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Comparison of Automated Urinalysis Parameter Atyp.C and Urine Cytology for Detecting Bladder Carcinoma *In Situ*

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Abstract

Background/Aim: Urine cytology is a standard non-invasive test for detecting atypical urothelial cells in bladder cancer, although its sensitivity remains limited. While Atyp.C reflects cytological atypia and may aid in detecting urothelial malignancy, its diagnostic performance in bladder carcinoma *in situ* (CIS) has not been specifically evaluated.

Patients and Methods: We retrospectively analyzed patients with pathologically confirmed bladder CIS treated from January 2022 to July 2025. The diagnostic sensitivities of urine cytology and Atyp.C were compared, and the performance of their combination was assessed using exact McNemar tests and paired bootstrap analyses. Additional analyses were performed for pure CIS, primary bladder cancer, and recurrent bladder cancer.

Results: This study included 61 patients. The overall sensitivity was 77% for urine cytology and 73.8% for Atyp.C, with only a small difference and bootstrap confidence intervals crossing zero. Combined testing showed a higher sensitivity (85.2%), but this increase was not statistically significant. Similar diagnostic performance and no significant incremental benefit were observed across the additional analyses.

Conclusion: Atyp.C demonstrated diagnostic sensitivity comparable to urine cytology for the detection of bladder CIS. As an automated and cost-neutral parameter, Atyp.C may be a useful complementary indicator in routine clinical practice.

Keywords: Bladder carcinoma *in situ*, urine cytology, automated urinalysis, Atyp.C, diagnostic sensitivity.

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Introduction

Bladder cancer is the ninth most commonly diagnosed malignancy worldwide and is the most frequent form of urothelial carcinoma (1). Carcinoma *in situ* (CIS) of the bladder is classified as a high-grade, flat lesion with a substantial risk of progression to muscle-invasive disease (2). Although CIS is categorized as nonmuscle-invasive bladder cancer, it is biologically aggressive, and inadequate diagnosis or delayed treatment may lead to progression to muscle-invasive carcinoma (2).

CIS often lacks a distinct papillary or elevated morphology and can therefore be difficult to detect using white-light cystoscopy (WLC) alone (3, 4). Despite these limitations, current diagnostic strategies for bladder cancer rely primarily on WLC in combination with urine cytology (3).

Urine cytology has long been regarded as the standard non-invasive diagnostic test for bladder cancer because of its high specificity (5). Although its sensitivity is limited in cases with low tumor burden or few atypical cells, urine cytology remains clinically valuable, particularly for the detection of high-grade urothelial carcinoma.

Nevertheless, urine cytology has several well-recognized limitations. In addition to suboptimal sensitivity, diagnostic interpretation is highly dependent on examiner experience, leading to interobserver variability (6, 7). Moreover, delayed result availability and variability in diagnostic reproducibility pose practical challenges in routine clinical practice. These limitations have driven increasing interest in automated urine analysis technologies as complementary tools that aim to enhance, rather than replace, conventional urine cytology.

The Sysmex UF-5000 is an automated urine particle analyzer based on fluorescence flow cytometry and includes a research-use parameter known as Atyp.C. This parameter quantitatively reflects the presence of atypical cells characterized by a high nuclear-to-cytoplasmic ratio and complex intracellular structures. Recent studies have suggested that Atyp.C correlates with histological tumor grade and depth of invasion in bladder cancer, indicating its potential value as a non-invasive diagnostic marker (8, 9).

However, the diagnostic utility of Atyp.C specifically for detecting bladder CIS – a clinically important and diagnostically challenging entity – has not been adequately investigated. Therefore, this study aimed to assess the diagnostic performance of Atyp.C in patients with bladder CIS and to determine whether combining Atyp.C with urine cytology improves sensitivity for CIS detection compared with either method alone.

Patients and Methods

Study design. This single-center, retrospective observational study was conducted at Kochi University Hospital. The study compared the diagnostic sensitivity of the automated urinalysis parameter Atyp.C with that of urine cytology for detecting pathologically confirmed bladder CIS and assessed the incremental detection rate when both tests were used in combination.

Study population. Medical records of patients who were histopathologically diagnosed with bladder CIS following transurethral resection of bladder tumor (TURBT) from January 2022 to July 2025 were retrospectively reviewed. Patients with a definitive diagnosis of pure CIS or CIS concomitant with papillary urothelial carcinoma were eligible for inclusion. Patients were excluded if urine specimens were inadequate or if corresponding urinalysis data or urine cytology results were unavailable.

Demographic and clinical data, including age, sex, prior history of bladder cancer, and previous intravesical bacillus Calmette–Guérin (BCG) therapy, were extracted from electronic medical records.

Definitions of diagnostic tests. Urine cytology was evaluated according to the Papanicolaou classification (10), with results of class III or higher considered positive. Atyp.C was measured using the UF-5000 automated urine particle analyzer (Sysmex Corporation, Kobe, Japan), which is based on fluorescence flow cytometry. As in previous studies (8, 9), an Atyp.C value ≥0.1/μl was defined as positive. For each patient, urine samples

obtained within 3 months before TURBT were used for urinalysis and urine cytology.

Endpoints and statistical analysis. The primary endpoints were the diagnostic sensitivity of urine cytology and Atyp.C for detecting bladder CIS, as well as the sensitivity of their combined use. Diagnostic sensitivity was defined as the proportion of pathologically confirmed CIS cases that produced a positive test result. Differences in diagnostic sensitivity between urine cytology alone and the combined use of urine cytology and Atyp.C were assessed using the exact McNemar test for paired binary data. Additionally, the difference in sensitivity between Atyp.C and urine cytology (Atyp.C minus urine cytology) was estimated, and the corresponding 95% confidence intervals were calculated using a paired bootstrap approach with 10,000 resamples.

Sensitivity estimates and their 95% confidence intervals were calculated using the Wilson method. Continuous variables were presented as medians with interquartile ranges (IQRs), and categorical variables as frequencies and percentages. All statistical analyses were performed using Jupyter Notebook (version 7.0) in a Python environment. A two-sided p-value <0.05 was considered statistically significant.

Ethical considerations. This study was approved by the Ethics Committee of Kochi Medical School (approval number: 2025-88) and conducted in accordance with the Declaration of Helsinki. Given the retrospective study design, the requirement for individual informed consent was waived, and an opt-out approach was implemented *via* the institutional website.

Results

Patient characteristics. This study included 77 patients with histopathologically diagnosed bladder CIS who subsequently underwent TURBT. Of them, 16 patients were excluded because corresponding urine cytology or automated urinalysis data were unavailable, leaving 61 patients for the final analysis. The study flow diagram is shown in Figure 1. The study cohort included 26 patients with pure CIS, 26 with primary bladder cancer, and 35 with recurrent bladder cancer.

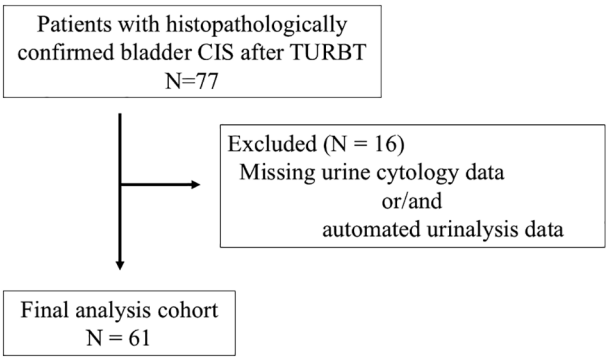

Figure 1. *Study flow diagram for patient selection and analysis sets. TURBT: Transurethral resection of bladder tumor; CIS: carcinoma in situ.*

Patient characteristics are summarized in Table I. The median age was 75 years [interquartile range (IQR)=70-81], and 53 patients (86.9%) were male. A prior history of bladder cancer and previous intravesical BCG therapy were documented in 35 (57.4%) and 7 patients (11.5%), respectively. A history of upper tract urothelial carcinoma and synchronous upper tract urothelial carcinoma was each observed in 5 patients (8.2%). Pure CIS was identified in 26 patients (42.6%), whereas the remaining 35 patients (57.4%) had CIS concomitant with papillary lesions or other pathological subtypes.

Analysis of the entire cohort. In the overall cohort of 61 patients, the sensitivity of urine cytology for CIS detection was 77.0% [95% confidence interval (CI)=65.1-85.8], while the sensitivity of Atyp.C was 73.8% (95% CI=61.6-83.2). The difference in sensitivity between Atyp.C and urine cytology (Atyp.C minus urine cytology) was −3.3%, with a paired bootstrap 95% CI ranging from −14.8% to +8.2%.

The sensitivity of the combined approach (positivity either urine cytology or Atyp.C) was 85.2% (95% CI=74.3-92.0). However, compared with urine cytology alone, this increase was not statistically significant based on the exact McNemar test (p=0.062) (Table II).

Table I. *Baseline characteristics of patients included in the analysis.*

Characteristics	Total (n=61)
Age, years, median (IQR)	75 (70–81)
Sex, n (%)	
Male	53 (86.9)
Female	8 (13.1)
Bladder cancer status, n (%)	
Primary	26 (42.6)
Recurrent	35 (57.4)
History of UTUC, n (%)	
Absent	56 (91.8)
Present	5 (8.2)
Synchronous UTUC, n (%)	
Absent	56 (91.8)
Present	5 (8.2)
Previous BCG treatment, n (%)	
Absent	54 (88.5)
Present	7 (11.5)
Urinary cytology class, n (%)	
I, II	14 (23.0)
III	18 (29.5)
IV, V	29 (47.5)
Atyp.C value, n (%)	
≥0.1	45 (73.8)
0.0	16 (26.2)
Pathological diagnosis, n (%)	
Pure CIS	26 (42.6)
Ta with CIS	13 (21.3)
T1 with CIS	17 (27.9)
Others	5 (8.2)

Values are n (%) unless otherwise indicated. IQR: Interquartile range; UTUC: upper tract urothelial carcinoma; BCG: bacillus Calmette–Guérin. The "Others" category included Tx with CIS or variant histology with CIS at the index procedure.

Analysis of patients with pure CIS. Among the 26 patients with pure CIS, the sensitivity of urine cytology was 69.2% (95% CI=49.1-84.9), whereas the sensitivity of Atyp.C was 61.5% (95% CI=42.0-78.5). The difference in sensitivity between the two tests was −7.7%, with a bootstrap 95% CI of −23.1% to +7.7%.

The sensitivity of the combined approach was 73.1% (95% CI=52.2-87.0). However, no statistically significant difference was observed between urine cytology alone and the combined approach according to the exact McNemar test (p=1.000) (Table II).

Analysis of primary bladder cancer. In the subgroup of patients with primary bladder cancer (n=26), the sensitivities of urine cytology and Atyp.C were identical at 84.6% (95% CI=66.5-93.8). The sensitivity of the combined approach was 92.3% (95% CI=75.9-97.9); however, this increase was not statistically significant compared with urine cytology alone based on the exact McNemar test (p=0.500). Atyp.C and urine cytology showed identical sensitivity, with a bootstrap 95% CI of −15.4% to +15.4% (Table II).

*Analysis of rec*urrent bladder cancer. Among the 35 patients with recurrent bladder cancer, the sensitivity of urine cytology was 71.4% (95% CI=54.9-83.7), whereas the sensitivity of Atyp.C was 65.7% (95% CI=49.2-79.2). The difference in sensitivity between the two tests was −5.7%, with a bootstrap 95% CI ranging from −22.9% to +11.4%.

The combined approach yielded a sensitivity of 80.0% (95% CI=64.1-90.0). However, no statistically significant incremental benefit over urine cytology alone was observed using the exact McNemar test (p=0.250) (Table II).

Discussion

This study demonstrated that the research-use parameter Atyp.C, derived from the automated urine particle analyzer UF-5000, showed diagnostic sensitivity comparable to that of urine cytology for detecting bladder CIS. Across the overall cohort and the subgroups of pure CIS, primary bladder cancer, and recurrent bladder cancer, differences in sensitivity between Atyp.C and urine cytology were small, and the corresponding 95% CIs from paired bootstrap analyses consistently crossed zero. Although combined testing with Atyp.C and urine cytology yielded a numerically higher sensitivity than urine cytology alone, this increase was not statistically significant. These findings indicate that Atyp.C may serve as a complementary diagnostic indicator with performance broadly comparable to urine cytology, rather than as a superior alternative.

Urine cytology has long been established as a standard non-invasive diagnostic modality in the management of bladder cancer because of its high specificity (11-13).

Table II. *Sensitivity of urine cytology and Atyp.C for detection of carcinoma in situ, stratified by pure CIS, primary bladder cancer, and recurrent bladder cancer.*

Group	n	Urine cytology sensitivity % (95% CI)	Atyp.C sensitivity % (95% CI)	Δ (Atyp-Cyt),% (bootstrap 95% CI)	Combined sensitivity† % (95% CI)	*p*-Value*
All patients	61	77.0 (65.1–85.8)	73.8 (61.6–83.2)	−3.3 (−14.8 to +8.2)	85.2 (74.3-92.0)	0.062
Pure CIS	26	69.2 (49.1–84.9)	61.5 (42.0–78.5)	−7.7 (−23.1 to +7.7)	73.1 (52.2-87.0)	1.000
Primary bladder cancer	26	84.6 (66.5–93.8)	84.6 (66.5–93.8)	0.0 (−15.4 to +15.4)	92.3 (75.9-97.9)	0.500
Recurrent bladder cancer	35	71.4 (54.9–83.7)	65.7 (49.2–79.2)	−5.7 (−22.9 to +11.4)	80.0 (64.1-90.0)	0.250

†Combined sensitivity was defined as positivity on either urine cytology or Atyp.C. **p*-Value was calculated using the exact McNemar test for the comparison between urine cytology alone and the combined approach.

However, its sensitivity remains limited, particularly for flat lesions such as CIS and tumors with a low tumor burden. Consequently, diagnostic confirmation often requires bladder or random biopsies, which are invasive and may still fail to identify all CIS lesions. These limitations highlight an unmet clinical need for complementary diagnostic markers that are reproducible, objective, and easily integrated into routine clinical practice (11).

The Sysmex UF-5000 is a fully automated urine particle analyzer that uses fluorescence flow cytometry to quantify the morphological characteristics of urinary cells. The Atyp.C parameter reflects the presence of cells with a high nuclear-to-cytoplasmic ratio and complex intracellular structures, which conceptually correspond to atypical urothelial cells identified by urine cytology. Recent studies by Zhang *et al*. demonstrated that Atyp.C correlates with histological tumor grade and depth of invasion in bladder cancer (9), suggesting its potential as a non-invasive indicator of tumor aggressiveness. Similarly, Okada *et al*. reported that combining Atyp.C with inflammatory parameters may improve diagnostic performance (8). In addition, recent studies have explored non-invasive bladder cancer detection using routinely available urine-derived data, underscoring continued interest in practical urine-based diagnostic strategies (14, 15). Nevertheless, studies focusing specifically on CIS – a clinically well-defined yet diagnostically challenging entity – and directly comparing Atyp.C with urine cytology, as well as their combined use, remain limited.

Our findings indicate that Atyp.C reflects cytological atypia in a manner comparable to urine cytology, resulting in similar diagnostic performance between the two approaches. At the same time, the incremental increase in sensitivity achieved by combining Atyp.C with urine cytology was limited. The overlap between the two tests may also have limited the additive effect. Therefore, this finding should be interpreted in the context of the relatively small sample size, particularly in the subgroup analyses, which limited the statistical power to detect modest differences in sensitivity. The relatively wide bootstrap confidence intervals observed across subgroups further support this limitation and highlight the need for cautious interpretation.

In recent years, several urinary biomarkers based on molecular techniques – such as NMP22 (16-18), Cxbladder (19, 20), Bladder EpiCheck (21, 22), UroSEEK (23, 24), and UroVysion FISH® (25, 26) – have demonstrated promising diagnostic performance in research settings. However, their widespread implementation in routine clinical practice is often constrained by the need for additional specimen processing, costly reagents, and specialized laboratory infrastructure. In contrast, Atyp.C is automatically generated as part of a standard urinalysis workflow without requiring additional sample collection, processing time, or cost, representing a distinct practical advantage (27, 28).

Notably, the potential applicability of Atyp.C may extend beyond urological settings. Compact automated urine analyzers, such as the UF-1500 (29), have demonstrated diagnostic performance comparable to that of the UF-5000, indicating that similar cytological information may be available in general outpatient or

primary care settings. Since these analyzers are widely used as part of routine urinalysis in non-urological clinical environments, Atyp.C can be generated without additional procedural burden.

In this context, Atyp.C should not be considered a stand-alone diagnostic test, but rather an auxiliary indicator that may prompt further urological evaluation. Particularly in settings where immediate access to specialized urological assessment is limited, elevated Atyp.C values may serve as an objective signal indicating the need for additional diagnostic procedures, including cystoscopy.

Several limitations of this study should be acknowledged. First, the single-center, retrospective design and relatively small sample size may limit the generalizability of our findings. Second, because the study population was restricted to pathologically confirmed CIS cases, diagnostic specificity could not be evaluated; inclusion of non-CIS control populations will be necessary to clarify the overall diagnostic accuracy of Atyp.C. Third, as Atyp.C reflects morphological atypia, it does not fully distinguish malignant changes from reactive or inflammatory alterations. Therefore, Atyp.C results should be interpreted in conjunction with cystoscopic findings and the broader clinical context.

Future prospective, multicenter studies that include non-CIS controls, as well as evaluations of cost-effectiveness and longitudinal clinical outcomes, are warranted to further define the clinical utility of this parameter. The automated urine analysis parameter Atyp.C demonstrated diagnostic sensitivity comparable to that of urine cytology for detecting bladder CIS. Although combining Atyp.C with urine cytology resulted in a numerical increase in sensitivity, this improvement was not statistically significant.

Since Atyp.C is generated automatically during routine urinalysis without additional cost or sample collection, it may serve as a practical complementary indicator to urine cytology for supporting the detection of flat, high-grade bladder lesions.

Conclusion

In conclusion, among patients with CIS, urine cytology and Atyp.C demonstrated comparable diagnostic sensitivity. Given its fully automated generation with same-day availability and no extra cost, Atyp.C may offer a clinically meaningful advantage in routine practice. Further multicenter prospective studies, including assessment of diagnostic specificity, are warranted to better define its clinical utility.

Conflicts of Interest

Keiji Inoue has received honoraria for lectures from Sysmex; however, this did not influence the research results or their interpretations.

Authors' Contributions

Ryu Shigehisa: Writing – original draft, project administration, methodology, investigation, formal analysis, data curation, conceptualization. Satoshi Fukata: Writing – original draft, project administration, methodology, conceptualization. Keisuke Sugimoto: Data curation, investigation, resources. Shiori Miyazaki: Data curation, investigation, resources. Shinji Tokuhiro: Data curation, investigation, supervision. Anantya Pustimbara: Formal analysis, methodology. Chiaki Kawada: Data curation, investigation, resources. Rie Yoshimura: Formal analysis, methodology. Keisuke Mizutani: Formal analysis, methodology. Daigo Takemori: Data curation, investigation. Yuhei Shiba: Formal analysis, methodology. Shinkuro Yamamoto: Methodology, conceptualization. Hiroto Osakabe: Investigation, formal analysis, data curation. Tomoya Nao: Investigation, formal analysis, data curation. Tsutomu Shimamoto: Investigation, formal analysis, data curation. Hideo Fukuhara: Investigation, formal analysis, data curation, conceptualization. Nobutaka Shimizu: Supervision. Shingo Ashida: Supervision, Keiji Inoue: Supervision.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, ChatGPT 5.4 (OpenAI, San Francisco, CA, USA) was used solely for language editing and stylistic improvements in select paragraphs under the supervision of the authors. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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