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Review Article

The Paris System for Reporting Urinary Cytology: An Updated Review

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Abstract

The Paris System for Reporting Urinary Cytology (TPS 1.0, published in 2016) is the first standardized, evidence-based reporting system established as an international reporting system for urine specimens after the International Congress of Cytology in Paris. Its primary purpose is to reduce the rate of unnecessary indeterminate diagnoses but maintain the excellent performance of urine cytology, in detecting high-grade urothelial carcinoma. The reporting system comprises six diagnostic categories, as well as each category's diagnostic criteria, estimated risk of malignancy, and management recommendations. After six years, TPS 2.0 was applied in 2022 upon the unfolding of new data. TPS 2.0 clarifies the diagnosis categories and updates the risk of malignancy in each category and developments of molecular tests. This review provides an updated summary of TPS 2.0. Some diagnostic pitfalls and molecular tests were also discussed.

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Introduction

For better communication between pathologists and urologists, the first edition of The Paris System for Reporting Urinary Cytology (TPSRUC, The Paris System [TPS] 1.0) was published in 2016 to standardize the reporting system.[1] After 5–6 years of practice based on the criteria of TPS 1.0 and prospective studies, the second edition (TPS 2.0) was published in 2022.[2,3] TPS highlights the need to focus on accurately identifying high-grade urothelial carcinoma (HGUC). After adopting TPS, there was an increase in false-negative rates and risk of malignancy (ROM) for negative for high-grade urothelial carcinoma (NHGUC).[4] Although the specificity and negative predictive value of TPS remains high (98.0–98.6% and 68.0–94.8%, respectively), the sensitivity and positive predictive value remain low (37.5–46.0% and 70.6–96.0%, respectively).[5,6]

TPS 2.0 comprises of six diagnostic categories: non-diagnostic, NHGUC, atypical urothelial cells (AUC), suspicious for high-grade urothelial carcinoma (SHGUC), HGUC, and other malignancies. Low-grade urothelial neoplasm (LGUN) was moved under the NHGUC category. An approach to diagnosis in urinary cytology was outlined in TPS 2.0 (Fig. 1).[2] Furthermore, three chapters were added in TPS 2.0: cytology of the upper urinary tract, risk of high-grade malignancies (ROHM), and the history of urine cytology: the long and winding road to Paris 2.0. The main goal of TPS was to lower the rates for indeterminate categories, particularly "atypia", and have the highest specificity and sensitivity for HGUC. In each chapter and diagnosis criteria, the further research direction was detailed, followed by sign-out samples, including formats and notes, making the clinical practice of urine cytology more uniform and efficient. Furthermore, TPS 2.0 further illustrates how to define the N/C ratio, which is almost the critical diagnostic criteria, and reduces the confusion after introducing TPS 1.0. The present study summarizes the updates for TPS 2.0, and the corresponding clinical practice.

Pathogenesis of urothelial carcinoma

Molecular pathways of the neoplastic transformation of urothelium

In TPS 2.0, the Cancer Genome Atlas was incorporated into the pathogenesis of low-grade (LG) and HGUC. A number of genomic alterations were identified in the pathogenesis of urothelial carcinoma (UC).[7–9] *FGFR* and *RAS* alterations were frequently identified in low-grade papillary carcinoma (LG-PUC), *FGFR* and *TP53* were frequently identified in HGUC,[10] and *TP53* and *RB* were frequently identified in carcinoma *in situ* (CIS). However, few genomic alterations were frequently identified in muscle invasive HGUC, such as the *RTK/RAS/PI3K* pathway (72%), *FGFR3* alterations, *ERBB2* enrichment, the histone modification pathway (89%), the *SWI/SNF* complex pathway (64%), and the *TP53/RB* pathway (93%).[11]

Adequacy of urine specimens

Adequacy criteria

- Any urine specimen with abnormalities (atypical, suspi-

Keywords: Urine cytopathology; Paris system; Diagnostic criteria; Risk of malignancy; Clinical management.
Abbreviations: AUC, atypical urothelial cells; HGUC, high-grade urothelial carcinoma; LGUN, low-grade urothelial neoplasm; ND/U, nondiagnostic/unsatisfactory; NHGUC, negative for high-grade urothelial carcinoma; SHGUC, suspicious for high-grade urothelial carcinoma; TPS, The Paris System for Reporting Urine Cytology.
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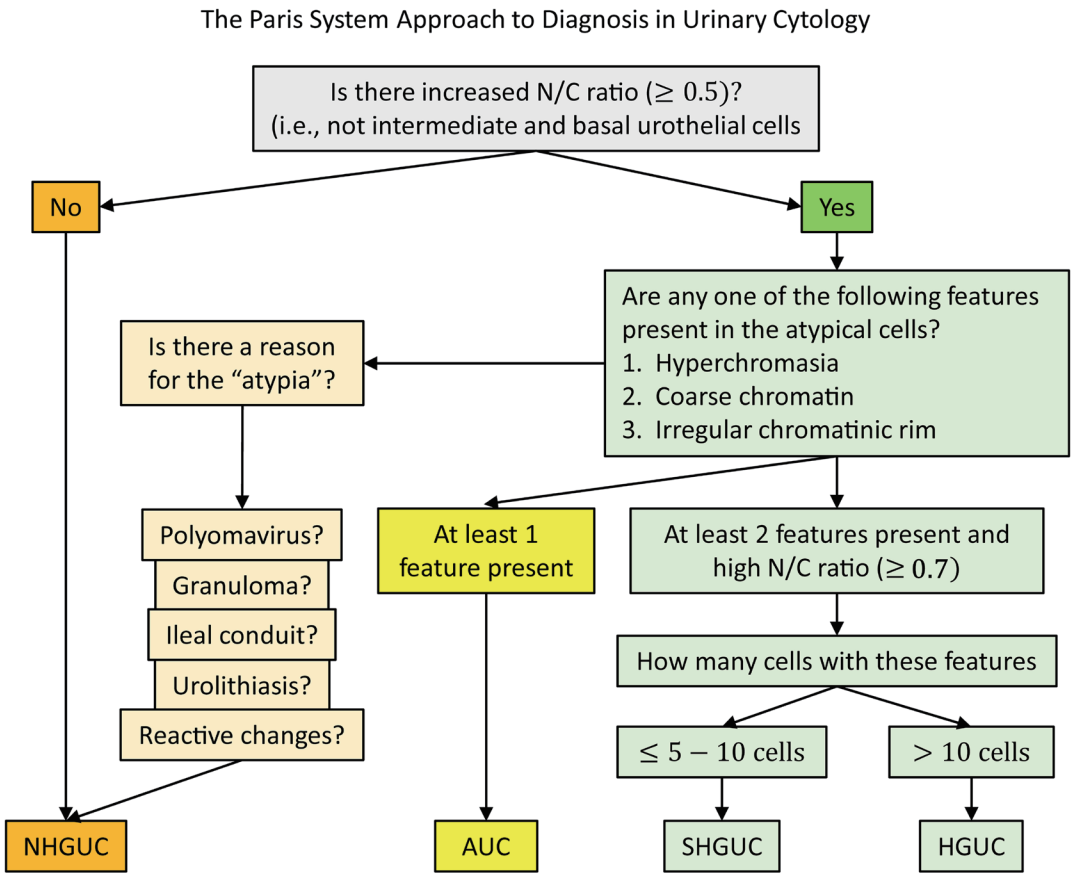

Fig. 1. Graphic algorithm of the Paris System for Reporting Urinary Cytology decision tree. TPS emphasizes the detection of HGUC. This snapshot conceptual flowchart illustrates the major points in the decision tree, including the evaluation of the N/C ratio, nuclear features, and cell quantity.[2]

cious, and positive for malignancy);
- Voided urine: >25–30 ml (25 ml with ThinPrep and 30 ml with SurePath preparation);[12]
- Instrumented urine urothelial cells: >20 cells/10 high-power fields (HPFs), satisfactory; 10–20 cells/10 HPFs, satisfactory but limited by low cellularity; <10 cells/10 HPFs, unsatisfactory/non-diagnostic.[13]

Unsatisfactory cases account for 0.3% of voided urine specimens.[6]

The less-than-optimal adequacy category[14]

Urine specimens that meet every adequacy criterion, except for urothelial cellularity, were assigned as "less-than-optimal" adequacy. It remains uncertain to assign such cases as adequate or non-diagnostic/unsatisfactory. More studies are needed.

Negative for high-grade urothelial carcinoma

A urinary specimen can be possibly categorized as NHGUC when it is adequate and lacks any cytomorphologic findings for HGUC. NHGUC cases accounted for 90.5% of voided urine specimens.[6]

Diagnostic criteria for NHGUC[15,16]

Benign urothelial cells

Benign urothelial cells were classified into superficial (umbrella), intermediate ("parabasal-like"), and deep (basal) urothelial cells. Superficial urothelial cells are large cells with one or multiple, large, centrally located round-to-oval nuclei, smooth nuclear membranes, abundant cytoplasm, cytoplasmic vacuoles for some cells, and low nuclear/cytoplasmic (N/C) ratios (<0.5) (Fig. 2a, b). Intermediate urothelial cells are intermediate in size, with round-oval nuclei, smooth nuclear membranes, and bland chromatin, but with less cytoplasm than superficial urothelial cells, and low N/C ratios (<0.5) (Fig. 2a). Deep urothelial cells are small cells with round nuclei, containing evenly distributed fine granular chromatin, scant cytoplasm, and high N/C ratios (Fig. 2b). Urothelial cells may present as single cells, in nests/sheets, or evenly in papillary-like fragments (especially in instrumented urinary specimens), without fibrovascular cores and cytologic atypia (Fig. 2c).

Squamous epithelial cells

Squamous cells are possibly from the urethra, squamous metaplasia, or contamination. The presence of benign squamous cells, including its parakeratotic or anucleate forms, is not specifically required for reporting (Fig. 2d).

Glandular cells

Glandular cells may be observed in urinary specimens, such as renal tubule cells observed in renal tubule casts (Fig. 3a), urachal remnants, endometriosis (Fig. 3b), cystitis cystica/glandularis (Fig. 3c), intestinal metaplasia, and prostatic cells with pigments (Fig. 3d). These would present as single cells

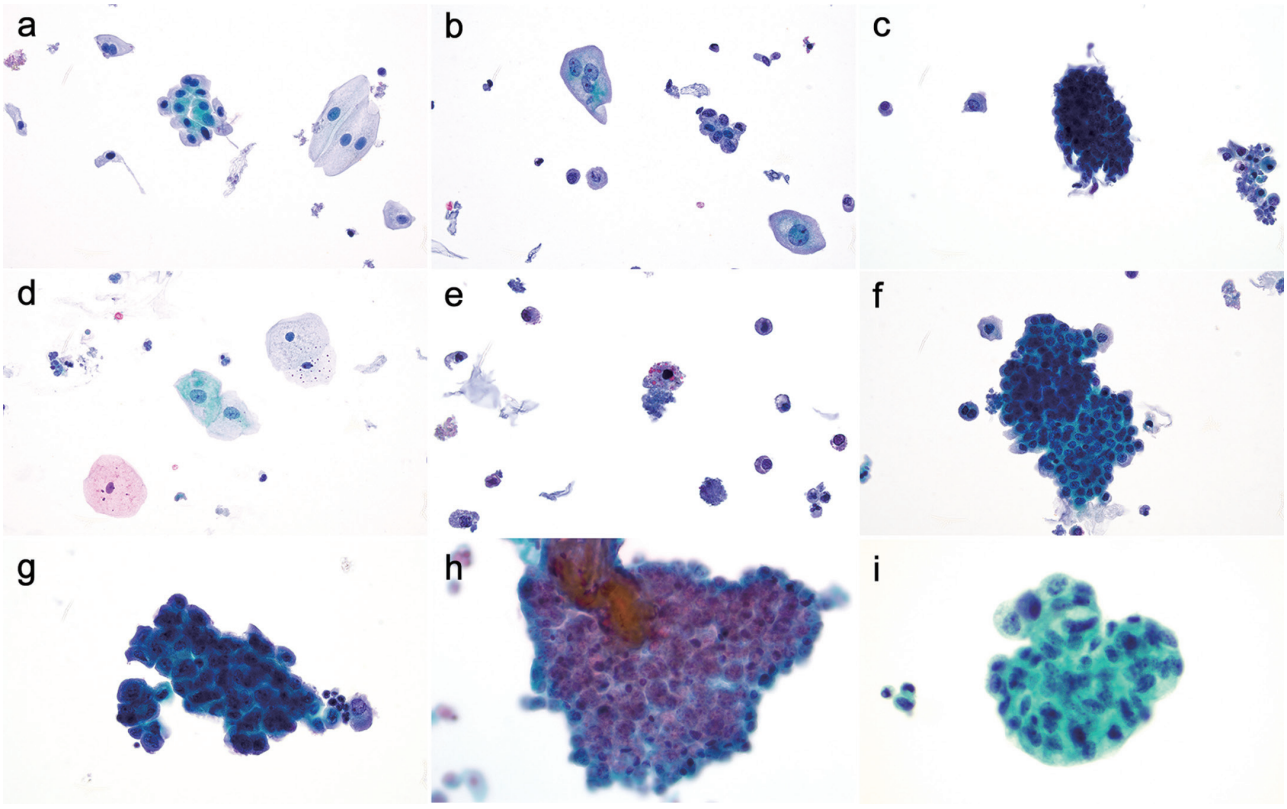

Fig. 2. Negative for high-grade urothelial carcinoma (NHGUC). Superficial urothelial (umbrella) cells have one or multiple nuclei with finely granular chromatin and conspicuous nucleoli, abundant cytoplasm, and low N/C ratios (a and b). For bladder washing specimens, urothelial cells may be arranged in papillary-like fragments without a fibrovascular core, but with small round or oval nuclei that contains finely granular chromatin, moderate cytoplasm, and low N/C ratios (<0.5) (c). Benign squamous cells are large polygonal cells with abundant dense cytoplasm, small round nuclei that contain finely granular chromatin or dark chromatin, and low N/C ratios (d). Degenerated urothelial cells present with shrunken (condensed), dark nuclei with mildly irregular nuclear borders, granular cytoplasm, and eosinophilic and/or cyanophilic intracytoplasmic inclusions (Melamed-Wolinska bodies) (e). Flat sheet of urothelial cells with low N/C ratios, scant-to-moderate cytoplasm, and small round nuclei that contain finely granular chromatin. Umbrella cells are present on the outer surface (f). Atypical urothelial tissue fragment (AUTF). Clusters of urothelial cells with nuclear overlapping: some had N/C ratios of ≥0.5, and slightly enlarged nuclei with nuclear membrane irregularity and finely granular chromatin (g). Low-grade papillary urothelial carcinoma. Three-dimensional clusters of innocuous urothelial cells with round nuclei, finely granular chromatin and inconspicuous nucleoli, low N/C ratios, and a surrounding fibrovascular core (h). Urolithiasis: clusters of urothelial cells with reactive changes, finely granular chromatin, conspicuous nucleoli, smooth nuclear contours, and low N/C ratios (i). Magnification: ×600.

or nests of columnar cells with small nuclei, and a vacuolated or granular cytoplasm.

Degenerative changes

The nuclei of degenerative cells are shrunken (condensed) and dark, with mildly irregular nuclear membranes. The cytoplasm may contain granules, and possibly large eosinophilic and/or cyanophilic intracytoplasmic inclusions (Melamed-Wolinska bodies, Fig. 2e). N/C ratios are low (<0.5).

Urothelial tissue fragments

Benign-appearing vs. atypical urothelial tissue fragments were clarified in TPS 2.0. Cohesive groups of urothelial cells arranged in honeycomb, without cytologic atypia, for HGUC were named as benign urothelial tissue fragments (BUTFs, Fig. 2f). Some mild atypia was allowed for this category. BUTFs may be observed in voided urine, and are always present in instrumented urinary specimens. Any cytological atypia observed from tissue fragments should be classified as atypical urothelial tissue fragments (AUTFs) under the AUC category (Fig. 2g).

Low-grade urothelial neoplasia

In TPS 2.0, LGUN was re-categorized under NHGUC. The diagnosis of LGUN was rendered only when the tissue fragments contained innocuous cells and fibrovascular cores (Fig. 2h). An explanatory note may be needed. The differential of LGUN includes urothelial papilloma, urothelial proliferation of unknown malignant potential (UPUMP), papillary urothelial neoplasm of low malignant potential (PUNLMP), and LGPUC.

Urolithiasis ("Stone atypia")

Urolithiasis can induce benign urothelial cells to form sheets or three-dimensional clusters. These cells may present with reactive changes, possibly mild hyperchromasia, low N/C ratios, and smooth nuclear membranes (Fig. 2i).

Urothelial change characteristics of infectious processes

Bacterial infection is the most common urinary tract infection. Acute inflammation (abundant neutrophils), bacteria, fungi, and reactive changes can be observed in acute bacterial infection. Viral cytopathic effects may be observed in infections with polyomavirus (Fig. 4a),[17–19] herpes simplex virus (HSV, usually type II, but also type I), cytomegalovirus (CMV), and human papillomavirus (HPV) (Fig. 4b). Among these, polyomavirus is the most frequent. Parasites are ex-

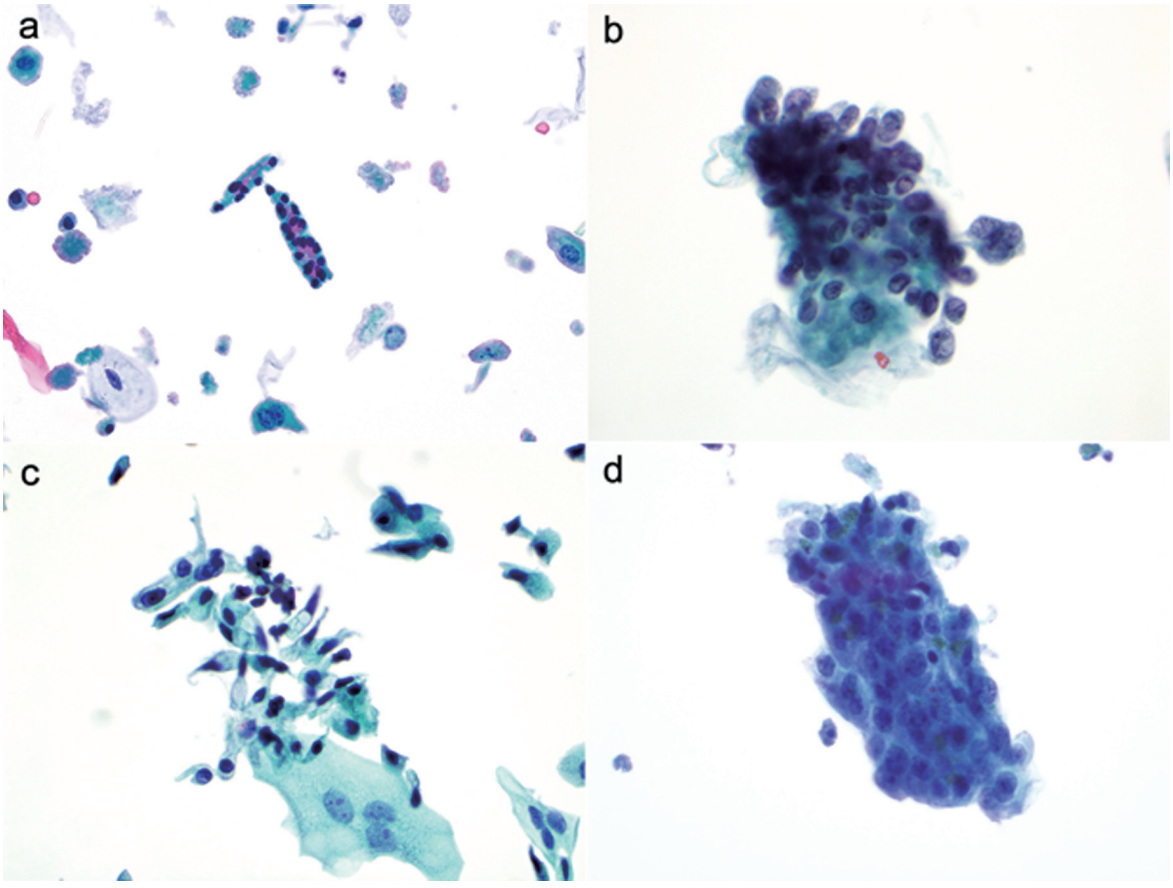

Fig. 3. NHGUC: benign glandular cells. Renal tubule cells, present in renal tubule casts (a). Endometriosis, columnar glandular cells with wispy and vacuolated cytoplasm, and small round or oval nuclei (b) Cystitis glandularis, columnar cells with moderate vacuolated cytoplasm, and small round nuclei (c). Prostatic cells, columnar glandular cells arranged in glandular formation, with cytoplasmic pigments (d). Magnification: ×600.

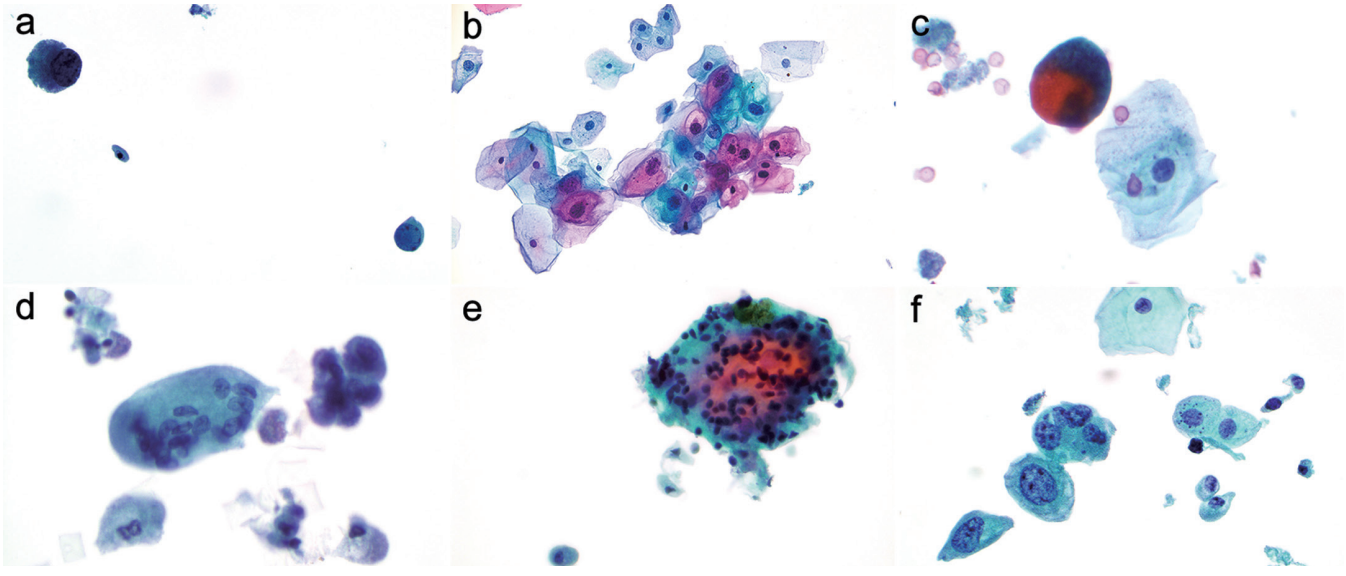

Fig. 4. Virus cytopathic effects. Polyoma virus-infected epithelial cells present with a large, ground-glass-like intranuclear viral inclusion (a). HPV-infected squamous cells present with hyperchromatic nuclei, with irregular nuclear membranes and perinuclear halos (b). Radiation effects: Affected cells present with cytomegaly, nucleomegaly, multinucleation, nuclear vacuoles, cytoplasmic polychromasia, and preserved N/C ratios (c). BCG effects: Reactive urothelial cells, multinucleated giant cells (d), and granuloma (e). Chemotherapy effects: the mitomycin and thiotepa caused the nuclear enlargement, multinucleation, and hyperchromasia of superficial cells (f). Magnification: ×600.

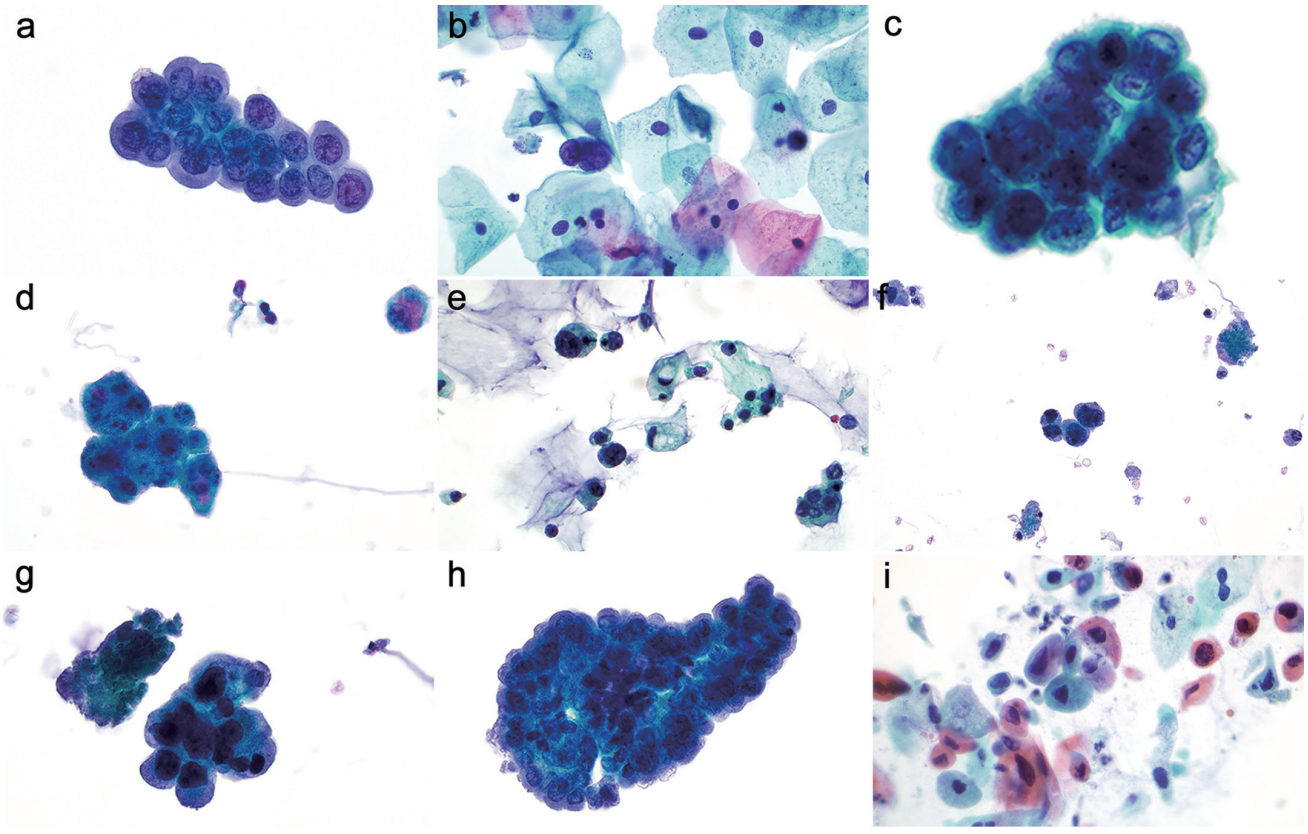

Fig. 5. Atypical urothelial cells (AUC), suspicious for high grade urothelial carcinoma (SHGUC), and high-grade urothelial carcinoma (HGUC). Atypical urothelial cells: A nest of urothelial cells with enlarged nuclei, irregular nuclear membranes, and N/C ratios of ≥0.5 (a). Suspicious for high-grade urothelial carcinoma: Rare urothelial cells with enlarged nuclei, hyperchromasia, irregular coarse chromatin, and high N/C ratios (≥0.7) (b). High-grade urothelial carcinoma: HGUC cells have enlarged nuclei, moderate hyperchromasia, irregular nuclear membrane, irregular coarse chromatin, and high N/C ratios (≥0.7) (c). HGUC cells with high N/C ratios (≥0.7), pleomorphism (variations in size and shape), dense cytoplasm, vacuolated cytoplasm, prominent nucleoli, mitosis, three-dimensional clusters (as observed in the nested variant of HGUC), and rare hypochromasia (d). HGUC cells present with a wide range of N/C ratios, from <0.5 to >0.7 (e). The degenerative changes include irregular nuclear membranes due to dehydration, and nuclear that has become dense due to pyknosis. Necrosis and inflammatory cells can be observed in the background (f). HGUC with extremely dark chromatin: extremely dark and opaque nuclei may equate with the combination of hyperchromatic nuclei and coarse/clumped chromatin, as criteria for malignancy (g). High-grade papillary urothelial carcinoma. A cluster of malignant urothelial cells surrounding the fibrovascular core in the center. Tumor cells have high N/C ratios (≥0.7), irregular nuclear membranes, and coarse chromatin (h). Squamous cell carcinoma: markedly pleomorphic squamous cells with pleomorphic hyperchromatic nuclei, abundant dense cytoplasm, orangeophilic colored stains for some cells, and sharp borders (i). Magnification: ×600.

tremely rare in the United States.

Urothelial changes associated with treatment effects

Radiation causes cytomegaly, nucleomegaly, multinucleation, nuclear and cytoplasmic vacuoles, finely granular/smudgy chromatin, and cytoplasmic polychromasia. N/C ratios are preserved and low (Fig. 4c). Bacillus Calmette-Guerin (BCG) causes granulomatous inflammation (Fig. 4d, e).[20] Chemotherapy with mitomycin and thiotepa causes nuclear enlargement, multinucleation, and hyperchromasia of superficial cells (Fig. 4f).[21] Seminal vesicle cells may be observed in urine specimens (Fig. 3d), especially after prostatic massage and digital rectal examination, and often together with the presence of spermatozoa. Furthermore, seminal vesicle cells have hyperchromatic, degenerated and smudgy nuclei, and golden-brown lipofuscin pigments in the cytoplasm.[22] Abnormal DNA content can also be present.[23]

Bladder diversion specimens

After cystectomy, the ileal conduit, Indiana pouch, or neobladder is used to replace the bladder to store urine. Urine specimens mainly contain degenerated glandular cells in a background of necrotic debris, mucin, bacteria, and inflammatory cells.[24] Urothelial cells and squamous cells may be present.

Ancillary testing

UroVysion may be helpful in the diagnosis.

Category performance[2]

The NHGUC category has a ROHM of 8.7–36.7%, a false-negative rate of 3.3%, and a negative predictive value (NPV) of 96.7%.

Atypical urothelial cells

A specimen that contains urothelial cells with mild-to-moderate cytologic (not architectural) changes for HGUC is categorized as AUC.[25] AUC cases accounted for 5.6% of voided urine specimens.[6]

Diagnostic criteria for AUC

The diagnostic criteria for AUC includes the major criterion and one minor criterion, which applies for all urine specimens, regardless of the preparation method (Fig. 5a).

- Major criterion: Increase in N/C ratio of ≥0.5, but <0.7,

due to nuclear enlargement;[26,27]
- Minor criteria:[28]
  - Nuclear hyperchromasia;
  - Irregular nuclear membranes (chromatinic rim or nuclear contour);
  - Irregular, coarse and clumped chromatin.[29,30]

Clarification of issues unresolved by TPS 1.0 regarding atypia

Urothelial degeneration presents with irregular cytoplasmic borders, cytoplasmic vacuolization, clumped, hazy, smudged, or indistinct chromatin, interrupted chromatin rim, or variable thickness and irregular contours, but rarely possesses sharp angles that are often observed in malignancies. The AUC category includes specimens, in which due to poor preservation and degeneration, the nature and degree of change in urothelial cells cannot be well-characterized, and there are concerns on HGUC.

Atypical squamous cells (ASCs) might be observed in urine specimens, in which cytomorphology would fall short of the definitive diagnosis of squamous cell carcinoma. It appears to be inappropriate to categorize ASCs in "atypical urothelial cells".

With the N/C ratio as the criterion, the maintenance of the TPS criteria for upper tract samples and all preparation types were discussed.[31]

Ancillary testing

FISH/UroVysion may be helpful in the diagnosis.

Suspicious for high-grade urothelial carcinoma

This diagnosis is restrictively used for cases of abnormal urothelial cells that quantitatively fall short of the definitive diagnosis of HGUC.[32,33] SHGUC cases accounted for 1.6% of voided urine specimens.[6]

Diagnostic criteria for SHGUC[2]

The diagnostic criteria for SHGUC includes the major criteria, and two of three features (Fig. 5b). The same criteria applies for all types of specimens.

A cut-off range of at least 5–10 abnormal cells for lower tract (LT) specimens and ≥10 cells for upper tract (UT) specimens is recommended for HGUC.[34]
- Major criteria: Increase in N/C ratio to ≥0.7 due to nuclear enlargement;
- Two of these three features:
  - Moderate-to-severe hyperchromasia;
  - Irregular clumpy chromatin;
  - Irregular nuclear membrane.

Clinical management recommendation.[35,36]

Patients with a diagnosis of SHGUC should be investigated, in order to determine the presence of HGUC, and manage this based on the patient's history, clinical setting, and cytologic findings.

High-grade urothelial carcinoma

The primary purpose of TPS is to have the highest positive predictive value for HGUC. HGUC cases accounted for 1.9% of voided urine specimens.[6]

Diagnostic criteria for HGUC[2]

At least 5–10 malignant cells are required for the diagnosis of HGUC for LT specimens, and ≥10 cells are required for UT specimens.
- The N/C ratio of ≥0.7 due to nuclear enlargement is the most restrictive and recommended benchmark for diagnosing HGUC (Fig. 5c).[37] However, a spectrum of N/C ratios was noted for HGUC, which ranged from <0.5 to >0.7;
- Moderate-to-severe hyperchromasia (Fig. 5c);
- Irregular nuclear membranes (Fig. 5c);
- Coarse/clumped chromatin (Fig. 5c);
- Additional cytomorphologic features:
  - Cellular pleomorphism, variation in size and shape, such as round, oval, elongated, and spindle;
  - Dense or vacuolated cytoplasm;
  - Prominent nucleoli (Fig. 5d);
  - Mitoses;
  - Necrosis (Fig. 5d, f);
  - Inflammation (Fig. 5f);
  - Hypochromasia (Fig. 5d).

Variances in the cytomorphology of HGUC[38]

N/C ratio

HGUC cells present with a wide range of N/C ratios, which range from <0.5 to >0.7. There are sufficient cells with N/C ratios of ≥0.7 and other cytologic features to interpret with confidence (Fig. 5e).

Hypochromasia in HGUC is rare, and a potential pitfall when diagnosing HGUC. Except for hypochromasia, these tumor cells should meet other criteria for HGUC (Fig. 5d).[39,40]

Degenerative changes

Degenerative changes are commonly identified in voided urine specimens, and these can be observed in HGUC. The features of these degenerative changes include loss of cytoplasm, "blown up" nuclei resulting in increased N/C ratio, irregular nuclear membrane due to dehydration, and dense nuclei due to pyknosis (Fig. 5f). Degenerative cells should not be evaluated for diagnosis. An extremely dark chromatin (a combination of hyperchromasia and coarse/clumped chromatin) is a well-recognized feature of HGUC, especially in degenerated HGUC cells. These cells are an independent predictor of malignancy, and should be counted as diagnosis criteria for HGUC (Fig. 5g).

Important histologic variants of HGUC in urine cytology

A total of 14 histologic variants of HGUC were recognized in the 2022 World Health Organization (WHO) classification of tumors of the urinary system.[41] It remains extremely challenging to diagnose some HGUC variants by urine cytology. The TPS 2.0 provides some images,and summarizes the cytomorphologic features of some subtypes.

Cytologic features of some variants

HGUC with squamous differentiation

In addition to HGUC cells, keratinized and/or non-keratinized (with intercellular bridges) squamous tumor cells would be present (Fig. 6a).[42]

HGUC with glandular differentiation

In addition to HGUC cells, malignant columnar glandular cells would be present, and present in a glandular formation. These tumor cells would have a vacuolated or mucin-filled cytoplasm, and hyperchromatic nuclei that contains coarse chromatin and nuclear membrane irregularities (Fig.

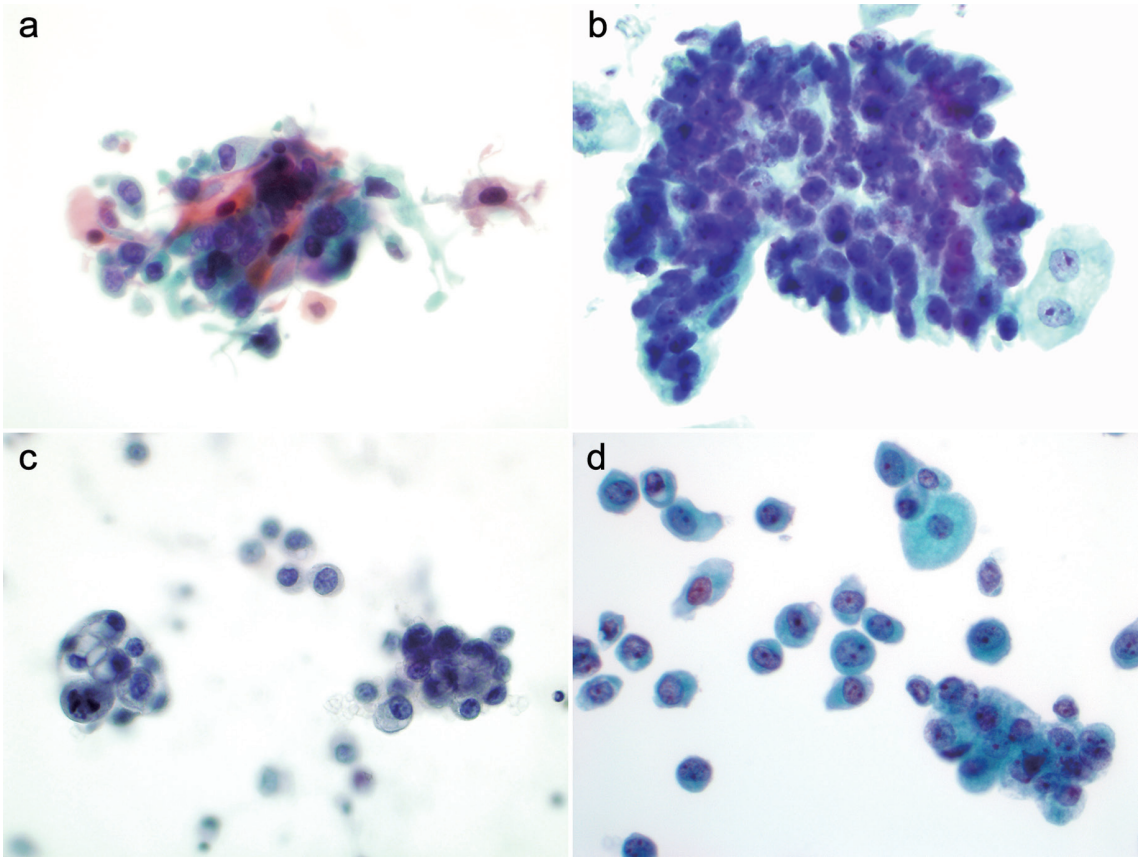

Fig. 6. Variants of HGUC. HGUC may present with squamous differentiation (a), glandular differentiation (b), micropapillary HGUC features (c), and plasmacytoid HGUC features (d). Magnification: ×600.

6b). The diagnosis of adenocarcinoma of the urinary tract can only be determined by extensive examination through biopsy or cystectomy tissue. If no definitive HGUC cells are identified in a urine specimen, it may be better to sign out as carcinoma with glandular differentiation, deferring the biopsy or cystectomy, and adding a note to provide the differentials.

The nested variant of urothelial carcinoma

These tumor cells present in nests/three-dimensional clusters. Furthermore, these tumor cells would have medium-sized, round-to-polygonal shapes, present with slightly increased N/C ratios, have HUGC nuclear features, and have a moderate-to-abundant granular-to-dense cytoplasm with distinct cell borders (Fig. 5d). Since its cytology features may overlap with reactive changes and other HGUC subtypes, it is nearly impossible to make a definitive diagnosis of nested variant on urinary cytology samples.

Micropapillary urothelial carcinoma

These tumor cells present in a micropapillary architecture without fibrovascular cores, but with peripheral or eccentric hyperchromatic nuclei, and cytoplasmic vacuoles. Furthermore, the N/C ratios would be elevated (Fig. 6c).[43] Other cytomorphologic features would overlap with HUGC.

Plasmacytoid urothelial carcinoma

These tumor cells are present as single cells, and have eccentrically placed, enlarged, hyperchromatic nuclei with irregular nuclear membranes, coarse chromatin and inconspicuous nucleoli, and an abundant and thick cytoplasm (Fig. 6d). The N/C ratio may be less than 0.7.[44]

Fibrovascular cores

Fibrovascular cores observed in HGUC are considered for the first time in TPS 2.0. Papillary tissue fragments can be observed in papilloma, LGPUC and HGPUC (Fig. 5h). Papillary-like clusters can also be observed in NHGUC, in both voided and instrumented urine (much more common). The diagnostic significance of papillary or papillary-like clusters entirely depends on the presence or absence of cytologic features for HGUC.

Effects of cytopreparation on the cytomorphology of HGUC

Alcohol fixation used in preparation clumps cells to form three-dimensional clusters, mimicking the papillary structure. Furthermore, alcohol fixation shrinks cells, and increases the N/C ratio. This allows the nuclei of alcohol-fixed, Papanicolaou-stained cells to be better preserved and visualized for evaluatingnuclear features that are critical for the diagnosis. Regardless of what kind of specimen preparation technique is used, the TPS criteria can be applied confidently.[45]

Cytopathology of the upper urinary tract

Definition of upper tract urothelial carcinoma (UTUC)

UTUC includes upper tract HGUC (UTHGUC), CIS, and LGUC

(UTLGUC) arising from the ureter or renal pelvis. TPS 2.0 focuses on detecting UTHGUC (CIS and HGUC).

UTUC prevalence

Synchronous UTUC and urothelial carcinomas of the bladder (UCB) can be observed in 17% of cases. Patients with primary UTUC develop recurrences in the bladder (22–47% of cases), which is likely due to the cancerization effect or intravesicular seeding, multifocal lesions, and the contralateral upper urinary tract (UUT) (2–6% of cases). Genomic mutations in FGFR3, KDM6A, and CCND1 are reported to be significantly associated with higher risk of subsequent UCB, and TP53 mutations are associated with lower risk.

Criteria for upper tract urothelial carcinomas[2]

The TPS cytomorphological criteria for UTHGUC are identical to those for LT specimens. For voided urine specimens, the origin (UT vs. LT) of the HGUC cannot be determined. For instrumented specimens, although the TPS cytomorphologic criteria for HGUC has been applied, a study reported that the cytologic features concerning HGUC included increased N/C ratios, hyperchromasia, and irregular nuclear membranes, as well as pleomorphism, mitoses and atypical degeneration. However, the difference was not statistically different between UTHGUC and UTLGUC. Coarse chromatin and bizarre single cells can be more frequently observed in UTHGUC when compared to UTLGUC.[46]

It remains challenging to make a diagnosis of UTLGNU, since the cytomorphologic features of UTLGUN tissue fragments overlaps with those observed in benign/reactive tissue fragments. The presence of urothelial tissue fragments with fibrovascular cores would be consistent with the clinical impression of LGUN, provided that the diagnostic features for high-grade lesions are not observed in the specimen.

Performance of urinary cytology for upper tract urothelial carcinoma

Urinary cytology has variable sensitivity (19–100%), specificity (86–100%), and positive predictive value (92–100%) for the diagnosis of UTHGUC.[47–49] The overall sensitivity for UTLGUN is significantly lower, when compared to that for HGUC, with reported sensitivities of 46% for UTLGUN prior to TPS vs. 0–34% (average 17%) after the implementation of TPS.[50–52]

Clinical management of upper tract urothelial carcinoma

Ideally, a diagnosis of HGUC in a selective cytology specimen should be confirmed through tissue diagnosis before any definitive treatment.[51] The decision to proceed with the nephroureterectomy solely based on the UT cytology result (HGUC or SHGUC), without an endoscopically or radiographically visible lesion, is generally not recommended. These patients should be closely monitored, to identify the source of the abnormal cells, and provide treatment accordingly, in a timely fashion.

Special consideration for collection, preparation and adequacy

UUT cytology is better than VU, since the usefulness of VU specimens remains limited. Tissue biopsy with uroscopy should be performed. All blocks prepared from instrumented specimens may contribute to the diagnosis of both HGUC and LGUN. More than 20 urothelial cells per 10 HPFs are required for the statement of adequacy for UT specimens.

Ancillary testing for upper tract urothelial carcinoma

FISH/UroVysion combined with a cytology morphology study would improve the diagnostic accuracy of UTUC.

Non-urothelial malignancies (NUM) and other miscellaneous lesions

Non-urothelial malignancies are rare in urine specimens, accounting for 0.1%.

Primary epithelial malignancies

Primary squamous cell carcinoma

Primary squamous cell carcinoma is characterized by exclusive squamous differentiation, without other associated malignant components.

- Cytologic criteria:[2]
  - Keratinizing squamous cell carcinoma: Pleomorphic large squamous cells that present as single cells, or in nests or three-dimensional clusters, and have polygonal, spindle, or bizarre (such as with a tadpole, etc.) shapes, with moderate-to-abundant keratinized/orangeophilic cytoplasm, well-defined sharp borders, and markedly atypical hyperchromatic/dark-ink nuclei. Squamous pearls and "cell in cell" patterns may be observed (Fig. 5i);
  - Non-keratinizing squamous cell carcinoma: Specimens that contain single and clusters of malignant squamous cells, with intercellular bridges, prominent nucleoli, and a scant-to-moderate dense cytoplasm;
  - Anucleated squamous cells ("ghost cells"), small atypical parakeratotic cells, necrosis and neutrophils may be observed in the background.

Atypical squamous cells

Atypical squamous cells are rarely observed in urine cytology (0.3–0.9%), and are possibly associated with bladder or cervical cancer in up to 20–30% of cases.[53] Atypical squamous cells can also be observed in HPV infection-associated lesions of the bladder and urethra.

- Cytologic criteria:
  - Atypical squamous cells with large and hyperchromatic nuclei, abnormal nuclear or cytoplasmic shapes, and densely orangeophilic cytoplasm;
  - Atypical squamous cells that quantitatively and/or quantitatively fall short of the diagnosis of squamous cell carcinoma.

Primary adenocarcinoma

Primary adenocarcinoma is characterized by exclusive glandular differentiation, without the association with other malignant elements.

Enteric adenocarcinoma

These tumor cells present with a similar morphology to colonic adenocarcinoma, clusters of columnar glandular cells arranged in glandular architectures, eccentric hyperchromatic nuclei, and moderate, delicate, or vacuolated cytoplasm, in the background of abundant necrosis. Signet-ring cells may be observed.

Mucinous adenocarcinoma

The atypical columnar cells would be arranged in rounded, three-dimensional clusters, and have small-to-moderate amounts of delicate or vacuolated cytoplasm, and medium-sized nuclei with a distinct nucleoli, in the background of

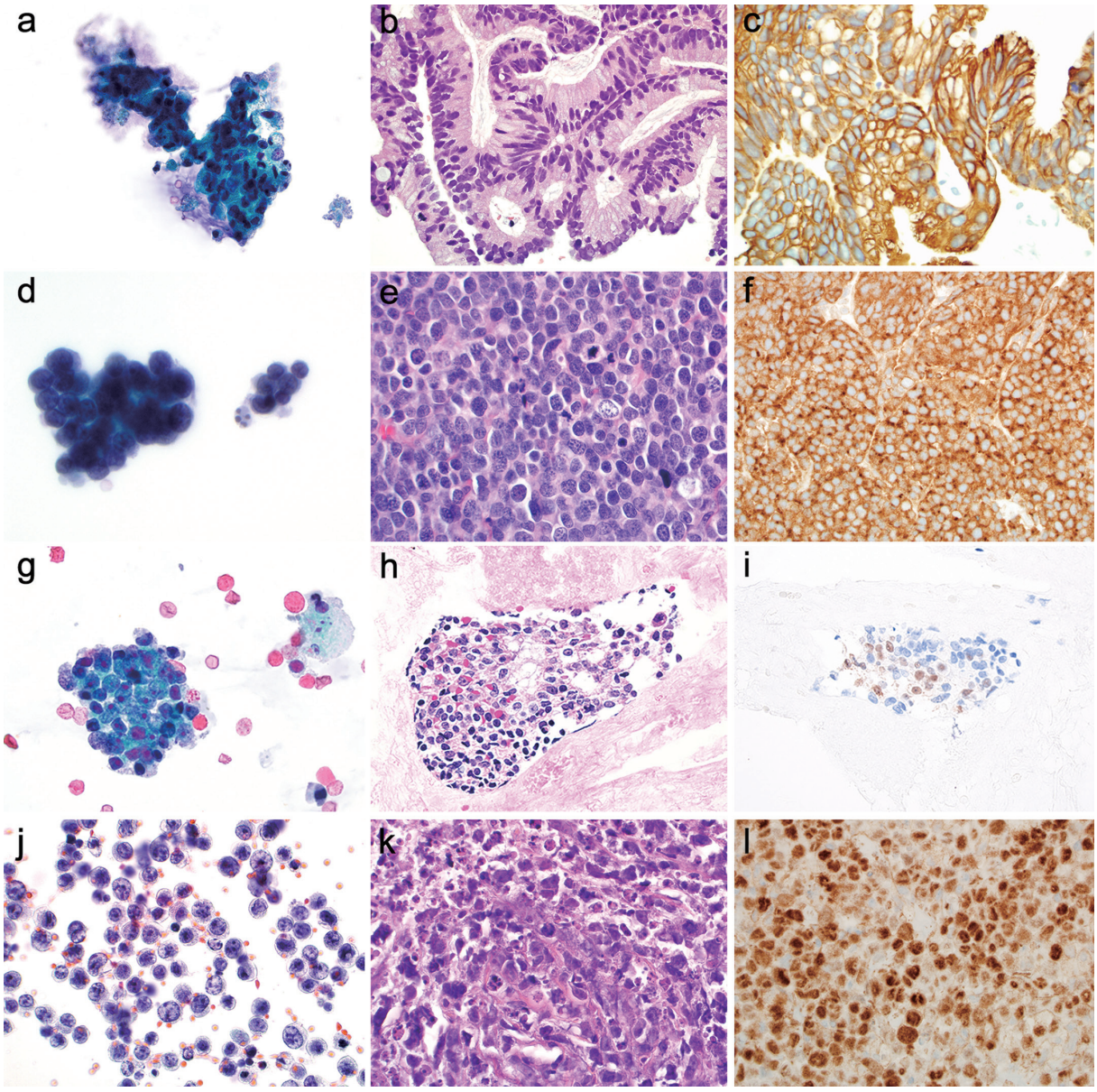

Fig. 7. Other malignancies. Adenocarcinoma: Malignant columnar cells are arranged in glandular formation, with elongated hyperchromatic nuclei (a), and moderate vacuolated or delicate cytoplasm (b), and present with low N/C ratios. The follow-up surgical resection shows the adenocarcinoma, which is positive for CK7 and CK20 (c). Small cell carcinoma: the cohesive cluster of cells with hyperchromatic round/oval nuclei, nuclear molding, and scant cytoplasm (d and e). The tumor cells are positive for synaptophysin (f). Prostatic adenocarcinoma: the cohesive nest of epithelial cells with prominent nucleoli and granular cytoplasm (g, h); Tumor cells are positive for NKX3.1 (i). Diffuse large B-cell lymphoma (DLBL): Discohesive cells with coarse chromatin, prominent nucleoli, irregular nuclear membrane, and minimal cytoplasm (j and k). Tumor cells are positive for PAX-5 (l). Magnification: ×600.

abundant mucin (Fig. 7a, b). The tumor cells may be positive for CK7 and/ or CK20 (Fig. 7c).

Clear cell adenocarcinoma

The large tumor cells present in clusters with occasional hobnail configurations, which have abundant vacuolated cytoplasm and centrally located nuclei that contain prominent nucleoli.

Notes

Since adenocarcinomas in urine cytology do not generally present with distinctive cytomorphologic features to allow for the determination of the subtype, it would be most appropriate to report these cases as adenocarcinoma, NOS, and draft a comment with differentials. Immunostains may be helpful for the definitive diagnosis in some cases, in order to distinguish primary adenocarcinoma from metastatic adenocarcinoma and subtyping adenocarcinoma.

Primary neuroendocrine tumors

Primary neuroendocrine tumors include well-differentiated neuroendocrine tumors (WDNETs), neuroendocrine carcino-

mas (NECs), including small-cell carcinoma (SmCC), large-cell NEC (LCNEC), and paraganglioma.

Small-cell carcinoma

SmCC is rare that often associated with HGUC or other subtypes of carcinoma.

- Cytologic criteria:[2]
  - Small-to-medium-sized tumor cells may be arranged in single, loose, or tight clusters, occasionally in linear pattern or rosette formation (Fig. 7d);
  - The tumor cells contain round/oval nuclei with granular or stippled hyperchromatic chromatin, and present with nuclear molding, scanty cytoplasm, and high N/C ratios. Mitoses, apoptosis, necrosis, crushing artifact, and hemorrhage may be observed (Fig. 7e);
  - The tumor cells are immunoreactive to neuroendocrine markers, synaptophysin (Fig. 7f), chromogranin A, CD56 and INSM1, and possibly immunoreactive to TTF1.

Paraganglioma

Paraganglioma arises from the embryonic nests of chromaffin cells in the sympathetic plexus of the detrusor muscle. Patients would commonly present with hypertension, headache, and hematuria. These tumor cells are rarely detected in urine.

- Cytologic features:
  - Large epithelioid cells that present in single or loose cohesive clusters. Tumor cells with round-to-oval nuclei, fine granular chromatin and inconspicuous nucleoli, and a moderate amount of cytoplasm;[54]
  - The differential diagnosis would include HGUC, plasmacytoid UC, lymphoma, melanoma, NET, and sarcoma.

Secondary epithelial malignancies

Metastatic carcinomas from the breast, gastrointestinal tract, gynecologic origin, liver, lungs, kidneys and prostate (Fig. 7g) are rarely detected in urine cytology. The cytomorphology of these metastatic carcinomas is similar to the primary tumor, and may mimic primary urothelial or non-urothelial malignancies. Immunostains performed on cell blocks (Fig. 7g, i), e.g., NKX3.1 for confirmation of prostatic primary or slides may help confirm the origin of the carcinoma.

Non-epithelial malignancies

Non-epithelial malignancies, such as sarcoma, melanoma and lymphoma, account for less than 0.5% of all bladder tumors.[55]

Sarcoma

Sarcoma with smooth muscle, skeletal muscle, endothelial, or no specific differentiation can arise in the urinary tract.[56,57] The diagnosis of sarcoma by urine cytology is seldom made.

- Cytologic criteria:
  - Pleomorphic spindle cells present as single cells, or in sheets or clusters, are pleomorphic, have hyperchromatic nuclei that possibly contains prominent nucleoli, and have a moderate amount of cytoplasm with ill-defined cytoplasmic borders;
  - The nuclei of leiomyosarcoma would have typical oval-to-spindle shapes with blunt ends;[58]
  - When high-grade or pleomorphic tumor cells, especially those with spindle shapes, are present in urine specimen, the differential should include primary or metastatic sarcoma, primary or metastatic HG carcinoma with sarcomatoid differentiation, melanoma, and lymphoma;
  - Immunostains and molecular studies would be helpful for the diagnosis.

Malignant melanoma

Melanoma is rarely detected in urine cytology[59–61]

- Cytologic criteria:
  - Atypical tumor cells present in single cells;
  - The tumor cells have an epithelioid, plasmacytoid, or spindle in shape, contain large, pleomorphic nuclei that contain prominent/macro-nucleoli and occasional intranuclear pseudoinclusions, and have moderate-to-abundant cytoplasm;
  - Intracytoplasmic, dark, finely dusty brown-to-black melanin pigments may be observed in tumor cells and macrophages;[59,62]
  - The tumor cells are immunoreactive to SOX10, Melan A, HMB45 and S100, but negative for cytokeratins.

Lymphoma

The most common primary lymphoma is low-grade, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) origin. This is commonly associated with chronic cystitis, and affects adults older than 60. The most common high-grade lymphoma is diffuse large B-cell lymphoma (DLBCL).[63]

- Cytologic criteria:
  - Atypical lymphoid cells with nuclear membrane irregularity are the general features of lymphoma. DLBCL is characterized by the presence of atypical large lymphoid cells, with large round-to-oval nuclei, dense chromatin, irregular nuclear membrane, prominent nucleoli, and moderate cytoplasm (Fig. 7j, k);
  - The differential diagnosis of high-grade lymphoma includes HGUC (especially plasmacytoid HGUC), SmCC, melanoma, and sarcoma;
  - Immunohistochemistry (IHC) and flow cytometry to detect lymphoid markers, such as Pax5 positivity in DLBCL (Fig. 7l), FISH, and molecular studies can help to confirm the diagnosis.

Primary plasmacytoma

Primary plasmacytoma is rare.[64]

- Cytologic criteria:
  - Neoplastic cells present as single cells, and have eccentric nuclei that contain peripheral clumping chromatin, binucleation, and prominent nucleoli, and dense basophilic cytoplasm with perinuclear hof;
  - The differential diagnosis includes HGUC, especially plasmacytoid UC, lymphoma, melanoma, NET, and sarcoma;
  - IHC and flow cytometry to detect CD138, CD38, CD56, kappa and lambda light chain are useful for the diagnosis.

Nephrogenic adenoma (NA)

NA is a common benign lesion that most commonly involves the urinary bladder. NA presents in various growth patterns, including tubular, cystic, tubulocystic, papillary, and flat. These tumor cells range from cuboidal to low columnar cells, with eosinophilic cytoplasm.[65] Clear cell change, degenerative atypia, and a hobnail appearance can occur.

- Cytologic criteria:
  - The tumor cells are arranged in small groups or papil-

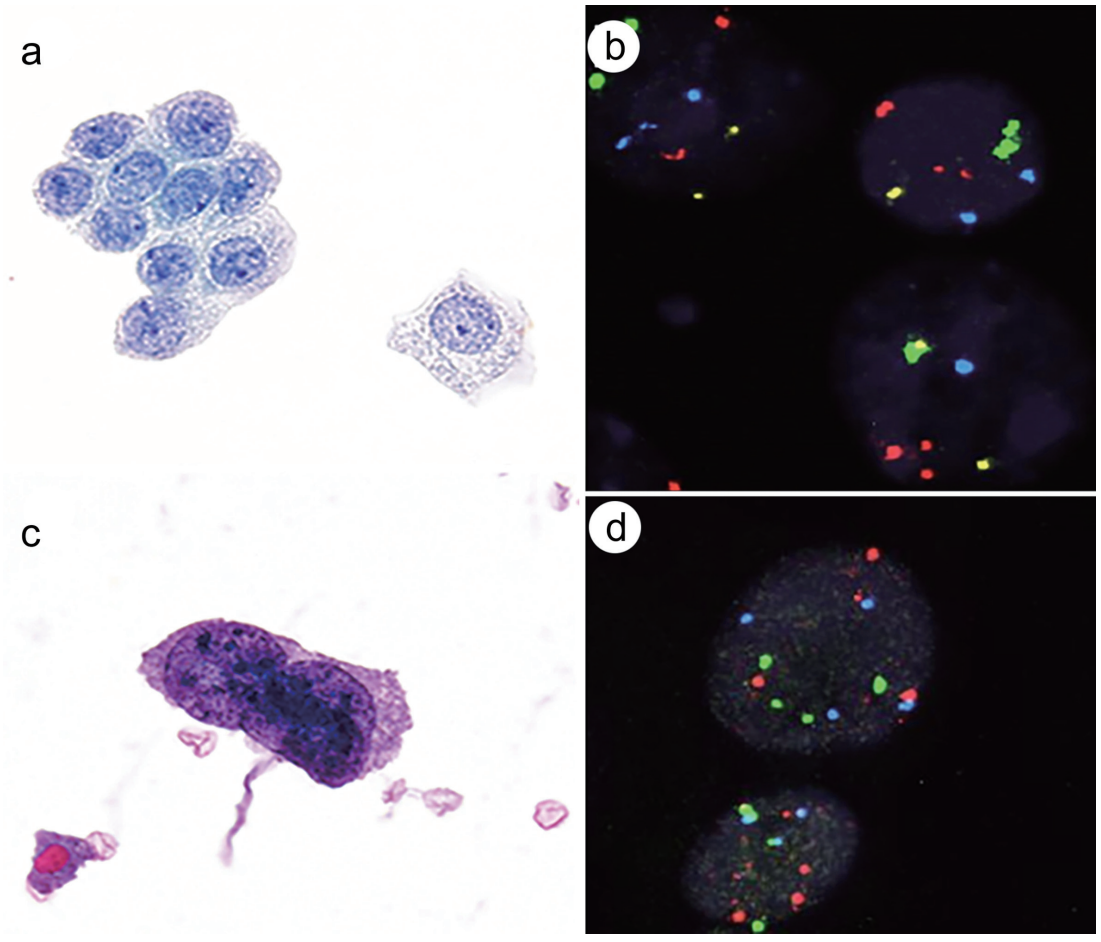

Fig. 8. UroVysion. Benign urothelial cells (a); UroVysion of benign urothelial cells (b); high-grade urothelial cells (c); UroVysion of high-grade urothelial cells (d). Magnification: ×400

lae, or present as isolated cells, have polygonal or columnar shapes, and moderate vacuolated cytoplasm, and present with no or mild nuclear atypia, with slightly increased N/C ratios, nuclear hyperchromasia, and prominent nucleoli;
- The tumor cells are diffusely positive for Pax-8, Pax-2 and AMACR;
- The differential diagnosis includes reactive changes, HGUC, clear cell adenocarcinoma, and low-grade RCC.

Ancillary studies in urinary cytology

Merely few tests have been approved by the US Food and Drug Administration (FDA) for diagnostic application, including UroVysion® fluorescence *in situ* hybridization (U-FISH), BTA™, and NMP22™. Furthermore, few tests have been studied and proposed, including tests for tumor-associated antigens, polymerase chain reaction (PCR)-based tests for mutations, and next-generation sequencing (NGS) to detect mutations or epigenetic changes in UC.

UroVysion FISH[66]

Papanicolaou-stained slides prepared from any urine sample can be used for the test.[67] U-FISH contains four single-stranded DNA probes, three chromosome enumeration probes (CEPs) that target the pericentromeric regions of chromosomes 2, 7, and 17, and another locus-specific identifier (LSI) probe that targets the 9p21 locus. After staining, the slides are analyzed using an epi-fluorescence microscope equipped with a 100 watt mercury lamp or LED light source, and appropriate filters to detect multicolor fluorescent signals,[2] and the magnification ranges from 600× to 1,000×. The number of signals for all four probes should be counted and recorded as abnormal when there is a gain (≥2 signals) for two or more chromosomes 3 (red), 7 (green), and 17 (aqua), or when there is a loss of both copies of 9p21 (gold), as suggested by the manufacturer. The test is considered positive when ≥4 of the 25 analyzed cells present with gains for two or more chromosomes, or ≥12 of these 25 cells have zero 9p21 signals (Fig. 8).

The imaging and automation of the UroVysion FISH analysis saves time, improves productivity, quality control, and the archiving of images, and increases accuracy.[68] Automated imaging systems consist of an automated scanning microscope coupled with software for image analysis. Target FISH is performed on Papanicolaou-stained monolayer preparations that have been pre-scanned by the imaging system, with atypical urothelial cells selected by the operator.

UroVysion FISH has a variable sensitivity of 89–100%, and a specificity of 60–100%.[66,69] A new category, "urothelial neoplasia diagnosed by U-FISH, not otherwise specified

(UNF-NOS)," was recently proposed. However, there have been concerns on its cost-effectiveness. Furthermore, there is a possibility of false-positive results in the UroVysion FISH analysis.[70]

FDA-approved liquid-based tests

Two versions of the bladder tumor antigen (BTA) test were approved by the FDA: quantitative ELISA test (BTA) TRAK™ and qualitative point-of-care test BTA stat. BTA stat and BTA TRAK™ have similar overall sensitivity (64% vs. 65%) and specificity (77% vs. 74%), respectively.[71] These tests have higher sensitivity, when compared to urine cytology. However, similar to NMP22, BTA assays suffer from a higher false-positive rate in patients with benign urinary tract diseases, limiting its use in clinical practice.[72]

The nuclear matrix protein (NMP22) test was approved by the FDA. However, this test should not be performed on voided urine samples obtained within five days after the instrumentation of the urinary bladder. False-positive results are common in patients with benign bladder conditions.[73]

Other liquid-based biomarkers

Various potential ancillary tests have emerged based on protein detection, microRNAs, gene expression profiling, epigenetic changes, and PCR-based detection.

Ancillary tests based on next-generation sequencing technology

NGS is a technique for acquiring the DNA sequence from each starting molecule of DNA in a sample. Various different mutations can be present in different cases of UC, permitting the simultaneous identification of multiple mutations.[74] Mutations, epigenetic alterations, and even copy number changes can be detected by NGS. Epigenetic changes (DNA methylation) can be detected using chemical treatment (bisulfite) to convert methylated cytosines to a nucleotide that is ultimately sequenced as thymidine. Then, the locations of these methylated cytosines can be computationally deduced. Copy number changes (which can represent aneuploidy) are deduced based on the number of individual reads. The commercially available NGS tests are uCAPP-Seq,[75] AssureMDx,[76] and UroSeek,[77,78] with a sensitivity of 83–93%, and a specificity of 86–99%.

Risk of high-grade malignancy[15]

The new term, ROHM, rather than ROM, was introduced in TPS 2.0. After applying TPS 1.0, various studies have been conducted to calculate the ROHM of each category, including five studies that retrospectively reclassified the previous diagnosis using TPS 1.0, and six studies that applied the TPS 1.0 criteria for the new urine cytology diagnosis.[2,6,32,33,35,79–86] The diagnosis criteria for LGUC in urine cytology remains very strict in TPS, resulting in significantly fewer diagnosed cases of LGUC. The calculation of ROHM of LGUC remains limited by the case number, which ranges from 0% to 54.1%.[2,24,32,35,38,79,81–89]

The weighted overall ROHM is calculated based on the sample size and standard deviation in each category (Table 1), presenting the overall updated performance of TPS 1.0.

Table 1. Estimated risk of high-grade malignancy (ROHM) for each category of The Paris System for Reporting Urinary Cytology[2]

TPS category	Risk of high-grade malignancy
ND	0–16%
NHGUC	8–24%
LGUN	0–44%
AUC	24–53%
SHGUB	59–94%
HGUC/malignant	76–100%

TPS, The Paris System for Reporting Urine Cytology; ND, nondiagnostic; NHGUC, negative for high-grade urothelial carcinoma; LGUN, low-grade urothelial neoplasm; AUC, atypical urothelial cells; SHGUC, suspicious for high-grade urothelial carcinoma; HGUC, high-grade urothelial carcinoma.

Clinical management

The implementation of TPS has standardized the diagnostic criteria, thereby limiting the interobserver variability in cytologic interpretation, creating a more reproducible diagnostic tool, and improving the communication among clinicians and cytopathologists.

Management of the unsatisfactory specimen[2]

The management of unsatisfactory specimens should be left at the clinician's discretion. The reasons for the unsatisfactory specimen should be investigated by cytopathologists and clinicians, and a repeat sample may be obtained depending on the risk for a significant lesion.

Management of negative for high-grade urothelial carcinoma[2]

The American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) proposed new guidelines that do not recommend the use of cytology in the initial evaluation of microscopic hematuria.[90] These guidelines recommend a patient-centered approach to diagnostic testing for microhematuria, based on the risk for urothelial malignancy. The AUA/Society of Urologic Oncology (SUO) proposed new guidelines that recommend a risk-stratified approach in the surveillance of non-muscle-invasive bladder cancer.[91] Urine cytology or other urinary biomarkers are not recommended for patients with a history of low-risk cancer, and a normal cystoscopy. Urine cytology is essential in the surveillance of patients for recurrences following therapy, since these patients remain at risk for recurrences in the remnant urothelium (upper tracts and urethra).[92–94] The role of additional molecular testing, such as UroVysion FISH and other urinary biomarkers (including ImmunoCyt and Cxbladder), remains to be determined. A patient with a diagnosis of NHGUC may continue the routine surveillance at intervals that commensurate with the risk of recurrence.

Management of atypical urothelial cells

The implementation of TPS has decreased the rate of AUC diagnoses.[36,95] The workup for AUC should be individualized based on the patient's risk assessment, and this may prompt a thorough evaluation. Patients with hematuria or persistent irritative voiding symptoms still require a thorough evaluation, with upper tract imaging and cystoscopy. Patients with known risk factors for urothelial carcinoma and atypical cytology should receive further investigation, in order to rule out any malignancies. For patients with a prior history of urothelial malignancy, the extent of the work-up would be dependent on the clinical suspicion of recurrent disease.[96] The role of additional molecular testing, such as UroVysion FISH and other urinary biomarkers, remains to be determined.[93,97,98] Some centers have instituted reflex UroVysion FISH testing for the adjudication of AUC diagnoses. A positive FISH assay

would be managed similar to a suspicious diagnosis, while a negative FISH test would be expectantly followed.[99–102]

Management of suspicious and positive for high-grade urothelial carcinoma

From a practical standpoint, the clinical management of "SHGUC" is identical to the HGUC diagnosis, requiring an active investigation to identify the source of the suspicious or positive cells by utilizing regular cystourethroscopy[103,104] (fluorescence cystoscopy, narrowband imaging, and directed/random bladder biopsies), and evaluate the prostatic urethra and upper tracts. The upper tract can be evaluated through imaging studies, computerized tomography (CT) urography, magnetic resonance (MR) urography, and ultrasound with retrograde pyelography.

Management of low-grade urothelial neoplasms

Most bladder cancers present as low-grade non-invasive papillary tumors, and diagnosing LGUC based on cytology can be challenging, with a relatively low sensitivity. Transurethral resection allows for the establishment of the histologic diagnosis, and is therapeutic for most solitary low-grade tumors. The AUA and European Association of Urology (EAU) recommends a risk-adapted surveillance protocol for non-muscle-invasive bladder cancer.[91,105] Routine surveillance cystoscopies may be performed at regular intervals.[106] The decision to provide adjuvant intravesical therapy (chemotherapy or immunotherapy) is based on the risk of recurrence and progression.[107] The stratification of patients into low-, intermediate-, and high-risk groups is essential for deciding the appropriate use of adjuvant intravesical chemotherapy (mitomycin, doxorubicin, or gemcitabine) or BCG instillation. Surgical removal of the bladder should be considered in case of BCG-unresponsive tumors, or NMIBCs with the highest risk of progression.[106]

Management of non-urothelial tumors

It may be difficult to distinguish primary non-urothelial malignancy from urothelial carcinoma with divergent histologic differentiation in urine cytology, which most often requires histology and ancillary studies on biopsy or resection specimens. The complete resection of all visible tumors, when appropriate, is recommended. A multidisciplinary approach, which employs surgery, systemic chemotherapy, and radiation on an individualized basis, should be considered. The standard treatment for primary squamous cell carcinoma of the bladder is radical cystectomy, followed by radiotherapy, with concurrent chemotherapy for unresectable or residual tumors.[108] Urachal carcinoma is treated through the wide local excision of the umbilicus and urachal remnant, with cystectomy and pelvic lymphadenectomy.[109] Primary adenocarcinoma is treated by partial cystectomy.[110] Neuroendocrine tumors should be managed using a multimodality approach, with neoadjuvant systemic chemotherapy, followed by radical cystectomy. The combination chemotherapy with definitive radiotherapy may be considered.[111,112]

Conclusions

The second edition of the Paris System for Reporting Urine Cytopathology further clarifies and defines the diagnostic criteria of each category. LGUN was re-categorized in NHGUC, and a new chapter, Cytology of the Upper Urinary Tract, was added. According to the feedback after the publication of TPS 1.0, the updated ROM and management suggestions in each category provides clarification for the communication among pathologists, radiologists and urologists. The primary purposes of TPS are to decrease the atypical category, and increase the specificity of the HGUC diagnosis from urine cytology. The measurement of the nuclear area may improve the accuracy of TPS. Future studies are needed, in order to further define the utilization of artificial intelligence (AI) and molecular testing in urine cytology, and refine AI, as well as the molecular basis of HGUC and biomarkers for AUS cases.

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Conflict of interest

The manuscript was submitted during Dr. Xiaoqi Lin's term from June 2021 to June 2023 serving as an editorial board member of *Journal of Clinical and Translational Pathology*. The authors have no other conflict of interests to declare.

Author contributions

Dr. Fei Chen wrote the draft of the manuscript, and Dr. Xiaoqi Lin conducted the final review and editing, and provided the figures with legends. Both authors significantly contributed to the study, and approved the final manuscript.

References

[1] Rosenthal DL, wojcik EM, Kurtycz DF. In: The Paris System for Reporting Urinary Cytology, 1st ed. Cham: Springer International Publishing Switzerland; 2016. doi:10.1007/978-3-319-22864-8.
[2] Wojcik EM, Kurtycz DF, Rosenthal DL. In: The Paris System for Reporting Urinary Cytology, 2nd ed. Cham: Springer Nature Switzerland AG; 2022. doi:10.1007/978-3-030-88686-8.
[3] Courtade-Saïdi M, Cochand-Priollet B, Vielh P, Piaton E, Sous l'égide de la Société Française de Cytologie Clinique. A new terminology for urinary cytopathology: The Paris System for Reporting Urinary Cytology (2015) (in French). Ann Pathol 2019;39(5):344–351. doi:10.1016/j.annpat.2019.04.003, PMID:31255415.
[4] Yuan LS, Gero M, Zia S, Aryal SC, Shetty S, Reynolds JP. Cyto-histo correlation and false-negative urine: Before and after the Paris system for reporting urinary cytology. Diagnostic Cytopathology 2022;50(8):404–410. doi:10.1002/dc.24982, PMID:35652594.
[5] Ulldemolins Aznar P, Muñoz Vicente E, Roselló-Sastre E. [How has the Paris System contributed to urine cytology? Evaluating the contribution of the Paris System to urine cytology. A comparative study of the Paris System and the Papanicolaou method in a tertiary centre]. Rev Esp Patol 2022;55(2):125–134. doi:10.1016/j.patol.2021.11.002, PMID:35483768.
[6] Lobo J, Lobo C, Leça L, Rodrigues Â, Henrique R, Monteiro P. Evaluation of the Implementation and Diagnostic Accuracy of the Paris Classification for Reporting Urinary Cytology in Voided Urine Specimens: A Cyto-Histological Correlation Study in a Cancer Center. Pathobiology 2022. doi:10.1159/000527980, PMID:36574757.
[7] Spruck CH 3rd, Ohneseit PF, Gonzalez-Zulueta M, Esrig D, Miyao N, Tsai YC, *et al*. Two molecular pathways to transitional cell carcinoma of the bladder. Cancer Res 1994;54(3):784–788. PMID:8306342.
[8] Al-Ahmadie H, Netto GJ. Molecular Pathology of Urothelial Carcinoma. Surg Pathol Clin 2021;14(3):403–414. doi:10.1016/j.path.2021.05.005, PMID:34373092.
[9] Lopez-Beltran A, Cimadamore A, Montironi R, Cheng L. Molecular pathology of urothelial carcinoma. Hum Pathol 2021;113:67–83. doi:10.1016/j.humpath.2021.04.001, PMID:33887300.
[10] Kamoun A, de Reyniès A, Allory Y, Sjödahl G, Robertson AG, Seiler R, *et al*. A Consensus Molecular Classification of Muscle-invasive Bladder Cancer. Eur Urol 2020;77(4):420–433. doi:10.1016/j.eururo.2019.09.006, PMID:31563503.
[11] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014;507(7492):315–322. doi:10.1038/nature12965, PMID:24476821.
[12] 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. doi:10.1002/cncy.21634, PMID:26524350.
[13] Richardson CJ, Pambuccian SE, Barkan GA. Split-sample comparison of urothelial cells in ThinPrep and cytospin preparations in urinary cytology: Do we need to adjust The Paris System for Reporting Urinary Cy-

tology criteria? Cancer Cytopathol 2020;128(2):119–125. doi:10.1002/cncy.22218, PMID:31774630.
[14] Prather J, Arville B, Chatt G, Pambuccian SE, Wojcik EM, Quek ML, *et al*. Evidence-based adequacy criteria for urinary bladder barbotage cytology. J Am Soc Cytopathol 2015;4(2):57–62. doi:10.1016/j.jasc.2014.09.206, PMID:31051710.
[15] Nikas IP, Seide S, Proctor T, Kleinaki Z, Kleinaki M, Reynolds JP. The Paris System for Reporting Urinary Cytology: A Meta-Analysis. J Pers Med 2022;12(2):170. doi:10.3390/jpm12020170, PMID:35207658.
[16] DeMay RM. In: Practice principles of cytopathology, Revised ed. Chicago: American Society for Clinical Pathology; 2007:96–99.
[17] Pinto M, Dobson S. BK and JC virus: a review. J Infect 2014;68(Suppl 1):S2–S8. doi:10.1016/j.jinf.2013.09.009, PMID:24119828.
[18] Gai M, Lanfranco G, Segoloni GP. "Decoy cells" in urine. Transplant Proc 2005;37(10):4309–4310. doi:10.1016/j.transproceed.2005.11.045, PMID:16387105.
[19] Koss LG. On decoy cells. Acta Cytol 2005;49(3):233–234. doi:10.1159/000326142, PMID:15966282.
[20] Knight A, Askling J, Granath F, Sparen P, Ekbom A. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis 2004;63(10):1307–1311. doi:10.1136/ard.2003.019125, PMID:15130900.
[21] Pierconti F, Rossi ED, Straccia P, Fadda G, Larocca LM, Bassi PF, *et al*. The risk of malignancy of atypical urothelial cells of undetermined significance in patients treated with chemohyperthermia or electromotive drug administration. Cancer Cytopathol 2018;126(3):200–206. doi:10.1002/cncy.21957, PMID:29360198.
[22] Terada T. Monstrous epithelial cell clusters in the seminal vesicle. Int J Clin Exp Pathol 2011;4(7):727–730. PMID:22076175.
[23] Wojcik EM, Bassler TJ Jr, Orozco R. DNA ploidy in seminal vesicle cells. A potential diagnostic pitfall in urine cytology. Anal Quant Cytol Histol 1999;21(1):29–34. PMID:10068772.
[24] Ajit D, Dighe SB, Desai SB. Cytology of Ileal conduit urine in bladder cancer patients: diagnostic utility and pitfalls. Acta Cytol 2006;50(1):70–73. doi:10.1159/000325897, PMID:16514843.
[25] Pambuccian SE. What is atypia? Use, misuse and overuse of the term atypia in diagnostic cytopathology. J Am Soc Cytopathol 2015;4(1):44–52. doi:10.1016/j.jasc.2014.10.004, PMID:31051673.
[26] Hang JF, Charu V, Zhang ML, VandenBussche CJ. Digital image analysis supports a nuclear-to-cytoplasmic ratio cutoff value of 0.5 for atypical urothelial cells. Cancer Cytopathol 2017;125(9):710–716. doi:10.1002/cncy.21883, PMID:28581671.
[27] McIntire PJ, Snow JT, Elsoukkary SS, Soong L, Sweeney J, Robinson BD, *et al*. Digital image analysis supports a nuclear-to-cytoplasmic ratio cutoff value below 0.7 for positive for high-grade urothelial carcinoma and suspicious for high-grade urothelial carcinoma in urine cytology specimens. Cancer Cytopathol 2019;127(2):120–124. doi:10.1002/cncy.22061, PMID:30395388.
[28] Kurtycz DFI, Barkan GA, Pavelec DM, Rosenthal DL, Wojcik EM, VandenBussche CJ, *et al*. Paris Interobserver Reproducibility Study (PIRST). J Am Soc Cytopathol 2018;7(4):174–184. doi:10.1016/j.jasc.2018.02.005, PMID:31043274.
[29] Frost JK. The cell in health and disease. An evaluation of cellular morphologic expression of biologic behavior. 2nd, revised edition. Monogr Clin Cytol 1986;2:1–304. PMID:3334075.
[30] McCroskey Z, Bahar B, Hu Z, Wojcik EM, Barkan GA. Subclassifying atypia in urine cytology: what are the helpful features? J Am Soc Cytopathol 2015;4(4):183–189. doi:10.1016/j.jasc.2014.11.002, PMID:31051752.
[31] Zhang ML, VandenBussche CJ, Hang JF, Miki Y, McIntire PJ, Peyton S, *et al*. A review of urinary cytology in the setting of upper tract urothelial carcinoma. J Am Soc Cytopathol 2021;10(1):29–35. doi:10.1016/j.jasc.2020.06.011, PMID:32792229.
[32] Stanzione N, Ahmed T, Fung PC, Cai D, Lu DY, Sumida LC, *et al*. The continual impact of the Paris System on urine cytology, a 3-year experience. Cytopathology 2020;31(1):35–40. doi:10.1111/cyt.12777, PMID:31596979.
[33] Rohilla M, Singh P, Rajwanshi A, Gupta N, Srinivasan R, Dey P, *et al*. Cytohistological correlation of urine cytology in a tertiary centre with application of the Paris system. Cytopathology 2018;29(5):436–443. doi:10.1111/cyt.12604, PMID:29920811.
[34] Brimo F, Xu B, Kassouf W, Ahmadi-Kaliji B, Charbonneau M, Nahal A, *et al*. Urine cytology: does the number of atypical urothelial cells matter? A qualitative and quantitative study of 112 cases. J Am Soc Cytopathol 2015;4(4):232–238. doi:10.1016/j.jasc.2015.01.003, PMID:31051759.
[35] Meilleroux J, Daniel G, Aziza J, d'Aure DM, Quintyn-Ranty ML, Basset CM, *et al*. One year of experience using the Paris System for Reporting Urinary Cytology. Cancer Cytopathol 2018;126(6):430–436. doi:10.1002/cncy.21999, PMID:29663682.
[36] Pastorello RG, Barkan GA, Saieg M. Experience on the use of The Paris System for Reporting Urinary Cytopathology: review of the published literature. J Am Soc Cytopathol 2021;10(1):79–87. doi:10.1016/j.jasc.2020.10.002, PMID:33160893.
[37] Cowan ML, Rosenthal DL, VandenBussche CJ. Improved risk stratification for patients with high-grade urothelial carcinoma following application of the Paris System for Reporting Urinary Cytology. Cancer Cytopathol 2017;125(6):427–434. doi:10.1002/cncy.21843, PMID:28272842.
[38] Anbardar MH, Monjazeb R. Reclassification of urinary cytology regarding The Paris System for Reporting Urinary Cytology with cytohistological correlation demonstrates high sensitivity for high-grade urothelial carcinoma. Diagn Cytopathol 2020;48(5):446–452. doi:10.1002/dc.24387, PMID:31976626.
[39] Pierconti F, Martini M, Straccia P, Fiorentino V, Musarra T, Larocca LM, *et al*. Hypochromatic large urothelial cells in urine cytology are indicative of high grade urothelial carcinoma. APMIS 2018;126(9):705–709. doi:10.1111/apm.12877, PMID:30160022.
[40] Renshaw AA, Gould EW. High-grade urothelial carcinoma with hypochromatic chromatin in urine cytology. J Am Soc Cytopathol 2021;10(1):25–28. doi:10.1016/j.jasc.2020.10.003, PMID:33132055.
[41] Amin MB, Berney DM, Comperat EM, Hartmann A, Menon S, Netto GJR, *et al*. Urinary and Male Genital Tumours. In: WHO Classification of Tumours, 5th, ed. Lyon: Internation Agency for Research on Cancer; 2022.
[42] Yoo Y, Choi E, Lee DH, Park S, Sung SH. Diagnostic value of urine cytology in detecting histologic variants of urothelial carcinomas in the urinary bladder: Cytopathologic correlation of 72 cases. Diagn Cytopathol 2021;49(3):367–373. doi:10.1002/dc.24660, PMID:33331144.
[43] Zhu B, Rohan SM, Lin X. Urine cytomorphology of micropapillary urothelial carcinoma. Diagn Cytopathol 2013;41(6):485–491. doi:10.1002/dc.22866, PMID:22623512.
[44] Gelarden I, Lin X. Urine cytology of high-grade plasmacytoid urothelial carcinoma. Journal of American Society of Cytopathology 2021;10(5):S32. doi:10.1016/j.jasc.2021.07.050.
[45] Straccia P, Bizzarro T, Fadda G, Pierconti F. Comparison between cytospin and liquid-based cytology in urine specimens classified according to the Paris System for Reporting Urinary Cytology. Cancer Cytopathol 2016;124(7):519–523. doi:10.1002/cncy.21709, PMID:26989867.
[46] Xu C, Zeng Q, Hou J, Gao L, Zhang Z, Xu W, *et al*. Utility of a modality combining FISH and cytology in upper tract urothelial carcinoma detection in voided urine samples of Chinese patients. Urology 2011;77(3):636–641. doi:10.1016/j.urology.2010.07.498, PMID:21256577.
[47] Potretzke AM, Knight BA, Vetter JM, Anderson BG, Hardi AC, Bhayani SB, *et al*. Diagnostic Utility of Selective Upper Tract Urinary Cytology: A Systematic Review and Meta-analysis of the Literature. Urology 2016;96:35–43. doi:10.1016/j.urology.2016.04.030, PMID:27151340.
[48] Wang L, Pambuccian SE, Wojcik EM, Barkan GA. Diagnosis of upper tract urothelial carcinoma-a comparative study of urinary cytology and surgical biopsy. J Am Soc Cytopathol 2015;4(1):3–9. doi:10.1016/j.jasc.2014.09.203, PMID:31051670.
[49] Williams SK, Denton KJ, Minervini A, Oxley J, Khastigir J, Timoney AG, *et al*. Correlation of upper-tract cytology, retrograde pyelography, ureteroscopic appearance, and ureteroscopic biopsy with histologic examination of upper-tract transitional cell carcinoma. J Endourol 2008;22(1):71–76. doi:10.1089/end.2007.9853, PMID:18315477.
[50] Zheng X, Si Q, Du D, Harshan M, Zhang Z, Haines K 3rd, *et al*. The Paris System for urine cytology in upper tract urothelial specimens: A comparative analysis with biopsy and surgical resection. Cytopathology 2018;29(2):184–188. doi:10.1111/cyt.12505, PMID:29251368.
[51] McIntire PJ, Snow JT, Robinson BD, Rao RA, Goyal A, Heymann JJ, *et al*. Improved correlation of urinary cytology specimens using The Paris System in biopsy-proven upper tract urothelial carcinomas. Cancer Cytopathol 2018;126(7):498–504. doi:10.1002/cncy.22005, PMID:29927548.
[52] Sassa N, Iwata H, Kato M, Murase Y, Seko S, Nishikimi T, *et al*. Diagnostic Utility of UroVysion Combined With Conventional Urinary Cytology for Urothelial Carcinoma of the Upper Urinary Tract. Am J Clin Pathol 2019;151(5):469–478. doi:10.1093/ajcp/aqy170, PMID:30668617.
[53] Hattori M, Nishimura Y, Toyonaga M, Kakinuma H, Matsumoto K, Ohbu M. Cytological significance of abnormal squamous cells in urinary cytology. Diagn Cytopathol 2012;40(9):798–803. doi:10.1002/dc.21645, PMID:21309015.
[54] Lee J, Park S, Cho MS, Sung SH, Kim KH. Urine cytology findings of primary paraganglioma of the urinary bladder: Case report. Diagn Cytopathol 2017;45(4):350–353. doi:10.1002/dc.23667, PMID:28110509.
[55] Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: a review. Eur Urol 2003;44(6):672–681. doi:10.1016/s0302-2838(03)00416-0, PMID:14644119.
[56] Mitra S, Kaur G, Kakkar N, Singh P, Dey P. Sarcoma in urine cytology; an extremely rare entity: A report of two cases. J Cytol 2017;34(3):171–173. doi:10.4103/0970-9371.208100, PMID:28701835.
[57] Iwa N, Ito S, Takegaki Y, Ikura Y, Kobayashi TK, Yasukawa S, *et al*. Cytologic features of sarcomatoid carcinoma of the urinary bladder: a case report. Diagn Cytopathol 2013;41(6):536–541. doi:10.1002/dc.21817, PMID:21953942.
[58] Hemachandran M, Nada R, Rajwanshi A. Leiomyosarcoma of the urinary bladder: a diagnostic challenge in urine cytology. Diagn Cytopathol 2004;31(4):281–282. doi:10.1002/dc.20053, PMID:15452910.
[59] Khalbuss WE, Hossain M, Elhosseiny A. Primary malignant melanoma of the urinary bladder diagnosed by urine cytology: a case report. Acta Cytol 2001;45(4):631–635. doi:10.1159/000327878, PMID:11480732.
[60] Martínez-Girón R. Melanoma cells in voided urine cytology. Cytopathology 2008;19(6):402–403.doi:10.1111/j.1365-2303.2008.00607.x,PMID:18713248.
[61] Hori T, Kato T, Komiya A, Fuse H, Nunomura S, Fukuoka J, *et al*. Primary melanoma of the urinary bladder identified by urine cytology: a rare case report. Diagn Cytopathol 2014;42(12):1091–1095. doi:10.1002/dc.23074, PMID:24574378.
[62] McIntire PJ, Kilic I, Wojcik EM, Barkan GA, Pambuccian SE. The color of urine: then and now-a comprehensive review of the literature with emphasis on intracytoplasmic pigments encountered in urinary cytology. J Am Soc Cytopathol 2020;9(1):9–19. doi:10.1016/j.jasc.2019.05.002, PMID:31551159.
[63] Sellman DP, Simpson WG, Klaassen Z, Jen RP, DiBianco JM, Reinstatler L, *et al*. Characterization and outcomes of local treatment for primary bladder lymphoma: A population-based cohort analysis. Urol Ann 2018;10(3):249–

253. doi:10.4103/UA.UA_106_17, PMID:30089981.
[64] Farinola MA, Lawler LP, Rosenthal D. Plasmacytoma with involvement of the urinary bladder. Report of a case diagnosed by urine cytology. Acta Cytol 2003;47(5):787–791. doi:10.1159/000326607, PMID:14526680.
[65] Piña-Oviedo S, Shen SS, Truong LD, Ayala AG, Ro JY. Flat pattern of nephrogenic adenoma: previously unrecognized pattern unveiled using PAX2 and PAX8 immunohistochemistry. Mod Pathol 2013;26(6):792–798. doi:10.1038/modpathol.2012.239, PMID:23328975.
[66] Hajdinjak T. UroVysion FISH test for detecting urothelial cancers: meta-analysis of diagnostic accuracy and comparison with urinary cytology testing. Urol Oncol 2008;26(6):646–651. doi:10.1016/j.urolonc.2007.06.002, PMID:18367109.
[67] Halling KC, Kipp BR. Bladder cancer detection using FISH (UroVysion assay). Adv Anat Pathol 2008;15(5):279–286. doi:10.1097/PAP.0b013e3181832320, PMID:18724101.
[68] Smith GD, Riding M, Oswald K, Bentz JS. Integrating a FISH imaging system into the cytology laboratory. Cytojournal 2010;7:3. doi:10.4103/1742-6413.62258, PMID:20436794.
[69] Gomella LG, Mann MJ, Cleary RC, Hubosky SG, Bagley DH, Thumar AB, *et al*. Fluorescence in situ hybridization (FISH) in the diagnosis of bladder and upper tract urothelial carcinoma: the largest single-institution experience to date. Can J Urol 2017;24(1):8620–8626. PMID:28263126.
[70] Tapia C, Glatz K, Obermann EC, Grilli B, Barascud A, Herzog M, *et al*. Evaluation of chromosomal aberrations in patients with benign conditions and reactive changes in urinary cytology. Cancer Cytopathol 2011;119(6):404–410. doi:10.1002/cncy.20171, PMID:21732550.
[71] Oliveira MC, Caires HR, Oliveira MJ, Fraga A, Vasconcelos MH, Ribeiro R. Urinary Biomarkers in Bladder Cancer: Where Do We Stand and Potential Role of Extracellular Vesicles. Cancers (Basel) 2020;12(6):1400. doi:10.3390/cancers12061400, PMID:32485907.
[72] Chou R, Gore JL, Buckley D, Fu R, Gustafson K, Griffin JC, *et al*. Urinary Biomarkers for Diagnosis of Bladder Cancer: A Systematic Review and Meta-analysis. Ann Intern Med 2015;163(12):922–931. doi:10.7326/M15-0997, PMID:26501851.
[73] Wang J, Batourina E, Schneider K, Souza S, Swayne T, Liu C, *et al*. Polyploid Superficial Cells that Maintain the Urothelial Barrier Are Produced via Incomplete Cytokinesis and Endoreplication. Cell Rep 2018;25(2):464–477.e4. doi:10.1016/j.celrep.2018.09.042, PMID:30304685.
[74] Hentschel AE, van der Toom EE, Vis AN, Ket JCF, Bosschieter J, Heymans MW, *et al*. A systematic review on mutation markers for bladder cancer diagnosis in urine. BJU Int 2021;127(1):12–27. doi:10.1111/bju.15137, PMID:32539176.
[75] Dudley JC, Schroers-Martin J, Lazzareschi DV, Shi WY, Chen SB, Esfahani MS, *et al*. Detection and Surveillance of Bladder Cancer Using Urine Tumor DNA. Cancer Discov 2019;9(4):500–509. doi:10.1158/2159-8290.CD-18-0825, PMID:30578357.
[76] van Kessel KE, Beukers W, Lurkin I, Ziel-van der Made A, van der Keur KA, Boormans JL, *et al*. Validation of a DNA Methylation-Mutation Urine Assay to Select Patients with Hematuria for Cystoscopy. J Urol 2017;197(3 Pt 1):590–595. doi:10.1016/j.juro.2016.09.118, PMID:27746284.
[77] Rodriguez Pena MDC, Springer SU, Taheri D, Li L, Tregnago AC, Eich ML, *et al*. Performance of novel non-invasive urine assay UroSEEK in cohorts of equivocal urine cytology. Virchows Arch 2020;476(3):423–429. doi:10.1007/s00428-019-02654-1, PMID:31482302.
[78] Springer SU, Chen CH, Rodriguez Pena MDC, Li L, Douville C, Wang Y, *et al*. Non-invasive detection of urothelial cancer through the analysis of driver gene mutations and aneuploidy. Elife 2018;7:e32143. doi:10.7554/eLife.32143, PMID:29557778.
[79] de Paula R, Oliveira A, Nunes W, Bovolim G, Domingos T, De Brot L, *et al*. Two-year study on the application of the Paris system for urinary cytology in a cancer centre. Cytopathology 2020;31(1):41–46. doi:10.1111/cyt.12780, PMID:31654587.
[80] Bakkar R, Mirocha J, Fan X, Frishberg DP, de Peralta-Venturina M, Zhai J, *et al*. Impact of the Paris system for reporting urine cytopathology on predictive values of the equivocal diagnostic categories and interobserver agreement. Cytojournal 2019;16:21. doi:10.4103/cytojournal.cytojournal_30_19, PMID:31741668.
[81] Wang Y, Auger M, Kanber Y, Caglar D, Brimo F. Implementing The Paris System for Reporting Urinary Cytology results in a decrease in the rate of the "atypical" category and an increase in its prediction of subsequent high-grade urothelial carcinoma. Cancer Cytopathol 2018;126(3):207–214. doi:10.1002/cncy.21958, PMID:29278461.
[82] Xing J, Monaco S, Pantanowitz L. The Ability of The Paris System to Stratify the Risk of High-Grade Urothelial Carcinoma. Journal of the American Society of Cytopathology 2018;7(5):S43. doi:10.1016/j.jasc.2018.06.102.
[83] Zare S, Mirsadraei L, Reisian N, Liao X, Roma A, Shabaik A, *et al*. A Single Institutional Experience With the Paris System for Reporting Urinary Cytology: Correlation of Cytology and Histology in 194 Cases. Am J Clin Pathol 2018;150(2):162–167. doi:10.1093/ajcp/aqy043, PMID:29878037.
[84] Suh J, Go H, Sung C, Baek S, Hwang H, Jeong S, *et al*. Modification of The Paris System for urinary tract washing specimens using diagnostic cytological features. Cytopathology 2017;28(6):516–523. doi:10.1111/cyt.12450, PMID:28816366.
[85] Granados R, Duarte JA, Corrales T, Camarmo E, Bajo P. Applying the Paris System for Reporting Urine Cytology Increases the Rate of Atypical Urothelial Cells in Benign Cases: A Need for Patient Management Recommendations. Acta Cytol 2017;61(1):71–76. doi:10.1159/000452092, PMID:27838683.
[86] Hassan M, Solanki S, Kassouf W, Kanber Y, Caglar D, Auger M, *et al*. Impact of Implementing the Paris System for Reporting Urine Cytology in the Performance of Urine Cytology: A Correlative Study of 124 Cases. Am J Clin Pathol 2016;146(3):384–390. doi:10.1093/ajcp/aqw127, PMID:27543983.
[87] Vallamreddy SKR, Vaheda BK, Pratima J. Implementation of the Paris system versus institutional diagnosis in the performance of urinary cytology: A 5 years correlative study of 74 cases. IP Arch Cytol Histopathol Res 2019;4(3):193–198. doi:10.18231/j.achr.2019.037.
[88] Rai S, Lali BS, Venkataramana CG, Philipose CS, Rao R, Prabhu GL. A Quest for Accuracy: Evaluation of The Paris System in Diagnosis of Urothelial Carcinomas. J Cytol 2019;36(3):169–173. doi:10.4103/JOC.JOC_67_18, PMID:31359918.
[89] Roy M, Kaushal S, Jain D, Seth A, Iyer VK, Mathur SR. An institutional experience with The Paris System: A paradigm shift from ambiguous terminology to more objective criteria for reporting urine cytology. Cytopathology 2017;28(6):509–515. doi:10.1111/cyt.12448, PMID:28833848.
[90] Barocas DA, Boorjian SA, Alvarez RD, Downs TM, Gross CP, Hamilton BD, *et al*. Microhematuria: AUA/SUFU Guideline. J Urol 2020;204(4):778–786. doi:10.1097/JU.0000000000001297, PMID:32698717.
[91] Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, *et al*. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol 2016;196(4):1021–1029. doi:10.1016/j.juro.2016.06.049, PMID:27317986.
[92] Picozzi S, Ricci C, Gaeta M, Ratti D, Macchi A, Casellato S, *et al*. Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. J Urol 2012;188(6):2046–2054. doi:10.1016/j.juro.2012.08.017, PMID:23083867.
[93] Xylinas E, Kluth LA, Rieken M, Karakiewicz PI, Lotan Y, Shariat SF. Urine markers for detection and surveillance of bladder cancer. Urol Oncol 2014;32(3):222–229. doi:10.1016/j.urolonc.2013.06.001, PMID:24054865.
[94] Chen H, Liu L, Pambuccian SE, Barkan GA, Quek ML, Wojcik EM. Urine cytology in monitoring recurrence in urothelial carcinoma after radical cystectomy and urinary diversion. Cancer Cytopathol 2016;124(4):273–278. doi:10.1002/cncy.21650, PMID:26566001.
[95] Kurtycz DFI, Sundling KE, Barkan GA. The Paris system of Reporting Urinary Cytology: Strengths and opportunities. Diagn Cytopathol 2020;48(10):890–895. doi:10.1002/dc.24561, PMID:32780564.
[96] Otsuka M, Taguchi S, Nakagawa T, Morikawa T, Maekawa S, Miyakawa J, *et al*. Clinical significance of random bladder biopsy in primary T1 bladder cancer. Mol Clin Oncol 2018;8(5):665–670. doi:10.3892/mco.2018.1587, PMID:29725532.
[97] Yafi FA, Brimo F, Steinberg J, Aprikian AG, Tanguay S, Kassouf W. Prospective analysis of sensitivity and specificity of urinary cytology and other urinary biomarkers for bladder cancer. Urol Oncol 2015;33(2):66.e25–66.e31. doi:10.1016/j.urolonc.2014.06.008, PMID:25037483.
[98] Kamat AM, Hegarty PK, Gee JR, Clark PE, Svatek RS, Hegarty N, *et al*. ICUD-EAU International Consultation on Bladder Cancer 2012: Screening, diagnosis, and molecular markers. Eur Urol 2013;63(1):4–15. doi:10.1016/j.eururo.2012.09.057, PMID:23083902.
[99] Bubendorf L, Piaton E. UroVysion® multiprobe FISH in the triage of equivocal urinary cytology cases. Ann Pathol 2012;32(6):e52–e56. doi:10.1016/j.annpat.2012.09.207, PMID:23244486.
[100] Gayed BA, Seideman C, Lotan Y. Cost-effectiveness of fluorescence in situ hybridization in patients with atypical cytology for the detection of urothelial carcinoma. J Urol 2013;190(4):1181–1186. doi:10.1016/j.juro.2013.03.117, PMID:23583531.
[101] Skacel M, Fahmy M, Brainard JA, Pettay JD, Biscotti CV, Liou LS, *et al*. Multitarget fluorescence in situ hybridization assay detects transitional cell carcinoma in the majority of patients with bladder cancer and atypical or negative urine cytology. J Urol 2003;169(6):2101–2105. doi:10.1097/01.ju.0000066842.45464.cc, PMID:12771727.
[102] Yoder BJ, Skacel M, Hedgepeth R, Babineau D, Ulchaker JC, Liou LS, *et al*. Reflex UroVysion testing of bladder cancer surveillance patients with equivocal or negative urine cytology: a prospective study with focus on the natural history of anticipatory positive findings. Am J Clin Pathol 2007;127(2):295–301. doi:10.1309/ADJL7E810U1H42BJ, PMID:17210520.
[103] Lotan Y, Bivalacqua TJ, Downs T, Huang W, Jones J, Kamat AM, *et al*. Blue light flexible cystoscopy with hexaminolevulinate in non-muscle-invasive bladder cancer: review of the clinical evidence and consensus statement on optimal use in the USA - update 2018. Nat Rev Urol 2019;16(6):377–386. doi:10.1038/s41585-019-0184-4, PMID:31019310.
[104] Lerner SP, Goh A. Novel endoscopic diagnosis for bladder cancer. Cancer 2015;121(2):169–178. doi:10.1002/cncr.28905, PMID:25132313.
[105] Babjuk M, Burger M, Compérat EM, Gontero P, Mostafid AH, Palou J, *et al*. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. Eur Urol 2019;76(5):639–657. doi:10.1016/j.eururo.2019.08.016, PMID:31443960.
[106] Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, *et al*. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol 2017;71(3):447–461. doi:10.1016/j.eururo.2016.05.041, PMID:27324428.
[107] Kamat AM, Witjes JA, Brausi M, Soloway M, Lamm D, Persad R, *et al*. Defining and treating the spectrum of intermediate risk nonmuscle invasive bladder cancer. J Urol 2014;192(2):305–315. doi:10.1016/j.juro.2014.02.2573, PMID:24681333.
[108] Rosiello G, Pecoraro A, Palumbo C, Knipper S, Luzzago S, Deuker M, *et al*. Radical cystectomy plus chemotherapy in patients with pure squamous cell bladder carcinoma: a population-based study. World J Urol 2021;39(3):813–822. doi:10.1007/s00345-020-03247-3, PMID:32424515.
[109] Szarvas T, Módos O, Niedworok C, Reis H, Szendröi A, Szász MA, *et*

al. Clinical, prognostic, and therapeutic aspects of urachal carcinoma-A comprehensive review with meta-analysis of 1,010 cases. Urol Oncol 2016;34(9):388–398. doi:10.1016/j.urolonc.2016.04.012, PMID:27267737.

[110] Davaro F, Schaefer J, May A, Raza J, Siddiqui S, Hamilton Z. Invasive non-urachal adenocarcinoma of the bladder: analysis of the National Cancer Database. World J Urol 2019;37(3):497–505. doi:10.1007/s00345-018-2411-7, PMID:30030660.

[111] Chau C, Rimmer Frcr Y, Choudhury A, Leaning Frcr D, Law A, Enting D, *et al*. Treatment Outcomes for Small Cell Carcinoma of the Bladder: Results From a UK Patient Retrospective Cohort Study. Int J Radiat Oncol Biol Phys 2021;110(4):1143–1150. doi:10.1016/j.ijrobp.2021.02.003, PMID:33561506.

[112] Siefker-Radtke AO, Dinney CP, Abrahams NA, Moran C, Shen Y, Pisters LL, *et al*. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of the M. D. Anderson cancer experience. J Urol 2004;172(2):481–484. doi:10.1097/01.ju.0000132413.85866.fc, PMID:15247709.