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ORIGINAL ARTICLE

Atypical urothelial cells classified according to the Paris System for Reporting Urinary Cytology: A 2-year experience with histological correlation from a Finnish tertiary care center—low rate and high risk of malignancy

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Abstract

Background: The Paris System for Reporting Urinary Cytology (TPS) was issued to shift the focus of urine cytology to high-grade lesions to increase the diagnostic accuracy of urine cytology. The aim of this study was to evaluate the power of TPS in the atypical urothelial cells (AUC) category with histological correlation and follow-up.

Methods: The data cohort consisted of 3741 voided urine samples collected during a 2-year period between January 2017 and December 2018. All samples were prospectively classified using TPS. This study focuses on the subset of 205 samples (5.5%) classified as AUC. All cytological and histological follow-up data were analyzed until 2019, and the time between each sampling was documented.

Results: Of the 205 AUC cases, cytohistological correlation was possible in 97 (47.3%) cases. Of these, 36 (12.7%) were benign in histology, 27 (13.2%) were low-grade urothelial carcinomas, and 34 (16.6%) were high-grade urothelial carcinomas. Overall, the risk of malignancy was 29.8% for all cases in the AUC category, and 62.9% in the histologically confirmed cases. The risk of high-grade malignancy was 16.6% in all the AUC category samples and 35.1% in the histological follow-up group.

Conclusions: The performance of 5.5% AUC cases is considered good and within the limits proposed by TPS. TPS is widely accepted by cytotechnologists, cytopathologists, and clinicians; it improves communication and patient management.

KEYWORDS
atypia, atypical urothelial cells, Paris System, urinary cytology, urine

INTRODUCTION

The Paris System for Reporting Urinary Cytology (TPS) was released in 2016. TPS aims to standardize the cytologic diagnostic criteria in urine cytology and focuses on high-grade malignancies to improve diagnostic output in cytology. TPS contains six diagnostic categories: negative for high-grade urothelial carcinoma (NHGUC), atypical urothelial cells (AUC), suspicious for high-grade urothelial carcinoma (SHGUC), high-grade urothelial carcinoma (HGUC), low-grade urothelial neoplasm (LGUN), and other malignances. Each category has strictly defined cytomorphological criteria, to ensure that the cytological evaluation is homogeneous and reproducible.[1]

The AUC category is frustrating for clinicians and especially for patients. On histological follow-up, it includes both benign and malignant entities.[2] Reviews by Pastorello et al.[3] and Cowan and VandenBussche[4] found that the number of atypical cytological samples decreased in most studies after the introduction of TPS. However, in one study, the number conversely increased from 3% to 24.2%.[5]

Our study is based on cases from a Finnish tertiary care university hospital and focuses on AUC category of TPS with cytohistological correlation and a follow-up of 2 years.

MATERIALS AND METHODS

All urine cytology samples were fixed in 50% ethanol, cytospun, and stained by Papanicolaou stain. The samples were first screened by a cytotechnologist, after which a cytopathologist evaluated the samples and signed them out. Three cytopathologists, each with at least 20 years of experience, signed out all the non-NHGUC cases. Only the NHGUC cases were signed-out by general pathologists. All cases were diagnosed at the Department of Pathology, Fimlab Laboratories, Tampere, Finland, during a 2-year period (January 2017–December 2018). The cytological diagnoses were made prospectively according to TPS, and the timeframe for histological follow-up lasted until 2019. The time spans between cytological and histological diagnoses were also calculated. Statistical analysis was performed using IBM SPSS Statistics 27 (IBM, Armonk, New York). This study was conducted according to the Declaration of Helsinki and approved by the Regional Ethics Committee of Pirkanmaa Hospital District (R17174). Informed consent from patients was not requested.

RESULTS

A total of 3741 voided urine cytology samples were analyzed in a 2-year period. Of these, 49 (1.31%) were insufficient, 3334 (89.1%) were placed in NHGUC category, 205 (5.5%) in the AUC category, 89 (2.4%) in the SHGUC category, 62 (1.66%) in the HGUC category, and two (0.01%) in the LGUN category (see Table 1).

Of the 205 samples diagnosed as AUC, 34 cases (16.6%) had no cytological or histological follow-up in the 0.5- to 2.5-years period (Figure 1). A repeated cytological sample was the most common primary follow-up, occurring in 111 (54.1%) cases. Biopsies were taken after an AUC-diagnosed sample in 44 (21.5%) cases. Both a biopsy and a cytological sample were taken simultaneously in 16 (7.8%) cases. Sometimes, multiple cytological and/or histological samples were taken at the same time; these are consolidated as one sample in Figure 1.

TABLE 1 Distribution of cytological diagnoses.

Diagnosis	No. of cases (%)
Insufficient material for diagnosis	49 (1.3)
Negative for high grade urothelial carcinoma	3334 (89.1)
Atypical urothelial cells	205 (5.5)
Suspicious for high grade urothelial carcinoma	89 (2.4)
High grade urothelial carcinoma	62 (1.7)
Low-grade urothelial neoplasms	2 (0.01)
Total	3741 (100.0)

The timespan between the first AUC diagnosis and the first follow-up sample (histological or cytological) was 2.9 months on average (range, 0–25 months).

A cytological sample was the only follow-up in 56 cases (27.3%). There were 160 cases with cytological follow-up samples available and 468 cytological urine follow-up samples in total. The first follow-up cytological sample was taken within 1 month of the AUC diagnosis in 56 cases (27.3%), between 1 and 2 months after diagnosis in 23 cases (11.2%), and after 2 months in the rest of the cases (45.5%). The longest time between AUC diagnosis and follow-up cytology sample was 25 months (1 case).

Of the 468 follow-up cytological samples 329 (70.3%) were categorized as NHGUC, 84 (17.9%) as AUC, 39 (8.3%) as SHGUC, and 13 (2.8%) as HGUC; three samples (0.6%) were insufficient. The distribution of TPS categories in the follow-up specimens is presented in Table 2.

At least one histological follow-up sample was available in 97 (47.3%) of the cases. In total, there were 152 histological follow-up samples. The first biopsy was taken within 1 month of the AUC diagnosis in 18 (8.8%) cases, between 1 and 2 months after diagnosis in 33 (16.1%) cases, and after 2 months in the rest (22.4%). The longest time between AUC diagnosis and follow-up histological sample was 25 months (one case).

The distribution of the time elapsed between AUC sample and histological follow-up sample was as follows: 1 month in 60 (29.3%) cases, 2 months in 23 (11.2%) cases, 3 months in 11 (5.4%) cases, 4 months in one (0.5%) case, and 5 months in two (1.0%) cases.

The distribution of histological diagnoses is presented in Figure 2. There were 34 (16.6%) high-grade papillary urothelial carcinomas and 27 (13.2%) low-grade papillary urothelial carcinomas. In the high-grade papillary urothelial carcinoma group, 17 (8.3%) samples were infiltrating carcinomas (15 [88.2%] cases originated from urinary bladder and two [11.8%] cases originated from ureter), and

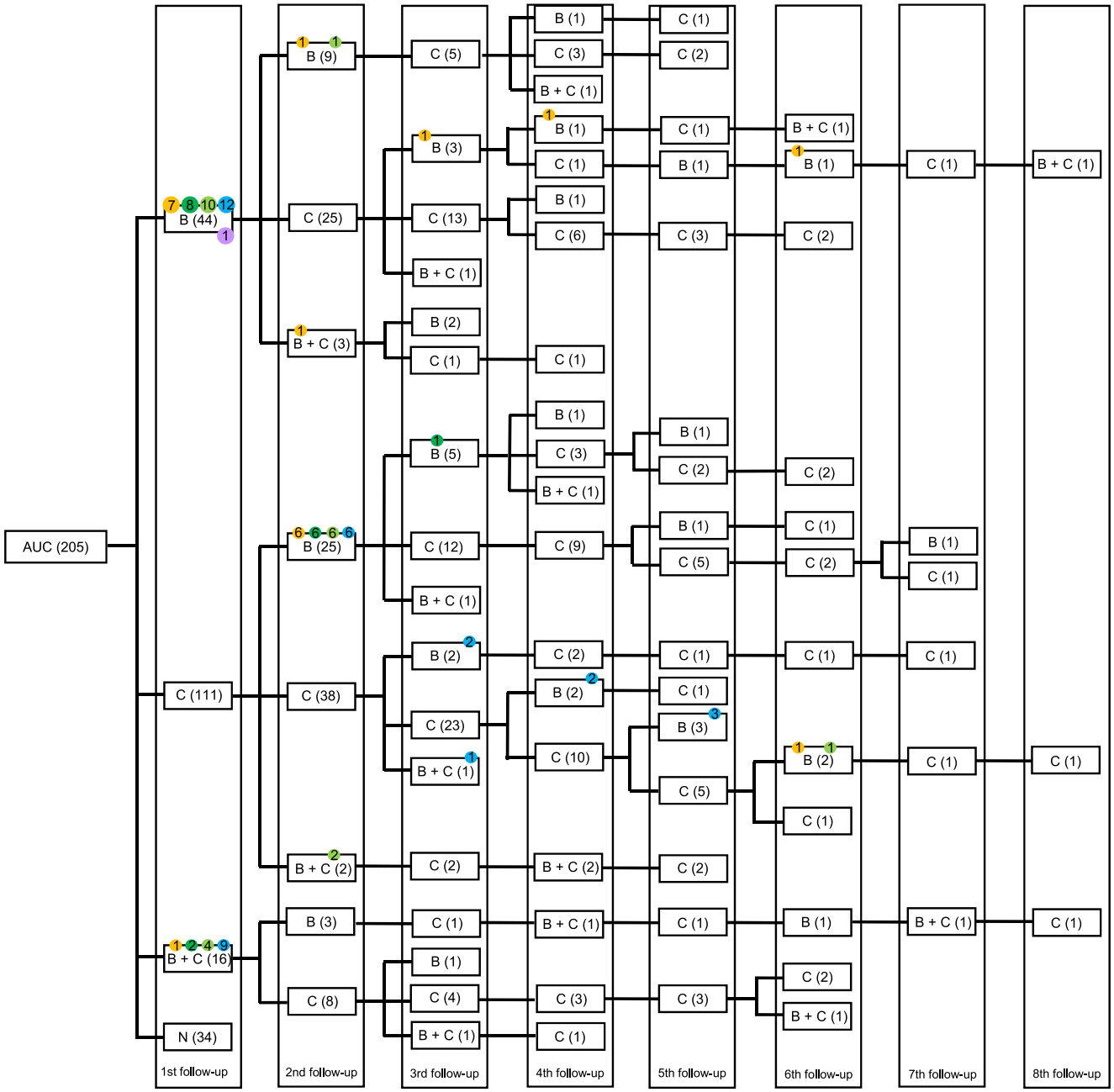

FIGURE 1 Diagnostic follow-up after cytological sample categorized as atypical urothelial cells (AUC). Follow-up was either histological sample (B), cytological sample (C), or both simultaneously (B + C). In some cases, there was no follow-up (N). Final histological diagnoses are color-coded as follows; yellow for infiltrating urothelial carcinoma, dark green for noninvasive high-grade urothelial carcinoma, light green for noninvasive low-grade urothelial carcinoma, blue for normal or reactive cells and purple for insufficient material for diagnosis.

17 (8.3%) were noninvasive carcinomas (13 [76.5%] cases originated from urinary bladder and four [23.5%] cases originated from renal pelvis/ureter). In the low-grade papillary urothelial carcinoma group, three (1.5%) samples were infiltrating carcinomas (two [66.7%] cases originated from urinary bladder and one [33.3%] case from renal pelvis) and 24 (11.7%) were noninvasive carcinomas (23 [95.8%] cases originated from urinary bladder and one case [4.2%] from renal pelvis) (Figure 2). Cytohistological correlation of an AUC case with final histopathological diagnosis of high-grade noninvasive papillary urothelial carcinoma is illustrated in Figure 3.

There were 36 (17.6%) benign histological diagnoses. The "no tumor" category contained both normal histological findings and various reactive and inflammatory changes (see Table 3). Cytohistological correlation of an AUC case with final histopathological diagnosis of inflammation is illustrated in Figure 4. The inflammation was granulomatous in four (2.0%) cases, acute in one (0.5%) case, and chronic in three (1.5%) cases. There were seven (3.4%) cases with metaplastic changes (Table 3).

The risk of malignancy (ROM) was 29.8% in all the AUC category samples and 62.9% in the histological follow-up group. The risk of

high-grade malignancy (ROHM) was 16.6% in all the AUC category samples and 35.1% in the histological follow-up group. Notably, the final histological diagnosis was found in the first biopsy in 90 cases (43.9%), as shown in Figure 1. In five (2.4%) cases, the infiltrating urothelial carcinoma was found only after several negative biopsies.

TABLE 2 Distribution of cytological diagnoses in follow-up samples after primary sample categorized as atypical urothelial cells.

Diagnosis	No. of cases (%)
Insufficient material for diagnosis	3 (0.6)
Negative for high grade urothelial carcinoma	329 (70.3)
Atypical urothelial cells	84 (17.9)
Suspicious for high grade urothelial carcinoma	39 (8.3)
High grade urothelial carcinoma	13 (2.8)
Total	468 (100.0)

TABLE 3 Distribution of histologically benign diagnoses after primary cytological sample categorized as atypical urothelial cells.

Diagnosis	No. of cases (%)
Granulation tissue	2 (1.0)
Hyperkeratosis	1 (0.5)
Metaplasia, squamous	7 (3.4)
Normal tissue or no malignancy	11 (5.4)
Inflammation	13 (6.3)
NOS	5 (2.4)
Granulomatous	4 (2.0)
Acute	1 (0.5)
Chronic	3 (1.5)
Insufficient material	1 (0.5)
Total	35 (17.1)

Note: The percentage (%) is calculated using only the samples with histological follow-up.

Abbreviation: NOS, not otherwise specified.

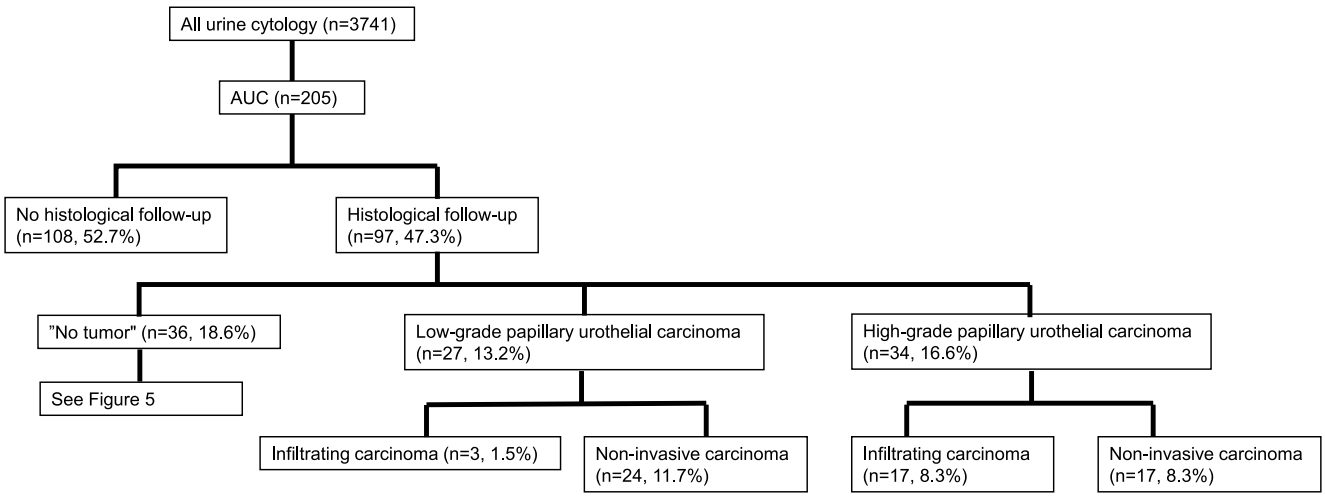

FIGURE 2 Distribution of histological diagnoses after primary cytological sample categorized as atypical urothelial cells (AUC). There were 34 (16.6%) samples categorized as high-grade papillary urothelial carcinomas and 27 (13.2%) as low-grade papillary urothelial carcinomas. In the high-grade papillary urothelial carcinoma group, 17 (8.3%) samples were infiltrating carcinomas, and 17 (8.3%) were noninvasive carcinomas. In the low-grade papillary urothelial carcinoma group 3 (1.5%) samples were infiltrating carcinomas, and 24 (11.7%) were noninvasive carcinomas.

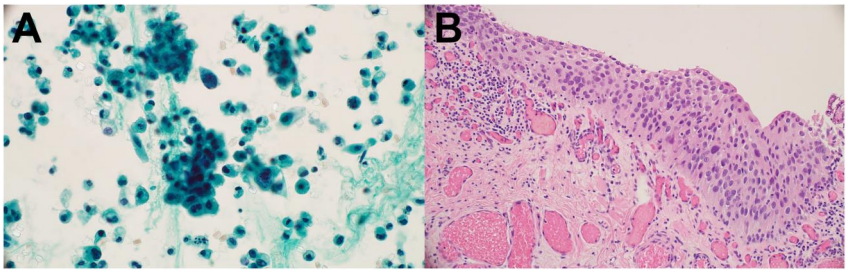

FIGURE 3 Cytohistological correlation of an AUC case (A) with final histopathological diagnosis of high-grade noninvasive papillary urothelial carcinoma (B).

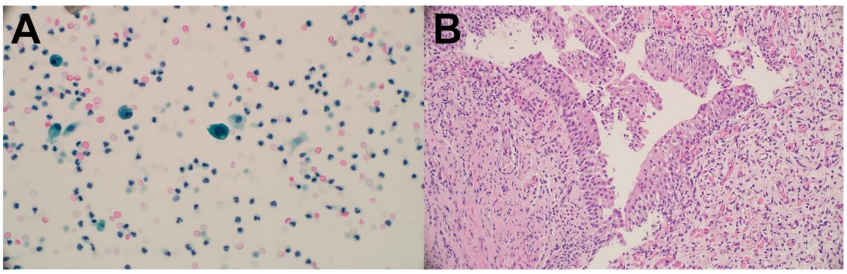

FIGURE 4 Cytohistological correlation of an AUC case (A) with final histopathological diagnosis of inflammation (B).

DISCUSSION

George Papanicolaou introduced the term atypia/atypical into cytology without a strict definition. As attempts at terminological standardization (e.g., TPS) progress, the term "atypia" has come to succeed due to well-defined criteria and ROM determination as well as close follow-up management.[2,6] The main goal of TPS is to reduce the atypia rate in urine cytology at the individual, laboratory, and community levels and consequently to increase clinicians' and the patients' confidence in cytological diagnoses.[2,6]

During the 2-year prospective study period, our rate of AUC diagnoses in urine cytology was 5.5%, which is considered good performance. In the second edition of TPS, the suggested frequency of AUC diagnosis is 5%–15%,[7] so our results are in the lower limit of the range. All our specimens, except the negative ones, were signed out by three cytopathologists. This may be one reason for the low rate of AUC diagnosis, because it is easier to keep the criteria strict and the threshold for consultations low among only a few cytopathologists.

In the pre-TPS era, there was high variability in the use of the atypia category with some studies reporting rates as high as 54.3%[8] and 59.8%.[9] A massive literature analysis of 30,802 cases produced a mean value of 23.2%, with a range of 4.7%–59.8%.[3] Importantly, the highest reported rates of atypia diagnoses each decreased in the post-TPS era to 8.5% and 41.5%, respectively.[8,9] Generally, there was a decrease in atypical samples after TPS implementation. The literature analysis of 30,802 cases revealed a post-TPS AUC range of 1.2%–41.5% with a mean value of 10.4%; this is within the limits suggested by TPS.[3] Another analysis showed a decrease in range from 18.6%–39% in the pre-TPS era to 14.4%–26% in the post-TPS era.[4] Single studies have shown lower rates of AUC results than ours: a French real-life study showed an AUC rate of 5.18%, a decrease from the 6.12% pre-TPS rate,[10] and an Indian university hospital-based reclassification study showed a 5.1% rate, a decrease from 11.9%.[11]

Surprisingly, a Spanish group reported an increase in AUC rates in their study: there was an 8-fold increase (from 3% to 24.2%) in histologically benign cases, a 10-fold increase (from 2.5% to 25%) in histologically low-grade carcinomas, and a 2.4-fold increase (from 6.6% to 15.8%) in histologically high-grade carcinomas. Their explanation was that increased nuclear/cytoplasmic (N/C) ratios of >0.5 were also found in benign and low-grade neoplasms and this consequently led to a 3.1-fold increase in false-positive cases.[5] The study failed to recognize that according to TPS AUC diagnosis requires more than just an elevated N/C ratio. A recent study importantly pointed out that enlarged nuclear size and the presence of nucleolus are also important diagnostic features in AUC cases.[12]

Several studies have investigated N/C ratio reproducibility. In one study, interobserver variance decreased with increased N/C ratio.[13] Similarly, Zhang et al.[14] observed 70% agreement with <0.5 N/C ratio images, 67.6% agreement with ≥0.5 and <0.7 N/C ratio images, and 93.9% agreement with ≥0.7 N/C ratio images. Nevertheless, findings by Layfield et al.[15] showed the opposite: with increased N/C ratio, the accuracy and precision of estimates decreased. Despite an absolute interrater agreement of 75%, cases with a true N/C ratio between 0.4 and 0.8 were accurately classified only 53% of the time. The Taiwan Society of Clinical Cytology organized an online survey on the cytomorphological TPS criteria that showed generally poor interobserver concordance. The overall agreement for N/C ratio was 65.9%, for hyperchromasia 58.1%, for nuclear membrane irregularities 60.2%, and for chromatin clumping 79.2% with Fleiss' κ coefficients of 0.386, 0.128, 0.152, and 0.239, respectively.[16] Three AUC cases surveyed in this study showed agreement of 40.88%, 44.53%, and 56.93% regarding AUC diagnoses.[16] In a study by Mikou et al.,[17] there was a diagnostic consistency rate of 93.27% in AUC cases. There were discrepancies between the AUC and NHGUC categories ($n = 3$) and between the AUC and SHGUC categories ($n = 4$).[17]

The accurate assessment of N/C ratio cutoff is crucial to avoid both over- and misdiagnosis. Our results show that this is not happening in our department. Continuous monitoring of rates is necessary as fluctuation in rates over 22 years was well documented in the Johns Hopkins Hospital follow-up study.[18] Reporting systems have an important role in both conserving and monitoring AUC rates.

Wang et al.[19] reported an increase in AUC diagnoses in instrumented samples from 10.2% to 13.6%. The overall figures decreased from 18.6% to 14.4% and in voided urine the decrease in AUC diagnoses was from 20% to 14.5%.[19] Still, other studies have shown a decrease in AUC diagnoses in both instrumented (36.6% to 9.1%) and voided (26.9% to 6.0%) urine samples,[20] although instrumented samples had a higher AUC rate. According to some authors, instrumentation artifacts may enhance nuclear border irregularities and

thus increase the number of cases fulfilling the AUC criteria.[19,21] In our laboratory, instrumented urine samples are rare.

Out of our 205 AUC cases, cytohistological correlation was available in 97 (47.3%) cases. Of these, 36 (12.7%) were histologically diagnosed as benign, 27 (13.2%) as low-grade papillary urothelial carcinomas, and 34 (16.6%) as high-grade papillary urothelial carcinomas. In the literature, low proportion of low-grade urothelial neoplasms has been associated with atypical features including tissue fragments, cytoplasmic tails, nuclear eccentricity, and enlarged nuclei,[22] although nuclei are most often monotonous and bland with only a slight increase in size.

Overall, the ROM was 29.8% and the ROHM was 16.6% for all cases in the AUC category, and 62.9% and 35.1%, respectively, in the histologically confirmed AUC cases. Our results are comparable with those of previous studies. A French institution with an AUC rate of 5.18% was comparable to ours and showed a 49.02% ROM in histologically verified cases.[10] Cowan et al.[4] reported the post-TPS ROM in the AUC category as 7%–53% in comparison to the pre-TPS range of 28.3%–33%. Another literature summary revealed a post-TPS ROM of 12.3%–60.9% and a pre-TPS ROM of 23.4%–71.4%.[3] The ROM of the AUC category showed an increase in the post-TPS era that can be explained by degenerative and inflammatory reactive changes being downgraded into the negative category. In the second edition of TPS, the ROM is supposed to be 24%–53%.[7] In light of this, our histologically confirmed cases with a ROM of 62.9% showed mild underdiagnosis. All the cytology terminology systems, including TPS, strongly recommend follow-up in the undetermined categories. Only 16.6% of the primarily AUC-diagnosed samples in our cohort did not have any follow-up samples. It is possible that in some of those cases the follow-up sample was taken in a private practice or in an institution not served by our pathology department. We agree with others that overcalling benign reactive cells as AUC may lead to unnecessary follow-up,[16] which may stress patients. The increases in the predictive value of AUC for the subsequent detection of HGUC from 28.3% to 46.1%[19] and of the ROM from 28.17% to 49.02%[10] are an important sign of the diagnostic value of the AUC category in TPS. Nevertheless, low-grade lesions are still detected histologically among the AUC cases, as shown in our analysis (13.2%) and the analyses of others: 12.5% as decreased from the pre-TPS rate of 46%,[20] 14.7%,[11] and 20%.[23] The percentage of benign findings among AUC cases is also variable, having been reported as 5%,[20] 11.6%,[11] 18.6% (present study), and 30%.[23] Importantly, there was a steep decrease in benign follow-up diagnoses in the AUC cases, from 53% in the pre-TPS era to 5% in a recent study.[20]

The main limitations of the present study are the sample-based (rather than patient-based) analysis and the limited follow-up time of 0.5–2.5 years. Nevertheless, the data are robust in volume and represent unselected material from community health care centers and from regional and university hospitals.

TPS has been endorsed by clinicians[24] worldwide. It has improved communication between health care professionals and, most importantly, the management of patients as shown by our present results and the literature review.

AUTHOR CONTRIBUTIONS

Emilia Pöyry: Conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing–original draft, and writing–editing. **Veera Nykänen:** Formal analysis, data curation, and writing–editing. **Johanna Pulkkinen:** Data curation and writing–editing. **Eliisa Viljanen:** Data curation and writing–editing. **Marita Laurila:** Data curation and writing–editing. **Ivana Kholová:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, visualization, supervision, validation, writing–original draft, and writing–editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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