# Diagnostic Advances in Urine Cytology

Juan Xing, MD[a], Jordan P. Reynolds, MD[b,*]

**KEYWORDS**

• Bladder cancer • Paris system • Urothelial carcinoma

**Key points**

- The Paris system for reporting urinary cytology is the most current classification method and it is based on both cytologic criteria and consensus on reporting schemes.
- The major diagnostic criterion for determining high-grade urothelial carcinoma is increased nuclear-to-cytoplasmic ratio, and the minor criteria include nuclear hyperchromasia, nuclear irregularity, and clumped chromatin.
- There are many benign entities that may mimic urothelial carcinoma, therefore leading to overdiagnosis.
- Ancillary testing is currently used with fluorescence in situ hybridization (UroVysion), the most commonly used test. Further validation is needed for ancillary testing for routine use in screening and detection of bladder cancer.

## ABSTRACT

The utility of urine cytology has shifted from the identification of red blood cells, crystals, or parasites to its currently used role of detection of cancer cells exfoliated in urine samples. A variety of ancillary tests have been developed to complement the diagnostic ability of urine cytology. Furthermore, urine testing will continue to evolve as the pathogenesis of genitourinary tract diseases in depth is understood. This article focuses on the diagnostic advances in urine cytology from the cytomorphological perspective, past and current reporting schemes, and the application of ancillary testing in urine samples.

## HISTORY OF URINE CYTOLOGY

Examination of urine is one of the oldest medical tests and has evolved from visual fluid inspection by ancient Egyptians and Greeks to routine microscopic examination conducted by cytopathologists.[1] Using urine cytology to detect cancer cells was first introduced by Dr Hermann Lebert in 1845 and Dr Vilem D. Lamble in 1856.[2,3] Dr William R. Sanders subsequently contributed to this subject in 1864.[4] Detection of cancer cells using urine cytology, however, did not gain mainstream popularity until 1945 after Drs George Papanicolaou and Victor F. Marshall[5] published their original work. Since then, urine cytology for identifying cancer cells has been integrated into routine urologic diagnosis and continues to play an important role in the diagnosis of urothelial carcinoma. Currently, urine cytology is still the best available test for diagnosing, screening, and monitoring bladder cancer and referred to as "good old cytology" by Dr DeMay.

## PAST URINE CYTOLOGY DIAGNOSTIC CRITERIA AND REPORTING SCHEMES

Although examination of urine has been used in medicine for centuries, the detailed

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[a] University of Pittsburgh Medical Center, UPMC Shadyside Hospital, 5150 Centre Avenue, POB2, Suite 201.2, Pittsburgh, PA 1523, USA; [b] Cleveland Clinic Foundation, Pathology and Laboratory Medicine Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44191, USA

* Corresponding author.

*E-mail address:* reynolj4@ccf.org

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cytomorphological description of cancer cells and reporting system were not proposed until Drs Papanicolaou and Marshall published their original work in 1945.[5,6] They studied cytologic findings of 240 cases and correlated the results with histologic diagnoses and found that urine cytology had high positive predictive value for urothelial carcinoma. The diagnostic criteria originally described included nuclear abnormalities, such as enlargement, anisonucleosis, hyperchromasia, coarse chromatin pattern, and prominence of nucleolus; cytoplasmic changes, including basophilia; and vacuolization as well as significant changes in their shape and size compared with their normal counterparts. In addition, a classification scheme consisting of 5 classes for reporting urine cytology was also proposed by Dr Papanicolaou: (1) absence of abnormal or atypical cells; (2) atypical cells present but without abnormal features; (3) cells with abnormal features but not sufficiently pathognomonic; (4) fair number of pathognomonic cells and cell clusters; and (5) large number of conclusive cells and cell clusters. Although the classification system was proposed, rigorous cytologic criteria for each specific category were not defined in this reporting scheme.

Although Dr Papanicolaou established the fundamental role of urine cytology in diagnosing bladder cancer, Dr Leopold G. Koss[7] made subsequent numerous contributions to the fields of urine cytology and cytopathology in general. Among his notable works, Koss first began to correlate the cytopathology and histopathology. He described the cytomorphologic features of urine cytology based on the 1973 World Health Organization classification of bladder cancer and pointed out that diagnosing of bladder cancers should depend on both architectural and nuclear abnormalities.[8] He also observed that it was extremely difficult to diagnose low-grade papillary tumors unless papillary fragments with fibrovascular cores were present.[9] The cytomorphologic features supporting malignancy included variable size and configuration with a very high nucleus-to-cytoplasmic (N:C) ratio, nuclear hyperchromasia, irregular nuclear membranes, abnormal chromatin texture, and high cellularity. Among them, hyperchromasia was the most important diagnostic feature.[9] He also addressed the issue of atypical urothelial cells and subclassified them into atypical 1 cells (ATY1) with hyperchromasia and predominantly round or oval contours and atypical 2 cells (ATY2) with hyperchromias and nuclear membrane irregularity. Based on his observation, Koss proposed his classification of scheme: (1) benign cells; (2) ATY1 cells and few clusters; (3) clusters, nuclear elongation, and few ATY2 cells; and (4) malignant tumor cells and many ATY2 cells. The first 2 classes corresponded to histologic benign conditions. Class 3 corresponded to histologic low-grade neoplasms (eg, papilloma and grade 1 papillary carcinoma) and class 4 to high-grade carcinomas (eg, grades 2 and 3 papillary carcinoma and carcinoma in situ).

A few recent urine cytology classification schemes have also been proposed in the literature (**Table 1**).[10–13] Murphy and colleagues[10] suggested a classification system in 1984. They described morphologic features that might be useful for identifying low-grade urothelial tumors in addition to the features of high-grade neoplasms. They observed that papillary and loose clusters, increased cellularity, eccentric nuclear location with more granular chromatin pattern, 1 or 2 nuclear indentions, and lack of prominent nucleoli were often associated with low-grade lesions. There was lack of consensus, however, on these features. Later, Ooms and Veldhuizen[11] proposed another classification scheme in 1993 and reported that more single cells and greater nuclear atypia were associated with increased tumor grade. In 2004, the Papanicolaou Society of Cytopathology Task Force published recommendations for reporting urine cytology in a format similar to the 2001 Bethesda System for reporting cervical cytology.[12] The Johns Hopkins Hospital template was published in 2013. They observed that the most common morphologic features that were associated with increased risk for high-grade urothelial carcinoma included hyperchromasia, irregular nuclear borders, increased N:C ratio, and anisonucleosis whereas hyperchromasia was the strongest predictor.[13,14]

Nevertheless, none of these reporting schemes gained broad acceptance due to lack of validated diagnostic criteria for each specific category and lack of consensus for indeterminant diagnoses.[15] The indeterminant diagnostic category may cause unnecessary stress to patients and create management dilemmas for clinicians. Therefore, there was a crucial need to develop a standardized terminology with specific diagnostic criteria in urine cytology.

## THE PARIS SYSTEM FOR REPORTING URINARY CYTOLOGY

The Paris system for reporting urinary cytology (TPSRUC) was initiated at the 2013 International Congress of Cytology in Paris and the final work was published in 2016.[16] The multidisciplinary