

# Therapeutic strategies for asymptomatic upper urinary tract urothelial carcinoma

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## Abstract

**Introduction:** Upper urinary tract epithelial carcinoma (UTUC) and bladder cancer are both sources of urinary epithelial cell. In our previous study of asymptomatic bladder tumors, we found that most of these tumors could be resected through the urethra without radical surgery. This study analyzed the treatment strategies for asymptomatic UTUC.

**Aim:** To investigate the clinicopathological features and surgical methods of these patients, thus choosing appropriate surgical treatment.

**Material and methods:** 136 patients with UTUC were recruited, of whom 21 patients with asymptomatic UTUC were group A, and 115 UTUC patients with hematuria or low back pain were group B. The clinicopathological features, oncologic outcomes, and surgical methods of patients were evaluated.

**Results:** Radical resection was the main surgical treatment which was included (group A 80.95%, group B 90.43%). Other patients were treated with kidney-retaining surgery. No statistically significant difference was observed in the pathological stage and grade between groups A and B ( $p > 0.05$ ). During a median follow-up period of 44.3 months, tumor-specific mortality of group A was 7.14%, and that of group B was 5.10%. In the same period, 106 patients with asymptomatic bladder tumor were recruited: 31 patients of them had asymptomatic bladder urothelial carcinoma. The asymptomatic UTUC group had a higher stage and grade of clinicopathological features than the asymptomatic bladder urothelial carcinoma group ( $p < 0.001$ ).

**Conclusions:** The principle of asymptomatic UTUC treatment is the same as that of symptomatic UTUC. Risk stratification should be carried out according to clinical staging and other parameters, and the corresponding surgical treatment should be selected.

**Key words:** upper urinary tract urothelial carcinoma, bladder urothelial carcinoma, symptom, diagnosis, surgical treatment.

## Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a malignant tumor derived from renal pelvis and ureter epithelium. The incidence is lower than that of bladder cancer, accounting for 5% to  $\leq 10\%$  of all urothelial carcinoma [1]. The most common symptom of UTUC is hematuria, and some patients may have low back pain or low back masses [2]. Patients with

advanced tumors may have systemic symptoms such as anemia, emaciation, hypertension, and poor appetite [3]. However, some patients have no clinical manifestations [4]. The lesions were accidentally found by imaging examination, i.e., asymptomatic UTUC.

In our previous study of asymptomatic bladder tumor, we found that the pathological stage and grade of asymptomatic bladder urothelial carcinoma were low, and the prognosis was good [5]. Most of these tu-

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mors could be resected through the urethra without radical surgery. Although UTUC and bladder cancer are both sources of urinary epithelial, they are highly heterogeneous malignancies with varying biological and clinical behaviors [6]. It is essential to study and analyze whether the staging and grading of UTUC are related to the existence of symptoms, so that we can correctly choose appropriate surgical treatment.

## Aim

The present study aims to investigate the clinicopathological features and surgical methods of these patients and improve the understanding of asymptomatic UTUC, thus helping in selecting a reasonable treatment plan.

## Material and methods

The clinical data of 136 patients with UTUC diagnosed and treated in our department from January 2014 to January 2021 were evaluated. The patients were divided into two groups: group A and group B. The patients without urinary tract irritation symptoms and no gross hematuria symptoms were included in group A (21 cases), and the patients with clinical symptoms of hematuria and low back pain were included in group B (115 cases). The exclusion criteria were as follows: patients with definite contraindications to surgery, advanced patients with multiple metastases, isolated kidney, contralateral renal insufficiency or contralateral severe renal insufficiency, bilateral renal pelvis/ureter carcinoma complicated with bladder tumor, medical record defect, or incomplete record. A total of 106 patients with asymptomatic bladder tumors were recruited in the same period; among them, 31 patients were pathologically confirmed as suffering from bladder urothelial carcinoma.

### Definition of asymptomatic UTUC

At present, there is a lack of a unified definition of asymptomatic UTUC. We defined it as a patient with no clinical symptoms, including “asymptomatic hydronephrosis” and “microscopic hematuria”. UTUC accidentally found by imageological examination or other operations.

### Pathological diagnosis and staging

Both UTUC and bladder cancer were graded using the WHO grading system (1973) [7]. Furthermore, postoperative staging was performed accord-

ing to the 2017 TNM classification developed by the International Union Against Cancer [8].

## Statistical analysis

Statistical software SPSS 19.0 was used for analysis. The measurement data were expressed by mean  $\pm$  standard deviation; an independent sample *t* test or  $\chi^2$  test was used for comparison. A *p*-value of  $< 0.05$  was considered statistically significant.

## Results

### Information

136 patients participated in this study, including 21 patients with asymptomatic UTUC in group A and 115 patients with hematuria or low back pain in group B (Table I). At the same time, 106 cases of patients with asymptomatic bladder tumor were treated with transurethral resection of bladder tumor (TURBt), including 31 cases of asymptomatic bladder urothelial carcinoma in 23 men and 8 women, with an average age of  $63.54 \pm 8.91$  years. Among 31 cases, there were 18 cases of single bladder cancer and 13 cases of multiple bladder cancer. The tumor size was 0.3–5.0 cm, with an average size of  $2.65 \pm 0.96$  cm. The results of urine exfoliative cytology were negative in 31 cases.

### Surgical treatment and postoperative chemotherapy

All 136 patients with UTUC were treated surgically, and the bladder tumors were excluded by cystoscopy before or during the operation. Surgical methods included open surgery, laparoscopic surgery, and flexible ureteroscopy (Table II).

In addition, all patients with upper urinary tract tumors underwent intravesical infusion chemotherapy with Pharmorubicin 50 mg + NS 50 ml for 1 h. Out of the 136 patients, 92 patients were treated with intravesical infusion chemotherapy once a week  $\times$  8 times, 1 h each time, followed by once a month  $\times$  10 times, a total of 18 times. Then, 18 patients underwent systemic intravenous adjuvant chemotherapy with gemcitabine combined with cisplatin postoperatively.

### Postoperative pathological stages and grades

Both groups were confirmed to be suffering from urothelial cell carcinoma (UCC) by pathology and

**Table I.** Basic information of patients in both groups

Variable	Group A	Group B	$\chi^2/T$ value	P-value
Total	21	115		
Gender:				
Male	14 (66.67%)	78 (67.83%)	0.011	0.917
Female	7 (33.33%)	37 (32.17%)		
Age [years]	67.29 $\pm$ 8.20	64.73 $\pm$ 9.45	1.161	0.248
Symptoms:				
Gross hematuria	0	90	–	–
Low back pain	0	7	–	–
Gross hematuria with low back pain	0	18	–	–
Renal pelvis tumor (cases):	9 (42.86%)	67 (58.26%)	1.709	0.191
Single (for example)	8 (38.10%)	60 (52.17%)	1.408	0.235
Size [cm]	2.84 $\pm$ 1.76	3.30 $\pm$ 1.67	–0.725	0.471
Multiple cases	1 (4.8%)	7 (6.1%)	0.000	1.000
Size* [cm]	2.2	3.07 $\pm$ 2.13		
Ureteral tumor (cases):	11 (52.38%)	41 (35.65%)	2.104	0.147
Size [cm]	3.05 $\pm$ 1.21	2.37 $\pm$ 1.05	1.859	0.069
Renal pelvis complicated with ureteral tumor (cases):	1 (4.76%)	7 (6.09%)	0.000	1.000
Size* [cm]	8	4.66 $\pm$ 1.01		
Urine exfoliative cytology (example):	20 (95.24%)	113 (98.26%)	–	0.398
Suspected cancer cells	2 (9.52%)	4 (3.48%)	0.439	0.507
Nuclear heterogeneous cells	1 (4.76%)	10 (8.70%)	0.030	0.863
Negative	17 (80.95%)	99 (86.09%)	0.076	0.783
Undetected	1 (4.76%)	2 (1.74%)	–	0.398
Preoperative or intraoperative examination by ureteroscopy/flexible ureteroscopy	21 (100%)	35 (30.43%)		
flexible ureteroscopy found tumor#				
Renal pelvis tumor	1 (4.76%)	2 (9.52%)	–	0.398
Ureter tumor	0	0		

\*The maximum diameter of multiple tumors is the largest in the case of the largest tumor; #Soft endoscopic surgery: 1 case in group A considered renal stones before operation; 1 case in group B had unknown causes of hematuria before operation; 1 case had symptoms of low back pain; and 1 case was misdiagnosed as kidney stone before operation.

showed negative surgical margins. No statistically significant difference was observed between the two groups in terms of postoperative pathological stage and grade comparison (all  $p > 0.05$ ) (Table III).

In this study, 55 patients underwent ureteroscopy/flexible ureteroscopy and biopsy before or during the operation, including 20 patients in group A and 35 patients in group B. In group A, 12 patients underwent preoperative tumor biopsy and pathological examinations for malignant urothelial tumors. Among them, 8 cases were low graded (LG), G1; 2 cases were graded G2; and 2 cases were high grad-

ed (HG), G3. Other 8 patients underwent biopsy of intraoperative tumors. Among them, 7 cases were considered malignant urothelial tumors based on pathological considerations, and in 1 case the nature of the tumor could not be determined. In group B, 18 patients underwent preoperative tumor biopsy and pathological examinations for malignant urothelial tumors. There were 13 cases graded G1, 3 cases graded G2, and 2 cases graded G3; 17 patients underwent biopsy of intraoperative tumors. Among them, 15 cases were considered to be malignant urothelial tumors based on pathological con-

**Table II.** Groups A and B

Grouping	Surgical mode	Specific method	Number of cases	Remarks
Group A (21 cases)	Open operation	Radical full-length renal ureterectomy + bladder sleeve resection	9	/
	Laparoscope	Laparoscopic radical resection of renal pelvis/ureter carcinoma	8	/
		Laparoscopic resection of ureter tumor and reanastomosis	1	Upper ureter tumor (patient insists on preservation of kidney)
		Laparoscopic resection of ureteral tumor and regeneration of ureteral bladder	2	Lower ureter tumor
	Flexible ureteroscopy	Holmium laser resection of renal pelvis tumor under flexible ureteroscopy	1	Pyelolithiasis
Group B (115 cases)	Open operation	Radical full-length renal ureterectomy + bladder sleeve resection	56	/
	Laparoscope	Laparoscopic radical resection of renal pelvis/ureter carcinoma	48	/
		Laparoscopic resection of ureter tumor and reanastomosis	0	/
		Laparoscopic resection of ureteral tumor and regeneration of ureteral bladder	9	Lower ureter tumor
	Flexible ureteroscopy	Holmium laser resection of renal pelvis tumor under flexible ureteroscopy	2	Hematuria/pyelolithiasis

**Table III.** Comparison of postoperative pathological stages and grades between the two groups

Project	Group A	Group B	$\chi^2/T$ value	P-value
Total	21	115		
Pathologic T stage:			0.165	0.685
a	0 (0%)	1 (0.87%)		
1	5 (23.81%)	28 (24.35%)		
2	5 (23.81%)	35 (30.43%)		
3	9 (42.86%)	39 (33.92%)		
4	2 (9.52%)	12 (10.43%)		
Pathologic N stage:			0.725	0.394
0	17 (80.95%)	101 (87.83%)		
1	4 (19.05%)	14 (12.17%)		
Pathologic M stage:			0.183	0.670
0	21 (100%)	114 (99.13%)		
1	0 (0%)	1 (0.87%)		
Pathological grade:			2.181	0.140
LG	8 (100%)	64 (99.13%)		
HG	13 (0%)	51 (0.87%)		

Because the pathological stages and grades were sequential, the CMH test function of the vcdExtra package in R language and the Cochran-Mantel-Haenszel  $\chi^2$  test were used.

siderations, and the nature of the tumor could not be determined in 2 cases. Among the 5 patients with grade G2, 2 patients underwent holmium laser resection of pelvis tumors under flexible ureteroscopy. The postoperative pathology was upgraded to grade G3. Three patients underwent radical surgery. One of them had a postoperative pathological upgrade to high grade (G3), and 2 cases were consistent with the grade of intraoperative pathological biopsy. The pathological grade of the remaining tumor biopsies was the same as that of the postoperative tumor.

### Follow-up

The recurrence rate of group A was 21.43% (3/14); the tumor-specific mortality rate was 7.14% (1/14); and the total mortality rate was 13.33% (2/15). In group B, the recurrence rate was 18.37% (18/98); the tumor-specific mortality was 5.10% (5/98); and the total mortality was 7.07% (7/99). No statistically significant difference was observed between the two groups in terms of bladder tumor recurrence rate and distant metastasis rate comparison ( $p > 0.05$ ) (Table IV).

In the previous study [5], 31 cases of asymptomatic bladder urothelial carcinoma were found to be low stage and LG tumors, including 25 cases of TaNOM0 stage, 6 cases of T1NOM0 stage, 29 cases of LG, and 2 cases of HG. Obviously, the asymptomatic UTUC group had a higher stage and grade of clinicopathological features ( $p < 0.001$ ), more aggressive than in the asymptomatic bladder urothelial carcinoma group (Table V).

### Discussion

UCC is a common tumor in developed countries, and its incidence ranks fourth [9]. It can be divided

into a lower urinary tract (bladder and urethra) and UTUC (renal pelvis cavity and ureter). Bladder cancer accounts for 90–95% of UCC [10]. The incidence of UTUC is lower than that of bladder cancer.

The best treatment for UTUC is surgical resection, including renal ureterectomy + bladder sleeve resection and kidney-retaining surgery. The choice of surgical plan depends on whether the tumor is high risk [11], tumor  $> 2$  cm, multiple tumors, hydronephrosis, exfoliative cytology for HG, urethroscopy for HG, previous history of radical operation of bladder cancer, histologic variation, etc. If any of them are high risk, radical surgery should be chosen. UTUC has the characteristics of complex heterogeneity, multicenter, and strong invasiveness. If renal pelvis carcinoma is resected only by kidney and partial ureter, the incidence of residual ureter tumor can be higher [12]. Therefore, renal ureterectomy + bladder sleeve resection is the gold standard for the treat-

**Table IV.** Follow-up results of the two groups

Project	Group A	Group B
Number of patients (example)	21	115
No recurrence	11	80
Lost visit	6	16
Recurrence (still alive and without metastasis)	2	12
Recurrence (no metastasis or death)	1	2
Recurrence (metastasis and death)	0	3
Recurrence and death (other cause)	0	1
Death (cause unknown)	1	1
Recurrence rate (%)	21.43	18.37
Tumor-specific mortality (%)	7.14	5.10
Total mortality rate (%)	13.33	7.07

**Table V.** Comparison of postoperative pathological stages and grades between asymptomatic UTUC and lower urinary urothelial carcinoma

Project	Asymptomatic UTUC group	Asymptomatic bladder urothelial carcinoma	<i>P</i> -value
Pathological stage:			$< 0.001$
Nonmuscular infiltration	5	31	
Muscle layer infiltration	16	0	
Pathological grade:			$< 0.001$
LG	8	29	
HG	13	2	

ment of UTUC [13]. The grading and staging of UTUC are not related to the presence or absence of symptoms. In fact, asymptomatic UTUC is also a tumor with HG stage, so radical surgery is recommended. In our study, the main treatment was radical full-length renal ureterectomy + bladder sleeve resection, including 64 cases of open radical resection of renal pelvis/ureter carcinoma and 57 cases of laparoscopic radical resection of renal pelvis/ureter carcinoma, and a small number of cases had kidney-retaining surgery.

In this study, 95.24% (20/21) of the asymptomatic UTUC group and 30.43% (35/115) of the symptomatic UTUC group underwent preoperative or intraoperative examination of rigid/flexible ureteroscopy biopsy. All of them were confirmed to be suffering from UCC. The reasons for the difference in the proportion of biopsies between the two groups are as follows: (1) The diagnosis of asymptomatic UTUC patients lacks the support of typical symptoms. We need more accurate examination to clarify the nature of space occupation to determine the surgical scheme and avoid excessive treatment; (2) some asymptomatic UTUC patients lack evidence of typical malignant tumors before the operation; (3) avoidance of medical disputes. The results show that most asymptomatic UTUC cases were HG and high stage UCC, not significantly different from symptomatic UTUC cases.

Notably, the rigid/flexible ureteroscopy biopsy cannot provide deep or full-thickness specimens due to the superficial appearance. They can only be diagnosed by grade and cannot be staged accurately, and some patients may be underestimated [14]. In this study, 5 cases with upper urinary tract tumors underwent preoperative/intraoperative pathological biopsies with moderate differentiation (G2). Therefore, two cases underwent holmium laser resection of renal pelvis tumors under a flexible ureteroscope. The pathological changes were upgraded to HG (G3) after the operation. Tumor recurrence occurred within 1 year, and final death occurred within 2 years. The other 3 cases were treated by radical surgery. Among them, 1 case was pathologically upgraded to HG (G3) after the operation, and no recurrence was found in 3 patients who were followed up for 2 years.

In addition, the holmium laser resection of the tumor may cause burning and destruction of surgical specimens, which may affect the accuracy of

postoperative pathology. Therefore, patients with moderately differentiated (G2) renal pelvis tumors undergoing holmium laser resection under a soft microscope should be vigilant. They should be followed up closely, and radical surgery should be performed if necessary.

In our previous study of asymptomatic bladder tumors, we found that most asymptomatic bladder urothelial carcinomas could be resected through the urethra without radical surgery [5]. In clinical work, some doctors may have inertial thinking similar to asymptomatic UTUC and asymptomatic bladder cancer, and they are more inclined to perform kidney-retaining surgery. On the other hand, fast-track surgery and enhanced recovery after surgery has been widely adopted in the field of general surgery [15]. However, we found that the stage and grade of UTUC were not related to the presence of symptoms. Although this and bladder cancer were both the sources of urinary epithelial, the pathological stage and grade were higher. Therefore, asymptomatic UTUC patients should be risk-stratified according to the clinical stage classification and other parameters and the corresponding surgical treatment method should be selected. The treatment principle and symptomatic UTUC should be the same; a radical operation is still the gold standard treatment. Conservative surgery can be considered with informed consent for patients who are old and weak, with poor tolerance to surgery, isolated kidney, etc.

Upper urinary urothelial carcinoma has the characteristics of multicentric growth and easy shedding implantation. The incidence of bladder tumor after UTUC is as high as 22–47% [16]. The high recurrence rate of bladder tumor severely affects the quality of life and threatens the life and health of patients. Therefore, how to reduce the recurrence rate of bladder tumor after UTUC is also a concern of urologists. Intravesical infusion chemotherapy after UTUC is mainly based on the choice of postoperative infusion chemotherapy for bladder urothelial carcinoma. However, at present, there is no consensus on the frequency and maintenance time of bladder perfusion after UTUC [17]. Although the morphology of UTUC is the same as that of bladder urothelial carcinoma, studies have shown some differences in biological characteristics and related gene expression [18, 19]. European Association of Urology (EAU) guidelines recommend that UTUC should be treated with single intravesical infusion chemotherapy im-

mediately after the radical resection of pyelopelvic carcinoma, which can reduce the risk of recurrence of bladder tumor in the first year after resection. At present, not much evidence is available for multiple perfusion. A study group demonstrated that the effect of multiple intravesical instillations may be superior to that of a single instillation [20]. High-quality evidence-based medical evidence is still needed to study the difference in efficacy between single and multiple perfusion. In view of the higher pathological stage and grade of UTUC than bladder cancer, intravesical perfusion therapy was regularly conducted with a standardized and full course of treatment after the operation in our study. For high-risk upper urinary tract tumors of stage T3/T4 or lymph node metastasis after UTUC, platinum-based adjuvant chemotherapy is recommended, while paclitaxel or gemcitabine chemotherapy can be considered in patients with renal insufficiency. The latest stage 3 randomized controlled clinical study showed that the survival time of patients with UTUC treated with gemcitabine combined with cisplatin was significantly better than that of the control group after the operation, further indicating that chemotherapy could reduce the risk of tumor recurrence and prolong the life of patients [21]. For asymptomatic UTUC one should also select the corresponding adjuvant treatment according to its stage and grade.

## Conclusions

Compared with asymptomatic bladder cancer, asymptomatic UTUC is more malignant and more aggressive. However, compared with symptomatic UTUC, asymptomatic UTUC does not show a lower grade of staging and should be taken seriously. The principle of asymptomatic UTUC treatment is the same as that of symptomatic UTUC. Risk stratification should be carried out according to clinical staging and other parameters, and the corresponding surgical treatment should be selected.

## Conflict of interest

The authors declare no conflict of interest.

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