Advantages of retrograde flexible ureteroscopy in determining the etiology of painless hematuria originating from the upper urinary tract

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Abstract. The present study investigated the use of retrograde flexible ureteroscopy (RFU) in the discrimination of the etiology of hematuria that originates from the upper urinary tract (UUT). The present study collected retrospective data for patients who presented with hematuria and cystoscopy-detected bleeding from the UUT between June 2006 and August 2018 in Ningbo First Hospital. All patients accepted RFU to determine the etiology of hematuria. Data regarding imaging examinations, surgery, pathology and complications were also collected and analyzed. In total, 65 patients (males, 38; females, 27) with a mean age of 63 years underwent RFU to determine the etiology of hematuria originating from the UUT. Using RFU, UUT tumors were found in 29 cases. Stones, polyps and atypical hyperplasia were found in two cases, and a definite diagnosis was not found in three cases. There were 17 cases without obvious abnormalities and nine cases were unable to undergo RFU due to ureteral stenosis. In patients who could not be diagnosed by imaging examination, 34.4% (11/32) were diagnosed with urothelial carcinoma by RFU, and these results were also confirmed by postoperative pathology. In the present study, no patient had severe complications after RFU. The present results suggested RFU may be used as a sensitive method to diagnose UUT tumors (78.4%; 29/37) and has strong specificity. RFU could be performed as a routine examination for patients with hematuria from the UUT.

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Introduction

Hematuria is the most common symptom of upper urinary tract urothelial carcinomas (UUTUC) (1). Early diagnosis of UUTUC is important, as early treatment of UUTUC increases overall patient survival (2). There are several established methods of evaluating hematuria from the UUT. Patients with hematuria can be diagnosed by radiology, urine cytology, cystoscopy or fluorescence *in situ* hybridization (3). Multi-detector computed tomographic urography (MDCTU) has replaced intravenous pyelography and has become the gold standard for detection of UUT tumors (4). The sensitivity of these methods is directly related to the tumor size (5,6): i) For tumors of 5-10 mm in diameter, the MDCTU sensitivity is 97%; ii) for tumors with a diameter of <5 mm, the sensitivity is reduced to 89%; and iii) when the tumor diameter is <3 mm, the sensitivity is ~40%. For patients who have hematuria of the UUT but negative MDCTU and cytology results, the probability of having urothelial carcinoma is 5-10% (7). As the muscularis of the renal pelvis and ureter is relatively weaker than the muscular layer of the bladder, tumors may easily invade the muscle layer, subsequently leading to metastasis (8). Therefore, early detection of UUT tumors is necessary to improve survival rates.

With the progression of endoscopic technology, ureteroscopy now provides a new way to detect UUTUC. Since retrograde flexible ureteroscopy (RFU) can observe the entire UUT directly, it is considered to be an important diagnostic method for judging the location of hematuria and finding early UUT carcinomas (9). According to the European Association of Urology guidelines, all patients with UUTUC should accept an ureteroscopy examination before treatment (9).

For the past few years, RFU has been widely performed in nearly all Grade IIIA hospitals in China; there were 1308

Grade IIIA hospitals nationwide by the end of 2016 (10). However, in most situations the flexible ureteroscope is used to search for stones in renal calices and renal pelvis (11). The present study investigated 65 cases with UUT bleeding who accepted RFU and 34 cases who were diagnosed as UUTUC at Ningbo First Hospital from June 2006.

Patients and materials

Patients. The ethics approval of the present study was obtained from the Ethics Committees of Ningbo First Hospital. All patient consent was obtained before undergoing RFU. Between June 2006 and August 2018, 65 patients (male, 38; female, 27; mean age, 63 years) underwent UUT examination by RFU to determine the etiology of hematuria originating from UUT in Ningbo First Hospital. The inclusion criteria were as follows: i) Patients had painless hematuria; and ii) patients underwent cystoscopy and MDCTU before the RFU. The exclusion criteria were as follows: i) Position of bleeding was located in bladder; and ii) patients could be diagnosed correctly for other diseases such as lower urinary tract infections or bladder carcinoma.

MDCTU revealed masses in 33 cases. There were 13 cases that exhibited ureteral dilatation, hydronephrosis or ureteral stenosis, but without evidence of UUT tumors. In total, five cases had renal cysts and 14 cases did not have obvious abnormalities. After a complete RFU examination of the entire UUT, patients with suspicious of neoplasms were biopsied. If the neoplasm was confirmed to be malignant, a nephroureterectomy would be performed directly or within 2 weeks after RFU. Patients who presented with negative findings were followed up regularly.

Hematoxylin-eosin staining. Tumor tissue was fixed with 4% PFA for 1 h at room temperature, embedded in paraffin and cut into samples of 5 μm thickness. H&E staining was conducted using a Hematoxylin and Eosin Staining kit (Shanghai Sixin Biotechnology Co., Ltd.) according to the manufacturer's protocol, Briefly, thin paraffin sections were deparaffinized in xylene and rehydrated in a graded series of aqueous ethanol solution. Following staining with hematoxylin and eosin, the tissue was sealed by neutral gum. Samples were observed under an Olympus CKX31 microscope (Olympus Corporation) at 10X objective.

Statistical analysis. The statistical software program SPSS 22.0 (IBM Corp.) was used to determine the statistical significance of the results by comparing the age/sex to the success ratio of flexible ureteroscopy examination (Table I). The relationship between age/sex and the ratio was analyzed by using an independent sample t-test and the Fisher test, respectively. $P<0.05$ was considered to indicate a statistically significant difference.

Results

All 65 patients received cystoscopy and imaging examination such as ultrasound and MDCTU before the RFU. All patients were found to be bleeding from the UUT by cystoscopy. In total, 33 patients who had positive MDCTU results were considered to have UUTUC or renal carcinoma. The remaining 32 patients were not detected to have obvious tumors by MDCTU; only stones, hydronephrosis, nephropyelitis or ureterostenosis were found.

Table I. Patient characteristics.

Characteristic	Patients with UUTUC or RCC	Patients without carcinoma	P-value
Number	35	30	
Age (years)	59.85±16.865	66.61±9.236	0.037
Success rate of RFU	0.857 (30/35)	0.867 (26/30)	0.004
Complications	2 (fever)	0	

RFU, retrograde flexible ureteroscopy; UUTUC, upper urinary tract urothelial carcinoma; RCC, renal cell carcinoma. Data are presented as the mean ± SD.

Table II. Positive and negative results detected by MDCTU or RFU.

	MDCTU results		
RFU	+	-	Total
+	19	11	30
-	9	17	26
Total	28	28	56

P=0.032. RFU, retrograde flexible ureteroscopy; MDCTU, multi-detector computed tomographic urography.

Among the 65 patients only 85.2% (56/65) patients were examined by RFU successfully. Urothelial masses were found in 37 cases (Fig. 1A and B). Renal calculi were found in two cases and no obvious abnormalities were found in 17 cases. The 37 patients with urothelial masses who received surgical treatment. Among them, 17 cases underwent immediate nephroureterectomy after the RFU and ureteroscopic biopsy. The other 19 patients accepted nephroureterectomy within 2 weeks after RFU (Fig. 1C). There was one patient who had renal cell carcinoma treated by radical nephrectomy. Among the 65 patients, 19 patients were considered to have UUTUC and 17 patients were found to be negative for UUTUC by both RFU and MDCTU (Table II). However, RFU found UUTUC in 11 patients who had negative results from MDCTU, and RFU found non-neoplastic diseases in nine patients who had positive results from MDCTU (Table II).

Pathology. Pathology (Fig. 1D) confirmed UUT epithelial carcinoma in 29 cases (Table III). There was one case was confirmed as renal clear cell carcinoma. In total, two cases were confirmed as atypical hyperplasia and two cases were confirmed as polyps. The present results identified three cases as undetermined for reasons such as lack of samples or that the pathological results were inconsistent with the clinical manifestation (data not shown).

Table III. MDCTU and RFU results in all patients.

Confirmed	UUTUC[a]	Other diseases	Normal	Failed	Total
MDCTU	33 (18)	21	11	0	65
RFU	37 (29)	2	17	9	65

[a]Numbers in parentheses indicate patients who were confirmed by pathology. RFU, retrograde flexible ureteroscopy; MDCTU, multi-detector computed tomographic urography; UUTUC, upper urinary tract urothelial carcinoma.

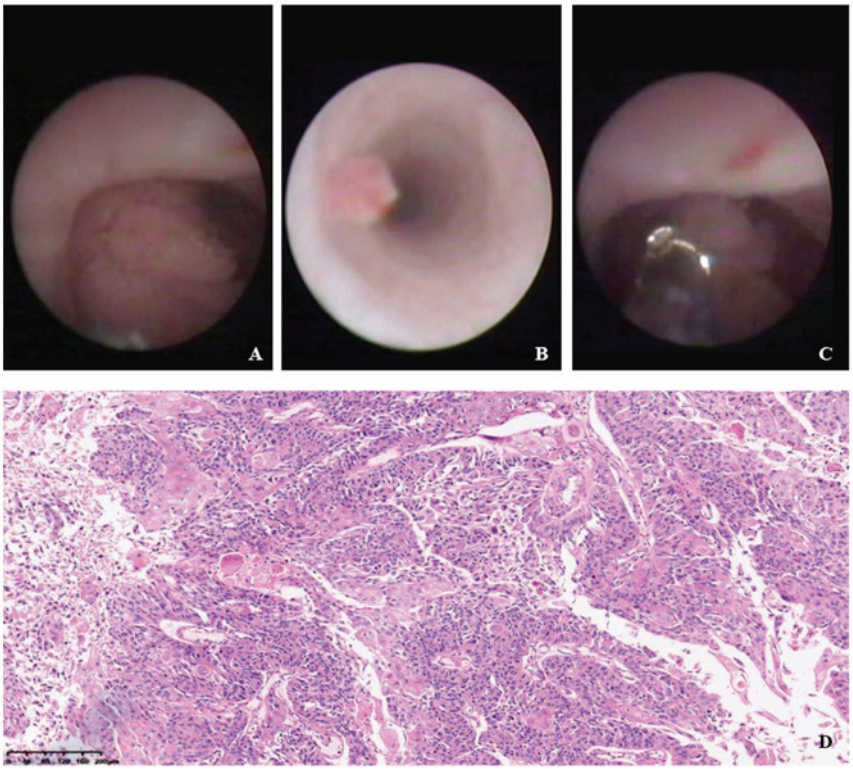

Figure 1. Images during the retrograde flexible ureteroscopy and pathological examination. (A) Renal pelvis cancer. (B) Ureter polyps. (C) Ureteroscopic biopsy. (D) A pathological image of confirmed upper urinary tract urothelial carcinoma. Scale bar, 200 μm.

Patients with RFU. RFU could not be performed in nine patients due to ureteral stenosis. There were five patients who had positive MDCTU results, received nephroureterectomy directly and were confirmed to have transitional cell carcinoma by pathology. In total, four patients who had negative MDCTU results did not receive surgical treatment and did not present with abnormalities during the 6 month follow-up. There were complications in three cases who presented with a slight fever after the RFU. No cases presented with severe complications after RFU.

Follow-up. With regards to postoperative follow-up, the present study did not follow up two patients who were diagnosed with ureteral stones. The remaining patients were followed up for 6-58 months (average for 34 months). Among them, five patients with UUTUC were lost to follow up. In total, four patients with UUTUC died; two succumbed to UUT carcinoma in the third and the fourth year after the operation and two died due to other diseases (one died due to prostate cancer after surgery, and the other died because of renal failure after 14 months). In total, two patients were found to have bladder tumors. There was one patient who received transurethral cystectomy 18 months after RFU and was followed up again for 2 years without recurrence. In total, one case occurred 14 months after the RFU and received both radical cystectomy and cutaneous ureterostomy; the patient was then followed up for 1 year and no obvious abnormalities were found. No tumor recurrence was detected in the remaining patients. The present results identified two patients with ureteral polyps who had no obvious abnormalities after the follow-up. There were two patients with negative RFU results who were followed up after 58 months and 10 months, and no obvious abnormality was found in either patient. Due to ureteral stricture, one patient who was not examined successfully by RFU was not found to have obvious abnormalities during the 6 months follow up.

Discussion

The most common symptom of UUT tumors is hematuria, which consists of either macroscopic or microscopic

hematuria, and occurs in 56-98% of patients with urothelial tumors (12,13). Other sources of hematuria include benign fibroepithelial polyps, angioma and stone disease (14,15). Upper urinary tract carcinoma has been prevalent in China in recent years (16). People with asymptomatic hematuria have a 3.3% risk of urinary tract malignancy (17) and multiple factors such as age, sex, environment or drug abuse have been reported to increase the risk of urinary tract malignancy (18). As hematuria from the UUT may be caused by benign or malignant disease, it is important to differentiate between these to avoid unnecessary surgical interventions.

In the present study, the sensitivity of RFU for the diagnosis of UUT tumors was ~78.4% (29/37; Table III) and the sensitivity of MDCTU was ~54.5% (18/33). In the present study, ureteral stenosis was the main reason for the failure of ureteroscopy. In nine patients with ureteral strictures, MDCTU revealed masses in four patients and these masses were confirmed to be ureteral urothelial carcinomas after the operation. In total, one patient presented with ureteral dilatation, hydronephrosis and ureteral stenosis in the preoperative imaging examination, which was later confirmed to be ureteral carcinoma after surgery. The present results identified four cases that were considered to be benign by preoperative imaging methods and received conservative treatment; no tumors were found during the follow-up.

Although the complication rate of RFU is low, complications reported included ureteral perforation, postoperative fever, impaired renal function and postoperative ureteral stenosis (19). Ureteral perforation is usually due to large tumor size or deep resection caused by the laser, and can generally be treated with an indwelling ureteral stent (20). Ureteral stricture is a long-term postoperative complication. The incidence of ureteral strictures is 0-13%, which has greatly increased in recent years due to holmium laser-induced thermal injuries to the ureter (21). In the present study, RFU was performed as a short-time medical procedure without the holmium laser treatment. Only three patients had a transient fever and all recovered within 24 h after antibiotic treatment. Complications such as renal impairment, ureteral perforation or ureteral stenosis were not observed in the present study.

Whether RFU increases the risk of tumor cell metastasis and decreases the survival rate is still inconclusive. Boorjian *et al* (22) reported the long-term follow-up results of 121 patients diagnosed with UUTUC with a mean follow-up time of 40 months. Boorjian *et al* (22) found that the number of disease-free patients who underwent nephroureterectomy with imaging and/or urinary cytology results was 81.3% (61/75), and those who underwent nephroureterectomy after ureteroscopy and laser ablation was 85.3% (29/34), and therefore concluded that there was no significant difference between the two methods. Ishikawa *et al* (23) conducted a retrospective study of UUTUC in 208 patients who underwent nephroureterectomy; 55 received ureteroscopy before surgery and the other patients only received surgery. Postoperative follow-up found no significant difference in tumor recurrence between the two groups (23). The estimated 5 year tumor-specific survival rate was 88.3% in patients receiving ureteroscopy and 78.1% in the control group; the difference between groups was not statistically significant (23). In the present study, 18 patients received nephroureterectomy immediately after the ureteroscopy and the remaining 19 patients received the operation within 2 weeks; surgical procedures were performed after the pathology results were returned. In the patients that were successfully followed up for 6-58 months (34 months on average), two patients died due to distant metastasis (5.4%) and two patients were diagnosed with bladder cancer during the follow-up. There was no evidence that the ureteroscopic procedure increased the risk of tumor metastasis in the present study. However, the present study had limitations such as a small sample size of patients, retrospective design and the lack of a control group.

The present results indicated RFU was highly sensitive and specific to the diagnosis of UUT tumors, and had few complications. The present results suggested RFY could be used as a routine examination for patients with hematuria originating from the UUT to improve the detection rate of UUT tumors and to avoid unnecessary surgeries.

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Availability of data and materials

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

Authors' contributions

KYW and JSH searched the literature, extracted the data and wrote the manuscript. JSH, LF, DXZ, QL and GHX performed the RFU. DMN and MH conducted literature search, analyzed the data and edited the manuscript. GHX and QM designed the study and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The ethics approval of this study was obtained from The Ethics Committees of Ningbo First Hospital. Patient consent was obtained before undergoing RFU.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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