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Diagnostic Value Comparison of Urothelium Carcinoma Among Urine Exfoliated Cells Fluorescent *In Situ* Hybridization (FISH) Examination, Computerized Tomography (CT) Scan, and Urine Cytologic Examination

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This study aimed to compare the clinical effectiveness of urine exfoliated cells FISH examination, CT scan, and urine cytologic examination on the diagnosis of upper urinary tract urothelium carcinoma with hematuresis symptom.

Material/Methods: A total of 30 patients with suspicious upper urinary tract urothelium carcinoma between Aug 2010 and Aug 2011 were enrolled, including 23 males and 7 females. All the subjects received urine exfoliated cells FISH examination, CT scan, and urine cytologic examination. Twenty-one cases were diagnosed as urothelium carcinoma, including 14 cases of carcinoma of renal pelvis and 7 cases of carcinoma of ureter. There were 6 cases in stage Ta/T1, 12 cases in stage T2, and 3 cases in T3/T4. The other 9 cases consisted of 1 case of neuroendocrine carcinoma of the renal pelvis, 2 cases of nephrotuberculosis, and 6 cases of renal clear cell carcinoma.

Results: The total sensitivity of FISH examination, CT scan, and urine cytologic examination on upper urinary tract urothelium carcinoma was 85.7%, 66.7%, and 28.6%, respectively (P<0.05). The tumor staging detection on Ta/T1, T2, and T3/T4 by FISH was 66.7%, 91.7%, 100%; by CT scan 33.3%, 75.0%, 100%; and by urine cytologic examination 0%, 25.0%, and 100%. Their diagnostic specificities were 88.9%, 77.8%, and 100%, respectively (P<0.05).

Conclusions: The diagnostic sensitivity on upper urinary tract urothelium carcinoma was highest in FISH examination, followed by CT scan and urine cytologic examination. FISH technique obviously improves the diagnosis of upper urinary tract urothelium carcinoma.

MeSH Keywords: Cells • Fishes • Urothelium

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Background

Upper urinary tract urothelial tumor is rare in clinical practice and only accounts for about 5% of all urothelial tumors. Its highest incidence is 10/100 000, and the incidence in males is twice that in females [1]. Urothelium carcinoma, namely transitional cell carcinoma, accounts for 95% of all the epithelial tumors in the urinary system and squamous cell carcinoma and adenocarcinoma accounts for the remaining 5%. Renal pelvis carcinoma, accounting for 7% of all renal tumors, can occur in any part of the renal pelvis and calyces. It most commonly appears in the upper pole of kidney, with low potential malignancy. It may grow as cauliflower, papillary, lumps, and infiltration [2]. Primary ureteral carcinoma is relatively rare, characterized as unilateral, accounting for about 1% of the urinary tract tumors. There are 3% located in the upper, 24% in the middle, and 73% in the lower ureter. The muscle layers of the renal pelvis and ureter are thinner than the bladder. The tumor easily penetrates the muscle layer to form the invasive tumor. Thus, the clinical prognosis of upper tract urothelial tumors is poor. Early prevention, screening, and diagnosis are extremely important for the prognosis. CT scan, ureteroscopy, and urine cytologic examinations are most widely used for detection. Due to anesthesia and pain, ureteroscopy cannot be tolerated by some patients. Although urine cytologic examination is noninvasive and has high specificity, it cannot be used clinically because of low sensitivity. CT scanning is gradually gaining more acceptance in clinical practice because of its simplicity, but it has poor diagnostic value for use in small lesions. Therefore, there is urgent need for a noninvasive, highly accuracy, and sensitive method to diagnose tumors. In recent years, several biomarkers were extracted and detected from urine, such as BTA, FDP, and NMP22. However, in spite of their higher sensitivity compared with urine exfoliative cytologic examination, their poor specificity and high false-positive rate restricted their clinical application [3]. Similar to other malignant tumors, the occurrence of urothelium carcinoma is accompanied with various genetic locus mutation. Sokolova and Halling explored use of the FISH detection kit (UroVysion) in targeting chromosomes 3, 7, 17, and 9p16. Many studies indicated that FISH demonstrated higher sensitivity and similar specificity compared with urine exfoliative cytologic examination [4]. The present study compared the clinical effectiveness of urine exfoliated cells FISH examination, CT scan, and urine cytologic examination in the diagnosis of upper urinary tract urothelium carcinoma with hematuresis symptom.

Material and Methods

Subjects

A total of 30 patients with suspicious upper urinary tract urothelium carcinoma between Aug 2010 and Aug 2011 were enrolled, including 23 males and 7 females with a median age of 63 (46–84) years. All subjects had hematuresis, including 27 cases of gross hematuria and 3 cases of microscopic hematuria. In addition, 19 cases had abdominal pain, 7 cases had irritative symptom of the bladder, and 17 cases had hydronephrosis on the affected side.

The study protocol was approved by the Research Ethics Committee of Hebei General Hospital and all patients gave their informed consent before study commencement.

Grouping

A total of 200 ml urine was collected for FISH examination, urine cytologic examination, and CT scan before cystoscopy. All the subjects were diagnosed by biopsy or surgery, including 21 cases diagnosed as transitional cell carcinoma. There were 13 cases on the left and 8 cases on the right. There were 21 cases diagnosed as urothelium carcinoma, including 14 cases of carcinoma of the renal pelvis and 7 cases of carcinoma of the ureter. There were 6 cases in stage Ta/T1, 12 cases in stage T2, and 3 cases in T3/T4. The other 9 cases consisted of 1 case of neuroendocrine carcinoma of the renal pelvis, 2 cases of nephrotuberculosis, and 6 cases of renal clear cell carcinoma.

Statistical analysis

McNemar test results were analyzed on SPSS 16.0 software. The specificity of urine cytology, FISH detection, and CT scan was based on the 9 cases excluding transitional cell carcinoma.

Results

Sensitivity analysis

All 30 hematuresis patients received FISH examination, CT scan, and urine cytologic examination. Different types of abnormal cells were counted according to the interpretation standard of FISH (Figures 1–4). The number of positive cases based on FISH, CT, and urine cytology were calculated to compare the sensitivity to tumor staging (Tables 1, 2).

There were 21 cases of urothelium carcinoma, 1 case of neuroendocrine carcinoma of the renal pelvis, 2 cases of nephrotuberculosis, and 6 cases of renal clear cell carcinoma in all of the 30 suspicious upper urinary tract urothelium carcinoma

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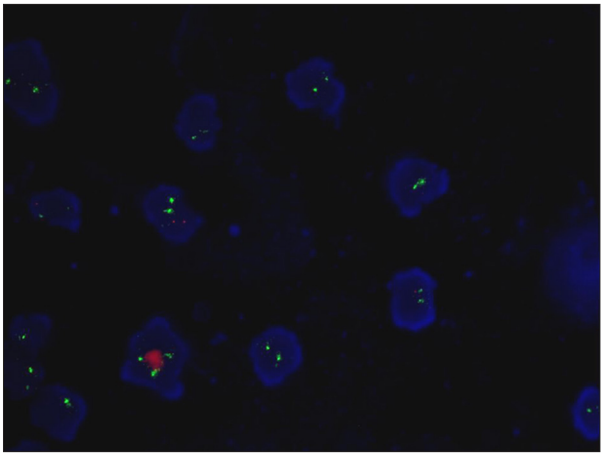

Figure 1. Chromosome 17 (green) show polysomy and 9q21 (red) show monosomy in 5 nuclei.

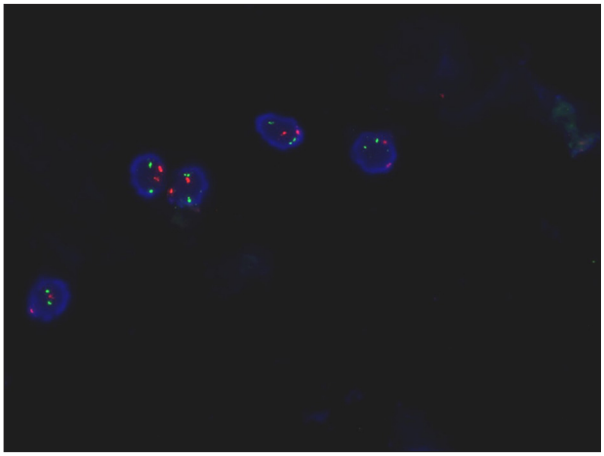

Figure 3. Chromosome 3 (green) and 7 (red) show polysomy in middle 2 nuclei.

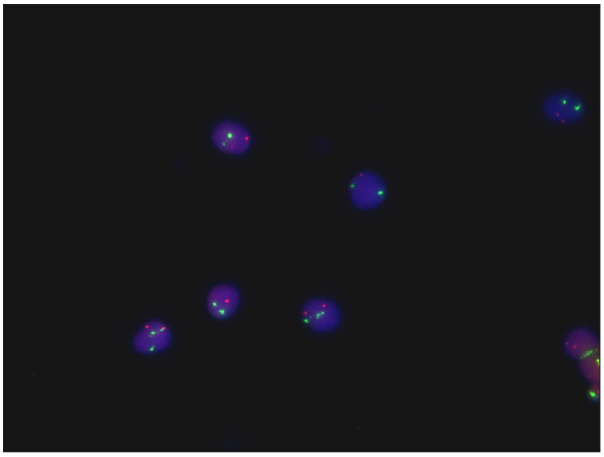

Figure 2. Chromosome 17 (green) show polysomy in 2 nuclei.

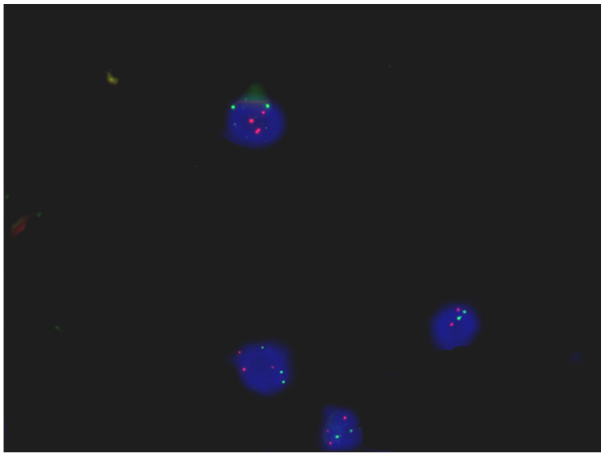

Figure 4. Chromosome 3 (green) and 7 (red) show polysomy in left 2 nuclei.

Table 1. The threshold of chromosomal abnormalities of 20 healthy controls.

	Chromosome 3 ≥3	Chromosome 7 ≥3	Chromosome 17 ≥3	Chromosome 0	9p16 1
Mean value	2.7	2.75	2.23	0.55	1.60
SD	1.03	0.94	1.22	0.61	0.75
Threshold value	5.79	5.58	6.00	2.40	3.90

Table 2. Comparison of sensitive and specificity obtained from urine cytology, cystoscopy and FISH analysis.

Tumor staging	Case/total (%)		
	FISH	CT	Urine cytology
$T_a/_1$	4/6 (66.7%)	2/6 (33.3%)	0/6 (0%)
T_2	11/12 (91.7%)	9/12 (75.0%)	3/12 (25.0%)
T_3/T_4	3/3 (100%)	3/3 (100%)	3/3 (100%)
Total	18/21 (85.7%)	14/21 (66.7%)	6/21 (28.6%)
Specificity	8/9 88.9%	7/9 77.8%	9/9 100%

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patients. The total sensitivity of FISH examination, CT scan, and urine cytologic examination on upper urinary tract urothelium carcinoma was 18/21 (85.7%), 14/21 (66.7%), and 6/21 (28.6%), respectively (P<0.05). The tumor staging detection on Ta/T1, T2, and T3/T4 by FISH was 4/6 (66.7%), 11/12 (91.7%), 3/3 (100%); by CT scan 2/6 (33.3%), 9/12 (75.0%), 3/3 (100%); and by urine cytologic examination 0/6 (0%), 3/12 (25.0%), and 3/3 (100%). McNemar test revealed that the 3 methods exhibited significant differences in total sensitivity.

Specific analysis

The diagnostic specificities of FISH, CT, and urine cytologic examinations were 88.9%, 77.8%, and 100%, respectively (P>0.05), indicating no significant difference in the diagnosis of upper urinary tract urothelium carcinoma.

Discussion

Upper urinary tract tumor is defined as a neoplasm involving the urinary tract between calyces and distal ureter [2]. Since upper urinary tract tumors cannot be observed directly, it is difficult to provide local treatment. Moreover, differences in individual anatomy makes the prognosis variable. Most urothelial tumors located in the renal pelvis are moderately differentiated but some are poorly differentiated. Well-differentiated tumors have local lesions and growth in nodular, polypoid, or cauliflower form, and may cause broadening of renal pelvis calyces following tumor enlargement. This type of cancer generally does not infiltrate out of renal parenchyma infiltration. Furthermore, it rarely appears as regional lymph node enlargement or distant metastasis, but is prone to lead to renal parenchyma thinning, resulting in relatively good surgical outcomes. Tumors with poor differentiation exhibit an invasive growth pattern along the renal pelvis and calyces wall; they may invade the renal parenchyma and easily to spread to regional lymph nodes or by distant metastasis. Ureteral urothelial tumors more easily infiltrate and metastasize than renal pelvis tumors because of the thinner muscle layer [5,6]. The Surveillance, Epidemiology, and End Results (SEER) database showed there were 9072 cases of urothelial tumor between 1973 and 1996, including 5379 cases of renal pelvis tumor and 3678 cases of ureter tumor [7,8]. The SEER database also demonstrated that the 5-year overall survival was significantly different among patients in different stages. Stewart reported that most upper urinary tract epithelial tumors are in advanced stage, leading to poor prognosis [9]. Thus, early screening is of great significance for the prognosis.

Ureteroscopy can directly observe the ureter and pelvis, and also is used to perform biopsy for diagnosis. However, it can only be applied under anesthesia and carries risk of ureter avulsion, perforation, and infection. In addition, it cannot be used in patients with ureter malformation or stenosis. Urine exfoliative cytological examination demonstrates high specificity and low sensitivity, especially in upper urinary tract urothelial carcinoma [10]. Oosterlinck suggested that its sensitivity is lower than 50% with high requirement for pathologist involvement in assessment [1].

Since an upper ureter tract lesion cannot be observed directly, imaging is widely used for the detection. CT can clearly display the tumor position, size, and density. It differentiates urothelium carcinoma from stone, blood clot, renal parenchyma cancer, and renal cyst in most cases. CT can help staging by confirming tumor infiltration and metastasis in advanced tumors. It was reported that the sensitivity of CT was 85.7% [11]. A study found that the positive rate of CT in primary ureteral carcinomas may reach 90.0% [12]. However, CT scan can miss small tumors in patients without ureterectasia or renal pelvis carcinoma invading the renal parenchyma [13].

FISH is a type of molecular genetic technique using a specifically binding fluorescently-labeled probe with single-stranded nucleotides to form hybrid double-stranded nucleotides. Numerous results showed that chromosome 3, 7, 9, 17 mutations are mostly found in urothelium carcinoma and are closely associated with staging [14,15]. Akkad first used FISH in urothelium carcinoma [16]. Mann-Aguilera and Luo compared FISH and urine exfoliative cytological examination in urothelium carcinoma, revealing that the total sensitivity and specificity of FISH are 76.7–87.5% and 80–100%, respectively. while they are 23.8–60% and 80–100%, respectively, in urine exfoliative cytological examination [17].

Our results demonstrated that the total sensitivity of FISH was significantly higher than CT scan and urine exfoliative cytological examination. FISH appeared to have higher sensitivity than CT scan and urine exfoliative cytological examination in early and advanced stages of upper urinary tract tumors (Ta/T1, T3/T4), but due to the small sample size, we were not able to perform statistical analysis. FISH showed obviously higher sensitivity than the other methods in determining T2 stage. No significant difference was observed in specificity of the 3 detection methods, which was similar to previous reports [17,18]. The sensitivity of CT scanning gradually increased with upstaging, which was incommensurable in FISH. However, FISH is noninvasive and can be used as a supplement for CT scan and urine exfoliative cytological examination [19,20].

Conclusions

The diagnostic sensitivity on upper urinary tract urothelium carcinoma was highest in FISH examination, followed by CT scan

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and urine cytologic examination. The difference was more significant following downstaging. No significant difference was observed in specificity. FISH technique obviously improves the diagnosis of upper urinary tract urothelium carcinoma.

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Conflict of interest

None.

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