Title

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Journal

Cancer Cytopathology, 133(1)

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Publication Date

2025

DOI

10.1002/cncy.22914

Peer reviewed

Received: 22 June 2024 | Revised: 5 September 2024 | Accepted: 23 September 2024

DOI: 10.1002/cncy.22914

ORIGINAL ARTICLE

Utility of The Paris System for Reporting Urinary Cytology in patients with HPV-positive urinary tract carcinoma

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Abstract

Background: Human papillomavirus (HPV)-positive urinary tract carcinomas (UTCas) have distinct morphology and molecular features with potential treatment implications. Cytomorphologic analysis of these tumors on urine cytology specimens has not yet been reported. The authors evaluated the cytomorphologic findings of HPV-positive UTCa on urine cytology using The Paris System for Reporting Urinary Cytology (TPS) criteria.

Methods: HPV-positive cases were identified by a retrospective review of surgical specimens that had UTCa confirmed by HPV in situ hybridization. Cases that had concurrent urine cytology were reviewed using TPS. Cytomorphologic features of high-grade urothelial carcinoma (HGUC) were evaluated as well as the presence of atypical squamous cells (ASCs) and basaloid features.

Results: Sixteen cytology specimens from eight patients with HPV-positive UTCa were included. On original diagnosis, none of the cytology specimens were suggested to be HPV-associated. TPS diagnostic criteria identified eight cases with at least atypical findings, including five HGUC cases, one case that was suspicious for HGUC, and two atypical urothelial cases. Common cytomorphologic features included basaloid clusters (six of eight cases; 75%) and ASCs (four of eight cases; 50%) that matched the corresponding surgical specimens. Most cases exhibited urothelial cell hyperchromasia (seven of eight cases; 88%), and hypochromasia was a frequently observed variant (four of eight cases; 50%), either alone or in addition to hyperchromasia.

Conclusions: HPV-positive UTCa can be identified reliably as HGUC by using TPS criteria; however, these cases may not be recognized as HPV-associated. The presence of basaloid cells or ASCs can help suggest screening for HPV in urine specimens. Larger scale studies are warranted to validate cytomorphologic differences and determine the impact of HPV infection on clinical outcomes for patients with UTCa.

KEYWORDS
atypical squamous cells, high-grade urothelial carcinoma, human papillomavirus-positive urethral and urothelial carcinomas, The Paris System for Reporting Urinary Cytology, urine cytology, urothelial carcinoma

INTRODUCTION

Urinary bladder cancer is the ninth most frequently diagnosed cancer worldwide[1] and the fourth most common malignancy in men within the United States, with over 80,000 new cases and approximately 17,000 deaths in the United States in 2022.[2] Urothelial carcinoma (UC), which accounts for about 90% of all bladder cancers, is by far the most common histologic type worldwide and is associated with risk factors that include smoking and exposure to various chemicals.[3] Human papillomavirus (HPV) is known to cause squamous cell carcinoma (SCC) of anogenital and oropharyngeal regions, and the coexistence of HPV has been reported in 96% of cervical cancers, 64% of anal cancers, 36% of penile cancers, and 41% of head and neck cancers.[4] Although some studies have suggested an association between HPV and urinary tract carcinoma,[5,6] the correlation between HPV and bladder cancer has remained a contentious issue. In 2011, a meta-analysis of 52 studies revealed that 16.88% of patients with bladder cancer tested positive for HPV.[5] However, recent research on this topic has yielded contradictory and inconclusive results, and reports on the coexistence of HPV and primary bladder cancer have reported various rates, ranging from 0% to 100%, with an overall prevalence of 16%.[7]

HPV-positive urethral and urothelial tract carcinomas (UTCas) are described sparsely in the literature[8,9] and, like HPV-positive SCCs in other regions, they have distinct morphology and molecular features with potential treatment implications.[10,11] An association between HPV infection and UTCa progression has been reported, particularly in terms of recurrence, which has been attributed to the presence of HPV E6 and E7 proteins in the urinary bladder, where the E6 and E7 proteins inhibit tumor-suppressing proteins and promote the development of cancer.[7] However, the clinical and prognostic significance of HPV detection in UTCa remains unclear.[12–15] A recent study evaluated the effect of HPV DNA on prognosis in UTCa and reported that, despite the lack of a statistically significant difference between HPV-positive and HPV-negative groups in terms of disease progression, patients with HPV-positive UTCa tended to have a higher frequency of tumor recurrence, unlike in other HPV-positive carcinomas.[7]

Urine cytology is a primary diagnostic modality for screening and surveillance of patients with UTCa. Urine cytology has high specificity for detecting high-grade UC (HGUC) using The Paris System for Reporting Urine Cytology (TPS).[16] TPS was first published in 2016 to propose a more standardized approach for UC detection. TPS defines clear cytomorphologic diagnostic criteria necessary for identifying atypical urothelial cells (AUCs), suspicious for HGUC (SHGUC), and HGUC, aiming for accurate HGUC diagnosis. To the best of our knowledge, cytomorphologic analysis and characterization of HPV-positive UTCa tumors in urine cytology specimens have not yet been reported in the literature. The goal of this study was to evaluate the cytomorphologic findings of HPV-positive UTCa on urine cytology using TPS criteria.

MATERIALS AND METHODS

Case selection

Approval of the study protocol was granted by the participating center's Institutional Review Board (IRB no. 17-21581). Cases of HPV-positive UTCa were identified by retrospective review of a pathology database for surgical specimens between 2015 and 2021 with histopathologic characterization and molecular testing, including high-risk HPV in situ hybridization (hrHPV-ISH) using the RNAscope 2.5 VS Probe-HPV-HR18 (Advanced Cell Diagnostics, Inc.) according to the manufacturer's instructions, in 4-μm formalin-fixed, paraffin-embedded tissue sections.

Prior signed-out surgical pathology reports in the anatomic pathology laboratory information system CoPathPlus (Cerner Corporation) were searched to identify qualified patients by using the search terms: "HPV positive," "HPV positive urothelial carcinoma," "HPV positive urethral and urothelial carcinoma," "atypical squamous cells," "high-grade urothelial carcinoma with squamous features," "carcinoma with squamous features," and/or "high-grade urothelial carcinoma with squamous differentiation." The original diagnoses for these cases included UC, carcinoma with urothelial and squamous features, and SCC.

After patient identification, HPV-positive cases that had concurrent urine cytology within 1 year of diagnostic surgical specimen collection were included (Figure 1). Patient demographics, indication for urine cytology, concurrent cystoscopy findings, specimen type, and primary tumor location were extracted from the electronic medical record system (EPIC; Epic Systems Corporation) by reviewing both clinical notes and demographic information.

Slide preparation and exclusion criteria

All urine cytology was processed using a liquid-based preparation (ThinPrep; Hologic, Inc.) and included one slide per case stained with the multichromatic histochemical Papanicolaou stain. Cell blocks and immunohistochemical stains were not performed on the urine specimens. Cases with urine cytology determined to be insufficient for

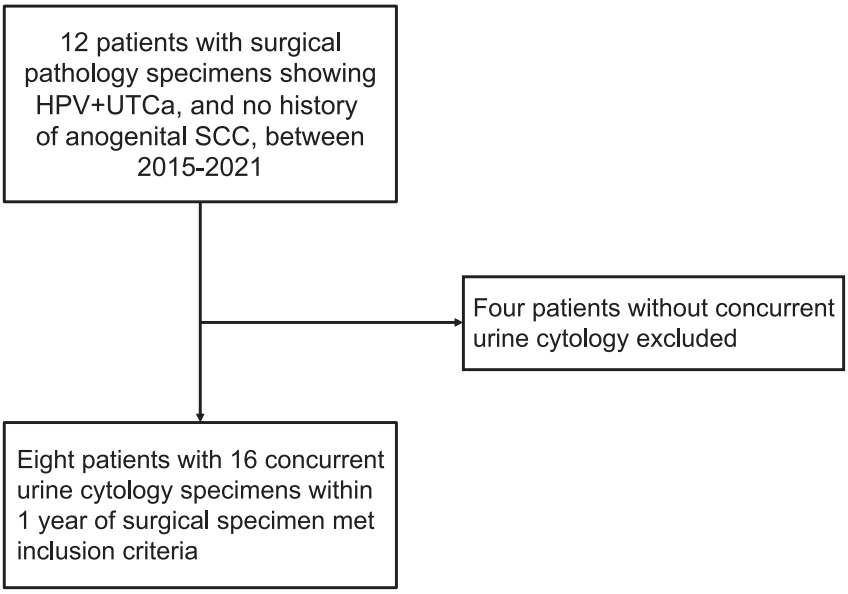

FIGURE 1 Inclusion and exclusion criteria. HPV+UTCa indicates HPV-positive urethral and urothelial tract carcinomas; SCC: squamous cell carcinoma.

evaluation, patients with a history of anogenital SCC, and cases with a suspicion of direct extension from the anogenital tract, including penile skin, vulva, cervix, and anus, were excluded.

Blinded review

The cases were randomized, and a blinded review of cytology slides was performed by a board-certified cytopathologist (P.V.) using TPS criteria.[16] A cytologic diagnosis was made by using TPS diagnostic categories, including negative for HGUC (NHGUC), AUCs, SHGUC, and HGUC. The following cytologic features, if present, were documented by the cytopathologist for each specimen: (1) increased nuclear-to-cytoplasmic (N:C) ratio, (2) nuclear hyperchromasia, (3) irregular nuclear membrane (nuclear border), and (4) irregular chromatin (coarse or clumped). In addition, the presence of nuclear hypochromasia, keratinization, basaloid cells, and atypical squamous cells was noted. The diagnosis of ASCs was reserved for keratinized squamous cells with spindle/tadpole morphology, enlarged hyperchromatic nuclei with irregular nuclear borders, and/or smudgy chromatin. Basaloid cells were defined as cohesive clusters of urothelial cells with smaller size, a minuscule amount of cytoplasm, a higher N:C ratio than the minimum TPS criteria for HGUC (N:C ratio, 0.8–0.9), and hyperchromatic, round-to-oval nuclei. Although basaloid cells in HPV-positive UTCa met HGUC criteria because of a high N:C ratio and hyperchromatic nuclei, their cytologic features, such as small cell size and minimal cytoplasm, were used to help distinguish them from conventional HGUC. Tumor quantitation was performed for cases with diagnoses of HGUC and SHGUC by using quantitation ranges previously used for assessing the number of malignant cells in urine cytology samples (less than five, from six to 10, 11–15, 16–20, 21–50, 51–100, or greater than 100 malignant cells).[17]

RESULTS

Twelve patients were identified who had HPV-positive UTCa surgical specimens; of these, four were excluded because of a lack of concurrent urine cytology specimens. The study cohort included the remaining eight patients with HPV-positive UTCa who had 16 urine cytology specimens (eight instrumented, eight voided urine). Cystoscopy indications were hematuria or surveillance of UC. The patients ranged in age at diagnosis from 56 to 72 years (mean age, 64.6 years) and included three women and five men (Table 1) with primary UTCa affecting the urinary bladder and/or the penile, prostatic, or female urethra. TPS criteria were not uniformly used by the original pathologists during the study period: the original urine cytology diagnoses included carcinoma, suspicious for carcinoma, SCC, malignant, or benign; and inflammation was frequently added as a qualifier in the diagnostic line. The original diagnoses did not suggest that any cytology specimens were HPV-associated. Three patients with HPV-positive UTCa exclusively had benign urine cytology classified as NHGUC.

On re-review, TPS diagnostic criteria identified eight cytology cases from five patients who had at least atypical findings, including five malignant cases (four HGUC with squamous features, one HGUC), one SHGUC, and two AUC cases (Table 1). The primary tumor location in these cases included the penile urethra, prostatic urethra, and female urethra. Seven cytology specimens had concordant diagnoses with the original pathologist despite language

TABLE 1 Cytomorphologic features in urine cytology of human papillomavirus-positive urethral and urothelial tract carcinoma.

Sex (age, years)	Surgical pathology diagnosis	Primary tumor location	Cytology specimen type	Cytology diagnosis	High N:C ratio[a]	Hyperchromasia	Hypochromasia (variant)[b]	Coarse chromatin	Irregular nuclear membranes	Keratinization	Atypical squamous cells	Basaloid cells
					TPS HGUC features					Additional features		
Male (56)	HGUC with extensive squamous features	Penile urethra	Instrumented (catheterized)	HGUC with squamous features	+	+	−	+	+	+	+	+
Male (70)	HGUC with focal squamous features	Penile urethra	Instrumented (bladder washing)	HGUC with squamous features	++	+	+	+	+	+	+	+
Male (64)	HGUC with focal squamous features	Prostatic urethra	Voided	HGUC with focal squamous features	++	+	−	+	+	+	+	+
			Instrumented (catheterized)	AUCs	+	+	−	+	+	−	−	−
			Voided	AUCs	+	+	+	+	+	−	−	−
			Voided	Suspicious for HGUC	++	+	−	+	+	−	−	+
Female (72)	HGUC	Female urethra	Instrumented (bladder washing)	HGUC	++	+	+	+	+	−	−	+
Male (65)	SCC	Penile urethra	Instrumented (bladder washing)	HGUC with squamous features	++	−	+	+	+	+	+	+

Note: Atypical squamous cells are defined as keratinized squamous cells with spindle/tadpole morphology, enlarged hyperchromatic nuclei with irregular nuclear borders, and/or smudgy chromatin. Basaloid cells are defined as urothelial cells with a high N:C ratio, scant cytoplasm, and hyperchromatic nuclei, arranged in cohesive clusters.

Abbreviations: AUCs, atypical urothelial cells; HGUC, high-grade urothelial carcinoma; HPV, human papillomavirus; N:C ratio, nuclear-to-cytoplasmic ratio; SCC, squamous cell carcinoma; TPS, The Paris System for Reporting Urinary Cytology.

[a]N:C ratio: ++ indicates >0.7, +, >0.5.

[b]Hypochromasia variant identified.

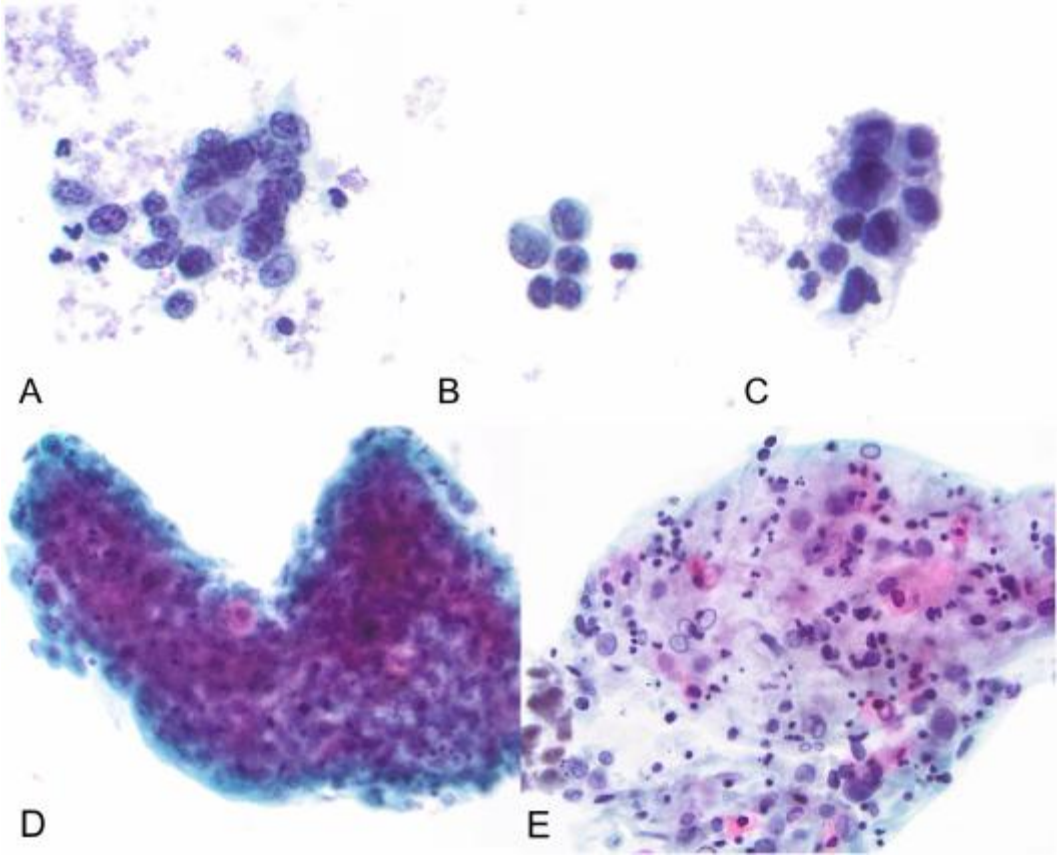

FIGURE 2 (A–E) Cytomorphologic features of HPV-positive UTCa, seen here on ThinPrep smears with Papanicolaou stain, include (A–C) basaloid features exhibiting cohesive clusters of cells with very scant cytoplasm (nuclear-to-cytoplasmic ratio, 0.8–0.9) and hyperchromatic nuclei, (D) basaloid clusters with squamous differentiation, and (E) mixed populations of hyperchromatic and hypochromatic nuclei with squamous features and atypical squamous cells (original magnification ×60 in A–C, ×40 in D and E). HPV indicates human papillomavirus; UTCa, urethral and urothelial tract carcinoma.

differences in diagnoses before and after implementing TPS criteria for reporting. One cytology specimen was upstaged from suspicious for carcinoma to HGUC with focal squamous features because of the presence of high-grade nuclear features and included focal keratinization and basaloid clusters. The eight cases initially diagnosed as NHGUC were again classified as NHGUC on re-review.

Common cytomorphologic features in urine specimens from patients with HPV-positive UTCa included basaloid clusters (six of eight patients; 75%; Figure 2) and ASCs (four of eight patients; 50%; Figure 3), matching the morphologic findings in corresponding, subsequent surgical resection specimens. Most cases showed urothelial cell hyperchromasia (seven of eight patients; 88%). Hypochromasia was a frequently observed variant (four of eight patients; 50%), either alone or in addition to hyperchromasia. No notable differences were observed regarding patient demographics or the method of specimen collection; there was a similar distribution in the 16 urine cytology specimens of positive and negative diagnoses in instrumented urine specimens (positive of in five eight specimens, negative in three of eight specimens) and voided urine specimens (positive in three of eight specimens, negative in five of eight specimens). Tumor quantitation revealed that the majority of the HGUC cases (four of five) had >100 malignant cells identified, whereas the remaining case (one of five) had between 51 and 100 malignant cells. In the single case diagnosed as SHGUC, from six to 10 malignant cells were identified. In addition, all HGUG and SHGUC cases displayed clusters of high-grade malignant cells with at least five cells per cluster, and most HGUC cases (four of five) also contained a single, high-grade malignant cell.

During the study period from 2015 to 2021, our institution received and reviewed a total volume of 11,065 urine cytology specimens, diagnosing 1050 cases of HGUC (detection rate of 9.5%). Among five HGUC specimens in our patient cohort, the incidence of HPV-positive UTCa with HGUC urine cytology was <1% (five of 1050).

DISCUSSION

HPV-associated UTCas are uncommon, and their clinical and pathologic features have been minimally described in the literature. These tumors in the urinary bladder are noted in association with neurogenic bladder and repetitive catheterization.[18] Like HPV-positive

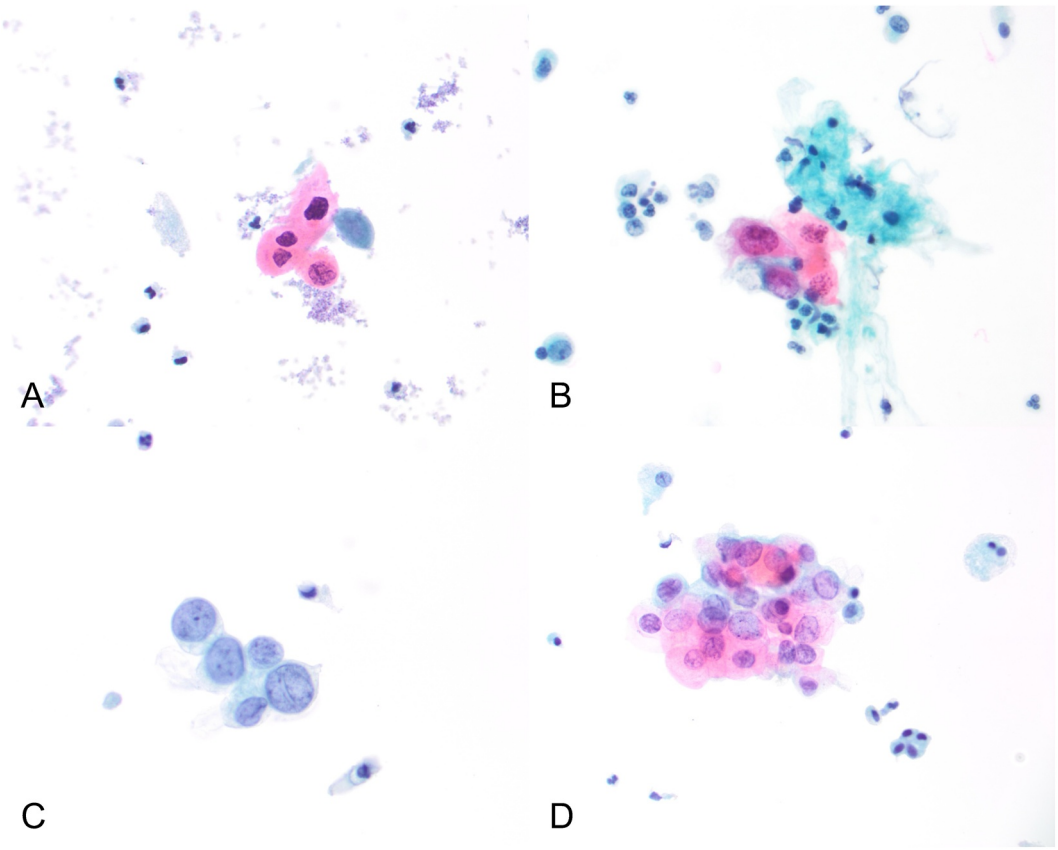

FIGURE 3 (A) Keratinizing cells and (B) atypical squamous cells were frequently seen in ThinPrep smears with human papillomavirus-positive urethral and urothelial tract carcinoma (Papanicolaou stain). Nuclear hypochromasia was a commonly seen variant in either (C) nonkeratinizing cells or (D) keratinizing cells (original magnification ×60 in A, C, and D; ×40 in B).

SCC found in oropharyngeal and anogenital regions, HPV-positive UTCa demonstrates a basaloid morphology and aberrant p16 expression by immunohistochemistry.[8,18] Accumulating evidence suggests that hrHPV has a distinct role in UTCa pathogenesis and that HPV-positive UTCa is a unique entity.[8]

A recent study reported that HPV-positive UC had a higher proportion of squamous differentiation, and the detection rate of HPV was six times greater in UTCa cases with squamous differentiation versus cases of usual and other histologic subtypes of UTCa. It also was reported that all HPV-positive cases had a high histologic grade and a greater proportion of muscle-invasive tumors.[19]

It is well documented that HPV-associated SCCs in anogenital and oropharyngeal regions exhibit basaloid morphology and reduced keratinization compared with their HPV-negative counterparts.[20] The histomorphologic and molecular characteristics of HPV-positive UTCa in the subsequent surgical specimens from these cases were published in another article from our institution,[8] which reported that HPV-positive UTCa displayed morphologic, immunohistochemical, and molecular characteristics similar to those of HPV-positive SCC found in other locations. In that study, all HPV-positive UTCas on histology displayed more prominent basaloid features compared with HPV-negative, squamous-predominant UTCa. In addition, fewer moderately differentiated to well differentiated squamous areas were observed in HPV-positive UTCas compared with HPV-negative UTCas. The remaining tumor areas often lacked squamous differentiation, resembling poorly differentiated carcinoma. This finding is reminiscent of previous studies from various anatomic locations, highlighting that HPV-positive UTCa shows characteristic basaloid and poorly differentiated morphology with fewer or absent squamous features, mimicking conventional HGUC.

In our study, the urine cytology specimens from patients with HPV-positive UTCa showed cohesive basaloid clusters of urothelial cells with smaller size, high N:C ratio (range, 0.8–0.9), scant cytoplasm, and hyperchromatic nuclei in 75% of cases, mirroring the morphologic findings observed in subsequent surgical specimens. All cases diagnosed as HGUC had readily identifiable high-grade malignant cells with the quantity of cells predominantly present in quantities of >100 per specimen and, at a minimum, in the range of 51–100 high-grade cells. It should be noted that nonkeratinizing basaloid cells can be indistinguishable from HGUC in cytology but are often smaller in size, with a minuscule amount of cytoplasm, compared with the cells seen in conventional HGUC. This similarity to conventional UC underscores the importance of further investigation, such as hrHPV-ISH or p16 staining with confirmatory hrHPV-ISH, to differentiate HPV-positive UTCa from its mimics.[8]

ASCs are scarcely reported in the UC literature, with an incidence of 0.3%–0.9% of urine specimens.[21,22] ASCs are defined as keratinizing squamous cells with large, hyperchromatic nuclei; a high N:C ratio; abnormal nuclear and cytoplasmic shapes; and dense, eosinophilic cytoplasm. These cells can appear singly or in clusters that are neither qualitatively nor quantitatively adequate for malignancy.[16] The majority of ASCs reportedly are associated with benign conditions, such as reactive changes, inflammation, and infection. However, they may be observed with malignancy in up to 20%–30% of cases; and in those with highly suspicious cytology that have extreme squamous atypia and pleomorphism, ASCs can be associated with cancer in up to 60% cases.[23] Malignancies associated with ASCs include HGUC with squamous differentiation and primary SCC; and, occasionally, they may result from involvement with other sites, such as the cervix or vagina.[24] The second edition of TPS[16] incorporates ASCs and recommends that a diagnosis of ASCs should be made in the presence of significant atypia and should be mentioned in cytology reports because occasionally isolated ASCs may represent the only evidence of an unsampled high-grade malignancy.[25,26] A recent study by Ho and Elsheikh evaluated the objective grading of squamous atypia in UC and the correlation of ASCs with concurrent UTCa and the risk of high-grade malignancy (ROHM). Those authors reported that the overall ROHM in ASCs ranged from 50% to 68%, and ASCs with high-grade atypia had a significantly higher ROHM versus ASCs with low-grade squamous atypia, with rates of 50% and 87%, respectively. Their findings emphasized the importance of noting ASCs and their grade of atypia in cytology reports, and clinicians should be alerted to the significance of these cells in urine cytology.[25] In our study, ASCs were noted in 80% (four of five) of HGUC cases, also suggesting that ASCs may represent morphologic evidence of an unsampled, HPV-positive UTCa.

Hypochromasia is a known nuclear variant observed in HGUC and was identified in 10.2% of HGUC specimens in a study of 117 cases by Stern and Siddiqui.[27] Similar to their findings of hypochromatic tumor cells seen either as an isolated feature of the tumor cells or in concert with hyperchromatic tumor cells, our study demonstrated nuclear hypochromasia in cases of both AUC and HGUC (four of eight cytology specimens; 50%). When present, hypochromasia was readily identified in tumor cells, including one case in which only hypochromasia was seen in conjunction with other TPS criteria for HGUC.

Limitations of our study include the rarity of HPV-positive UTCa, the retrospective analysis of cases, the small number of surgical cases identified as HPV-positive UTCa with an incidence <1% of HGUC diagnoses, and a lack of concurrent urine cytology for all cases. As a tertiary care center, concurrent urine cytology may be performed at outside medical institutions and may not be submitted concurrently with surgical biopsy, resection, or consultation review of surgical pathology slides. The identification of cytomorphologic features on urine cytology may prompt prospective workup of tumors for HPV status.

HPV-positive UTCa can be identified reliably, from at least AUCs up to HGUC, by using TPS. However, these cases may not be recognized as HPV-associated. Identifying the presence of basaloid cells, which are reflective of tumor morphology on surgical resection,[18] or ASCs in urine cytology specimens can help suggest screening for HPV on urine specimens or on concurrent surgical biopsy or resection specimens by hrHPV-ISH testing. Our findings further support the recommendation by TPS that ASCs should be consistently reported when identified. The cytomorphologic features in urine cytology in HPV-positive UTCa have not been reported previously; therefore, our study provides new findings on these cases. Because HPV-positive UTCa is a distinct entity[9] with possible divergent treatment regimens, more extensive studies are warranted to validate cytomorphologic differences and determine the impact of HPV infection on the clinical outcomes of patients with UTCa.

AUTHOR CONTRIBUTIONS

Kara Tanaka: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing–original draft, and writing–review and editing. **Neslihan Kayraklioglu**: Conceptualization, data curation, formal analysis, investigation, methodology, and writing–review and editing. **Emily Chan**: Conceptualization, formal analysis, investigation, methodology, and writing–review and editing. **Chien-Kuang C. Ding**: Conceptualization and writing–review and editing. **Poonam Vohra**: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, writing–original draft, and writing–review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest.

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How to cite this article: Tanaka K, Kayraklioglu N, Chan E, Ding C-KC, Vohra P. Utility of The Paris System for Reporting Urinary Cytology in patients with HPV-positive urinary tract carcinoma. *Cancer Cytopathol*. 2025;e22914. doi:10.1002/cncy.22914