INTRODUCTION

Tumors arising from the urothelium may exfoliate readily into the urinary stream. Voided urine, therefore, is potentially representative of the entire urinary tract and thus useful in the detection of tumors of the bladder, kidneys, ureters, or urethra. Specimens from particular anatomic sites may also be obtained through instrumentation (i.e., catheterization, brushings, and washings).

Urine cytology samples represent a significant percentage of the daily non-gynecologic case volume. Sometimes, it remains one of the challenging specimens to be interpreted due to delayed processing, suboptimal preservation, inadequate cellularity, nuclear degeneration, as well as unrealistic expectations for the cytological diagnosis of LGUN, which is the most prevalent neoplasms visualized by urologists during cystoscopy procedure. Historically, there was significant interobserver variability, a lack of standardized definitions, definitive criteria, and universal acceptance of the existed urine cytology classification systems.\(^\text{[1]}\)
In view of the wide-ranging diagnosis of hematuria (gross as well as microscopic), urine cytology is considered to be the initial diagnostic study in routine practice. Hematuria is caused by several benign conditions. Hence, this screening procedure is crucial for patients at higher hazard for bladder cancer (senior smoker males and vocational exposure). Urologists rely on cytology for a routine radiographic and endoscopic urinary tract evaluation to ensure that the malignancy is detected. At present, urinary cytology is the most common test used in detecting and monitoring urothelial carcinoma. The urine cytology reading accuracy depends on the specimen type, clinical condition, and tumor configuration.

Seven diagnostic categories were proposed by TPS in 2013, first, for patients with non-diagnostic specimens. The unsatisfactory group is followed by, negative for high-grade urothelial carcinoma (NHGUC), atypical urothelial cells (AUC), suspected of having high-grade urothelial carcinoma (SHGUC), high-grade urothelial carcinoma (HGUC), low-grade urothelial neoplasm (LGUN), and other primary and secondary malignancies. According to strict criteria, these entities are well defined with association to a known risk of malignancy and clinical consequences. The previously listed standards lead to improved diagnostic sensitivity and specificity HGUC.

TPS does not aim only to define morphological standards for different categories of cytopathology on urinary tracts but also standardize the reportable system so that it is acceptable universally and globally.

As for the morphological criteria established by TPS, they were based on studies conducted using ThinPrep and SurePath methods. However, participants responses from the latest published CAP questionnaire showed that the cytospin method is used to assess urine cytology as second in ranking following ThinPrep. Therefore, the cytospin preparation needs to be assessed and validated for the applicability of morphological standards indicated in the TPS.

**MATERIALS AND METHODS**

After obtaining institutional approval from unit of biomedical ethics – research committee, electronic archives at King Abdulaziz University Hospital were searched from 2015 through 2020 for all urine specimens. These specimens included voided (i.e., non-catheterized) urine, bladder washings, catheterized urine, ureteral washings, renal pelvis washings, and/or renal cyst fluids. On processing level, the specimen was poured into a labeled tube to be centrifuged by Thermo Scientific™ centrifuge at 2000 rpm for 5 min. The resulted button was prepared by cytospin using Epredia™ Single Cytofunnel™ with white filter cards. Following slides were stained with the Papanicolaou method. All cases were reviewed board certified cytopathologists using TPS criteria.

To achieve analytical characterization, surgical histological diagnosis has been considered the gold standard with which diagnostic cytopathological urine samples were compared. In addition, test performance statistics (i.e., sensitivity, specificity, accuracy, and positive and negative predictive values) were calculated. Furthermore, Chi-square test was used to compared variables. $P < 0.05$ was considered statistically significant.

**RESULTS**

Out of 1371 obtained urine samples, 316 (23%) had a concurrent or subsequent surgical pathology specimen. The mean age of all patients was 62 years. As of patients for whom a surgical specimen was available, their mean age was 63 years. Of the 316 cases for which histologic specimens were available, 256 were male (81.3%) and 60 were female (19%). In the present study, reclassifying urine cytology specimens according to the TPS criteria yielded the following diagnoses in ascending order: 101 AUC (32%), 95 NEG (30%), 59 HGUC (18.7%), 31 SHGUC (9.8%), and 30 (9.5%) others. There are 263 concordant (86.8%) and 40 discordant cases (13.2%), resulting from the association of cytology review with the original histomorphological diagnosis. Examples on cyto-histo correlation are depicted in [Figures 1-6]. The non-diagnostic cytology samples were excluded from the calculation. Cytology cases were tabulated as follows: Benign (NHGUC), atypical (AUC), low-grade neoplasm (LGUN), and high-grade malignancy (SHGUC, HGUC, metastasis, and other primary malignancies). Histology diagnosis of benign cases was rendered as false positive for the lesional entities on cytology. The overall sensitivity, specificity, and accuracy of urine cytology cytospin in the present study were 94.7%, 73.9%, and 86.8%, respectively. The positive predictive value

![Figure 1: Pleomorphic and hyperchromatic urothelial cells exhibiting >0.7 N:C with background hematuria (×40).](image-url)
was 85.6% and negative predictive value was 89.5% [Table 1]. It is evident from the Chi-square table that there is a statistically important relationship at the standard of significance 0.05% for TPS and histomorphological diagnosis [Table 2].

**DISCUSSION**

TPS classification is based on liquid base preparation as it is the most used method in daily cytology practice because it delivers optimal morphological details besides filtering all the non-desirable debris.[6] However; a considerable number of laboratories have maintained the conventional cytospin technique according to the College of American Pathologists Survey.[5] In this study, we demonstrated the performance characteristics of the second most popular type of preparation in urine cytology.

Gray zone (AUC) cases are one of the most complex cases encountered in daily practice. All ancillary data are put together to approach the full picture of the puzzle. Type of urine sample, endoscopic finding, and clinical information along with radiological images should be available with every case. Any mass lesion observation in the above input is considered to be a red flag. On the other hand, non-neoplastic scenarios such as urinary tract infection and stone-related cases are treated with low threshold. Grungy background and high cellularity seen in the first glance promotes a careful analysis. If a corresponding biopsy is present, cytospin correlation is conducted. Requesting to repeat the cytospin and optimizing stains quality helps in some cases to clear the
fine details. In addition, ×60 objective is used to magnify the nuclear membrane irregularity and chromatin appearance as well. The algorithmic approach to atypical urine specimens is summarized in [Figure 7].

Goutas et al. concluded that there are no comparable statistical differences in sensitivity and specificity for cytospin versus ThinPrep when TPS standards were applied. It was found that the analytical parameters of the cytospin method were 76.9% and 80%, for sensitivity and specificity, respectively. In addition, positive predictive value was 90.9% and negative predictive value was 57%. The overall accuracy was 79.8%. Our values show similar percentages to their identified concordant and discordant cases as well as other analytical parameters, except from sensitivity and negative predictive value, which are significantly lower than what we calculated.

The Paris Working Committee concluded at their first meeting that TPS has a high sensitivity to HGUC.[3]

- **Table 1:** Cytohistopathology correlation of all cases.

| Type of cases          | Number of cases | Cytology diagnosis (PARIS) | Concordant histology | Discordant histology |
|------------------------|-----------------|---------------------------|----------------------|----------------------|
| Benign                 | 95              | 85 (TN)                   | 10 (FN)              |
| Atypical               | 101             | 73 (TP)                   | 28 (FP)              |
| Low-grade neoplasm     | 13              | 13 (TP)                   | 0 (FP)               |
| Malignant, high grade  | 94              | 92 (TP)                   | 2 (FP)               |
| Total                  | 303             | 263                       | 40                   |

- **Table 2:** Correlation between TPS and histomorphological diagnosis.

| Chi-square tests       | Value      | Df  | Asymptotic significance (two sided) |
|------------------------|------------|-----|-----------------------------------|
| Pearson Chi-square     | 531.640*   | 132 | 0.000                             |
| Likelihood ratio       | 283.594    | 132 | 0.000                             |
| No. of valid cases     | 315        |     |                                   |

*149 cells (92.5%) have expected count <5. The minimum expected count is 5. TPS: The Paris System

**Figure 6:** Subsequent biopsy showed HGUC of the bladder (×20). HGUC: High-grade urothelial carcinoma.

**Figure 7:** An algorithmic approach to atypical looking urine specimens.
Likewise, Straccia et al. and Richardson et al. have shown that TPS criteria can be successfully applied in laboratories processing cytospin and ThinPrep preparations because the HGUC cytomorphology appears similar in both techniques with no differences in sensitivity or specificity.[8,9] In parallel, our observations yielded a 97.9% concordant cytohistology in high-grade malignancy group. The cytological diagnosis of HGUC or SHGUC, regardless of cystoscopy findings, should be thoroughly investigated and closely followed. It is critical to have dual communications between urologists and cytologists to optimize the clinical outcome.[10-13]

CONCLUSION
Urine cytology evaluation is a non-invasive and cost-effective method for urothelial carcinoma detection. TPS has been designed to improve urine cytology diagnostic accuracy and standardize reporting terms. In this study, we demonstrated that TPS criteria are applicable on cytohistology.

COMPETING INTEREST STATEMENT BY ALL AUTHORS
No potential competing interest was reported by all authors.

AUTHORSHIP STATEMENT BY ALL AUTHORS
All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the CytoJournal.

ETHICS STATEMENT BY ALL AUTHORS
This study was approved by the Committee of Biomedical Ethics at King AbdulAziz University, Jeddah, KSA (No. 392-21). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

LIST OF ABBREVIATIONS (IN ALPHABETIC ORDER)
AUC - Atypical urothelial cells
HGUC - High-grade urothelial carcinoma
LGUN - Low-grade urothelial neoplasm
NHGUC - Negative for high-grade urothelial carcinoma
SHGUC - Suspected of having high-grade urothelial carcinoma
TPS - The Paris system.

EDITORIAL/PEERREVIEW STATEMENT
To ensure the integrity and highest quality of cytojournal publications, the review process of this manuscript was conducted under a double-blind model (authors are blinded for reviewers and vice versa) through automatic online system.

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