Predictive factors of recurrence and survival of upper tract urothelial carcinomas.

Grégory Verhoest, Shahrokh Shariat, Thomas Chromecki, Jay Raman, Vitaly Margulis, Giacomo Novara, Christian Seitz, Mesut Remzi, Morgan Rouprêt, Douglas Scherr, et al.

Predictive factors of recurrence and survival of upper tract urothelial carcinomas

Grégory Verhoest[1,*] Shahrokh F. Shariat[2,3,*], Thomas F. Chromecki[2,4], Jay D. Raman[5], Vitaly Margulis[5], Giacomo Novara[6], Christian Seitz[7], Mesut Remzi[8], Morgan Rouprêt[9], Douglas S. Scherr[2], Karim Bensalah[1,+]

[1]Department of Urology, CHU Rennes, University of Rennes, Rennes, France
[2]Departments of Urology and [3]Division of Medical Oncology, Cornell University Medical College, New York, USA
[3]Department of Urology, Penn State College of Medicine, Hershey, USA
[4]Department of Urology, Medical University Graz, Graz, Austria
[5]Department of Urology, University of Texas Southwestern Medical Center, Dallas, USA
[6]Department of Urology, University of Padua, Padua, Italy
[7]Department of Urology, Hospital Barmherzige Brüder Vienna, Vienna, Austria
[8]Department of Urology,Hospital Weinviertel-Korneuburg, Korneuburg, Austria
[9]Department of Urology, La Pitié Salpétrière Hospital, Paris, France

[*]Authors of equal contribution

[+]**Corresponding author:**
Karim Bensalah, MD
Department of Urology
Rennes University Hospital
Rue Henri Le Guillou
35033 RENNES CEDEX, FRANCE
karim.bensalah@chu-rennes.fr
Tel: +33 2 99 28 42 70
Fax: +33 2 99 28 41 13

Key words: transitional carcinoma, upper tract, nephro-ureterectomy, predictive factors, recurrence, urothelial carcinoma

Word count: Text - 2815
Abstract - 195

Abbreviations:
CIS = Carcinoma In Situ
CSM = Cancer Specific Mortality
LN = Lymph Node
LVI = Lymphovascular Invasion
RNU = Radical Nephroureterectomy
SEER = Surveillance Epidemiology and End Results
TNM = Tumor, Nodes, and Metastases
UTUC = Upper Tract Urothelial Carcinoma
UTUCC = Upper Tract Urothelial Carcinoma Collaboration

Abstract

Objective: UTUCC is a rare tumor and most reports on prognostic factors come from small single centers series. The objective of this article was to provide an updated overview of current clinical, pathological and biological prognostic factors of UTUC.

Methods: PubMed was searched for records from 2002 to 2010 using the terms “prognostic factors”, “recurrence”, “survival”, and “upper tract urothelial carcinoma”. Among identified citations, papers were selected based on their clinical relevance.

Results: Classical clinical factors that influence UTUC prognosis include age, presence of symptoms, hydronephrosis and interval from diagnosis. Many biomarkers have shown promises to better appraise the natural course of UTUC although none is currently used in clinical practice. Stage, grade, lymph node metastases, lymphovascular invasion, tumor necrosis, and tumor architecture are strong pathological parameters. RNU is the standard treatment of localized UTUC. Both laparoscopic and open approaches seem to offer similar cancer control. Lymph node dissection increases staging accuracy and might confer a survival benefit.

Conclusion: RNU is the standard treatment for most patients with UTUC. Recent multicenter studies confirmed the prognostic value of classical prognostic parameters. Better survival prediction might be obtained with prognostic systems including clinical data and new biomarkers.

Introduction

Upper tract urothelial carcinoma (UTUC) is a rare tumor that represents 5% of all genitourinary malignancies.[1] It occurs more frequently in the renal pelvis than in the ureter with a ratio of 3:1.[2, 3] Classical risk factors for the development of UTUC include smoking, abuse of analgesics, chronic urinary tract infection, stone disease, and oncologic agents such as cyclophosphamide.[2] UTUC can develop after primary bladder cancer in up to 10% of cases. Secondary bladder cancer after primary UTUC is more common with a risk of 20 to 50%.[3-5]

Radical nephro-ureterectomy (RNU) with ipsilateral bladder cuff excision is the surgical standard of care for patients with non metastatic UTUC. Despite effective local therapy, disease recurrence and progression remain common. The most important prognostic factor of UTUC is disease stage. Five-year survival rates approach 90% for low stage tumors and decrease to < 30% in cases of regional nodal metastases and < 10% in case of distant metastases.[5] Endoscopic management can be an option for patients with small, unilateral low stage and low grade tumors [6, 7].

Because of the rarity of UTUC, most of the publications concerning UTUC were single center series, until recently. Although they largely contributed to the understanding of the disease, they were limited by small size and heterogeneous populations. To overcome this limitation and in an effort to better understand the natural history, a comprehensive database (UTUCC; the Upper Tract Urothelial Carcinoma Collaboration) incorporating the clinico-pathologic characteristics and outcomes of more than 1300 patients treated with RNU for UTUC at 13 academic centers worldwide was created in 2008.[8] Many publications focusing on prognostic

factors came out of this collaborative effort. To externally validate the findings of these studies, a validation cohort based on over 700 RNU cases was created.

In the light of data, the objective of this review was to investigate prognostic factors of UTUC outcomes.

Clinical factors

Age. There is very limited data on the impact of age on clinical outcomes in UTUC. In a retrospective study from the UTUCC including 1453 patients, Shariat et al. reported that older age was an independent predictor of cancer-specific mortality (CSM).[9] This finding could be explained by a change in the biological potential tumor cells, a decrease in the host's defense mechanisms, or differences in care patterns.[10] However, advanced age alone should not be an exclusion criterion for the aggressive treatment of potentially curable UTUC. A large proportion of elderly patients can be cured with RNU.[9] Therefore, chronological age alone is an inadequate indicator of outcomes in older UTUC patients and should not be used to deny a potentially curative intervention to elderly patients.[9]

Gender. No difference has been shown in histopathological features and outcomes between men and women treated with RNU for UTUC.[11, 12]

Symptoms. The presence of symptoms is a classical prognostic factor in renal cell carcinoma (RCC) patients.[13] The UTUCC studied 654 patients managed by RNU and found no difference in terms of recurrence-free survival between patients with incidental tumors and patients with local symptoms. However, patients with systemic symptoms had a significantly higher risk of disease recurrence (p<0.001).[14] Nevertheless, systemic symptoms could not predict recurrence or cancer death in multivariable analysis. Yet, symptom classification improved the accuracy of a

predictive model comprising stage, grade and lymph node status. In a smaller series of 168 patients, Inman and colleagues built a preoperative model, where presence of constitutional symptoms (pain or weight loss) was a predictor of overall survival (p=0.007), and trended towards predicting cancer mortality (p=0.064).[15]

Hydronephrosis. In bladder cancer, hydronephrosis is a sign of advanced disease and a predictor of poor outcome.[16] In UTUC, two previous studies reported that non-visualization of the urinary tract, delayed excretion, or hydronephrosis were associated with invasive ureteral cancer.[17, 18]

Interval from diagnosis. As suggested in bladder cancer[19], a recent study showed that longer interval from diagnosis of UTUC to RNU was associated with aggressive features, such as more advanced stage and higher tumor grade, but not with disease recurrence or cancer-specific mortality. However, in the subgroup of patients with stage ≥ pT2, longer delay was associated with higher risk of disease recurrence and cancer-specific mortality.[20]

Biomarkers

Conventional serum markers. Recent research into the profiling of UTUC at the molecular level has begun to shed light on important mechanisms of pathogenesis, as well as providing a number of potential diagnostic and prognostic markers. Molecular markers have the potential to be used clinically to screen for, diagnose, or monitor the activity of diseases and to guide molecular targeted therapy or assess therapeutic response. The prognostic value of proteins implicated in the regulation of cell cycle (p53 and p27), apoptosis (bcl2, survivin), cell adhesion (E-Cadherin) and cell proliferation (Ki67) have been suggested in small single-center series.[3, 21, 22] E-Cadherin and Ki67 were shown to be independent prognostic factors of tumor

recurrence in multivariable analysis.[21, 22] Microsatellite instability has also been identified as an independent prognostic parameter, mainly among patients with pT2-T3 N0 M0 UTUC.[3, 23] Although these markers are promising, none are used in clinical practice. Tissue microarray studies are currently ongoing as part of the UTUCC biomarker and validation project. Based on the lower tract urothelial carcinoma experience, a combination of complementary and yet independent molecular markers will likely better capture the biologic potential of each individual urothelial tumor, resulting in improved clinical decision-making.

Laparoscopic versus open RNU

There has been a controversy regarding the laparoscopic treatment of UTUC because of the fear of potential tumor seeding. Most of the studies are retrospective and it is unlikely that a large randomized analysis will be performed due to the rarity of UTUC. However, the retrospective series suggest that the laparoscopic approach is safe and effective in appropriately selected patients.

While some authors reported a higher risk of intravesical disease recurrence with laparoscopic approach [24], the studies were small, monocentric and multivariable analyses failed to characterize treatment modality as an independent risk factor for disease recurrence.[25, 26] A recent publication from the UTUCC including 1249 patients reported that laparoscopic RNU offered equivalent oncologic efficacy to open surgery in selected patients. There was no difference between the two approaches with respect to disease recurrence or cancer-specific mortality; although patients treated laparoscopically had significantly more favorable cancer characteristics which might have resulted in selection biases.[27] Other retrospective reports confirmed these findings.[27-29] There is only one prospective randomized

study that included 80 patients treated with either laparoscopic or open RNU. With a follow-up of 44 months, the authors found comparable oncologic outcomes between the laparoscopic and open group. However, in patients with pT3 and high grade UTUC, there was a slight advantage in cancer specific survival in favor of the open RNU.[30] Results were comparable with the retroperitoneal approach, with low complications rate suggesting that it was also a safe procedure.[31, 32]

Endoscopic treatment

Endoscopic surgery can be considered in imperative situations (solitary kidney, bilateral disease, significant comorbidities) but also in selected patients with a small low grade tumor. Both retrograde and antegrade approaches can be used depending on tumor volume and location.[7] Retrograde uretersocopy has a low morbidity but requires smaller instruments that limit the size of the tumor that can be treated.[6] In addition, some portions of the upper urinary tract, such as the lower pole calyces, can sometimes not be reliably reached with working instruments. The antegrade approach allows the treatment of larger tumors but with the potential risk of tumor seeding. Only limited monocentric series report on the endoscopic treatment of UTUC with a recurrence risk of about 30%.[6, 7]

Adjuvant instillations

Because of the high local recurrence rate of patients managed endoscopically (around 30%), adjuvant topical chemotherapy has been utilized. The instillation can be accomplished via a nephrostomy tube or through a ureteral catheter. The same agents used to treat urothelial carcinoma of the bladder are used to treat tumors of the upper tracts (i.e., BCG, mitomycin and other chemotherapies). Although the

cumulative experience appears encouraging, no long-term study has shown statistical improvement with relation to survival and recurrence rates.[33, 34] This may be due to insufficient numbers to show clinical significance, given the relative rarity of the disease, differential biology of upper urinary tract versus bladder tumors, or inadequate delivery systems that do not allow for uniform delivery and adequate dwell times to enable a clinical response.

Pathological factors

Tumor location. Historically, the prognostic impact of tumor location resulted in contradictory results. Tumors within the renal pelvis are more common than ureteral lesions, but small single-institution series have suggested that ureteral disease confers worse prognosis.[35] A European study, including 269 patients from three academic centers who underwent RNU at three academic centers, noted that tumor location was not independently associated with clinical outcomes.[36] A larger series from the UTUCC showed that in 1249 patients that there is no difference in terms of recurrence or cancer-specific mortality between ureteral and renal pelvic tumors (p=0.133).[37] This was confirmed in nine SEER registries relying on 2824 patients; Isbarn et al. failed to detect an association of tumor location with cancer-specific survival.[38] Finally, Favaretto et al. confirmed the lack of prognostic importance of tumor location when adjusted for the effects of standard pathologic variables in RNU patients.[28]

Tumor architecture. Tumor architecture (infiltrative or papillary) was found to be associated with disease recurrence in international multicenter analyses.[8, 39, 40] Five years after RNU, 40% of patients with papillary vs. 77% with infiltrative tumors had disease recurrence.[39] Langner at al. showed that infiltrative pattern was

significantly associated with the development of metastatic disease and was an independent prognostic factor of survival.[41] Combining this parameter with histological grade and tumor location in 1453 patients, a preoperative prognostic model achieved 76.6% accuracy in predicting non-organ confined UTUC.[40]

Tumor stage. Tumor stage is currently the most important prognostic indicator of UTUC. Upper tract urothelial carcinomas can spread by direct invasion, mucosal seeding, hematologic and lymphatic routes. The metastatic potential, and therefore the prognosis, worsens with advancing tumor stage. All the largest series validated tumor stage as a prognostic indicator.[3, 5, 8] Patients with pTa-pT1 tumors have a 5-year cancer-specific survival > 90%, whereas patients with pT3-4 tumors have a 5-year cancer-specific survival of 40.5% and 19% respectively.[4, 36] Tumor stage is also associated with a higher risk of local recurrence in many studies.[8, 42-44] In the UTUC studies, advanced pathological stage was consistently associated with disease recurrence and cancer specific survival.[8, 45, 46]

Lymph node invasion. Up to 30% of patients with muscle-invasive UTUC present with lymph node (LN) metastasis at diagnosis, which is associated with poor prognosis.[2, 3] Lymph node invasion has been demonstrated to be one of the most important predictors of poor outcome in patients treated with RNU.[8, 36, 40, 43, 47] There are no definitive data supporting the survival benefit of lymph node dissection in UTUC patients. Indications for lymphadenectomy are extrapolated from bladder cancer data that advocate extensive pelvic lymph node dissection to improve both staging and survival in patients undergoing radical cystectomy.[48] In a study comprising 1130 patients from the UTUCC, 5 year specific survival was lower in patients with pN+ disease compared to those with pNx disease (35% vs. 69%, $p<0.001$).[47, 49, 50] Interestingly, patients with pNx disease had a worse prognosis

than pN0 patients, particularly in patients with advanced T stage. Therefore, the authors recommend that patients suspected to have pT2-T4 disease should undergo lymphadenectomy to improve staging and eventually help guide decision-making regarding adjuvant chemotherapy. Based on patients from the same cohort, the authors further studied the importance of the extent of lymphadenectomy. [47, 49, 50] In the entire population, the number of LNs removed was not associated with cancer mortality. However, in the subgroup of pT0 patients, the extension of lymph node dissection seemed to be associated with better cancer-specific survival.[50] A minimum of 8 LNs seemed to be the most informative cut-off with 75% probability of detecting one or more positive LN, and accurate prediction of cancer-specific mortality.[49, 50] Finally, Bolenz et al. demonstrated that LN density (using a threshold of 30%) significantly affected cancer-specific mortality in UTUC patients. [51]

Lymphovascular invasion (LVI). LVI has been shown to have an important prognostic role, and assessment of this feature may help identify patients who could benefit from multimodal therapy after RNU.[43, 52] Lymphatic vessels serve as the primary pathway for metastatic tumor cell spread in many types of cancer.[53] Early studies reported that LVI is an independent prognostic factor in UTUC.[43, 54, 55] More recently, the UTUCC confirmed that patients with LVI had worse cancer-specific survival than their counterparts without LVI.[56] LVI was an independent predictor of both disease recurrence and cancer-specific mortality, even among patients who had either negative lymph nodes or who did not undergo lymphadenectomy [56]. LVI was associated with established features of biologically aggressive UTUC, such as advanced stage, high tumor grade, metastasis to lymph nodes, infiltrative tumor architecture, tumor necrosis, and concomitant carcinoma in

situ (CIS).[36, 57] In addition, lymphovascular invasion was an independent predictor of both disease recurrence and cancer-specific mortality. When evaluated in all patients, addition of LVI to standard pathologic features improved their predictive accuracy for both disease recurrence and cancer-specific mortality by a statistically significant but clinically small margin. This margin was significantly larger and clinically significant when the analyses were restricted to patients without lymph node metastasis and those who did not undergo a lymphadenectomy. Besides inclusion in predictive tools for selecting adjuvant therapy, LVI could be considered for inclusion in the TNM staging system such as in hepatic and testicular cancer. However, a limitation is the inherent difficulty in determining the presence of LVI at the morphological level, with significant differences between pathologists. Retraction artifacts of the surrounding stromal tissue can mimic vascular invasion. Therefore, experts have recommended reporting LVI only in unequivocal cases, and to make use of immunohistochemistry, if necessary. The use of immunohistochemical staining to identify the vessels remains controversial and not practical for everyday clinical use. It is of utmost importance that strict morphological criteria are established to standardize and make the diagnosis of LVI reproducible, and consequently allow its recommendation in daily clinical setting.[43]

Tumor grade. Tumor grade is currently divided into papillary urothelial neoplasia of low malignant potential, low-grade carcinomas and high-grade carcinomas. Until 2004, the most common classification used was the WHO classification of 1973, which distinguished three grades (G1, G2, G3).[58] High-grade tumors are more likely to invade the underlying connective tissue, muscle, and surrounding tissues and are also more likely to be associated with concomitant CIS.[16, 51] The prognostic role of pathological grade is controversial. Several authors did not find any

prognostic role for tumor grade [36, 52, 59], whereas others reported an effect of grade on UTUC recurrence and/or progression.[42, 44] These discrepancies might be related to similarities between grade 1 and 2 tumors and to the well-known intra- and interobserver variability to assign grade. Most recent series, including the one from UTUCC, used a 2-tiered grading system and found that high tumor grade was a strong independent prognostic factor in patients treated with RNU.[8, 39, 40]

Tumor necrosis. Only a few reports have addressed the prognostic value of tumor necrosis in UTUC. Langner et al. showed that tumor necrosis was an independent predictor of clinical outcomes and could predict distant metastasis after RNU.[60] This was subsequently confirmed by Simone [61] and by two large UTUCC series.[62, 63] In multivariable analyses, tumor necrosis was an independent predictor of both disease recurrence and cancer-specific mortality.[62] Assessment of tumor necrosis may help to identify patients who could benefit from multimodal therapy. Therefore, evaluation of extensive tumor necrosis has been suggested to become part of standard pathologic reporting.[62] Further extended validation is needed before tumor necrosis can be used to guide clinical decision-making after RNU.

Carcinoma in situ (CIS). Carcinoma in situ is a cytological lesion of the urothelium and the basal membrane, with pre-invasive and invasive potential. In bladder cancer, CIS is associated with an increased risk of disease recurrence and progression.[64] In a series including 79 patients, CIS was a significant independent parameter of subsequent bladder recurrence (p=0.005).[65] The UTUCC confirmed these findings in 1387 patients; the presence of concomitant CIS in patients with organ confined UTUC (≤ pT2 N0M0) was associated with worse outcomes and a significantly increased risk of both cancer recurrence and cancer-specific mortality.[66-68]

Conclusion

Radical nephroureterectomy is the standard treatment for most patients with UTUC. Both laparoscopic and open approaches offer similar cancer control in appropriately selected patients. Lymphadenectomy seems to offer both a staging and survival benefit. The recent worldwide collaborative efforts confirmed classical clinical and pathological prognostic parameters (i.e. stage, grade, lymph node metastases) and new ones (LVI, necrosis, architecture). To better appraise the course of UTUC, there is a need to identify new biomarkers that could serve as prognostic indicators to include patients into clinical trials or help guide the clinical decision making regarding the type of treatment, integration of multimodal treatment and, response to treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

References

[1] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009 Jul-Aug: **59**:225-49

[2] Oosterlinck W, Solsona E, van der Meijden AP, et al. EAU guidelines on diagnosis and treatment of upper urinary tract transitional cell carcinoma. Eur Urol. 2004 Aug: **46**:147-54

[3] Roupret M, Wallerand H, Traxer O, et al. [Checkup and management of upper urinary tract tumours in 2010: An update from the committee of cancer from the French National Association of Urology]. Prog Urol. 2010 Apr: **20**:260-71

[4] Zigeuner R, Pummer K. Urothelial carcinoma of the upper urinary tract: surgical approach and prognostic factors. Eur Urol. 2008 Apr: **53**:720-31

[5] Raman JD, Scherr DS. Management of patients with upper urinary tract transitional cell carcinoma. Nat Clin Pract Urol. 2007 Aug: **4**:432-43

[6] Cornu JN, Roupret M, Carpentier X, et al. Oncologic control obtained after exclusive flexible ureteroscopic management of upper urinary tract urothelial cell carcinoma. World J Urol. 2010 Apr: **28**:151-6

[7] Bagley DH, Grasso M, 3rd. Ureteroscopic laser treatment of upper urinary tract neoplasms. World J Urol. 2010 Apr: **28**:143-9

[8] Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009 Mar 15: **115**:1224-33

[9] Shariat S, Godoy G, Lotan Y, et al. Advanced patient age is associated with inferior cancer-specific survival after radical nephroureterectomy. BJU Int. 2010 Jun: **105**:1672-7

[10] Jeldres C, Sun M, Lughezzani G, et al. Highly predictive survival nomogram after upper urinary tract urothelial carcinoma. Cancer. 2010 Aug: **116**:3774-84

[11] Lughezzani G, Sun M, Perrotte P, et al. Gender-related differences in patients with stage I to III upper tract urothelial carcinoma: results from the Surveillance, Epidemiology, and End Results database. Urology. 2010 Feb: **75**:321-7

[12] Shariat SF, Favaretto RL, Gupta A, et al. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol. 2010 Oct (in press)

[13] Patard JJ, Leray E, Cindolo L, et al. Multi-institutional validation of a symptom based classification for renal cell carcinoma. J Urol. 2004 Sep: **172**:858-62

[14] Raman JD, Shariat SF, Karakiewicz PI, et al. Does preoperative symptom classification impact prognosis in patients with clinically localized upper-tract urothelial carcinoma managed by radical nephroureterectomy? Urol Oncol. 2010 Jan (in press)

[15] Inman BA, Tran VT, Fradet Y, Lacombe L. Carcinoma of the upper urinary tract: predictors of survival and competing causes of mortality. Cancer. 2009 Jul 1: **115**:2853-62

[16] Brien JC, Shariat SF, Herman MP, et al. Preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology can improve prediction of advanced upper tract urothelial carcinoma. J Urol. 2010 Jul: **184**:69-73

[17] Cho KS, Hong SJ, Cho NH, Choi YD. Grade of hydronephrosis and tumor diameter as preoperative prognostic factors in ureteral transitional cell carcinoma. Urology. 2007 Oct: **70**:662-6

[18] Ng CK, Shariat SF, Lucas SM, et al. Does the presence of hydronephrosis on preoperative axial CT imaging predict worse outcomes for patients undergoing nephroureterectomy for upper-tract urothelial carcinoma? Urol Oncol. 2011 Jan-Feb: **29**: 27-32

[19] Gore J, Lai J, Setodji C, Litwin M, Saigal C, Project UDiA. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results-Medicare analysis. Cancer. 2009 Mar: **115**:988-96
[20] Waldert M, Karakiewicz PI, Raman JD, et al. A delay in radical nephroureterectomy can lead to upstaging. BJU Int. 2010 Mar: **105**:812-7
[21] Fromont G, Roupret M, Amira N, et al. Tissue microarray analysis of the prognostic value of E-cadherin, Ki67, p53, p27, survivin and MSH2 expression in upper urinary tract transitional cell carcinoma. Eur Urol. 2005 Nov: **48**:764-70
[22] Eltz S, Comperat E, Cussenot O, Roupret M. Molecular and histological markers in urothelial carcinomas of the upper urinary tract. BJU Int. 2008 Aug 5: **102**:532-5
[23] Roupret M, Azzouzi AR, Cussenot O. Microsatellite instability and transitional cell carcinoma of the upper urinary tract. BJU Int. 2005 Sep: **96**:489-92
[24] Matsui Y, Utsunomiya N, Ichioka K, et al. Risk factors for subsequent development of bladder cancer after primary transitional cell carcinoma of the upper urinary tract. Urology. 2005 Feb: **65**:279-83
[25] Huang WW, Huang HY, Liao AC, et al. Primary urothelial carcinoma of the upper tract: important clinicopathological factors predicting bladder recurrence after surgical resection. Pathol Int. 2009 Sep: **59**:642-9
[26] Hattori R, Yoshino Y, Komatsu T, Matsukawa Y, Ono Y, Gotoh M. Pure laparoscopic complete excision of distal ureter with a bladder cuff for upper tract urothelial carcinoma. World J Urol. 2009 Apr: **27**:253-8
[27] Capitanio U, Shariat SF, Isbarn H, et al. Comparison of oncologic outcomes for open and laparoscopic nephroureterectomy: a multi-institutional analysis of 1249 cases. Eur Urol. 2009 Jul: **56**:1-9
[28] Favaretto R, Shariat S, Chade D, et al. Comparison Between Laparoscopic and Open Radical Nephroureterectomy in a Contemporary Group of Patients: Are Recurrence and Disease-Specific Survival Associated with Surgical Technique? Eur Urol. 2010 Aug (in press)
[29] Roupret M, Smyth G, Irani J, et al. Oncological risk of laparoscopic surgery in urothelial carcinomas. World J Urol. 2009 Feb: **27**:81-8
[30] Simone G, Papalia R, Guaglianone S, et al. Laparoscopic versus open nephroureterectomy: perioperative and oncologic outcomes from a randomised prospective study. Eur Urol. 2009 Sep: **56**:520-6
[31] Liapis D, de la Taille A, Ploussard G, et al. Analysis of complications from 600 retroperitoneoscopic procedures of the upper urinary tract during the last 10 years. World J Urol. 2008 Dec: **26**:523-30
[32] Hemal AK, Kumar A, Gupta NP, Seth A. Retroperitoneal nephroureterectomy with excision of cuff of the bladder for upper urinary tract transitional cell carcinoma: comparison of laparoscopic and open surgery with long-term follow-up. World J Urol. 2008 Aug: **26**:381-6
[33] Thalmann GN, Markwalder R, Walter B, Studer UE. Long-term experience with bacillus Calmette-Guerin therapy of upper urinary tract transitional cell carcinoma in patients not eligible for surgery. J Urol. 2002 Oct: **168**:1381-5
[34] Nonomura N, Ono Y, Nozawa M, et al. Bacillus Calmette-Guérin perfusion therapy for the treatment of transitional cell carcinoma in situ of the upper urinary tract. Eur Urol. 2000 Dec: **38**:701-4;discussion 5
[35] Akdogan B, Dogan HS, Eskicorapci SY, Sahin A, Erkan I, Ozen H. Prognostic significance of bladder tumor history and tumor location in upper tract transitional cell carcinoma. J Urol. 2006 Jul: **176**:48-52

[36] Novara G, De Marco V, Gottardo F, et al. Independent predictors of cancer-specific survival in transitional cell carcinoma of the upper urinary tract: multi-institutional dataset from 3 European centers. Cancer. 2007 Oct 15: **110**:1715-22
[37] Raman JD, Ng CK, Scherr DS, et al. Impact of Tumor Location on Prognosis for Patients with Upper Tract Urothelial Carcinoma Managed by Radical Nephroureterectomy. Eur Urol. 2010 Jun: **57**: 1072-9
[38] Isbarn H, Jeldres C, Shariat SF, et al. Location of the primary tumor is not an independent predictor of cancer specific mortality in patients with upper urinary tract urothelial carcinoma. J Urol. 2009 Nov: **182**:2177-81
[39] Remzi M, Haitel A, Margulis V, et al. Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. BJU Int. 2009 Feb: **103**:307-11
[40] Margulis V, Youssef RF, Karakiewicz PI, et al. Preoperative multivariable prognostic model for prediction of nonorgan confined urothelial carcinoma of the upper urinary tract. J Urol. 2010 Aug: **184**:453-8
[41] Langner C, Hutterer G, Chromecki T, Rehak P, Zigeuner R. Patterns of invasion and histological growth as prognostic indicators in urothelial carcinoma of the upper urinary tract. Virchows Arch. 2006 May: **448**:604-11
[42] Li WM, Li CC, Ke HL, Wu WJ, Huang CN, Huang CH. The prognostic predictors of primary ureteral transitional cell carcinoma after radical nephroureterectomy. J Urol. 2009 Aug: **182**:451-8; discussion 8
[43] Kim DS, Lee YH, Cho KS, Cho NH, Chung BH, Hong SJ. Lymphovascular invasion and pT stage are prognostic factors in patients treated with radical nephroureterectomy for localized upper urinary tract transitional cell carcinoma. Urology. 2010 Feb: **75**:328-32
[44] Li CC, Chang TH, Wu WJ, et al. Significant predictive factors for prognosis of primary upper urinary tract cancer after radical nephroureterectomy in Taiwanese patients. Eur Urol. 2008 Nov: **54**:1127-34
[45] Novara G, De Marco V, Gottardo F, et al. Independent predictors of cancer-specific survival in transitional cell carcinoma of the upper urinary tract: multi-institutional dataset from 3 European centers. Cancer. 2007 Oct: **110**:1715-22
[46] Huben RP, Mounzer AM, Murphy GP. Tumor grade and stage as prognostic variables in upper tract urothelial tumors. Cancer. 1988 Nov: **62**:2016-20
[47] Roscigno M, Shariat SF, Margulis V, et al. Impact of lymph node dissection on cancer specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. J Urol. 2009 Jun: **181**:2482-9
[48] Capitanio U, Suardi N, Shariat SF, et al. Assessing the minimum number of lymph nodes needed at radical cystectomy in patients with bladder cancer. BJU Int. 2009 May: **103**:1359-62
[49] Roscigno M, Shariat SF, Freschi M, et al. Assessment of the minimum number of lymph nodes needed to detect lymph node invasion at radical nephroureterectomy in patients with upper tract urothelial cancer. Urology. 2009 Nov: **74**:1070-4
[50] Roscigno M, Shariat SF, Margulis V, et al. The extent of lymphadenectomy seems to be associated with better survival in patients with nonmetastatic upper-tract urothelial carcinoma: how many lymph nodes should be removed? Eur Urol. 2009 Sep: **56**:512-8
[51] Bolenz C, Shariat SF, Fernandez MI, et al. Risk stratification of patients with nodal involvement in upper tract urothelial carcinoma: value of lymph-node density. BJU Int. 2009 Feb: **103**:302-6
[52] Hong B, Park S, Hong JH, Kim CS, Ro JY, Ahn H. Prognostic value of lymphovascular invasion in transitional cell carcinoma of upper urinary tract. Urology. 2005 Apr: **65**:692-6

[53] Shariat SF, Svatek RS, Tilki D, et al. International validation of the prognostic value of lymphovascular invasion in patients treated with radical cystectomy. BJU Int. 2010 May: **105**:1402-12
[54] Saito K, Kawakami S, Fujii Y, Sakura M, Masuda H, Kihara K. Lymphovascular invasion is independently associated with poor prognosis in patients with localized upper urinary tract urothelial carcinoma treated surgically. J Urol. 2007 Dec: **178**:2291-6; discussion 6
[55] Bolenz C, Fernandez MI, Trojan L, et al. Lymphangiogenesis occurs in upper tract urothelial carcinoma and correlates with lymphatic tumour dissemination and poor prognosis. BJU Int. 2009 Apr: **103**:1040-6
[56] Novara G, Matsumoto K, Kassouf W, et al. Prognostic Role of Lymphovascular Invasion in Patients with Urothelial Carcinoma of the Upper Urinary Tract: An International Validation Study. Eur Urol. 2010 Jun: **57**: 1064-71
[57] Kikuchi E, Margulis V, Karakiewicz PI, et al. Lymphovascular invasion predicts clinical outcomes in patients with node-negative upper tract urothelial carcinoma. J Clin Oncol. 2009 Feb 1: **27**:612-8
[58] Lopez-Beltran A, Bassi P, Pavone-Macaluso M, Montironi R. Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. Eur Urol. 2004 Mar: **45**:257-66
[59] van der Poel HG, Antonini N, van Tinteren H, Horenblas S. Upper urinary tract cancer: location is correlated with prognosis. Eur Urol. 2005 Sep: **48**:438-44
[60] Langner C, Hutterer G, Chromecki T, Leibl S, Rehak P, Zigeuner R. Tumor necrosis as prognostic indicator in transitional cell carcinoma of the upper urinary tract. J Urol. 2006 Sep: **176**:910-3; discussion 3-4
[61] Simone G, Papalia R, Loreto A, Leonardo C, Sentinelli S, Gallucci M. Independent prognostic value of tumour diameter and tumour necrosis in upper urinary tract urothelial carcinoma. BJU Int. 2009 Apr: **103**:1052-7
[62] Zigeuner R, Shariat S, Margulis V, et al. Tumour necrosis is an indicator of aggressive biology in patients with urothelial carcinoma of the upper urinary tract. Eur Urol. 2010 Apr: **57**:575-81
[63] Seitz C, Gupta A, Shariat S, et al. Association of tumor necrosis with pathological features and clinical outcome in 754 patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma: an international validation study. J Urol. 2010 Nov: **184**:1895-900
[64] Shariat SF, Palapattu GS, Karakiewicz PI, et al. Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ-confined TCC at radical cystectomy. Eur Urol. 2007 Jan: **51**:152-60
[65] Pieras E, Frontera G, Ruiz X, Vicens A, Ozonas M, Piza P. Concomitant carcinoma in situ and tumour size are prognostic factors for bladder recurrence after nephroureterectomy for upper tract transitional cell carcinoma. BJU Int. 2010 Nov: **106**: 1319-23
[66] Wheat JC, Weizer AZ, Wolf JS, Jr., et al. Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ confined urothelial carcinoma following radical nephroureterectomy. Urol Oncol. 2010 May (in press)
[67] Karam JA, Margulis V, Montorsi F, et al. Carcinoma in situ of the upper urinary tract treated with radical nephroureterectomy--results from a multicenter study. Eur Urol. 2008 Oct: **54**:961-3
[68] Otto W, Shariat SF, Fritsche HM, et al. Concomitant carcinoma in situ as an independent prognostic parameter for recurrence and survival in upper tract urothelial carcinoma: a multicenter analysis of 772 patients. World J Urol. 2011 Jan (in press)