Cytopathology in Focus: Paris System: a new paradigm for urinary cytology

Güliz A. Barkan, MD
Eva M. Wojcik, MD
Dorothy L. Rosenthal, MD
Daniel F.I. Kurtycz, MD

May 2016—The Paris System Working Group has proposed and published a standardized reporting system that redefines the primary purpose of urinary cytology: the detection of high-grade urothelial carcinoma (HGUC).[1] A program to address standardization of urine cytology reporting was conceived at the 18th International Congress of Cytology in Paris in May 2013 where a number of people of like interest assembled and formed the Paris System Working Group. This consortium was composed of an international group of cytopathologists, surgical pathologists, and urologists. The reporting system is grounded in the current understanding of the pathogenesis and clinical significance of urothelial carcinoma (UC).

Morphology divides UC into two general groups, low grade and high grade. Not surprisingly, the two groups also have different genetic pathways and vastly different biologic behavior.[2-4] Approximately 70 percent of UC arising in the urinary bladder are non-muscle invasive (WHO/ISUP stage pTaT1) papillary tumors, usually observed via cystoscopy, that are generally categorized as low-grade urothelial carcinoma (LGUC) on biopsy. They have a good prognosis but have been associated with a high recurrence rate. Although early studies have suggested up to 10 to 15 percent of LGUC progress to HGUC, current literature indicates that earlier studies5 likely overstated the amount of progression. The remaining 30 percent are muscle-invasive (≥T2) tumors, which are histologically categorized as HGUC and associated with worse overall survival than LGUC. In situ flat urothelial lesions are by definition noninvasive HGUC. Their flat nature causes them to be more difficult to detect on cystoscopy, but their high-grade cytomorphology necessitates biopsy and close follow-up.

Urine cytology has a high sensitivity of detecting HGUC because the morphological features of HGUC are well defined and easily identifiable in urine cytology. Conversely, urine cytology has poor sensitivity for identifying low-grade urothelial lesions since the cytomorphology of these lesions closely resembles that of normal/benign urothelium. Therefore, the Paris System Working Group members unanimously agreed that the new reporting system would concentrate primarily on what is important: the detection of HGUC. In the Paris System, the low-grade urothelial lesions are combined under the title Low-Grade Urothelial Neoplasm (LGUN). LGUC is a diagnosis that is reserved for the rare occasion in which fibrovascular cores combined with bland urothelial cells are readily identified in urine cytology. LGUN also serves as a placeholder for future technologic development. Factors may be found that would improve the performance characteristics of LGUN detection, but at present they are unavailable.

Urine cytology specimens make up an important percentage of the nongynecologic caseload in most cytopathology laboratories. It is a notoriously challenging specimen type for the following reasons: lack of a quantitative definition of adequacy, the subjective nature of “atypia,” marked degenerative changes seen in voided urine specimens, and the unrealistic expectation of making an LGUC diagnosis.

The stated focus of the Paris System Working Group was to improve the reporting and performance of urinary

cytology. The group also worked on identifying the value of ancillary testing in the screening and diagnosis of urinary neoplasms. The initial meeting was followed by the creation of a Web-based survey directed at the pathology community, with questions based on concepts and problems brought to light by group participants. The survey was promoted through the websites of the International Academy of Cytopathology and American Society of Cytopathology and the ASC Listserv.

Paris System diagnostic categories and criteria

The Paris System Working Group created a reporting system with defined diagnostic categories and reproducible morphologic criteria such that this system could be universally accepted and used worldwide. The reporting system and atlas were published in early 2016 (Springer Press, New York and Heidelberg, Germany).

Here is a look at the chapters:

Chapter 1. Pathogenesis: A discussion of our current understanding of urothelial neoplasia.

Chapter 2. Adequacy: The definition of adequacy in urinary cytology. A statement of adequacy provides confidence that the specimen is representative of the target site/lesion. Specimen adequacy pertains to the quantitative (cellularity, volume, or both) and qualitative nature (degeneration, presence of obstructive elements, etc.) of the specimen. Urinary cytology samples that are completely obscured by inflammatory cells, peripheral blood elements, extracellular material (mucin, for example), or lubricant are unsatisfactory or non-diagnostic. As in any cytology sample, any evidence of abnormality (atypia and higher) automatically qualifies a sample as "adequate for diagnosis." The chapter includes a flowchart for determination of specimen adequacy which provides guidance for establishing adequacy based on specimen type, presence of urothelial cells, obstructive elements, etc. In this chapter, the Paris System Working Group sets forth the rationale that 2,600 cells or two well-visualized urothelial cells per high-power field in 10 consecutive high-power fields may be used as an objective measure of adequacy in instrumented urine specimens.[6] For voided urine, preliminary studies indicate that specimens over 30 mL are more likely to be cellular/satisfactory.[7,8] As further investigations are conducted into the nature of adequacy in urinary cytology, the authors believe that the murky area of adequacy will be clarified.

Chapter 3. Negative for High-Grade Urothelial Carcinoma (NHGUC): The object of urinary cytology is the identification of HGUC. In the new formulation, many samples that may have been called "atypical" now fall into this category. Reactive cells, cells with instrumentation artifact, cells with changes due to nephrolithiasis, benign urothelial tissue fragments, and polyomavirus now belong here.[9] This will help rectify much of the unease experienced by clinicians and their patients who found the interpretation of "atypia" unsettling, and which may have led to unwarranted intervention in lesions that were either non-neoplastic or were not going to progress to invasive disease.

Chapter 4. Atypical Urothelial Cells (AUC): The outcome analysis of "atypia" defined. Since the criteria of atypia have varied among institutions and even among individual pathologists within the same institution, it's not surprising that the reported outcome analysis of this diagnosis has been variable.

Morphology is an imperfect reflection of neoplasia and biologic behavior. Insecurity with a given diagnosis breeds atypical interpretations. Atypia frustrates clinicians and pathologists and impairs a clear therapeutic pathway. One of the major goals was to confine the atypia category by making the object of the Paris System the search for HGUC. Thus, many cases of minor atypia or those with known causes of "atypia"—calculus, for example—get shifted to NHGUC; cases with significant atypia are moved into "Suspicious for HGUC (SHGUC)." The latter has a management scheme akin to HGUC. Small numbers of major and minor criteria to constrain AUC are offered. For a diagnosis of AUC, the sine qua non criterion is high nuclear cytoplasmic ratio (N/C)(> 0.5) in non-superficial and non-degenerated urothelial cells. In addition, one of the following criteria must also be present: mild to moderate nuclear hyperchromasia (compared with a benign urothelial cell or a squamous cell, used as an internal control), irregular nuclear membranes (chromatinic rim or nuclear contour), and irregular, coarse chromatin pattern.

To date, patients with a diagnosis of AUC have been managed in a manner similar to patients assigned a "negative" diagnosis. With the refocus by the Paris System on relative risk of all categories predicting HGUC, and clear criteria provided for the diagnosis of AUC, the hope is that the "atypia" rate of urinary cytology will be reduced universally. As this concept becomes more accepted worldwide, a shift in the management strategy of AUC will inevitably follow, perhaps requiring a much closer follow-up and evaluation of patients carrying this diagnosis.

Chapter 5. Suspicious for High-Grade Urothelial Carcinoma (SHGUC): The definition and outcome analysis of the "suspicious" category. This group contains cases with significant cytologic abnormality but falling numerically short of an overt call of HGUC. Follow-up of cases diagnosed as SHGUC reveals a higher rate of biopsy-proven HGUC compared with AUC. To provide this diagnosis there needs to be clearly identifiable non-superficial and non-degenerated urothelial cells with an increased N/C (>0.7) and severe nuclear hyperchromasia (compared with benign urothelial cells or squamous cells, used as an internal control). In addition, at least one of the following cytomorphologic criteria should be seen: irregular nuclear membranes (chromatinic rim or nuclear contour) and/or coarse, clumped chromatin pattern. The main dividing criterion between SHGUC and HGUC is a minimum of five to 10 malignant urothelial cells in the latter. The category of SHGUC has a higher positive predictive value compared with that of the AUC category, and therefore the recommended Paris System management strategy is similar to that of HGUC.

Chapter 6. High-Grade Urothelial Carcinoma (HGUC): The morphologic criteria and outcome analysis of the purpose of the Paris System. This group includes samples with unequivocal HGUC as defined by the presence of a minimum of five to 10 severely abnormal urothelial cells with an N/C ratio of 0.7 or greater, with moderate to severe hyperchromasia, coarse chromatin, and markedly irregular nuclear membranes (chromatinic rim or nuclear contour).

Patients carrying this diagnosis should be evaluated carefully with cystoscopy and upper tract evaluation and staging biopsies.

Chapter 7. Low-Grade Urothelial Neoplasm (LGUN): The definition and outcome analysis of low-grade urothelial neoplasms, including papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade urothelial carcinoma (LGUC), and low-grade urothelial dysplasia categories proposed by WHO/ISUP. While urologic cytology does not perform well in the diagnosis of LGUC, this category may be used in cases in which the criteria are strictly fulfilled. Under the Paris System, the interpretation of LGUC can be made only if papillary groups composed of relatively bland cells with fibrovascular cores are observed.

This category should be used as a subcategory in combination with NHGUC. It is not even AUC. In addition, this category serves as a placeholder for future genetic/molecular knowledge. While we may not be able to currently diagnose LGUN in many cases, there may be a future marker or genetic disruption that could be detected on a urologic sample.

Chapter 8. Other Malignancies Primary and Metastatic, and Miscellaneous Lesions: The background, etiology, diagnostic cytomorphological criteria, and use of ancillary studies for the diagnosis of these rare neoplasms. The chapter includes epithelial and non-epithelial tumors, including hematogenous neoplasms, direct extension of tumors into the urinary bladder, metastatic neoplasms, and benign neoplasms as well as tumor-like conditions.

Chapter 9. Ancillary Studies in Urinary Cytology: Noninvasive or minimally invasive tests to identify UC (low grade or high grade) that are more specific, sensitive, and economical than cytologic tests alone. To date, such a test does not exist. In the past, methods such as special stains and ploidy analysis failed to give sufficient resolution or were economically unrealistic. In the modern era there are a number of techniques that are FDA approved only for voided urine, including UroVysion FISH (Abbott Molecular, Des Plaines, Ill.), ImmunoCyt (DiagnoCure, Québec City), BTA stat (Polymedco, Cortland Manor, NY), and NMP 22 (Alere, Waltham, Mass.). The methods and their utility in specific clinical scenarios are discussed.

Chapter 10. Cytopreparatory Techniques: Collection techniques, various preparatory methods, and the staining

used in preparing urine cytology specimens. Based on a CAP survey, the majority of U.S. institutions use the ThinPrep (Hologic, Marlborough, Mass.) method, followed by the CytoSpin method (Thermo Fisher Scientific, Waltham, Mass.).[10] The chapter describes how concentration techniques are used in the preparation of urine specimens.

Chapter 11. Clinical Management: The clinical use and role of urine cytology in the management of patients with hematuria and patients with a history of UC. Effective communication between pathologists and urologists is essential for optimal patient care. Urologists and pathologists have important responsibilities: Urologists should provide the clinical history and cystoscopic findings to the pathologist, and pathologists should provide a clear, concise cytology report following the published Paris System guidelines.

Conclusion

The intention of the Paris System is to provide standardized, universally acceptable, outcome evidence including relative risk of HGUC, and consensus-based guidelines for reporting urinary cytology. The atlas chapters make a convincing case for a paradigm shift in the reporting of urologic cytology, putting HGUC as the primary focus. In addition, the concluding pages point the way to the future and suggest a number of studies that need to be performed to explore as yet unanswered questions regarding urinary cytology. This ensures that in time there will be a "Paris 2.0" as the quest for improved urologic diagnosis and care continues.

1. Rosenthal DL, Wojcik EM, Kurtycz DFI, eds. *The Paris System for Reporting Urinary Cytology.* New York: Springer; 2016.
2. Netto GJ. Molecular genetics and genomics progress in urothelial bladder cancer. *Semin Diagn Pathol.* 2013;30(4):313–320.
3. Cheng L, Zhang S, MacLennan GT, Williamson SR, Lopez-Beltran A, Montironi R. Bladder cancer: translating molecular genetic insights into clinical practice. *Hum Pathol.* 2011;42(4):455–481.
4. Knowles MA. Molecular pathogenesis of bladder cancer. *Int J Clin Oncol.* 2008;13(4):287–297.
5. van Rhijn BW. Combining molecular and pathologic data to prognosticate non-muscle-invasive bladder cancer. *Urol Oncol.* 2012;30(4):518–523.
6. Prather J, Arville B, Chatt G, et al. Evidence-based adequacy criteria for urinary bladder barbotage cytology. *Journal of the American Society of Cytopathology.* 2015;4(2):57–62.
7. VandenBussche CJ, Rosenthal DL, Olson MT. Adequacy in voided urine cytology specimens: the role of volume and a repeat void upon predictive values for high-grade urothelial carcinoma. *Cancer Cytopathol.* 2016;124(3):174–180.
8. Barkan GA. Enough is enough: adequacy of voided urine cytology. *Cancer Cytopathol.* 2016;124(3):163–166.
9. Wojcik EM. What should not be reported as atypia in urine cytology. *Journal of the American Society of Cytopathology.* 2015;4(1):30–36.

10. Barkan GA, Tabatabai L, Sturgis C, Kurtycz DFI, Souers RJ, Nayar R. In preparation for the Paris System for Reporting Urinary Tract Cytopathology (TPSRUTC): observations from the 2014 supplemental questionnaire of the College of American Pathologists (CAP) Cytopathology Interlaboratory Comparison Program (CICP) [abstract]. *Mod Pathol.* 2015;28(suppl 2):83A.

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Dr. Barkan is an associate professor of pathology and urology, vice chair of education, and director of cytopathology, Loyola University Medical Center, Maywood, Ill. Dr. Wojcik, president of the American Society of Cytopathology, is chair of pathology and the Helen M. and Raymond M. Galvin professor of pathology and urology, Loyola University Medical Center. Dr. Rosenthal is a professor emerita of pathology, Division of Cytopathology, Johns Hopkins School of Medicine. Dr. Kurtycz is a professor of pathology and laboratory medicine, University of Wisconsin-Madison, and medical director, Wisconsin State Laboratory of Hygiene. Dr. Kurtycz is a member of the CAP Cytopathology Committee.