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ORIGINAL ARTICLE

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Cyto-histo correlation and false-negative urine: Before and after the Paris system for reporting urinary cytology

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Abstract

Background: The impact of implementing the Paris system (TPS) on the rate of discrepant cases in the negative for high-grade urothelial carcinoma (NHGUC) category that had a subsequent diagnosis of high-grade urothelial carcinoma (HGUC) on histology is not well studied.

Methods: We adopted TPS in May 2019. We searched discrepant cases with negative urine cytology 2017–2019 in our cyto-histo correlation database. The urine cytology and follow-up biopsy/resection were reviewed by a cytopathologist who also did Genitourinary (GU) Pathology subspecialty sign-out. Voided urine and instrumented urine were included in this study.

Results: There were total of 70 discrepant cases with negative cytology interpretation but HGUC on the subsequent biopsy or resected specimen. Following the TPS criteria, the rate of discrepant negative cytology cases increased from 6 cases between January 2017 and May 2019 to 64 cases after May 2019 when we adopted TPS. There were 2 discrepant negative cases in 2017, 3 cases in 2018, and 65 cases in 2019. Out of 65 cases in 2019, 64 cases were identified after May 2019. Additional 55 urine cytology slides were reviewed according to the TPS criteria, of which, the diagnoses remained unchanged in 45 (82%) cases and 10 (19%) cases were reassigned to either atypical or suspicious categories. The discrepancy was noted more on the instrumented urine and the upper tract urine. However, the false-negative rate rose faster in voided urine and lower tract urine. The risk of HGUC with the category of NHGUC was 0.03% in 2017, 0.05% in 2018, and 1.06% in 2019 at our institution. The increase in false-negative rate could not be attributed to a single cytopathologist.

Conclusion: After adopting TPS for reporting urine cytology, there was an increase in HGUC from negative urine cytology which was subsequently confirmed on histology as cases of HGUC. The quality control of negative urines could be important monitoring the process when implementing TPS.

KEYWORDS
cyto-histo correlation, false-negative case, false-negative urine, the Paris system for reporting urinary cytology, TPS

1 | INTRODUCTION

Urinary cytology is currently the most common technique used for screening and monitoring urothelial carcinoma. It is non-invasive and cost effective when compared to other modalities. The Paris system (TPS) for reporting urinary cytology provides standardized cytomorphologic criteria and diagnostic categories. Uniform reporting facilitates in patient stratification and the subsequent clinical management. The principle objective of TPS was to reliably diagnose high-grade urothelial carcinoma (HGUC).[1]

TPS proposes the following diagnostic categories: (1) unsatisfactory/nondiagnostic; (2) negative for HGUC; (3) atypical urothelial cells (AUC); (4) low-grade urothelial neoplasia; (5) suspicious for HGUC; (6) positive for HGUC; and (7) positive for other primary and metastatic malignancies. This reporting system has been adopted worldwide. Multiple studies have been published exploring the advantages and disadvantages of the system since its implementation. TPS seems to have reduced indeterminate diagnosis and improved sensitivity of urine cytology reporting[2]. TPS was implemented in our institution in May 2019. The aim of the study was to evaluate the impact of implementing TPS on the rate of discrepant cases in the negative for high-grade urothelial carcinoma (NHGUC) category that had a subsequent diagnosis of high-grade urothelial carcinoma (HGUC) on histology.

2 | MATERIALS AND METHODS

We adopted TPS in May 2019. We searched discrepant cases with negative urine cytology from 2017 to December 2019 in our cyto-histo correlation database (all cases in this database were reviewed by different cytotechnologists, fellows, and cytopathologists; a subset were presented at intradepartmental consensus meetings if significant deviation found). The urine cytology and follow-up biopsy/resection were then re-reviewed by a cytopathologist who also did Genitourinary (GU) Pathology subspecialty sign-out. ThinPrep was used for urine cytologic preparation at our institution. The interval between the urine cytology specimens and the subsequent biopsy or excision was generally within half a year, on average 1–3 months. Due to TPS is designed for the diagnosis of high-grade urothelial carcinoma and the known limitations in the diagnosis of other types of urothelial neoplasms and other carcinomas, we excluded cases with the following final diagnoses on surgical pathology: urothelial proliferation with uncertain malignant potential, low-grade urothelial carcinoma, low-grade urothelial carcinoma with focal high-grade features, small cell carcinoma, prostatic adenocarcinoma, metastatic carcinoma, and any cases with suspicious but not definitive diagnoses. We included all specimen types: voided urine and instrumented urine including bladder wash, ureter wash, ureter brushing, and other types of instrumented urine. We also investigated whether a single cytopathologist or a few outliers were responsible for the increase in the false-negative rate by tracing back the staff who signed out the individual discrepant cases. Of note, we had 21 practicing cytopathologist during our study period. We received 7791, 7806, and 7699 urine cytology cases in 2017, 2018, and 2019, respectively; including 6026 (in 2017), 6188 (in 2018), and 6342 (in 2019) cases signed out as NHGUC.

The diagnostic criteria for AUC under TPS: (1) Major criterion (required): Non superficial and nondegenerated urothelial cells with an increased N/C ratio (>0.5). (2) Minor criteria (one required): nuclear hyperchromasia, irregular nuclear membranes, irregular, coarse, and clumped chromatin.

The diagnostic criteria for HGUC under TPS: (1) Cellularity; at least 5–10 abnormal cells. (2) N/C ratio: 0.7 or greater. (3) Nucleus: moderate-to-severe hyperchromasia. (4) Nuclear membrane: markedly irregular. (5) Chromatin: coarse/clumped.

3 | RESULTS

A total of 70 discrepant cases with negative cytology interpretation but high-grade urothelial carcinoma on subsequent biopsy or resection were identified. After adopting TPS for reporting urinary cytology, the rate of discrepant negative cases increased: 6 cases January 2017–May 2019 to 64 cases after May 2019 when we adopted TPS. We had 2 discrepant negative cases in 2017, 3 discrepant cases in 2018, but 65 cases in 2019, of which 64 were after May 2019 (Figure 1).

A total of 55 available urine cytology slides were re-reviewed based on the TPS criteria, and the diagnoses remained unchanged in 45 (82%) cases according to the TPS criteria. 10 (19%) cases were reassigned to the atypical categories; of which, one case was before May 2019. Example discrepant cases that were reassigned to the atypical categories are demonstrated in Figure 2. One of the cases being illustrated in Figure 2 was before TPS (Figure 2A), the rest were after TPS (Figure 2B–D), they are representative of the findings seen in the bulk of the discrepant cases. Per TPS, an increased N/C ratio (>0.5) in nonsuperficial and nondegenerated urothelial cells is a major and required criterion, which is challenging to evaluate in the illustrated cases. Figure 2 A shows a binucleated hyperchromatic cell with coarse chromatin, nuclear groove, and small nucleoli; however, it was a bladder wash, it might be difficult to identify rare diagnostic cells in a very cellular specimen and assessment for n/c ratio in a binucleated cell is difficult. Figure 2B shows a group of urothelial cells with higher n/c ratio and enlarged nuclei but they were not well-preserved. Figure 2C is again an instrumented urine, these groups of urothelial cells are small but with seemingly high n/c ratio and focal hyperchromasia, somehow resembling of hyperchromatic crowded groups (HCG) in cervical cytology. However, the n/c ratio is difficult to evaluate in a tight group. Figure 2D shows very large glandular appearing cells, with small nucleoli and possible cell in cell morphology; however, they do not show hyperchromasia, irregular nuclear contours, or coarse chromatin, n/c ratio is likely increased but difficult to assess due to 3D configuration, possible binucleation, or cell in cell morphology.

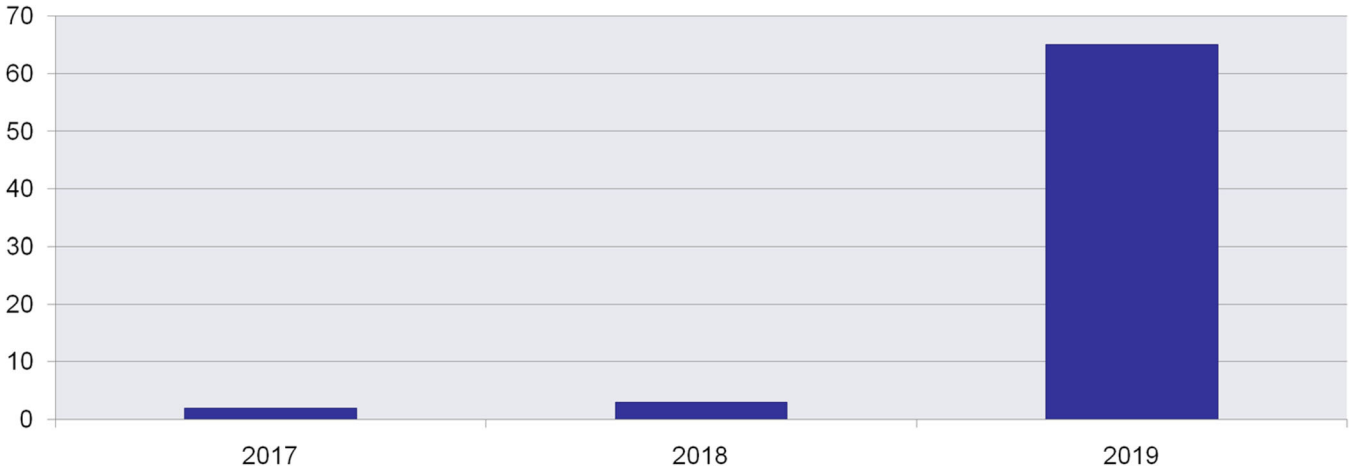

FIGURE 1 After adopting TPS, the rate of discrepant negative cases increased. Two discrepant negative cases in 2017, 3 discrepant cases in 2018, but 65 cases in 2019, of which 64 were after May 2019 [Color figure can be viewed at wileyonlinelibrary.com]

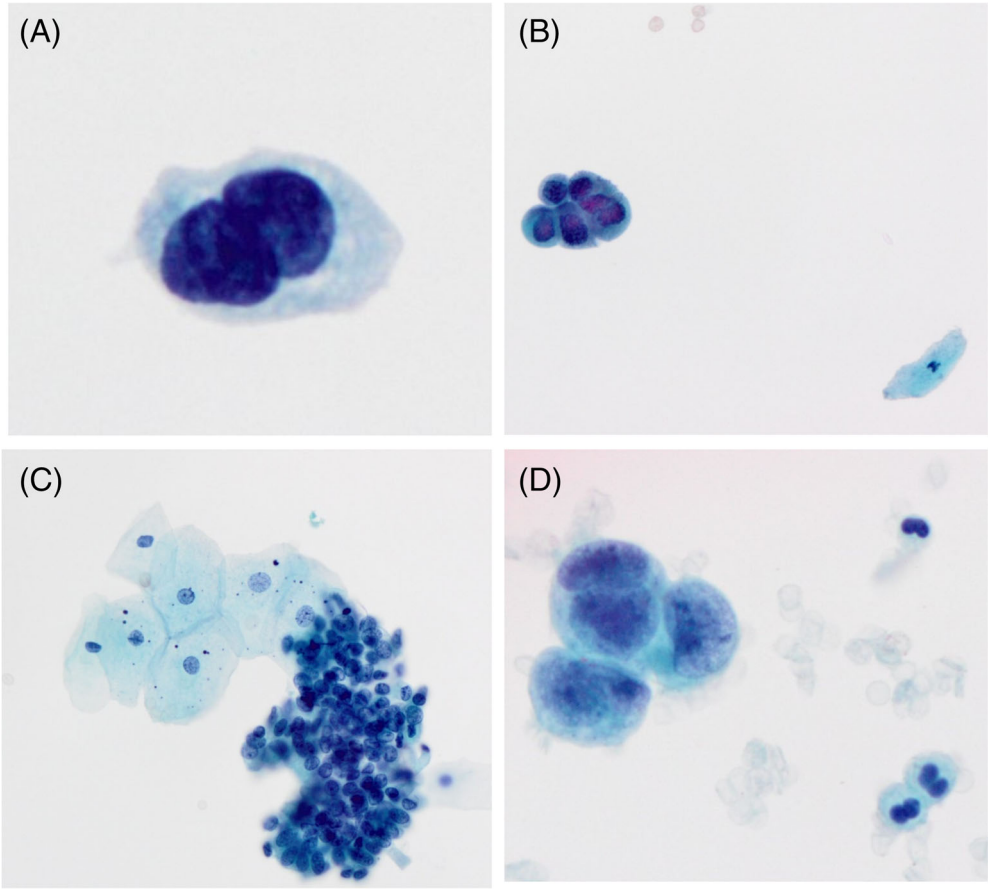

FIGURE 2 Representative discrepant cases. A: Bladder wash. Initial cytology diagnosis: NHGUC. Re-review: AUC. Follow-up biopsy: Flat CIS. B: Voided urine. Initial cytology diagnosis: NHGUC. Re-review: AUC. Transurethral resection: Non-invasive papillary urothelial carcinoma, high grade. C: Instrumented urine. Initial cytology diagnosis: NHGUC. Re-review: AUC. Follow-up resection: Non-invasive papillary urothelial carcinoma, high grade. D: Voided urine. Initial cytology diagnosis: NHGUC. Re-review: AUC. Follow-up resection: Invasive papillary urothelial carcinoma, high grade. The initial cytology diagnosis is how the case was signed out initially. Figure 2A was before TPS era, Figure 2B–D was after TPS era [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 The rate of negative, atypical, suspicious, and malignant diagnosis at our institution for urine cytology cases 2017–2019

Urine	Negative	AUC	Suspicious for HGUC	HGUC
2017	6026 (77.3%)	1464 (18.8%)	149 (1.9)	152 (2.0%)
2018	6188 (78.4%)	1536 (19.7%)	29 (0.4%)	121 (1.6%)
2019	6342 (82.4%)	1101 (14.3%)	136 (1.8%)	117 (1.5%)

TABLE 2 The false negative rate of void urine versus instrumented urine 2017–2019

Urine	Voided	False-negative rate	Instrumented	False-negative rate
2017	7089	2 (0.028%)	702	0 (0)
2018	7144	1 (0.014%)	662	2 (0.3%)
2019	7176	50 (0.7%)	523	17 (3.3%)

Note: The study institution switched to the TPS in May 2019, only one discrepant case identified January–April 2019.

TABLE 3 The false negative rate of upper tract urine versus lower tract urine 2017–2019

Urine	Upper tract	False-negative rate	Lower tract	False-negative rate
2017	221	0	7570	2 (0.03%)
2018	168	1 (0.6%)	7638	2 (0.03%)
2019	185	1 (0.5%)	7514	17 (0.23%)

Note: The study institution switched to the TPS in May 2019, only one discrepant case identified January–April 2019.

TABLE 4 The risk of high-grade urothelial carcinoma with the category of NHGUC 2017-2019

Urine	Negative	False-negative cases	Risk of HGUC with the category of NHGUC
2017	6026	2	0.03%
2018	6188	3	0.05%
2019	6342	67	1.06%

Note: The study institution switched to the TPS in May 2019, only one discrepant case identified January–April 2019.

The rate of negative, atypical, suspicious, and malignant diagnosis at our institution for urine cytology cases during the years of the study is shown in Table 1, indicating an increase in negative diagnoses was at the expense of the atypical category. The discrepancy was noted more on the instrumented urine (2018 vs. 2019). However, the false-negative rate rose faster in voided urine (50 times) than instrumented urine (11 times) (Table 2). Similarly, the discrepancy was noted more on the upper tract urine. However, the false-negative rate rose faster in lower tract urine (9 times) than upper tract urine (essentially no change) (Table 3). The risk of HGUC with the category of NHGUC was 0.03% in 2017, 0.05% in 2018, and 1.06% in 2019 at our institution (Table 4). The risk of HGUC with the category of NHGUC increased 20–30 times after implementation of TPS; although the risk is still small.

No single cytopathologist was found to be responsible for the increase in the false negative rate (Figure 3A). A total of 4 cytopathologist had discrepant negative cases before and after the implementation of TPS, while the rest 17 cytopathologists only had discrepant negative cases afterwards (Figure 3B). Analysis of the other discrepant cases with negative cytology interpretation but neoplasm or carcinoma other than HGUC, low-grade urothelial carcinoma, or urothelial proliferations on subsequent histology revealed one small cell carcinoma (bladder), four prostatic adenocarcinoma, one renal clear cell carcinoma, and one metastatic adenocarcinoma (upper GI/pancreaticobiliary tract) within the study period.

4 | DISCUSSION

Urinary cytology was proposed by Papanicolaou and Marshall as a clinically useful method with which to diagnose urothelial cancer in 1945.[3] Voided urine specimens generally are used in the clinical setting of hematuria and persistent irritative voiding symptoms, whereas washing specimens, in conjunction with cystoscopy, are more commonly used in patients with a history of urothelial carcinoma. Urinary cytology in general has a higher sensitivity for the diagnosis of HGUC, which is especially useful for flat carcinomas that may be cystoscopically occult.

In 2016, TPS for reporting urinary cytology was created as an international effort to standardize urine cytology.[1,4] By placing the main emphasis on the detection of HGUC, the implementation of TPS has led to a reduction in the rate of indeterminate diagnoses and to an increase in the number of positive cases.[5–8] It has shown better concordance with follow-up histology, and thus improves the overall performance and accuracy of urinary cytology.[9] However, because urinary cytology is used primarily for screening purposes, it needs to have a high sensitivity and good negative predictive value (NPV) to be an effective test. We therefore performed a 3-year retrospective study and found that the rate of false-negative urine had increased after the implementation of TPS at our institution. Our false-negative rate was low at the rate of approximately two to three cases per year before the implementation of TPS but reached to 64 cases in the 8-month period right afterwards. These findings suggest that after

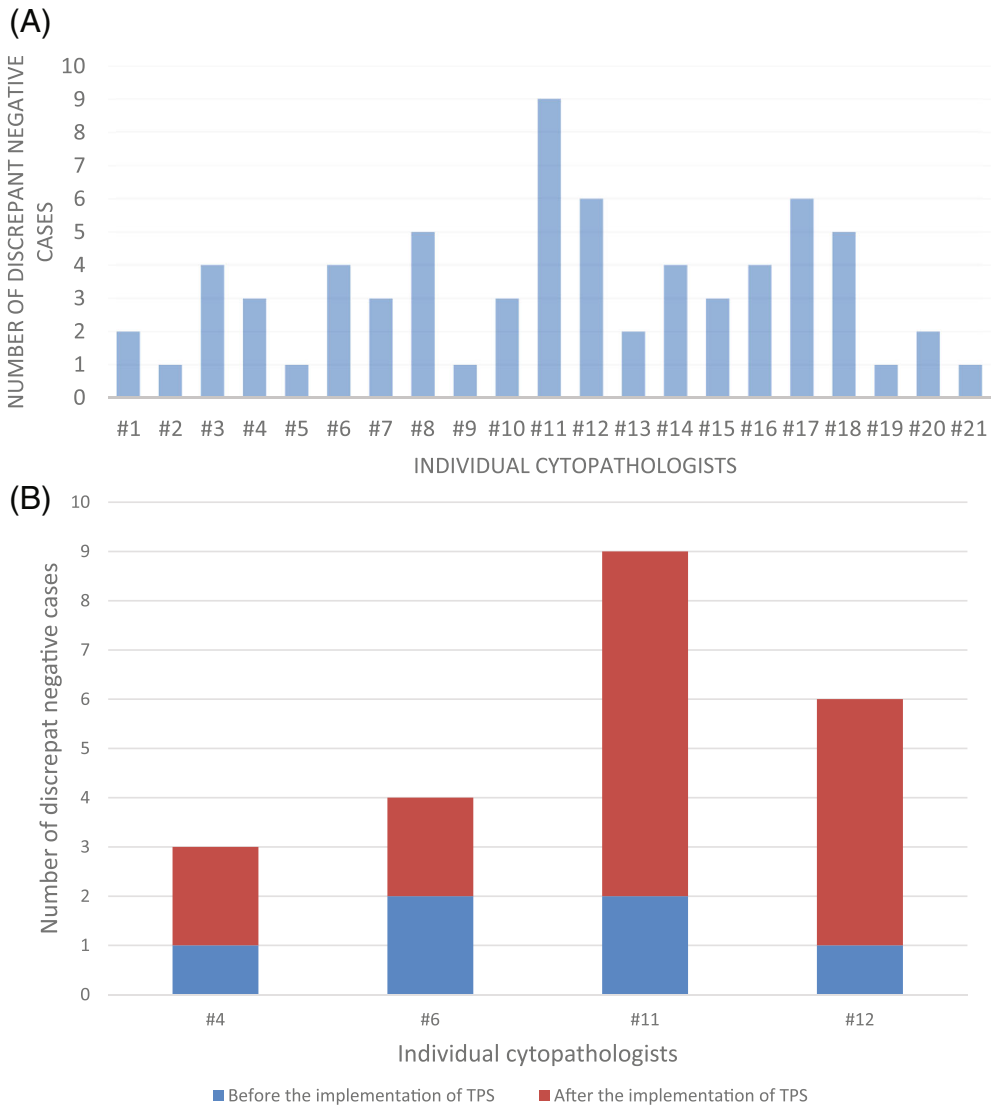

FIGURE 3 A. No single cytopathologist was found to be responsible for the increase in the false-negative rate. B. Four cytopathologist had discrepant negative cases before and after the implementation of TPS, they had 6 discrepant negative cases in total before TPS (2- and 1/4-year period) and 16 discrepant negative cases in total after TPS (8-month period). Pathologist #4, #6, #11, and #12 had 1, 2, 2, and 1 discrepant cases before TPS and 2, 2, 7, and 5 discrepant cases after TPS, respectively [Color figure can be viewed at wileyonlinelibrary.com]

implementing TPS at our institution, a subset of cases with "atypical" features, including somewhat worrisome for an underlying malignancy, were lumped into NHGUC category. On re-review, by applying strict TPS criteria, a small portion (19%) of these discrepant cases was reassigned to the atypical category while the majority was unchanged (82%).

Zare et al. reported that applying TPS guidelines increased the number of NHGUC diagnoses.[10] However, the authors argued that this finding reflected all the cases with benign/reactive features, as well as all entities with cytologic changes that are not concerning for HGUC were now being classified in the NHGUC category according to the TPS. The authors concluded TPS showed slightly better sensitivity (72.5% and 74.5%) and NPV (87% vs. 90%), and thus classifying more cases as NHGUC by TPS had not raised concern about the sensitivity of urinary cytology. However, this overall slightly improved sensitivity and NPV might be resulted from the better performance of other categories.

Stanzione et al. performed a retrospective study of 381 cases to evaluate the diagnostic accuracy of urine cytology after implementation of TPS. Their analysis showed a significant increase in urine cytology specificity (12.5–95.9% and 100% in 2016 and 2017, respectively) and PPV (83.5% to 96.4% and 100% in 2016 and 2017, respectively) after switching to TPS. Whereas, the sensitivity and NPV gradually decreased, which is consistent with our findings.[11] In their study, the sensitivity was 100% before TPS, this dropped to 87.1% in 2016 and 81.7% in 2017, respectively, after TPS. Similarly, NPV was 100% before TPS, this dropped to 85.4% in 2016 and 81.4% in 2017, respectively, after TPS. Notably, the recent study published by Paula R. et al found the overall negative predictive value of TPS for urinary cytology was 88.2%; risk of malignancy (ROM) was 11.1% for the category of "negative for HGUC".[12] Rohilla et al. similarly reported the risk of HGUC with the category of negative for HGUC was 11.6%.[13] These results indicated roughly 1 in 10 negative urines will be proven to have HGUC on subsequent specimens. Our results indicate the risk of HGUC with the category of NHGUC was 1.1% in 2019 at our institution. However, we only followed patients for 0–6 months (average 1–3 months) and only patients who had a positive biopsy at our institution during that time frame were included in this study.

It's worth mentioning that the overall sensitivity for urine cytology is low in the literature, with various studies reporting values rarely >80%.[11-14] Although all patients with gross hematuria should undergo cystoscopy, upper tract imaging, and urinary cytology; it is no longer recommended to use urine cytology in the initial evaluation of patients with microscopic hematuria unless the patient has risk factors for carcinoma in situ. An article by Lee et al.[15] discussed causes of false-negative for high-grade urothelial carcinoma in urine cytology. They found that the 19 cases with confirmed HGUC was characterized by eight cases with paucity of candidate tumor cells, four cases with poor preservation, and six cases with obscuring inflammation/blood, and one case with interpretation error, with many cases have overlapping features. However, these are frequent issues with urine cytology, which could not explain the increase of false-negative rate after implementing the TPS at our institution.

We observed no difference among 21 cytopathologists with different levels of experience. The vast majority of our cytopathologists was cytopathology fellowship trained. No single cytopathologist was found to be responsible for the increase in the false-negative rate. Except for four cytopathologists, all others only had discrepant negative cases after TPS. The four cytopathologists who had discrepant negative cases before and after TPS also showed an upward trend after TPS (almost 3 times more discrepant negative cases during the 8-month period after TPS comparing to 2- and 1/4-year period before TPS). Although we did not study the interobserver variability among our cytopathologists, Paris Interobserver Reproducibility Study (PIRST) showed diagnostic categories with the best agreement was NHGUC (71%), followed by low-grade urothelial neoplasm (62%) and HGUC (57%), while practice type (academics versus non-academic) was not major factors in concordance.[16] It was noticed there was a notable interobserver variability for evaluation of N/C ratio,[5] this is intrinsic to TPS and may not be easily overcome. Although previous data supports a N/C ratio cutoff value of 0.5 for atypical urothelial cells, the area under the curve (AUC) in this study was 79%,[17] a value that is not optimal as an AUC of 0.5 corresponds to a model that is not better than random and an area of 1 corresponds to perfect predictions. Zhang et al reported that morphologists tend to overestimate the nuclear-to-cytoplasmic ratio especially for images with an N/C ratio of 0.4 and 0.6 (> 40.0%); however, the majority of our negative discrepant cases was felt not meeting the diagnostic criteria of N/C ratio of 0.5 for AUC under re-review.[18] Similarly, Layfield et al.[19] reported that in the critical range, N/C ratio of 0.5 to 0.7, interobserver correlation (75%), and correlation with true N/C ratio (53%) may be insufficiently accurate for precise category assignment in TPS.

One limitation of this study was although the cytology re-review was blinded to the histologic diagnosis. The case series were composed of negative discrepant cases after histo-cyto correlation; therefore, we knew the cases were upgraded on histology and correspondingly some of the upgrade from NHGUC form AUC could be due to retrospective review bias. However, only a small portion of cases (19%) have been upgraded after re-review, the majority of cases were not reassigned to a different category, reflecting the issue could be intrinsic to TPS. Per TPS, an increased N/C ratio (>0.5) in non-superficial and non-degenerated urothelial cells is a major and required criteria, which presents the most challenges when we re-reviewed the discrepant cases (illustrated in Figure 2). Another limitation is that only cases with follow-up surgical pathology were included in the study, the clinical suspicion might be higher in this subset of cases. The results may have been affected by the study's limitations. Thirdly, an increase in negative diagnoses at the study institution was seemly at the expense of the atypical category rather than the suspicious/malignant category; one may argue that it is not significant as clinicians often treat atypical diagnoses as negative for patient management. However, we believe as patients will also be followed by urine cytology after surgery or other modalities of treatment, it is important that the false-negative rate is being kept low enough to avoid significant number of unexpected findings on the subsequent tests to ensure urine cytology continue to be trusted as an effective screening test. We suggest that in a case with higher pretest probability such as a urothelial cancer history, persistent symptoms/abnormal urine analysis despite treatment, abnormal findings on cystoscopy, or extensive degeneration, cases may be managed on a case-by-case basis especially when the n/c ratio is difficult to assess. Since it was reported that a history of UC and washing specimens had lower NPV,[20] it is prudent to pay extra attention in these clinical scenarios in an effort to increase the sensitivity and NPV after TPS.

In summary, adopting TPS for reporting urine cytology results in an increase in discrepant negative cases with the subsequent histologic diagnoses of HGUC at our institution. When implementing TPS, quality control of negative urines could be important monitoring the process. Abnormal cystoscopic findings may warrant histologic confirmation, as a negative urine cytology test cannot confidently eliminate the possibility of the presence of a high-grade urothelial carcinoma or the presence of a low-grade urothelial carcinoma or other types of carcinoma such as prostatic adenocarcinoma and metastatic carcinoma from elsewhere.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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