



ORIGINAL ARTICLE

Evidence-based adequacy criteria for urinary bladder barbotage cytology

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KEYWORDS

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Introduction Adequacy criteria are well established in some areas of cytopathology to prevent false negative diagnoses. To date, no such criteria have been proposed and validated for urinary tract specimens. Our aim was to determine a cellularity cutoff point that significantly affects the sensitivity of detecting high-grade or in situ urothelial carcinoma (HGUC or UCIS) in bladder barbotage/washing specimens.

Materials and methods Bladder barbotage specimens collected in liquid-based media were selected. Specimens diagnosed as “positive for HGUC” (with histologic confirmation) composed the study group, with negative cases as control specimens. Samples were serially diluted and ThinPrep slides of decreasing cellularity were made and reviewed for diagnosis and cellularity. In a retrospective validation study, we identified cases with a “negative for malignancy” bladder barbotage/washing and a surgical pathology diagnosis of UCIS or HGUC (ie, false negative cytology). Cellularity was assessed.

Results A distinct difference in sensitivity was noted at a cutoff point of 2644 (20 per 10 high-power fields) urothelial cells. Sensitivities increased for atypical or higher (68.3% versus 100%) and HGUC (43.3% versus 88.0%) after application of this cutoff point with high statistical significance ($P = 0.001$ and 0.0001 , respectively). For the retrospective review, cases below the cutoff point were reclassified as unsatisfactory, and sensitivity rose from 76.3% to 84.8% ($P = 0.0027$).

Conclusions Our results indicate that, in the absence of atypical or malignant cells, an adequate bladder barbotage specimen should have a minimum of 2644 (20 per 10 high-power fields) well-visualized, well-preserved urothelial cells to increase the positive predictive value of this test.

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Introduction

Urinary tract cytology (UTC) is widely used for the evaluation of hematuria, irritative voiding symptoms, and in the

follow-up of urothelial carcinoma (UC).¹ The continued use of UTC in the detection of UC, despite numerous proposed alternatives (BTA [Bladder tumor antigen] STAT and BTA TRAK [Polymedco, Courtlandt Manor, NY], Nuclear Matrix Protein/NMP22 [Matritech Inc., Newton, MA], Immunocytology/ImmunoCyte/uCyt+ [Diagnocure, Sainte-Foy, Quebec, Canada], and others²), is due to its high specificity, ranging from 78% to 100%.³ Nonetheless, the reported sensitivity of UTC for the detection of UC is low, especially in studies including low-grade UCs, for which reported detection rates can be as low as 10%.³ Even for high-grade UC (HGUC), the reported sensitivity of UTC ranges from 38% to 100%.³⁻⁵ This large variation in reported sensitivities of UTC in the detection of HGUC is most likely related to multiple factors, including the diagnostic criteria used for the grading of UC on histologic evaluation,⁶ the type of specimen used (voided urine, bladder barbotage, etc),⁷ cytopreparatory method, the experience and skill of the interpreter, and the quality of the sample. The quality of the specimen can affect the sensitivity of UTC and may be, at least in part, responsible for its low sensitivity in the detection of HGUCs reported in some studies. However, the impact of the quality of the specimen on the performance of UTC cannot be assessed in the absence of quantifiable adequacy criteria. Unfortunately, such adequacy criteria have not been defined to date.

The aim of this study was to determine what constitutes an adequate bladder washing/barbotage specimen. To reach this goal, we determined the minimum cellularity that allows a cytologic diagnosis to be rendered by using a 2-step approach. In the first step, we serially diluted residual bladder barbotage specimens known to be positive for malignancy to determine the minimum cellularity at which the cytologic preparation could still be diagnosed as abnormal (atypical urothelial cells [AUC] and above). In the second step of this study, we used the cellularity criteria determined in the first step to retrospectively assess the impact on the sensitivity in a large cohort of previously diagnosed bladder barbotage specimens. To our knowledge, this is the first evidence-based study to determine adequacy criteria for bladder washing/barbotage cytology.

Materials and methods

Prospective determination of adequacy criteria

Nineteen bladder barbotage specimens were selected for the study. Cases were selected based on the cytologic diagnosis, the availability of residual material, and adequate histologic follow-up. The study group was composed of 10 consecutive specimens diagnosed as "positive for HGUC" that had histologic confirmation as either HGUC or UC in situ (UCIS). The control group consisted of 9 consecutive cases diagnosed as negative for UC or diagnosed as atypical or suspicious with reactive or low-grade UC on a subsequent histology specimen. In our institution, the bladder barbotage

specimens are collected by urologists and processed in our laboratory following a standard protocol that has been in place for over 15 years.⁸ Briefly, vigorous irrigation of the bladder with 80 to 100 ml³ of sterile saline solution is performed during cystoscopy and the resultant fluid is then sent to the cytology laboratory, where the volume and gross appearance of the fluid are noted. The 50 to 100 ml³ of fluid are then centrifuged for 5 to 10 minutes at 2000 rpm, then fixed with 30 ml of CytoLyt solution (Hologic, Inc, Bedford, Mass), and recentrifuged for another 2 minutes at 2000 rpm. The resulting cell sediment is processed using a ThinPrep 3000 Processor (Hologic, Inc) and stained according to the Papanicolaou (Pap) method. On average, we receive 1600 UTC per year in our laboratory.

The residual cellular samples left over in the container after the preparation of the diagnostic ThinPrep slide were serially diluted with repetitive 2-fold dilutions in PreservCyt solution (Hologic, Inc) to achieve the desired cellularity. ThinPrep slides were prepared from each dilution using the ThinPrep 3000 Processor according to the abovementioned procedure. The slides were then reviewed by 1 of the authors (J.P.) to check for the presence of cellular material; acellular slides were discarded. The resulting 6 to 11 slides per case, together with the original diagnostic slide, for a total of 146 slides (85 from cases positive for UC, and 61 from control cases), were included in the study. The slides were deidentified, assigned a study number, and placed in a random order into trays of 20 slides that were circulated among 5 observers. The 5 observers participating in the study were a cytotechnologist, a cytopathology fellow, and 3 board-certified cytopathologists with 10 to 20 years of experience and interest in UTC. The observers were only informed of the age, sex, and medical history of the patient, but not of the exact design of the study or of the composition of the cases entered into the study. Each slide was diagnosed independently as negative for HGUC, AUC, suspicious for HGUC, or positive for HGUC. All diagnoses were entered into a spreadsheet. Slides that had the same diagnosis rendered by ≥ 3 observers were considered diagnostically concordant. Slides with discordant diagnoses were reviewed around a multiheaded microscope to achieve a consensus diagnosis.

In each slide, 1 observer counted the number of urothelial cells (excluding nonurothelial cells such as inflammatory cells and squamous cells) in 10 consecutive nonadjacent 40 \times objective high-power fields (hpf) on an Olympus BX40 microscope (Olympus America, Center Valley, Pa) with 10 \times /FN22 ocular. Counting was done along the horizontal diameter of the ThinPrep preparation, including the center of the slide, and the cell counts were averaged per 10 hpf. The formula used for calculating the cellularity of the whole preparation was $n \times 1322$, where n represents the average cell count per hpf and 1322 represents the number of hpf per 20-mm diameter ThinPrep slide for a FN22 ocular/40 \times objective.^{9,10} For cases with <10 cells per 10 hpf, the cell count was extended to 40 hpf over the entire

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