

# Microscopic hematuria predicts lower stage in patients with upper tract urothelial carcinoma

Nienie Qi<sup>1,\*</sup>  
Jiufeng Zhang<sup>2,\*</sup>  
Yue Chen<sup>1</sup>  
Rumin Wen<sup>1</sup>  
Hailong Li<sup>1</sup>

<sup>1</sup>Department of Urology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China;  
<sup>2</sup>Department of Urology, Peking University First Hospital, Institute of Urology, Peking University, National Urological Cancer Center, Beijing, China

\*These authors contributed equally to this work

**Background:** The aim of this study was to assess the association between the severity of hematuria (microscopic or gross) and the tumor stage and grade in a population of histopathologically confirmed upper tract urothelial carcinoma (UTUC) patients.

**Patients and methods:** We conducted a multicenter, observational study of patients who were newly diagnosed with UTUC between January 2011 and December 2016. Demographic information, pathology, and the status of hematuria were retrospectively reviewed. The association between the severity of hematuria and the tumor stage and grade was evaluated using logistic regression.

**Results:** The UTUC patients presented with gross hematuria (GH, 76.7%), microscopic hematuria (MH, 11.1%), and no hematuria (12.2%) at the time of diagnosis. The pathological stages at diagnosis for those with MH were Ta in 5.1%, T1 in 47.5%, and  $\geq$ T2 in 47.5%. The stages at diagnosis for those with GH were Ta in 1.7%, T1 in 35.5%, and  $\geq$ T2 in 62.7%. On univariate and multivariate logistic regression analyses, after adjusting for clinical factors such as age, gender, and smoking history, GH was an independent risk factor for muscle-invasive UTUC ( $\geq$ T2 disease) at diagnosis (OR 1.89, 95% CI 1.073–3.329;  $P=0.027$ ). High-grade tumor was found in 47.8% of patients with GH and 39.0% of those with MH. The severity of hematuria was not associated with tumor grade.

**Conclusion:** We are the first to report evidence that microscopic hematuria at presentation accurately predicts lower pathological stage in patients with newly diagnosed UTUC. Earlier detection of disease, before the development of GH, may influence the treatment decision and survival. The type of hematuria at the time of diagnosis does not impact the tumor grade.

**Keywords:** upper tract urothelial carcinoma, gross hematuria, microscopic hematuria, stage

## Introduction

Urothelial carcinomas (UCs) are the fifth most common tumors.<sup>1</sup> They can be located in the lower or upper urinary tract. Compared to bladder cancer, upper tract UCs (UTUCs) are relatively uncommon and account for only 5%–10% of UCs.<sup>2</sup> UTUC includes renal pelvic carcinoma and ureteral carcinoma. Approximately 60% of patients with UTUC are invasive at diagnosis.<sup>3</sup> Radical nephroureterectomy (RNU) with bladder cuff excision is the standard treatment for high-risk UTUC, regardless of tumor location.<sup>4</sup> However, chronic kidney disease is prevalent after RNU as there is a substantial decline in the estimated glomerular filtration rate.<sup>5</sup> Upper tract UCs that invade the muscle wall usually have a poor prognosis. The 5-year specific survival rate is <50% for patients with pT2/pT3 tumors and <10% for those with pT4.<sup>6–8</sup> Therefore, earlier detection before invasion and conservative management of small, low-grade, and non-invasive

Correspondence: Hailong Li; Rumin Wen  
Department of Urology, The Affiliated Hospital of Xuzhou Medical University, No. 99 Huaihai West Road, Quanshan District, Xuzhou 221100, China  
Email [wwwvivi163@163.com](mailto:wwwvivi163@163.com);  
[1102485781@qq.com](mailto:1102485781@qq.com)

UTUCs are important for preserving kidney function and improving survival for patients with UTUC. Currently, UTUC is often detected after the occurrence of gross hematuria (GH) or microscopic hematuria (MH), which is the most common symptom of UTUC (70%–80%).<sup>9</sup> It is often assumed that MH tends to occur before GH in the disease development process. However, this has not been fully explicated and it is unknown whether GH at the time of diagnosis predicts a more invasive disease than MH.

In the present study, we investigated the status of hematuria at presentation to predict the disease stage and tumor grade. To the best of our knowledge, there is no available study regarding the association of the severity or presence/absence of hematuria and the stage and grade of UTUC patients.

## Patients and methods

We conducted a multicenter, observational cohort study of patients diagnosed with UTUC between January 2011 and December 2016. A total of 532 patients with histologically confirmed UTUC were retrospectively enrolled in the present study. Informed consent was obtained from all the participants. Clinicopathologic parameters were collected from the medical records, including age at initial diagnosis, gender, smoking history, and severity or presence/absence of hematuria at the time of diagnosis, to evaluate their impact on the stage and grade. All of the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review board of Peking University First Hospital and The Affiliated Hospital of Xuzhou Medical University. All the patients provided written informed consent.

GH was defined as visible blood in the urine reported by the patient, while MH was defined as more than three red blood cells/high-power field on urine analysis. All the pathological specimens were reexamined by an experienced urological pathologist to confirm the original diagnosis. The tumor stage was assessed according to the UICC 2009 TNM classification of malignant tumors. The tumor grade was assessed according to the 2004 WHO classification grading system.

For statistical analysis, numerical variables were compared using independent *t*-tests and categorical variables were compared using chi-square tests. The association between variables and tumor grade or stage was examined by using

univariate and multivariate logistic regression analyses. The stage was categorized as a dichotomous variable based on the presence of invasion ( $\geq T2$  vs  $T1+Ta$ ). All the statistical analyses were conducted using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA). All the reported *P*-values were two sided, and statistical significance was set at  $<0.05$ .

## Informed consent

Written informed consent was obtained from the patient for the publication of this report.

## Ethical approval

The study was approved by the institutional review board from Peking University First Hospital and The Affiliated Hospital of Xuzhou Medical University.

## Results

Exactly 532 consecutive UTUC patients were enrolled in the present study and their clinicopathologic characteristics are described in Table 1. There were 273 male and 259 female patients with a mean age of 66.8 years. The diagnosis of UC was pathologically confirmed in all the patients. A total of 214 patients had non-muscle-invasive diseases ( $\leq pT1$ ) and 318 patients had muscle-invasive diseases ( $\geq pT2$ ), while 286 patients had low-grade tumors and 246 patients had high-grade tumors. The patients presented with GH (408, 76.7%), MH (59, 11.1%), and no hematuria (65, 12.2%). Women were more likely to present with MH than men (14.3% vs 8.1%,  $P=0.003$ ). Most of the patients with UTUC had no history of smoking, and GH was prevalent in those with a history of smoking.

After excluding the patients with no hematuria, the pathological stages at diagnosis for those with MH were  $Ta$  in 5.1%,  $T1$  in 47.5%, and  $\geq T2$  in 47.5%. The stages at diagnosis for the patients with GH were  $Ta$  in 1.7%,  $T1$  in 35.5%, and  $\geq T2$  in 62.7%. On univariate and multivariate logistic regression analyses, after adjusting for clinical factors such as age, gender, and smoking history, GH was an independent risk factor for muscle-invasive UTUC ( $\geq T2$  disease) at diagnosis (OR 1.89, 95% CI 1.073–3.329;  $P=0.027$ ), as shown in Table 2.

After excluding the patients with no hematuria, high-grade tumor was found in 47.8% of those with GH and 39.0% of those with MH. The severity of hematuria was not associated with the tumor grade. None of other clinical factors predicted the grade of disease.

In the 467 patients who presented with hematuria, the type of hematuria (MH or GH) after stratification by both pathological stage and grade is shown in Table 3. MH had

**Table 1** Clinical and pathological characteristics of UTUC patients according to the type of hematuria

Variable		Type of hematuria, n (%)			Total, n	P-value
		Gross	Microscopic	None		
Age (mean, years)		67.0	66.8	65.0	66.8	0.388
Gender	Male	226 (82.8)	22 (8.1)	25 (9.2)	273	0.003
	Female	182 (70.3)	37 (14.3)	40 (15.4)	259	
Smoking	Yes	102 (85.0)	4 (3.3)	14 (11.7)	120	0.007
	No	306 (74.3)	55 (13.3)	51 (12.4)	412	
Grade	High	195 (79.3)	23 (9.3)	28 (11.4)	246	0.385
	Low	213 (74.5)	36 (12.6)	37 (12.9)	286	
Stage	Ta	7 (58.3)	3 (25.0)	2 (16.7)	12	0.044
	T1	145 (71.8)	28 (13.9)	29 (14.4)	202	
	T2	126 (79.7)	14 (8.9)	18 (11.4)	158	
	T3	115 (82.1)	12 (8.6)	13 (9.3)	140	
	T4	15 (75.0)	2 (10.0)	3 (15.0)	20	

**Abbreviation:** UTUC, upper tract urothelial carcinoma.

**Table 2** Multivariate logistic regression analysis of factors predicting high grade or stage ( $\geq T2$ )

	Stage		Grade	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	0.993 (0.976–1.011)	0.444	1.003 (0.986–1.020)	0.753
Gender	0.837 (0.555–1.261)	0.394	1.253 (0.838–1.873)	0.272
Smoking	0.861 (0.517–1.434)	0.565	0.787 (0.483–1.283)	0.336
GH	1.766 (1.011–3.084)	0.046	0.695 (0.394–1.224)	0.208

**Abbreviation:** GH, gross hematuria.

**Table 3** Positive and negative predictive values of MH for predicting low-grade and non-muscle-invasive UTUC

	Hematuria (n=467)
Non-muscle-invasive cancer (Ta+T1)	
Positive predictive value	52.5%
Negative predictive value	62.7%
Low-grade cancer	
Positive predictive value	61.0%
Negative predictive value	47.8%

**Abbreviations:** MH, microscopic hematuria; UTUC, upper tract urothelial carcinoma.

a positive predictive value (PPV) and negative predictive value of 52.5% and 62.7% for non-muscle-invasive UTUC, respectively. MH had a PPV and negative predictive value of 61.0% and 47.8% for low-grade UTUC, respectively.

## Discussion

Currently, UC is often detected on evaluation of patients who present with GH or MH. Much attention has been paid to determine which patients should or should not be referred to urologists for further assessment.<sup>10–12</sup> However, the association between the status of hematuria at presentation and the tumor stage or grade is not clear. It is unknown whether presentation with GH at diagnosis means a worse prognosis than having MH. A previous study reported that local symptoms (including flank/lumbar pain, GH, or a palpable mass)

did not confer a worse prognosis compared to patients with incidentally detected UTUC.<sup>13</sup> Ramirez et al found that GH at the time of diagnosis was associated with a more advanced stage in patients with newly diagnosed bladder cancer.<sup>14</sup> The association of the UTUC stage or grade at diagnosis with GH vs MH has never been explored.

In our multicenter study, we tried to describe the impact of the severity of hematuria on the stage and grade of UTUC. We found that MH at diagnosis predicted a lower tumor stage of UTUC in multivariate logistic regression analysis. In fact, there was an ~80% higher risk for invasive ( $\geq pT2$ ) disease at the time of diagnosis when patients presented with GH. However, patients with low and high grade of disease had a similar distribution of MH and GH.

The management and survival of UTUC is stage dependent, and patients who are diagnosed when their disease is muscle invasive have a significantly worse survival than those with non-muscle-invasive UTUC.<sup>15</sup> However, it is difficult to accurately determine the stage of UTUC using currently available methods. Urinary cytology and radiography are unable to accurately predict muscle-invasive disease in UTUC patients. Su et al retrospectively assessed the diagnostic accuracy of fluorescence in situ hybridization (FISH) for detecting aggressive UTUC and found that the overall sensitivity of FISH for detecting advanced UTUC was 62.4%.<sup>16</sup> They suggested that voided urine FISH results might predict advanced

UTUC. Although ureteroscopy is more sensitive and specific for diagnosing UTUC than urine cytology and radiography, it may not be accurate for predicting tumor stage. Straub et al found that the accuracy of preoperative ureteroscopy for predicting the correct tumor grade in UTUC patients was only 58%; this accuracy increased to only 68% when urinary cytology was also considered.<sup>17</sup> Furthermore, ureteroscopy is an invasive procedure that requires general anesthesia and involves the accompanying surgical complications, and a recent study indicated that patients were at a higher risk of intravesical recurrence after RNU when they had undergone ureteroscopy before RNU.<sup>18</sup>

Because of the inaccurate preoperative or transurethral staging of UTUC, many RNUs are performed unnecessarily. Preoperative prediction of the pathological stage or patients' prognosis may reduce this overtreatment by selecting patients for nephron-sparing surgery. Diagnostic tools, or combinations of tools, which are effective for determining the UTUC stage are urgently needed to identify patients for whom conservative management is the most appropriate treatment strategy. The present study found that many risk factors associated with the detection of UTUC, including gender and smoking history, were not associated with the stage at presentation. Only MH at presentation was independently associated with lower stage. Combined with other diagnostic techniques, the severity of hematuria may be helpful for distinguishing tumors best treated using conservative management from those that should be treated with RNU.

Some studies suggested that some patients had low risk of cancer and could avoid extensive evaluations using a stratifying risk of urinary tract malignant tumors in patients with MH.<sup>19</sup> However, the current evidence showed that most patients with MH were not appropriately referred to an urologist for further evaluation and did not undergo imaging examination.<sup>20,21</sup> Delays in the diagnosis of UTUC can lead to upstaging of tumor and delay in surgery, which may result in the change of management and worse prognosis.<sup>22,23</sup> Therefore, the appropriate evaluation of UC in patients with MH may improve the survival of those with UTUC.

Some limitations of our study should be considered when interpreting the results. First, this study is retrospective, with all the attendant imprecisions associated with the large recollection of data. The data were collected in two centers and there were certainly biases related to differences in pathologic assessment between the two centers. In addition, the sample size of the patients with MH at diagnosis was relatively small. Only 15% patients with hematuria (GH or MH) presented with MH, which may influence the reliability of the PPV of MH for predicting non-muscle-invasive UTUC. Finally, we

were unable to evaluate the relationship between the severity of hematuria and oncologic prognosis due to the short follow-up period. Similar studies evaluating the relationship between the status of hematuria and tumor stage of UTUC in additional populations are needed to confirm our findings. Despite these limitations, to the best of our knowledge, this is the first study to provide the correlation between the severity of hematuria and the tumor stage of UTUC.

## Conclusion

We are the first to report evidence that MH at presentation accurately predicts lower pathological stage in patients with newly diagnosed UTUC. Earlier detection of disease, before the development of GH, may influence the treatment decision and survival. The type of hematuria at the time of diagnosis does not impact the tumor grade.

## Data sharing statement

Please contact the author for data requests.

## Acknowledgments

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## Disclosure

The authors report no conflicts of interest in this work.

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