Diagnostic Value Comparison of CellDetect, Fluorescent In Situ Hybridization (FISH) and Cytology in Urothelial Carcinoma

Donghao Shang
Friendship hospital https://orcid.org/0000-0002-6624-6834
Xiuhong Xu
Capital Medical University Affiliated Beijing Friendship Hospital
Yuting Liu
Capital Medical University
Zhenghao Chen
Capital Medical University Affiliated Beijing Friendship Hospital
Daye Wang (wangdaye@ccmu.edu.cn)
Capital Medical University https://orcid.org/0000-0002-3932-2037

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Abstract

Background To evaluate clinical effectiveness of a novel CellDetect method, when compared with Fluorescent In Situ Hybridization (FISH), and urine cytology, in the diagnosis of urothelial carcinoma (UC).

Methods A total of 264 patients with suspicious UC were enrolled in this study, all tissue specimens were collected by biopsy or surgery. Urine was obtained for examinations prior to the surgical procedure, CellDetect staining was carried out with CellDetect kit and FISH was performed with UroVysion detection kit according to the manufacturer's instructions. All urine cytology specimens were centrifuged and obtained by cytospin method, the slides were stained by standard Papanicolaou method.

Results There were 128 cases of UC and 136 cases of non-UC in this study, with no significant difference in gender and age between the two groups. Our results indicated that the sensitivity of CellDetect, FISH, and urine cytology was 82.8%, 83.6%, and 39.8%, respectively. In addition, the specificity of the three examinations was 88.2%, 90.4%, and 86.0%, respectively. The sensitivity of CellDetect and FISH are significantly superior compared to conventional urine cytology, however, there was no significant difference in specificity among three staining techniques. In addition, the sensitivity of CellDetect in lower urinary tract UC, upper urinary tract UC, NMIBC, and MIBC was 83.3%, 81.8%, 83.5%, and 72.0%, respectively, the screening ability of CellDetect has no correlation with tumor location and stage. Sensitivity of CellDetect in low grade and high grade UC was 51.6% and 92.8%, screening ability of CellDetect in high grade UC is significantly superior compared to that in low grade UC.

Conclusions CellDetect and FISH show equal value in diagnosing UC, both are superior to that of conventional urine cytology. Compared to FISH, CellDetect is cost-effective and easier to operate, it has extensive clinical application value in monitoring recurrence of UC and screening of indetectable UC.

Background

Urothelial carcinoma (UC) is the second most common urologic malignancy after prostate cancer, which accounts for approximately 90% of all bladder cancer[1]. Upper urinary tract UC is rare in clinical practice and only accounts for about 5% of all UC [2]. Although transurethral resection (TUR) is the primary regimen for patients with non-muscle-invasive bladder cancer (NMIBC), and the reported 5-year overall survival rate has been 90%, once disease progressed, the 5-year overall survival rate drops to 25%-60% for muscle-invasive bladder cancer (MIBC) [3, 4]. With up to an 80% recurrence rate, a routine endoscopy surveillance is essential for early tumor detection, UC is considered one of the costliest malignancies in terms of lifetime follow-up[5, 6]. Due to pain and anesthesia, cystoscopy and ureteroscopy can not be tolerated by some patients. Thus, early noninvasive screening and diagnosis are extremely important for the prognosis of UC patients, imaging and urine cytologic examinations are widely used for detection.

Urine cytology is the most common noninvasive examination for UC detection, however, a large scale study provides further evidence that cytology has low sensitivity for UC detection [7]. In recent years, several biomarkers have been discovered from urine of patients with UC, such as FDP, BTA and NMP22.

Despite their higher sensitivity compared with cytology examination, high false-positive rate and poor specificity restricted their clinical application[8]. Fluorescence in situ hybridization (FISH) is also frequently performed in the surveillance of patients with a history of UC [9, 10]. FISH is a multicolor and multitarget examination that has been established for the detection of UC in the urine[11]. Many studies have compared the performance characteristics (sensitivity and specificity) of FISH to conventional cytology, and results indicated that FISH demonstrated higher sensitivity and similar specificity compared with conventional urine cytology[12, 13].

CellDetect is a novel cell staining technique by Zetiq Technologies Ltd (Israel) for cancer screening and diagnosis[14]. CellDetect staining system is composed of generic dyes and a unique plant extract (Ficus elastica), the active component of the plant extract was a class of polyphenols present in a variety of plants. CellDetect staining display dual color, more cyto-morphological details compared to hematoxylin and eosin (HE) staining. In CellDetect-stained sections, normal cells generally present blue/green after staining, contrasting with tumor cells, which stained red/purple. Due to its excellent staining characteristics, CellDetect could distinguish normal cells from tumor cells even in small tumor foci. CellDetect has the potential to become one of the most effective examinations for cervical cancer screening and early diagnosis [15].

In this study, we compared the clinical effectiveness of CellDetect, FISH, and urine cytology in the diagnosis of UC. The results showed that CellDetect provided a uniquely useful tinctorial clue for the detection of UC. CellDetect used in urine exfoliated cell screen would provide an effective technique for early diagnosis of human UC.

Patients And Methods

Sample collection

A total of 264 patients with suspicious UC were enrolled in the Department of Urology of Beijing Friendship Hospital from Jan 2020 to Mar 2021. All subjects had hematuresis, irritative symptom of the bladder, abdominal pain, and hydronephrosis on the affected side. No patient received neoadjuvant chemotherapy, all tissue specimens were diagnosed by biopsy or surgery, histological cell type of the resected UC samples was determined by two experienced pathologists, tumor stage was evaluated according to the Union for International Cancer Control (UICC) 2017 TNM classification system, and histological grade was also assessed according to the World Health Organization (WHO) 2004 grading system for UC. Urine was obtained for CellDetect, FISH and urine cytology prior to the surgical procedure. Study protocol was approved by the Research Ethics Committee of Beijing Friendship Hospital and all patients gave their informed consent before study commencement.

Celldetect Staining

Cell staining was carried out with CellDetect kit (Zetiq Techoogies Ltd., Tel Aviv, Israel) according to manufacturer's instruction. Briefly, urine sample (minimum of 50 ml) was collected from each patient and smeared onto slide. After fixation with 10% trichloroacetic acid, nuclease was stained first with hematoxylin followed by differentiation with HCL/ethanol. CellDetect kit was then used to further staining with the red and the green dye in the kit. Between the staining, conditioning was performed with the plant extract and further differentiation was carried out as mentioned above. With this kit, normal, inflammatory, and malignant cells can easily be differentiated. Malignant cells show a red nucleus and pink cytoplasma; normal urothelial or squamous epithelial cell typically will have a dark purple or green nucleus and green cytoplasma; infalmmatory cells show a purple nucleus and red cytoplasma, and also can be distinguished morphologically. Each slide was accessed under microscope by 2 cytologists (a third cytologist was assigned as necessary if discrepancies occur), and assigned to categories 2 according to best practice from pathology department: negative, and positive[16].

Fish And Cytology

A total of 200 ml urine was collected for FISH and cytology examination.In brief, after centrifugation for 5 min at 2000 rpm, two slides were prepared with the ThinPrep5000 processor® (Hologic, Inc, Marlborough, MA): one slide was used for FISH and the other was used for urine cytology stained using Papanicolaou staining. FISH was performed with UroVysion detection kit (Abbott Molecular, Chicago, IL, USA) according to the manufacturer's instructions. Positivity was determined by the criteria as listed in the package insert after all cells were evaluated. ≥4 abnormal cells that had chromosomal gain for at least two of chromosomes 3, 7 or 17, samples with ≥ 10 tetraploid cells with normal morphology or ≥ 12 cells with homozygous loss of 9p21 were considered positive. All cytology specimens were centrifuged and obtained by cytospin method, slides were stained by standard Papanicolaou method. For diagnosis of negative or positive UC, refer to CellDetect staining.

Statistical analysis

Data was collected and compiled using SPSS 16.0. All results are expressed as mean ± standard deviation (SD), statistical significance was determined by Student's t-test, chi-squared test was performed for comparisons among CellDetect, FISH and urine cytology examination. A p value of ≤ 0.05 was considered significant.

Results

A total of 264 patients (190 male (72%) and 74 female (28%)) with suspicious UC received CellDetect, FISH, and urine cytology examination. All participants received cystoscopy or ureteroscopy, and pathological results were derived from biopsy, TUR, radical cystectomy and nephroureterectomy, baseline characteristics of the study population are listed in Table 1. There were 128 cases of UC and 136 cases of non-UC in this study, and no significant difference was found in gender and age between the two groups.

In UC patient's group, 84 patients were detected in lower urinary tract and 44 patients were detected in upper urinary tract, tumor grade was low grade in 31 patients (24.2%), and high grade in 97 patients (75.8%), in addition, tumor stage enrollment into the study was NMIBC in 103 patients (80.5%), MIBC in 25 patients (19.5%).

Table 1
Baseline characteristics of the study population

	CellDetect		FISH		Cytology	
	□	-	□	-	□	-
UC	106	22	107	21	51	77
Non-UC	16	120	13	123	19	117
Sensitivity (%)	82.8		83.6		39.8	
Specificity (%)	88.2		90.4		86.0	

Compared to conventional urine cytology, CellDetect showed superior features: 1. nuclear/cytoplasmic ratio is maintained; 2. nuclear irregularity is clearly seen; 3. hyper-chromic nucleus. The unique plant extract adds color-a valuable feature that is easily and accurately targetable on the suspicious areas. The urine smears stained by CellDetect were shown in Fig. 1.

We evaluated the diagnostic value of CellDetect, FISH and cytology in UC (Table 2), total sensitivity of CellDetect, FISH, and urine cytology in UC was 106/128 (82.8%), 107/128 (83.6%), and 51/128 (39.8%), respectively, this indicated that CellDetect and FISH have similar sensitivity in the diagnosis of UC, and both examinations are superior to urine cytology. In addition, diagnostic specificity of CellDetect, FISH, and urine cytology in UC was 120/136 (88.2%), 123/136 (90.4%), and 117/136 (86.0%), respectively, indicating no significant difference in the diagnosis of UC. Thus, in the diagnosis of UC, CellDetect has the same screening ability as FISH and significantly efficient than conventional urine cytology.

Table 2
Diagnostic value of CellDetect, FISH and cytology in UC

	CellDetect				
	n	□	-	Sensitivity (%)	p
Tumor location					
Lower urinary UC	84	70	14	83.3	
Upper urinary UC	44	36	8	81.8	0.975
Grade					
Low grade	31	16	15	51.6	
High grade	97	90	7	92.8	< 0.001
Stage					
NMIBC	103	86	17	83.5	
MIBC	25	18	7	72.0	0.301

We further evaluated the diagnostic value of CellDetect in UC (Table 3), total sensitivity of CellDetect in lower urinary tract UC and upper urinary tract UC was 70/84 (83.3%), 36/44 (81.8%), respectively (p = 0.975). Tumor staging detection on NMIBC, and MIBC by CellDetect was 86/103 (83.5%), 18/25 (72.0%), respectively (p = 0.301), it demonstrated that the screening ability of CellDetect has no correlation with tumor location and clinical stage. However, total sensitivity of CellDetect in low grade and high grade was 16/31 (51.6%), 90/97 (92.8%), respectively (p < 0.001), we can draw the conclusion that the screening ability of CellDetect in high grade UC is significantly superior to that in low grade UC.

Table 3
Diagnostic value of CellDetect in UC.

	UC	Non-UC	*p*
No.	128	136	
Gender			
Male	90	100	
Female	38	36	0.657
Age			
Range	32–89	35–84	
Average ± SD	67.5 ± 10.2	68.9 ± 13.0	0.741
Tumor location			
Lower urinary UC	84		
Upper urinary UC	44		
Grade			
Low grade	31		
High grade	97		
Stage			
NMIBC	103		
MIBC	25		

Discussion

Currently, an estimated 429,000 new cases of UC were diagnosed, with 165,000 deaths per year in the world[17]. Moreover, there are 80,000 new cases of UC with 33,000 deaths in China per year [18]. Despite the improvement in diagnostic techniques and the progress in surgical therapies, UC has a high recurrence rate risk and the prognosis remains poor in UC patients with high grade or MIBC [19]. UC is considered a life-threatening disease, and routine cystoscopic check is usually performed to screen the recurrence of UC following TUR [20].

Although some noninvasive examinations have been applied to UC detection and screening the recurrence of UC, such as urine cytology and biomarkers, many studies still show low sensitivity of UC diagnosis [21, 22]. Therefore, novel examination and diagnosis innovations are needed for patients with UC. At present, various studies have suggested that FISH, an examination which uses four-colored fluorescence in situ hybridizations, is superior to conventional urine cytology and can improve the

diagnosis of UC[23, 24]. Thus, FISH can assist in improving UC detection compared to those using urine cytology. However, FISH also has many disadvantages, which limit its application in UC diagnosis: it requires special supporting equipment; the experimental procedures are relatively complicated and costly; final decision of UC requires pathologists with rich experience in diagnosis.

CellDetect staining is a unique platform for cancer diagnosis,the proprietary plant extract and dyes enable color distinction between benign and malignant cells based on staining color and morphology. CellDetect was able to spot CIS cases even when cystoscopy missed, and for some cases of high grade UC, the nucleus of tumor cells shrinked while inflammatory cells enlarged, it's easy to confuse pathologist. However we found that the nuclei of high grade UC tend to be smaller, they also lose their round shape and smooth nuclear membrane, which can be easily observed with CellDetect. A previous study indicated that 94% sensitivity and 89% specificity to detect UC using CellDetect, which had overall superior sensitivity compared to urine cytology[25]. Another study also suggested that the sensitivity of CellDetect was 84%, which is more efficient than that of BTA stat in detecting UC[16].

In this study, we compared diagnostic value among CellDetect, FISH, and urine cytology in UC. Our results indicated that CellDetect and FISH have equal-level sensitivity in the diagnosis of UC, and both are significantly superior to conventional urine cytology. However, there was no significant difference in specificity between the three staining techniques. In addition, the sensitivity of CellDetect has no correlation with tumor location and clinical stage. However, the sensitivity of CellDetect in low grade and high grade UC was 51.6% and 92.8%, which suggests that the screening ability of CellDetect in high grade UC is significantly superior to that in low grade UC. In a previous study on the diagnostic value of FISH and cytology in UC, the sensitivity of FISH in low grade and high grade UC was 25% and 73%, and the sensitivity of cytology was 36% and 75%[25]. Studies have found that the expression of E-cadherin was down-regulated in high-grade, invasive and distant metastatic UC, suggests that reduced expression of adhesion-related protein weakens cell-cell adhesion, and causes tumor cells to detaches from the primary site and develop invasion and metastasis [26, 27]. These also explains why the detection rate of high grade UC is generally higher than that of low grade UC by different staining methods based on urine exfoliation cytology.

Due to the high recurrence of bladder cancer after TUR, bladder infusion chemotherapy combined with regular cystoscopy is the conventional strategy in the management of lower urinary tract UC, however, cystoscopy has some recognized limitations, such as, small or occult tumor lesions are not easy to visualize and diagnose[28]. In addition, the morphological characteristics of CIS under cystoscopy usually appear as erythematous areas, make it difficult to distinguish CIS from inflammatory lesions[29]. Finally, some patients cannot tolerate cystoscopy, thus, noninvasive monitoring and diagnostics are extremely important for the screening of patients with lower urinary tract UC. We predicted that novel urine stain for exfoliated cells will have an expectable clinical application prospect, CellDetect combined imaging examination may play an important role in monitoring recurrence of lower urinary tract UC, it is worth of further study in the future. Moreover, upper urinary tract UC is defined as a tumor involving the urinary tract between pelvis and ureter. The muscle layers of upper urinary tract are thinner than the

bladder, so the UC cells can easily penetrates the muscle layer to form invasive disease, and the prognosis of upper tract UC is poor. Unlike lower urinary tract UC, imaging diagnosis of upper urinary tract UC is usually difficult to determine the diagnosis, patients generally have poor tolerance to ureteroscopy, which also could cause local and distant spread of UC cells. Therefore, early noninvasive screening and diagnosis are extremely important for the prognosis. In our study, the diagnostic value of CellDetect in upper urinary tract UC was equal to that in lower urinary tract UC, which suggests that CellDetect also plays an important role in screening of upper urinary tract UC.

Conclusions

In conclusion, CellDetect and FISH show equal value in diagnosing UC, both are superior to that of conventional urine cytology. CellDetect can obviously improve ability in monitoring recurrence of UC, and it also can be applied in screening of indetectable upper urinary tract UC. Compared to FISH, CellDetect technique is cost-effective and easier to operate, so CellDetect has extensive clinical application value in the diagnosis of UC and postoperative follow-up in future.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Beijing Friendship Hospital and all patients gave their informed consent before study commencement.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests There are no competing interests associated with this study.

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Authors' contributions

Donghao Shang: project development, Data collection，Manuscript writing; Xiuhong Xu: Data collection， Data analysis; Yuting Liu: Data management, Manuscript editing; Zhenghao Chen: Manuscript writing; Daye Wang: project development, Data analysis, Manuscript editing

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Figures

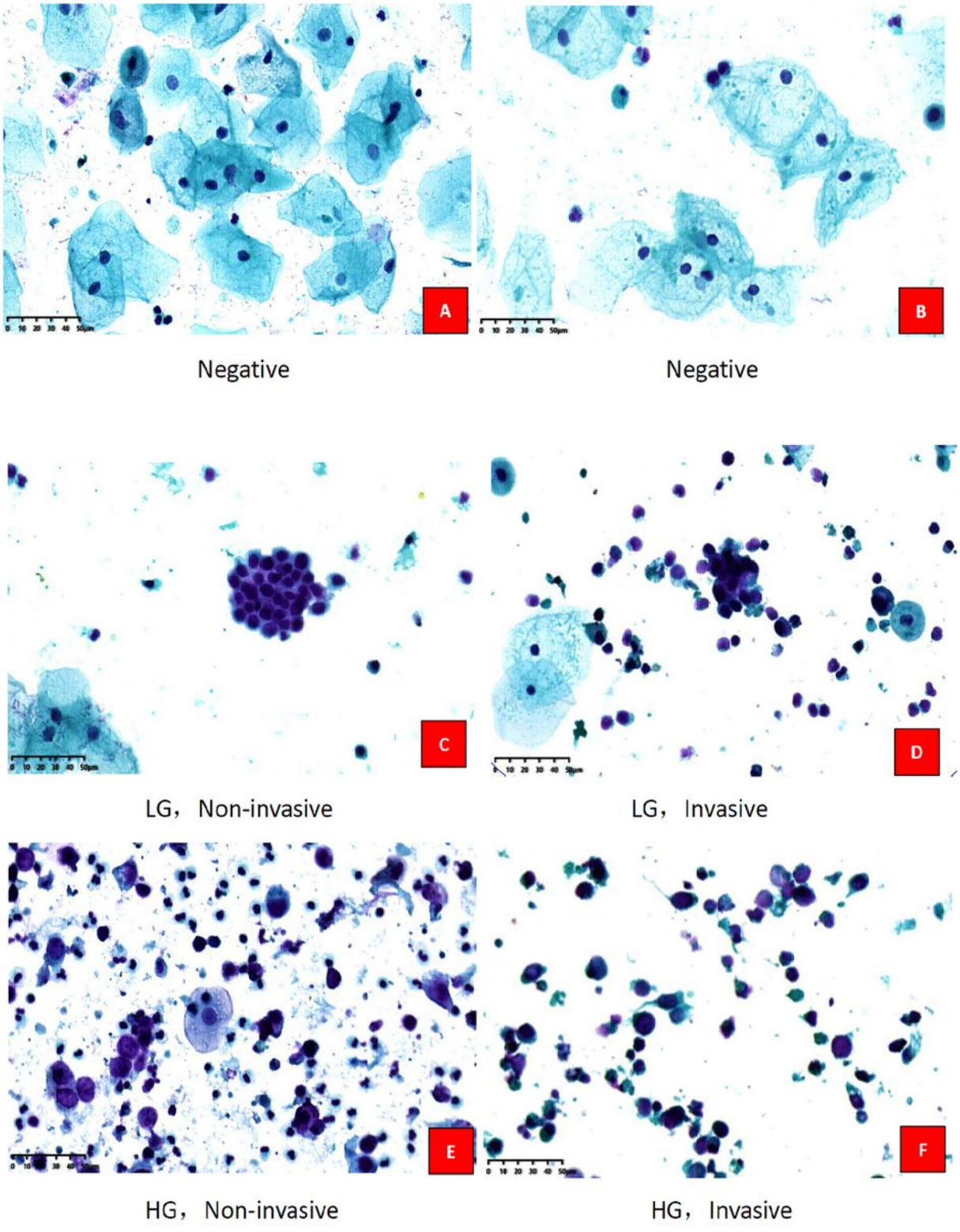

Figure 1

Urine smears stained by CellDetect. (A) and (B) show microscopic features of negative case from non-UC patients. Nuclei of epithelial cells are stained in either green, blue or dark purple, and usually do not show hyperchromasia (with the exception of the pycnotic nuclei of superficial cells), and inflammatory cells are stained in purple. (C-F) show UC cells exhibiting reddish-purple nuclei, cytoplasm is either transparent, pink or green. Magnification: ×40HG = high grade; LG = low grade.