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

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Key Words
The Paris System · Urine · Standardized reporting terminology · Bladder cancer

Abstract
The main purpose of urine cytology is to detect high-grade urothelial carcinoma (HGUC). 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 cytomorphic criteria for the reliable diagnosis of HGUC. This paper outlines the essential elements of TPS and the process that led to the formation and rationale of the reporting system. The Paris System Working Group, organized at the 2013 International Congress of Cytology, conceived a standardized platform on which to base cytoclogic interpretation of urine samples. The widespread dissemination of this approach to cytoclogic 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 the 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.

Introduction

More than five decades ago, Dr. George Papanicolaou hypothesized that microscopic evaluation of exfoliated cells in the urine was a potentially useful method to detect HGUC. 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 cytomorphic criteria for the reliable diagnosis of HGUC. This paper outlines the essential elements of TPS and the process that led to the formation and rationale of the reporting system. The Paris System Working Group, organized at the 2013 International Congress of Cytology, conceived a standardized platform on which to base cytoclogic interpretation of urine samples. The widespread dissemination of this approach to cytoclogic 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 the 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.

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Published online: June 18, 2016
DOI: 10.1159/000446270

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urinary tract malignancies. Since then, urinary tract cytophology has been plagued by less than 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 constitute 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 prior to 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 via cystoscopy. Additionally, 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]. 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 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-Fle-zar, 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 two major groups, low-grade and high-grade, based on two separate pathogenetic pathways and biologic behavior [3–5].

Approximately 70% of bladder UCs are non-muscle-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 10–15% of cases. The remaining 30% are muscle-invasive (≥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 fibroblast growth factor receptor 3 (FGFR3). This mutation is associated with overall favorable disease characteristics [6]. On the other hand, 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 TCS1, with resultant identification of 2 separate neoplastic pathways with 2 intrinsic molecular signatures [4]. This genetic evidence has led to the provocative question of whether these are two 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 Working Group was that the new reporting system would concentrate primarily on the detection of HGUC while minimizing the detection of LGUC, since 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 (TPS).

**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 aspirates [FNAs]) and for the education of clinicians on that terminology. Although pathologists have paid attention to all elements of the pathology report (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 Web sites 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, ensures that important diagnostic criteria are considered, standardizes information between institutions, and provides essential therapeutic and prognostic details. For example, surgeons modernizing the disease processes, would correlate patient management with optimal clinical outcomes, and would be understood and accepted by the healthcare team taking care of the patient.

In the United States, widespread implementation of electronic health records is central to federal government goals for improving healthcare 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 been successful, realizing widespread international implementation leading to the desired standardized terminology and 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 remains disparate and complex.

In order 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; and avoid 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 healthcare 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 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 symp-
tom of neoplasia [23]. Nevertheless, in the appropriate clinical setting, urine cytology may play an important ad-

junctive role, because the test is relatively cheap and col-

lection methods are either minimally invasive or nonin-

vasive. The initial evaluation for patients at higher risk for

bladder cancer (older age, male, smoking history, occu-

pational exposures) and those with unexplained irritative

urinary symptoms (potentially due to carcinoma in situ)

should include urine cytology. Several groups also advo-

cate the use of cytology in the initial diagnosis and surveil-

lance for HGUC [24–26]. This can be performed at the
time of cystoscopy, during which a bladder washing/bar-
bottage may be obtained, thus increasing the cellular yield

available for cytologic interpretation. Even for patients

who have undergone radical cystectomy with urinary di-

version, urine cytology represents an important means to

survey the remnant extra-vesical 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 and the cytopathologist, as

well as the clinical suspicion. Knowledge of the results of

a urinary marker has been shown to influence how sub-
tle urothelial abnormalities may be viewed [27]. The de-
cision to perform a biopsy of an equivocal lesion is justi-

fied if the cytologic diagnosis is Suspicious for HGUC

(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 ‘suspi-
cious’ urine cytology should be thoroughly investigated

and followed closely, regardless of the cystoscopic find-
ings [29]. The conundrum rests with the ‘atypical’ diag-
nostic 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 neo-

plastic 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 laborato-

ry’s frequency of ‘atypical’ interpretations, the more

meaningful that category is to the clinician. Clearly, there

are limitations to urine cytology. Microscopic morphol-

ogy is not a perfect reflection of biologic behavior. This

may be due to disease-related factors (poor sensitivity for

low-grade noninvasive tumors), the method of sampling

(voided versus instrumented), and the experience of the

cytopathologist. Urologists should understand these lim-

itations when interpreting the reports. In order to im-

prove the clinical utility of urine cytology, it is important

for both urologists and cytopathologists to communicate
effectively with each other. The clinical history (sym-

toms, prior treatments) and cystoscopic findings should

be readily available to the cytopathologist in order to op-
timize the usefulness of the cytology report.

### Diagnostic Categories and Morphologic Criteria of

The Paris System

A universally accepted and utilized system for report-
ing urinary tract cytopathology does not exist. This was eloquently demonstrated and documented by Glatz et al.
[30] via an international teleytology quiz on urinary cy-
tology, 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 in order to be universally acceptable and globally
utilized. The published diagnostic categories are shown
in table 1, and figure 1 shows the algorithmic approach to
TPS.

### Adequacy

Unlike surgical pathology, adequacy of the cytopathol-
ogy specimen is an integral part of the report. For some
specimen types, adequacy has been clearly defined (i.e.,
for cervicovaginal cytology [31, 32] and FNA specimens
of the thyroid [33–35]); in others, adequacy criteria have
been proposed (pancreaticobiliary system cytology [36],
EBUS/EUS-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, univer-
sally accepted adequacy criteria. Adequacy, in general,
ensures that the specimen is representative of what is

<table>
<thead>
<tr>
<th>Table 1. Diagnostic categories for The Paris System for Reporting Urinary Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nondiagnostic/unsatisfactory</td>
</tr>
<tr>
<td>2. Negative for high-grade urothelial carcinoma (NHGUC)</td>
</tr>
<tr>
<td>3. Atypical urothelial cells (AUC)</td>
</tr>
<tr>
<td>4. Suspicious for high-grade urothelial carcinoma (SHGUC)</td>
</tr>
<tr>
<td>5. High-grade urothelial carcinoma (HGUC)</td>
</tr>
<tr>
<td>6. Low-grade urothelial neoplasm (LGUN)</td>
</tr>
<tr>
<td>7. Other: primary and secondary malignancies and miscellaneous lesions</td>
</tr>
</tbody>
</table>
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 (Papanicolaou 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 2,600 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 proposes guidelines for estimating cellularity in instrumented urinary tract specimens. Another study evaluated the volume of voided urine, concluding that specimens larger than 30 ml are more likely to be cellular/satisfactory [41, 42].

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.

Fig. 1. Algorithmic approach to diagnosis of urinary cytology in The Paris System.
The majority of urinary tract specimens fall in this category, negative for high-grade urothelial carcinoma (NHGUC). 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 outnumber 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 vesical cells also fall into this category. Groups or fragments of urothelial cells that may be seen in both instrumented and non-instrumented 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 NHGUC [43].

Figure 2A, B depicts benign urothelial cells classified under the NHGUC category.

### Table 2. Guidelines for estimating cellularity in instrumented urinary specimens

<table>
<thead>
<tr>
<th>Prep diameter, mm</th>
<th>Area, mm²</th>
<th>FN20 eyepiece 10× objective number of fields at FN20, 10×</th>
<th>number of cells/field for 2,644 cells total</th>
<th>FN20 eyepiece 10× objective number of fields at FN20, 40×</th>
<th>number of cells/field for 2,644 cells total</th>
<th>FN20 eyepiece 10× objective number of fields at FN20, 10×</th>
<th>number of cells/field for 2,644 cells total</th>
<th>FN20 eyepiece 10× objective number of fields at FN20, 40×</th>
<th>number of cells/field for 2,644 cells total</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>132.7</td>
<td>42.3</td>
<td>62.5</td>
<td>676</td>
<td>3.9</td>
<td>1,600</td>
<td>1.7</td>
<td>82.6</td>
<td>32</td>
</tr>
<tr>
<td>20</td>
<td>314.2</td>
<td>100</td>
<td>26.4</td>
<td>1,600</td>
<td>1.7</td>
<td>559</td>
<td>4.7</td>
<td>1,322</td>
<td>2</td>
</tr>
</tbody>
</table>

Adapted from Solomon and Nayar [32] (page 8).
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 wide interobserver and intraobserver variability, which is the reason why the rates of atypia vary from 1.9 to 23.2% among institutions [44, 45]. 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 [46–48] and surveys sent out to TPS groups responsible for the AUC and SHGUC chapters concurred on the 4 cytomorphologic 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 (see fig. 1, table 3).

Therefore, the criteria for diagnosing atypical urothelial cells include one major and one 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 one 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 The Bethesda System 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, 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 towards 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 in order 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—although 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 N/C ratio (>0.7) and severe nuclear hyperchromasia. The minor criteria, of which only one is required,

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**Table 3. Comparison of morphologic criteria of abnormal cells in The Paris System for Reporting Urinary Cytology**

<table>
<thead>
<tr>
<th>Category</th>
<th>N:C ratio (1)</th>
<th>Nuclear chromasia (2)</th>
<th>Chromatinic rim/nuclear membrane (3)</th>
<th>Chromatin quality (4)</th>
<th>Mandatory (major) features</th>
<th>Minor features</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCa</td>
<td>&gt;0.5</td>
<td>similar to umbrella cells or dark/very darka</td>
<td>fine and even or uneven shape and thicknessa</td>
<td>finely granular or coarsely clumpedb</td>
<td>1</td>
<td>2–4 (one of the features 2–4 noted with ‘a’ must be a second feature identified in the cells of interest in addition to number 1)</td>
</tr>
<tr>
<td>SHGUCb</td>
<td>&gt;0.7</td>
<td>very dark</td>
<td>uneven shape and thickness</td>
<td>coarsely clumped</td>
<td>1, 2</td>
<td>3, 4 (at least one of the above must be a third feature identified)</td>
</tr>
<tr>
<td>HGUCb</td>
<td>&gt;0.7</td>
<td>very dark</td>
<td>uneven shape and thickness</td>
<td>coarsely clumped</td>
<td>1, 2</td>
<td>3, 4 (at least one of the above must be a third feature identified)</td>
</tr>
</tbody>
</table>

*a Only one minor feature required. b Only difference is the quantity: SHGUC = very few cells, 5–10 cells.
include: (1) irregular nuclear membranes (chromatinic rim or nuclear contour), and (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 one 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 irregularity, and severe hyperchromasia [49, 50]. 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 [51]. According to TPS, the necessary morphological features to diagnose HGUC include: a minimum of 5 to 10 severely abnormal urothelial cells with an N/C ratio of 0.7 or greater, with cells showing moderate to severe hyperchromasia, coarse chromatin, and markedly irregular nuclear membrane. Figure 5 depicts a classic HGUC.

**Low-Grade Urothelial Neoplasm**

The main goal of TPS is to detect a HGUC, but 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 [52–55]. TPS, however, 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. [56], 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

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Fig. 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. In this atypical cell 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’.

Fig. 4. Suspicious for high-grade urothelial carcinoma (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 invasive HGUC in the urinary bladder.
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 of urothelial origin, are rare and typically represent fewer than 5% of bladder tumors. They include squamous cell carcinoma, 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 fewer than 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, and carcinomas of stomach, breast, kidney, and lung. Figure 7 is an example of adenocarcinoma of the prostate involving the urinary bladder.

The Use of Ancillary Diagnostic Testing in Urine Cytology

As mentioned earlier, 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 ureteroscopy. There have been many ancillary studies used for urine cytology, but only a few are currently US Food and Drug Administration (FDA)-approved to be used in the laboratory setting; namely: UroVysion FISH (Abbott Molecular Inc, Des Plaines, Ill., USA), ImmunoCyt (Scimedx, Denville, N.J., USA), BTA stat (Polymedco, Cortlandt Manor, N.Y., USA), and NMP 22 (Allere, Waltham, Mass., USA). The FDA approval for these tests are for voided urine specimens only.
Of these, one of the most commonly used to clarify inconclusive cytological findings is the UroVysion FISH test, likely because of its morphologic applicability to the cytopathology laboratory. This multiprobe FISH test was initially developed to improve the detection of invasive HGUC in voided urine and is now FDA-approved for initial diagnosis and surveillance of patients with hematuria [57]. 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 [58]. 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 versus 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 greater than 90% for the diagnosis of HGUC. In this scenario, the ancillary test does not add any additional clinical benefit, only unnecessary cost. The UroVysion FISH test can increase the sensitivity of cytology for the detection of LGUC from 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 [59].

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. Nonetheless, 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.
Table 4. Relative risk of the diagnostic categories outlined in The Paris System, based on studies to date.

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of malignancy, %</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory/nondiagnostic</td>
<td>&lt;5–10</td>
<td>repeat cytology, cystoscopy in 3 months if increased clinical suspicion</td>
</tr>
<tr>
<td>Negative for high-grade urothelial carcinoma</td>
<td>0–10</td>
<td>clinical follow-up as needed</td>
</tr>
<tr>
<td>Atypical urothelial cells</td>
<td>8–35</td>
<td>clinical follow-up as needed; potential use of ancillary testing</td>
</tr>
<tr>
<td>Suspicious for high-grade urothelial carcinoma</td>
<td>50–90</td>
<td>more aggressive follow-up, cystoscopy, biopsy</td>
</tr>
<tr>
<td>Low-grade urothelial neoplasm</td>
<td>~10</td>
<td>need cystoscopy and biopsy to further evaluate grade and stage</td>
</tr>
<tr>
<td>High-grade urothelial carcinoma</td>
<td>&gt;90</td>
<td>more aggressive follow-up, cystoscopy, biopsy, staging</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>&gt;90</td>
<td>more aggressive follow-up, cystoscopy, biopsy, staging</td>
</tr>
</tbody>
</table>

Conclusions

Important ongoing work by The Paris System 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.

Acknowledgements

The authors would like to thank all who were involved in creating The Paris System of Reporting Urinary Cytology. This was truly a team effort.

Funding Sources

The authors have not received any grant funding for this paper or for developing The Paris System of Reporting Urinary Cytology.

Disclosure Statement

The authors do not have any financial conflict of interest to disclose.

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