

# Predictive models and prognostic factors for upper tract urothelial carcinoma: a comprehensive review of the literature

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**Abstract:** In the context of customized patient care for upper tract urothelial carcinoma (UTUC), decision-making could be facilitated by risk assessment and prediction tools. The aim of this study was to provide a critical overview of existing predictive models and to review emerging promising prognostic factors for UTUC. A literature search of articles published in English from January 2000 to June 2016 was performed using PubMed. Studies on risk group stratification models and predictive tools in UTUC were selected, together with studies on predictive factors and biomarkers associated with advanced-stage UTUC and oncological outcomes after surgery. Various predictive tools have been described for advanced-stage UTUC assessment, disease recurrence and cancer-specific survival (CSS). Most of these models are based on well-established prognostic factors such as tumor stage, grade and lymph node (LN) metastasis, but some also integrate newly described prognostic factors and biomarkers. These new prediction tools seem to reach a high level of accuracy, but they lack external validation and decision-making analysis. The combinations of patient-, pathology- and surgery-related factors together with novel biomarkers have led to promising predictive tools for oncological outcomes in UTUC. However, external validation of these predictive models is a prerequisite before their introduction into daily practice. New models predicting response to therapy are urgently needed to allow accurate and safe individualized management in this heterogeneous disease.

**Keywords:** Upper tract urothelial carcinoma (UTUC); prognosis; prognostic factors; predictive tools; nomograms; risk stratification; biomarkers; survival; disease recurrence

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## Introduction

Until recently, management and surveillance of upper tract urothelial carcinoma (UTUC) was patterned after that of bladder cancer (BC). But reports have demonstrated that, despite their pathological similarities, BC and UTUC

had distinct biological behaviors, and therefore, required individualized recommendations (1,2).

However, due to the low incidence of UTUC [it accounts for only 5–10% of all urothelial carcinomas (3)], the majority of studies is mainly made of single-institution

small cohorts. The resulting low-level of evidence did unfortunately not allow high-grade recommendations for UTUC management (2).

In a context where personalized patient care is necessary with kidney-sparing surgery (KSS) for localized tumors, neoadjuvant chemotherapy before radical nephroureterectomy (RNU), and lymph node (LN) dissection for high-risk tumors (2,4), accurate assessment of tumor aggressiveness is necessary for clinical decision-making.

Beyond the established prognostic factors such as tumor stage, grade and LN metastasis, numerous patient-, surgery- and pathology-related factors have been recently identified thanks to intense research based on collaborative studies. The integration of these factors in predictive tools has permitted to guide decision-making for customized/personalized care delivery.

The aim of this review was to provide a critical overview of existing predictive models and to review emerging promising prognostic factors for UTUC. We have previously reported on International Consultation on Urologic Diseases—Société Internationale d'Urologie (ICUD-SIU) guidelines (5). In this review, we updated the data and added non-consensus-based opinions of authors.

### Evidence acquisition

A non-systematic literature search was conducted using PubMed/Medline database. Articles published in English between January 2000 and June 2016 were collected by using a combination of the following terms: “prognostic factor”, “predictive tool”, “nomograms”, “risk stratification”, “survival”, “biomarker” together with “upper tract urothelial carcinoma” or “upper tract transitional cell carcinoma”. All published studies on predictive tools or predictive/prognostic biomarkers were retained for the purpose of this review. In order to explore other emerging prognostic factors and biomarkers, retrospective studies and meta-analyses involving more than 300 patients were also retained.

### Evidence synthesis

#### *Preoperative prediction of disease invasiveness and oncological outcomes after surgery*

RNU with bladder-cuff excision remains the gold standard for high-risk UTUC (2). However, indication of KSS has slowly shifted from absolute indication in patients

with solitary kidney, bilateral disease or patient-related comorbidities towards elective indication for a broader spectrum of patients with low-risk UTUC (2,4). Therefore, before considering KSS, preoperative assessment of tumor invasiveness but also after risk of extra-luminal recurrence, metastasis and cancer-specific mortality are essential to support an evidence-based assessment of the risks, benefits and alternatives in a shared decision-making process.

#### **Imaging and ureteroscopy findings: cornerstones of preoperative prediction in UTUC**

Several predictive models based on preoperative imaging and diagnostic ureteroscopy findings have been designed to assess muscle-invasive and/or non-organ-confined (NOC) UTUC (Table 1).

Hydronephrosis (6,10-12) and local invasion (7) are both features associated with advanced disease that can be detected on high definition computed tomography (CT) urography. Hydronephrosis is also associated with an increased risk of tumor metastasis (6).

The increased use of high-definition flexible digital ureteroscopes has facilitated the preoperative identification of features associated with high-risk UTUC such as sessile architecture (13-17) and tumor multifocality (18-20). When combined with biopsies, ureteroscopy also permit to identify high-grade tumors with high accuracy and reproductibility (14,16,21,22).

#### **Predictive tools for advanced-stage and NOC UTUC assessment**

Brien *et al.* showed that the knowledge of hydronephrosis, ureteroscopic grade and urinary cytology can predict muscle-invasive and NOC with a positive predictive value (PPV) of 89% and 73%, respectively (8). More importantly, if all three are negative, the negative predictive value (NPV) was 100%.

Chen *et al.* constituted a nomogram based on gender, tumor architecture, multifocality, tumor location, grade and hydronephrosis that reached an accuracy of 79% for both NOC and muscle-invasive disease assessment (6). Even if gender appeared as a predictor of advanced-stage disease in this dataset, its influence on tumor aggressiveness and oncological outcomes in UTUC is controversial with most studies showing no effect (23-27). Therefore, international guidelines on UTUC do not consider gender as a predictor of oncological outcomes in UTUC (2).

By combining tumor grade, architecture and tumor location in a nomogram, Margulis *et al.* reached an

Table 1 Preoperative predictive models for advanced-stage and NOC disease in UTUC

Authors	Model	Gender	Imaging		Ureteroscopy findings			Histology		Accuracy (%)	Validation
			Hydronephrosis	Invasion	Location	Multifocality	Architecture	Grade	Cytology		
<b>Muscle-invasive disease</b>											
Chen et al., 2013 (6)	Nomogram	✓	✓	✓	✓	✓	✓	✓	79	Internal	
Favaretto et al., 2012 (7)	Risk group stratification		✓	✓	✓	✓	✓	✓	71	-	
Brien et al., 2010 (8)	Risk group stratification		✓				✓	✓	PPV: 89; NPV: 100	-	
<b>NOC disease</b>											
Chen et al. 2013 (6)	Nomogram	✓		✓	✓	✓	✓	✓	79	Internal	
Favaretto et al., 2012 (7)	Risk group stratification		✓	✓	✓	✓	✓	✓	70	-	
Margulis et al., 2010 (9)	Nomogram			✓	✓	✓	✓	✓	77	Internal	
Brien et al., 2010 (8)	Risk group stratification		✓				✓	✓	PPV: 73; NPV: 100	-	

NOC, non-organ-confined; UTUC, upper tract urothelial carcinoma; PPV, positive predictive value; NPV, negative predictive value.

accuracy of 77% for NOC-disease assessment (9). However, the impact of tumor location on UTUC prognosis is still debated. Contradictory findings have been reported concerning its correlation with advanced UTUC (6,22,28,29), disease recurrence (19,22,26,29,30) and cancer-specific survival (CSS) (18-20,22,28,30,31). Even if meta-analyses found no correlation between NOC disease and tumor location (20), ureteral tumors seem associated with shorter recurrence-free survival (RFS) in various studies (20,24,25). However, the current meta-analyses suffer from poor quality as they are based on methodologically weak studies.

From a dataset of 274 UTUC patients treated with RNU, Favaretto *et al.* constituted a risk group stratification model for muscle-invasive UTUC with an accuracy of 71% (7). From the same dataset, the association of tumor grade, location, invasion and hydronephrosis on imaging predicted NOC-UTUC with an accuracy of 70%. Unfortunately, these findings are still waiting for external validation.

### Emerging demographic and preoperative prognostic factors

As in most diseases, patient's physical condition influences immediate postoperative outcomes such as time of recovery, duration of hospitalization and surgery-related complications (32). Few patient-related factors are associated with UTUC aggressiveness and oncologic outcomes (Table 2).

### Advanced-age & ECOG-PS

For a long-time, advanced chronological age was thought to be an independent factors associated with invasive tumor patterns (33), tumor recurrence (34,35) and shorter CSS (16,33,34,36) based on nationwide epidemiologic studies. However, large multi-institutional studies have shown that advanced-age was not a predictor of survival anymore when it was adjusted for the effect of performance status (34,36-38). Therefore, international guidelines do not recommend age as reason to not offer RNU with potential curable intent (2). However, assessment of performance status helps identify patients who are likely to have serious morbidity and therefore not benefit from RNU.

### Symptoms

At the time of diagnosis, patient's physical condition can also be altered by systemic symptoms related to advanced-stage disease such as night sweat, anorexia and weight loss (48). Flank pain, when related to hydronephrosis, is also a marker of NOC disease (12). Similarly to all cancers, symptoms of systemic disease portend metastatic cancer with poor outcomes.

**Table 2** Prognostic factors in UTUC

Factors	High tumor stage	High tumor grade	Lymph node metastasis	IVR	RFS	MFS	CSS	OS	Level of evidence	Ref.
<b>Preoperative factors</b>										
Advanced age	✓	✓		✓	✓		✓	✓	3	(16,33-36)
ECOG-PS							✓	✓	3	(37,38)
Obesity (BMI ≥30)					✓		✓	✓	3	(39)
Smoking	✓	✓	✓	✓	✓		✓		3	(40-42)
DM with poor glycemic control				✓	✓		✓	✓	3	(35,43-47)
History of bladder CIS/BC		✓		✓					3	(35,43-45)
Hydronephrosis	✓	✓	✓					✓	3	(6,10)
Symptoms	✓	✓	✓						3	(48)
Local invasion on imaging	✓		✓						4	(7)
<b>Postoperative factors and pathological features</b>										
High tumor stage				✓	✓	✓	✓	✓	3	(15-17,21,35,39,49,50)
High tumor grade					✓		✓		3	(14,16,21,22)
Lymph node metastasis				✓	✓		✓	✓	3	(15,16,35,39)
Concomitant CIS	✓	✓	✓	✓	✓		✓		3	(35,49,51)
LVI	✓	✓	✓		✓	✓	✓	✓	3	(15,16,52-54)
Ureteral location				✓	✓	✓	✓		3	(18,20,35,50)
Multifocal tumor	✓	✓	✓		✓	✓	✓	✓	3	(6,18-20,55)
Tumor size >3 cm				✓					3	(56)
Sessile architecture	✓	✓	✓		✓		✓		3	(6,13-16)
Tumor necrosis	✓	✓	✓						3	(57,58)
Concomitant histology variant	✓	✓	✓		✓	✓	✓	✓	3	(59-61)
Positive surgical margins				✓		✓			3	(24,62,63)
Extravesical BCE				✓	✓				3	(24,35,64)
Endoscopic BCE				✓	✓				3	(35,64)
Lack of BCE							✓		3	(65)
Laparoscopic RNU				✓					3	(24)

UTUC, upper tract urothelial carcinoma; IVR, intravesical recurrence; RFS, recurrence-free survival; MFS, metastasis-free survival; CSS, cancer-specific survival; OS, overall survival; BMI, body mass index; DM, diabetes mellitus; CIS, carcinoma *in situ*; BC, bladder cancer; LVI, lymphovascular invasion; BCE, bladder cuff excision; RNU, radical nephro-ureterectomy.

**Ethnicity**

Data on the influence of ethnicity on UTUC-related oncologic outcomes are very sparse. While a population-based US study found that African-American patients with UTUC had a shorter survival than other ethnic groups (66), an international study comparing Japanese with European and US Caucasian patients did not find any difference

in survival between these two groups (67). Further investigations on both biological and sociological factors underlying these results must be performed. Access to care could also influence the worse outcomes of African-American patients.

**Smoking status**

Similarly to BC, cumulative smoking exposure is a well-

established predictor of poor outcomes in UTUC. Heavy long-term smokers (more than 20 cigarettes per day for more than 20 years) were more likely to have advanced-stage disease, and experience disease recurrence and cancer-specific mortality after RNU (40,41). Interestingly, after 10 years of smoking cessation, former smokers had similar outcomes to non-smokers (40,42). Therefore, counseling smoking cessation should be strongly encouraged.

### History of BC

Despite being recognized as separate entities, the upper urinary tract and bladder share the same fertile soil for development of urothelial carcinoma. Therefore, it is not surprising that history of BC is associated with higher tumor grade and increase risk of intravesical recurrence after treatment of UTUC (35,43-45). In general, BC recurrence after UTUC treatment is as high as 30–40% (35).

### Metabolic disorders

Obese patients [body mass index (BMI) >30] (39) or diabetes mellitus (DM) with poor glycemic control (46,68,69) are more likely to develop tumors with aggressive behavior and suffer, therefore, from worse survival. On the other hand, underweight, defined as BMI in the lowest quartile of a cohort, is also associated with worse survival (70). These findings need to be confirmed in all ethnic groups and in large controlled studies.

### Tumor necrosis

Tumor necrosis is a pathological feature that is associated with muscle-invasive UTUC. However, after adjustment for the effects of established pathologic features, its association with oncological outcomes either weakened or totally disappeared (57,58,67).

Preoperative assessment of tumor aggressiveness remains challenging despite the identification of solid new predictors/prognosticators. Clinical use of existing predictive models is mostly questioned due to the lack of external validation. However, the combination of emerging prognostic factors together with high definition imaging and ureteroscopically-obtained biopsies might help building more accurate predictive models for a more accurate customized care delivery.

### Postoperative assessment of survival outcomes in UTUC

After surgery, accurate risk estimation would allow optimal decision-making regarding adjuvant chemotherapy and follow-up scheduling.

### Postoperative predictive models for disease recurrence and distant metastasis

Several predictive tools have been designed to assess the risk of intravesical recurrence, local and distant recurrence after RNU (Table 3). These models share several factors that have been described as independent predictors for each outcome.

Concomitant carcinoma *in situ* (CIS) is a well-known predictor of worse survival in BC. In UTUC, concomitant CIS is associated with advanced-stage UTUC (49,51), intravesical and loco-regional recurrence (35,49,51) as well as CSS (49,51).

Lymphovascular invasion (LVI) is also an independent predictor of worse oncologic outcomes after RNU (52-54,73).

Positive surgical margins and lack of complete bladder cuff excision (BCE) are associated with higher risk of both intravesical recurrence and shorter survival (24,62,65,74).

Latest meta-analyses demonstrated that endoscopic and extravesical BCE resulted in higher recurrence rates compared to complete intravesical removal (22,35,64,74,75).

Xylinas *et al.* identified prognosticators of intravesical recurrence from a cohort study including more than 1,900 patients (35). Independent prognostic factors for nomogram building were patient age, gender, history of BC, tumor location, clinical stage, concomitant CIS, LN metastasis, BCE and surgical approach. The combination of these factors helped to reach an accuracy of 69% for prediction of intravesical recurrence risk at 2 years.

Ishioka *et al.* also proposed a risk group stratification model and a nomogram predicting intravesical recurrence after RNU (17). By combining, tumor architecture, tumor stage, LVI and gender, they obtained an accuracy of 62%.

For the prediction of 5-year RFS in patients with high grade UTUC after RNU, Youssef *et al.* developed a simplified risk stratification model called TALL score. Based on tumor stage, architecture, LVI and LN metastasis, this predictive scoring model reached an accuracy of 73% (71).

Colin *et al.* published a risk group stratification model that assessed 2- and 5-year metastasis-free survival (MFS) by combining tumor location, stage, LVI and surgical margin (50).

### Postoperative predictive models for CSS

Existing postoperative models predicting CSS are mostly constructed from established prognosticators such as tumor stage, grade or LN metastases (Table 4). They reach an accuracy up to 82% for prediction of 5-year CSS. However, they almost all suffer from the same limitation: lack of external validation and lack of decision-analysis.

**Table 3** Postoperative predictive models for disease recurrence and metastasis after RNU for UTUC

Authors	Model	Outcome	Demographic features			Ureteroscopic and pathological features					Surgery-related features			Accuracy (%)	Validation		
			Age	Gender	Previous UCB	Location	Architecture	Stage	Grade	LN metastasis	LN density	CIS	LVI			Surgical approach	BCE
Youssef <i>et al.</i> 2015 (71)	Risk group stratification	5-year RFS for high grade non-metastatic RNU			✓	✓	✓	✓	✓							73	External
Colin <i>et al.</i> 2014 (50)	Risk group stratification	2- and 5-year MFS for pT2-3 pNx				✓	✓	✓							✓	-	-
Xylinas <i>et al.</i> 2014 (35)	Risk group stratification & nomogram	3, 6, 9, 12, 18, 24 and 36 months IVR	✓	✓	✓	✓	✓	✓	✓						✓	69	External
Ishioaka <i>et al.</i> 2015 (17)	Risk group stratification & nomogram	1- and 5-year IVR	✓			✓	✓							✓		62	-
Cha <i>et al.</i> 2012 (15)	Nomogram	2- and 5-year RFS for RNU without perioperative chemotherapy	✓			✓	✓	✓	✓					✓		77	External
Bolenz <i>et al.</i> 2009 (72)	Risk group stratification	5-year RFS for RNU with lymphadenectomy							✓	✓				✓		70	Internal

RNU, radical nephro-ureterectomy; UTUC, upper tract urothelial carcinoma; UCB, urothelial carcinoma of the bladder; LN, lymph node; CIS, carcinoma *in situ*; LVI, lymphovascular invasion; BCE, bladder cuff excision; RFS, recurrence-free survival; MFS, metastasis-free survival; IVR, intravesical recurrence.

Table 4 Postoperative models for CSS after RNU for UTUC

Authors	Model	Outcome	Age	Ureteroscopic and pathological features							Accuracy (%)	Validation	
				Location	Architecture	Stage	Grade	LN metastasis	LN density	CIS			LVI
Youssef <i>et al.</i> 2015 (71)	Risk group stratification	5-year CSS for high grade non-metastatic RNU			✓	✓		✓				72	External
Seisen <i>et al.</i> 2014 (76)	Nomogram	5-year CSS for pT1-3/N0-x M0 without preoperative chemotherapy	✓	✓	✓		✓					81	External
Rouprêt <i>et al.</i> 2013 (77)	Nomogram	5-year CSS	✓	✓	✓		✓					80	External
Ku <i>et al.</i> 2013 (78)	Nomogram validation	3- and 5-year CSS for RNU without neoadjuvant chemotherapy	✓	✓	✓		✓					72	External
Chia <i>et al.</i> 2012 (15)	Nomogram	2- and 5-year CSS for RNU without perioperative chemotherapy	✓	✓	✓		✓			✓		82	External
Yates <i>et al.</i> 2012 (79)	Nomogram	3- and 5-year CSS	✓	✓	✓		✓					78	External
Jeldres <i>et al.</i> 2010 (80)	Nomogram	5-year CSS	✓	✓	✓		✓					75	External
Bolenz <i>et al.</i> 2009 (72)	Risk group stratification	5-year CSS for RNU with lymphadenectomy		✓	✓		✓		✓		✓	68	Internal

CSS, cancer-specific survival; RNU, radical nephro-ureterectomy; UTUC, upper tract urothelial carcinoma; LN, lymph node; CIS, carcinoma *in situ*; LVI, lymphovascular invasion.

The exception is the study from Ku *et al.* (78) who performed an online external validation of Yates *et al.*'s (79) model in a dataset of patients from a Korean institution. This permitted to confirm that Yates *et al.*'s model based on age, tumor stage, grade, location and LN metastasis had an accuracy of more than 70% from 3- and 5-year CSS prediction.

### Emerging prognostic factors of disease RFS or MFS

Some more prognostic factors of disease recurrence have been described and would benefit from more in depth investigations (Table 2).

#### Tumor size

Surgeons' experimental knowledge has demonstrated that large tumors were not necessarily muscle-invasive tumors. However, no large multicenter study has investigated this question yet. A meta-analysis gathering seven studies showed that tumor larger than 3 cm were more likely to recur (56). However, these results are limited by the small number of patients included and the heterogeneity of studies.

#### Variant histology

Non-pure urothelial carcinoma with the presence of variant histology is another marker of aggressive disease that can sometimes be assessed on ureteroscopically-obtained biopsies (59,60,81). Variant histology has been associated with intravesical and loco-regional recurrence (60). A large retrospective study compared survival of patients presenting variant histology versus pure urothelial carcinoma. At 5-year, patients with variant histology had a 30% lower CSS compared to patients with pure urothelial carcinoma (60).

Before integration of the described predictive tools in clinical decision-making, external validations in independent cohorts such as Ku *et al.* (78) performed should be done. Variant urothelial carcinoma also appears to be a pathological feature associated with high risk UTUC and should therefore be emphasized on pathological reports and during multidisciplinary discussions for patient care management. Similarly to BC, it will/can change management significantly (82).

### Biomarkers predicting oncologic outcomes after RNU

The increase in UTUC research has permitted to identify numerous tissue-, blood- and urine-based biomarkers associated with UTUC survival outcomes (Table 5). Through a better understanding of biological mechanisms associated with UTUC carcinogenesis, progression and metastasis, UTUC diagnosis, surveillance and treatment are

likely to be improved.

### Blood-based predictive tools for survival outcomes

Inflammatory response and immune system reaction toward cancer are well-described phenomenon in various types of malignancies. Changes in level of biomarkers such as hemoglobin (102), CRP (103) or neutrophil-to-lymphocyte ratio (NLR) (104,105) have been correlated with muscle-invasiveness and/or NOC disease as well as worse oncologic outcomes after RNU (Table 5).

Kim *et al.* integrated NLR in a postoperative nomogram for RFS and CSS (109). When combined with tumor stage, LVI and BCE, the model predicted 2- and 5-year RFS with an accuracy of 78%, and CSS with an accuracy of 80%.

Fujita *et al.* (102) and Sakano *et al.* (110) both also integrated inflammatory biomarkers (hemoglobin level and white blood cell count) in the construction of a preoperative risk group stratification model predicting CSS.

Preoperative estimated glomerular filtration rate (eGFR) is also a predictor of disease recurrence and CSS (111,112). By adding eGFR to tumor stage, grade and LN metastasis, Ehdiaie *et al.* constructed a nomogram predicting RFS and CSS with an accuracy of 82% and 83%, respectively (112).

### Upcoming prognostic molecular biomarkers

Numerous prognostic molecular biomarkers in UTUC have been described (Table 5). These biomarkers are implicated in every steps of tumorigenesis and progression from cell-cycle regulation [mTOR pathway (99)] to cell-proliferation [HER2 (91), Ki-67 (95-97,113), BCAT1 (83), CDCA5 (84)] and apoptosis [p53 (100)]. Unfortunately, most of them have been described in single-institution cohorts and very few factors benefited from external validation.

Ki-67 seems to be, to date, the most promising biomarker. High proliferation based on Ki67 staining has been associated with disease invasiveness, disease recurrence and CSS in both retrospective and prospective studies (95-97,113,114).

Potentially, the combination of tissue-based biomarkers such as Ki-67 and inflammation-related blood-based preoperative markers could constitute the future of UTUC prognostication and prediction.

### Conclusions

Current international guidelines encourage a risk-adapted approach to UTUC management. Whether it is for preoperative tumor invasiveness assessment when considering KSS or for postoperative determination of

**Table 5** Prognostic biomarkers associated with advanced stage disease and oncological outcomes in UTUC

Factors	High tumor stage	High tumor grade	Lymph node metastasis	IVR	RFS	MFS	CSS	OS	Level of evidence	Ref.
Tissue-based biomarkers										
BCAT1	✓	✓	✓			✓	✓		4	(83)
CDCA5	✓	✓	✓			✓	✓		4	(84)
COX2 and EP4R co-expression	✓	✓					✓		4	(85)
CSF2	✓					✓	✓		4	(86)
FGF7	✓	✓	✓		✓	✓			4	(87)
FOXA1									4	(88)
GPX2 (under-expressed)	✓	✓	✓			✓	✓		4	(89)
HAS3	✓	✓	✓			✓	✓		4	(90)
HER2				✓					4	(91)
IGFBP5	✓	✓	✓			✓	✓		4	(92)
IMP3	✓	✓	✓		✓		✓	✓	4	(93)
INHBA	✓	✓	✓			✓	✓		4	(94)
Ki-67	✓		✓	✓	✓		✓		3	(95-97)
MMP-11	✓	✓	✓			✓	✓		4	(98)
mTOR pathway	✓	✓	✓		✓		✓		4	(99)
p53					✓		✓	✓	4	(100)
PTP4A3	✓		✓			✓	✓		4	(101)
Blood-based biomarkers										
Anemia					✓	✓	✓		4	(102)
High CRP					✓		✓		4	(103)
High NLR	✓	✓	✓		✓	✓	✓		3	(104,105)
Fibrinogen	✓	✓					✓	✓	3	(106)
Low sodium							✓		4	(102)
Red cell distribution width								✓	4	(107)
White blood cell count							✓	✓	4	(107)
Urine-based biomarkers										
Cytology				✓					3	(108)

UTUC, upper tract urothelial carcinoma; IVR, intravesical recurrence; RFS, recurrence-free survival; MFS, metastasis-free survival; CSS, cancer-specific survival; OS, overall survival; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio.

patients who could benefit from adjuvant intravesical instillations or chemotherapy, predictive models and prognostic factors have been described. However, due to their low level of evidence and lack of external validation, none of these predictive tools has been recommended

in daily decision-making yet (2,4). Still, noteworthy developments have been achieved thanks to international collaborations, and more accurate predictors are highly likely to change current practice.

We expect the combination of patient-, pathology-,

surgery- and biomarkers-related factors will eventually reach an accuracy high enough for a wide-spread use for customized decision-making in UTUC.

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None.

### Footnote

*Conflicts of Interest:* Shahrokh F. Shariat owns or co-owns the following patents: methods to determine prognosis after therapy for prostate cancer. Granted 2002-09-06; methods to determine prognosis after therapy for bladder cancer. Granted 2003-06-19; prognostic methods for patients with prostatic disease. Granted 2004-08-05; soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma. Granted 2010-07-20. He is advisory board member of Astellas, Cepheid, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanofi, Wolff. He is speaker for Astellas, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanochemia, Sanofi, Wolff. Romain Mathieu is consultant for Astellas, Ipsen, Janssen; and he is speaker of Janssen, Sanofi, Novartis, Takeda. The other authors have no conflicts of interest to declare.

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