, but falls quantitatively short of a definitive HGUC diagnosis. However, the atypia present is beyond the atypia defined in the AUC category. Naturally, the follow-up of cases diagnosed as SHGUC will reveal a higher rate of HGUC compared with that of AUC.

The major or required criteria are the presence of nonsuperficial and nondegenerated urothelial cells with an increased nuclear cytoplasmic (N/C) ratio (> 0.7) and severe nuclear hyperchromasia. The minor criteria, of which only 1 is required, include: (1) irregular nuclear membranes (chromatinic rim or nuclear contour), (2) very dark, irregular, coarse, clumped chromatin. Figure 4 depicts a urine specimen with significant cytologic atypia in a few cells, hence classified under SHGUC.

High-grade Urothelial Carcinoma

Although urine cytomorphology reporting has evolved over time from the days of George Papanicolaou and Leopold Koss, perhaps the 1 concept that has remained unchanged is the cytomorphologic characteristics of HGUC. HGUC has been well recognized in urinary tract cytopathology as having the following features: High N/C ratio, nuclear pleomorphism, nuclear membrane

TABLE 3. Comparison of Morphologic Criteria of Abnormal Cells in The Paris System for Reporting Urinary Cytology

Category	N-C Ratio (1)	Nuclear Chromasia (2)	Chromatinic Rim/Nuclear Membrane (3)	Chromatin Quality (4)	Mandatory (Major) Features	Minor Features
AUC†	> 0.5	Similar to umbrella cells Or Dark/very dark†	Fine and even Or Uneven shape and thickness†	Finely granular Or Coarsely clumped†	1	2, 3, 4 (one of the features 2-4 noted with "†" must be a second feature identified in the cells of interest in addition to number 1)
SHGUC*	> 0.7	Very dark	Uneven shape and thickness	Coarsely clumped	1, 2	3, 4 (at least one of the above must be a third feature identified)
HGUC*	> 0.7	Very dark	Uneven shape and thickness	Coarsely clumped	1, 2	3, 4 (at least one of the above must be a third feature identified)

*Only difference is the quantity: SHGUC = very few cells, < 5 cells; HGUC > 5 to 10 cells.
†Only 1 minor feature required.
HGUC indicates high-grade urothelial carcinoma; SHGUC, suspicious for high-grade urothelial carcinoma.

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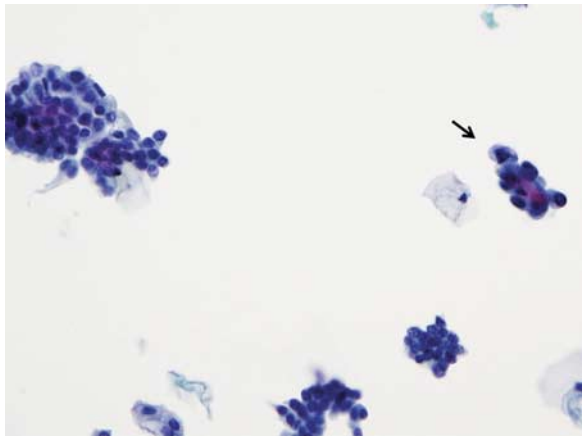

FIGURE 3. Atypical urothelial cells (bladder washing, ThinPrep, Papanicolaou stain ×600). This urine specimen has very rare cells with slightly higher N:C ratio (>0.5), in addition to hyperchromasia. This atypical cluster (arrow) cells are enlarged compared with the neighboring clusters of benign urothelial cells. Degenerative changes make it difficult to further characterize the chromatin pattern. However, the cytomorphologic changes are sufficient to classify this case under "AUC." Please see this image in color online.

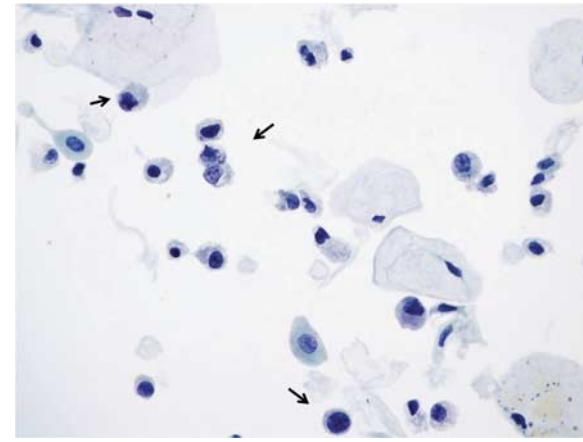

FIGURE 4. Suspicious for high-grade urothelial carcinoma(HGUC) (bladder washing, ThinPrep, Papanicolaou stain ×600). This urine specimen contains rare cells with high N:C ratio (>0.7), irregular nuclear contours, and coarse chromatin. Compared with the benign urothelial cells, the abnormal urothelial cells are hyperchromatic and are all features of HGUC; however, the paucity of abnormal urothelial cells (arrows) precludes a definitive diagnosis of HGUC. On follow-up this patient had an invasive HGUC in the urinary bladder. Please see this image in color online.

irregularity, and severe hyperchromasia.[50,51] In addition, coarse chromatin patterns are well described and illustrated. Other features, such as nuclear and cytoplasmic pleomorphism, eccentrically located nuclei, dense cytoplasm, presence of mitotic figures, and apoptotic bodies are also seen in these cases. Prominent nucleoli, isolated malignant cells with enlarged nuclear size and extensive necrosis have been described as features of HGUC in urine cytology specimens, with necrosis increasing the possibility for invasive disease.[52] According to TPS, the necessary morphologic features to diagnose HGUC include: a minimum of 5 to 10 severely abnormal urothelial cells with an N/C ratio of ≥ 0.7, with cells showing moderate to severe hyperchromasia, coarse chromatin, and markedly irregular nuclear membrane. Figure 5 depicts a classic HGUC.

Low-grade Urothelial Neoplasm

Although the main goal of TPS is to detect a HGUC, low-grade urothelial lesions cannot be discounted. Previous studies list a number of morphologic features that enabled the diagnosis of LGUC, such as minimal nuclear enlargement, nuclear membrane irregularity, density of cytoplasm, and elongated nuclei.[53–56] However, TPS acknowledges that in the majority of cases a reliable diagnosis of low-grade carcinoma cannot be made, even with the morphologic features listed above. In a recent study by McCroskey et al,[57] most of the features described previously as diagnostic for LGUC were observed almost equally in cases negative for LGUC regardless of whether the specimens were from the upper or lower urinary tract. Presence of fibrovascular cores, a feature extremely rare in urine specimens, is the only instance when the diagnosis of low-grade papillary lesion in instrumented urine can be made with confidence. Fibrovascular cores can be seen in any low-grade papillary lesion, including papillomas, papillary urothelial neoplasia of low malignant potential and LGUC. Therefore, for reporting purposes, "low-grade urothelial neoplasm (LGUN)" is recommended as a diagnostic category. This category is to be used sparingly, and in conjunction with the NHGUC category in order to clarify the conspicuous absence of HGUC. Figure 6 demonstrates LGUN, where the surgical follow-up was noninvasive LGUC. In TPS, LGUN also serves as a placeholder, awaiting further understanding of the molecular biology of the lesion.

Other Malignancies: Primary, Metastatic, and Miscellaneous Lesions

Primary malignancies of the urinary bladder, other than urothelial origin are rare, and typically represent <5% of bladder tumors. They include squamous cell carcinoma,

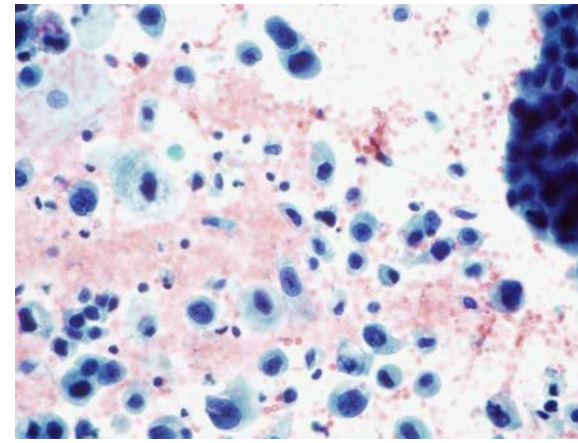

FIGURE 5. High-grade urothelial carcinoma (bladder washing, cytospin, Papanicolaou stain ×600). This urine specimen has numerous cells with high N:C ratio (>0.7), demonstrating nuclear hyperchromasia, coarse chromatin, and irregular nuclear membranes. Most cells have a plasmacytoid appearance with eccentrically placed nuclei. The background has a significant number of red blood cells, which is commonly seen in cytospin preparations. Please see this image in color online.

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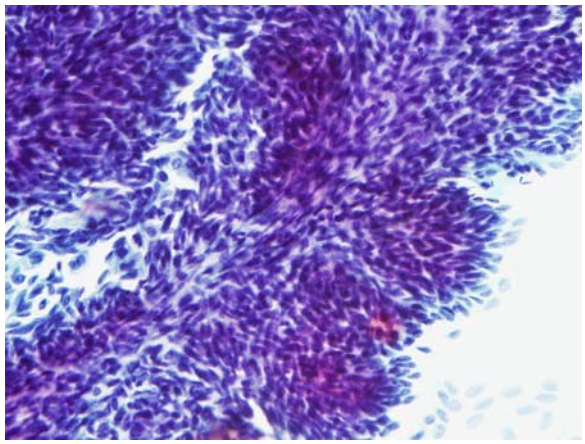

FIGURE 6. Low-grade urothelial neoplasm (LGUN) (renal pelvis brushing, conventional preparation, Papanicolaou stain ×400). This is a very cellular urine specimen composed of monomorphic cells. The most striking morphologic features are the presence of fibrovascular cores lined by the monomorphic urothelial cells. This is the only sine qua nonmorphologic feature to render a diagnosis of LGUN. On follow-up this patient did have a subcentimeter low-grade papillary urothelial carcinoma. Please see this image in color online.

adenocarcinoma, and small cell carcinoma. Their cytologic features are the same as those in other parts of the body.

Secondary malignancies in the bladder occur in < 10% of bladder tumors. Most of these are direct invasion from prostate, cervix, uterus, or gastrointestinal tract. The most common distant metastases are malignant melanoma, carcinomas of stomach, breast, kidney, and lung. Figure 7 is an example of adenocarcinoma of the prostate involving the urinary bladder.

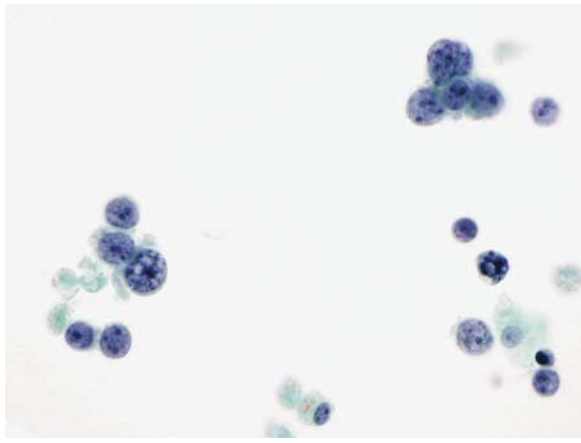

FIGURE 7. Prostatic adenocarcinoma involving urinary bladder (bladder washing, ThinPrep, Papanicolaou stain ×600). This urine specimen demonstrated mostly clusters of cells with high N:C ratio and prominent nucleoli. Although high-grade urothelial carcinoma can show clustering and prominent nucleoli, these features are more commonly observed in adenocarcinomas, especially of prostatic origin. This patient did have a history of prostatic adenocarcinoma, Gleason score 4 + 4 = 8, and the cell block sections showed PSA-positive tumor cells. Please see this image in color online.

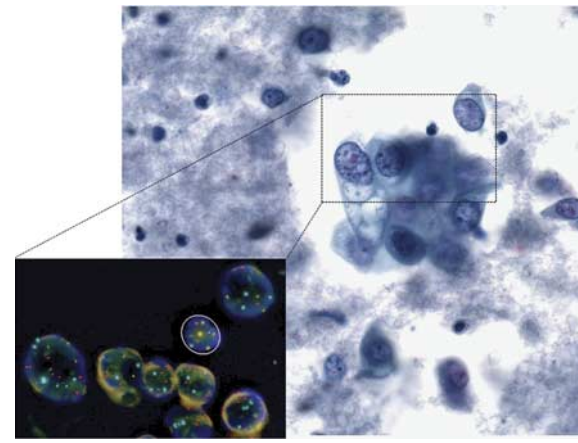

FIGURE 8. FISH TEST: (Cytospin, original magnification Papanicolaou stain, ×600). Bladder washing 3 months after intravesical BCG-treatment for pT1, high-grade urothelial carcinoma. Atypical urothelial cells in a background of inflammation support the diagnosis of AUC. However, morphology cannot distinguish between neoplastic cells and reactive cellular changes. Inset of the same atypical cell group: UroVysion FISH clearly shows a positive result with gain of the centromeric signals (blue, red, and green) and homozygous deletion of 9p21 (no yellow signals). Encircled is an inflammatory cell that shows a regular disomic signal pattern and serves as internal negative control (original magnification ×600). Please see this image in color online.

THE USE OF ANCILLARY DIAGNOSTIC TESTING IN URINE CYTOLOGY

As mentioned above, the diagnosis of "atypical urothelial cells" is inconclusive for malignancy, and creates a dilemma for the urologist, especially in patients with negative or equivocal findings on ureterocystoscopy. There have been many ancillary studies used for urine cytology, but only a few are currently FDA approved to be used in the laboratory setting; namely: UroVysion FISH (Abbott Molecular Inc., Des Plaines, IL), ImmunoCyt (Scimedx, Denville, NJ), BTA stat (Polymedco, Cortlandt Manor, NY), and NMP 22 (Allere, Waltham, MA). The FDA approval for these tests are for voided urine specimens only.

Of these, one of the most commonly used to clarify inconclusive cytologic findings is the UroVysion FISH test likely due to its morphologic applicability to the cytopathology laboratory. This multiprobe FISH test was initially developed to improve the detection of invasive HGUC in voided urines and is now FDA approved for initial diagnosis and surveillance of patients with hematuria.[58] The reported sensitivity and specificity of the test for detection of HGUC vary widely in the literature and have been reported from 8% to 100% and 29% to 100%, respectively.[59] This variability in the reported performance of the test may be due to lack of standardization of the technical testing procedure and test evaluation. These vulnerabilities include the definition for UroVysion FISH positivity, prevalence of disease in the population tested, the specimen type (voided urine vs. instrumented specimens), and the cellularity of the urinary specimen used for FISH testing.

A cytologic diagnosis of "positive for malignancy" has a high specificity and positive predictive value of > 90% for the diagnosis of HGUC. In this scenario, the ancillary tests does not add any additional clinical benefit, but only unnecessary cost. The UroVysion FISH test can increase the sensitivity of cytology for the detection of LGUC from

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TABLE 4. Relative Risk of the Diagnostic Categories Outlined in the Paris System, Based on Studies to Date

Category	Risk of Malignancy (%)	Management
Unsatisfactory/nondiagnostic	< 5-10	Repeat cytology, cystoscopy in 3 mo if increased clinical suspicion
Negative for high-grade urothelial carcinoma	0-10	Clinical follow-up as needed
Atypical urothelial cells	8-35	Clinical follow-up as needed Potential use of ancillary testing
Suspicious for high-grade urothelial carcinoma	50-90	More aggressive follow-up, cystoscopy, biopsy
Low-grade urothelial neoplasm	~10	Need cystoscopy and biopsy to further evaluate grade and stage
High-grade urothelial carcinoma	> 90	More aggressive follow-up, cystoscopy, biopsy, staging
Other malignancy	> 90	More aggressive follow-up, cystoscopy, biopsy, staging

25% to 60% to 75%, but usually low-grade neoplasms are clearly visible by cystoscopy and the FISH result will not impact the clinical management. Conversely, in the setting of atypia with negative or inconclusive findings on cystoscopy, a negative UroVysion FISH test makes it very unlikely that these abnormal cells derive from a HGUC and this additional information will help the urologist in further management of the patient.[60]

In general, the ancillary test might be of potential use for clarifying atypia in urinary cytology (Fig. 8) and may be able to assist the urologist in clinical management. However, testing must be well standardized, performed in the hands of experienced cytomorphologists (if it is a morphology-based assay), under consideration of cystoscopy findings, and the patient's medical history.

CONCLUSIONS

Important ongoing work by TPS Working Group will provide a standardized platform for reporting cytologic interpretation of urine samples. The relative risk of the diagnostic categories outlined in The Paris System, based on studies to date are outlined in this paper (Table 4). Prospective studies to establish successful prediction of HGUC by all categories, and clinical outcomes relative to each morphologic category will be essential to the successful acceptance and implementation of TPS. For urologists, understanding the diagnostic criteria, their clinical implications, and appreciating the limitations of TPS is necessary if we are to utilize urine cytology and ancillary tests in a thoughtful and practical manner.

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