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Prognostic Factors in Upper Urinary Tract Urothelial Carcinomas: A Comprehensive Review of the Current Literature

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Abstract

Context: The heterogeneity of upper tract urothelial carcinoma (UTUC) biology and prognosis, as well as the presence of different treatment options, makes the clinical decision-making process extremely challenging.
Objective: Provide an overview of the currently available prognostic factors for UTUC, focusing on clinical and pathologic characteristics, as well as on molecular markers.
Evidence acquisition: A systematic literature search was conducted using the PubMed, Scopus, and Embase databases to identify original articles, review articles, and editorials regarding prognostic factors in patients with UTUC. Keywords included *urothelial carcinoma, renal pelvis, ureter, upper urinary tract urothelial carcinoma, upper urinary tract transitional cell carcinoma, prognosis, prognostic factors, markers*, and *survival.* Articles published between 2000 and 2011 were reviewed and selected with the consensus of all the authors.
Evidence synthesis: Prognostic factors can be divided into four different categories: preoperative/clinical factors, intraoperative/surgical factors, postoperative/pathologic factors, and molecular markers. Because of the rarity of the disease, only a small amount of level 1 evidence information from prospective randomized trials is available. Conversely, several single-institutional and multi-institutional studies have been published providing level 3 evidence information on various prognostic factors. Tumor stage and grade represent the best-established predictors of prognosis in patients with UTUC, but controversies still exist regarding the prognostic impact of tumor location and tumor necrosis. Several promising biomarkers have also been evaluated, but further studies evaluating their prognostic role are still needed. Finally, few prognostic models have been developed to provide clinicians with accurate estimates of the outcome of interest.
Conclusions: In the past few years, several prognostic factors have been identified to help clinicians dealing with patients with UTUC in the decision-making process. However, well-designed multi-institutional studies are still needed to provide stronger evidence and to promote the use of these prognostic factors in clinical practice.

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1. Introduction

Urothelial carcinomas are derived from the urothelium and can be located either in the lower urinary tract (bladder, urethra) urinary tract or in the upper urinary tract (pyelocaliceal cavities, ureter). Although the mechanisms of carcinogenesis are thought to be similar throughout the urinary tract, recent epidemiologic data and genetic studies suggest otherwise. It is now obvious that strong differences exist regarding tumor location and behavior between the upper and the lower urinary tract. Upper tract urothelial carcinoma (UTUC) is a rare and heterogeneous disease that accounts for approximately 5% of all urothelial tumors, with an estimated incidence of 2.08 cases per 100 000 person-years in the United States [1]. Improvements in imaging and endoscopic techniques, as well as improvements in bladder cancer (BCa) control outcomes, have recently led to a stage migration toward earlier-stage tumors [1]. Despite this stage migration, UTUC still represents an aggressive disease with high recurrence and progression rates. Radical nephroureterectomy (RNU) with bladder-cuff removal is considered the gold standard treatment of UTUC [2,3]. According to the National Comprehensive Cancer Network guidelines, regional lymphadenectomy and neoadjuvant chemotherapy should also be considered in selected patients with high-risk disease [3]. Conversely, some patients with low-risk disease may benefit from a more conservative approach (eg, endoscopic ablation, segmental resection) [3].

Preoperatively, the correct identification of those patients harboring a low-risk UTUC versus individuals harboring a more aggressive disease is critical in the counseling of UTUC patients. Until recently, there were few high-quality data to guide physicians and patients in the management of UTUC. This lack of data is largely because of the low incidence of this disease, resulting in single-center small study cohorts. This situation, together with the heterogeneity of UTUC biology and prognosis and the presence of different treatment options, makes the decision-making process extremely challenging. Several single- and multi-institutional efforts have been made to determine the prognostic factors that may help in selecting the best treatment and follow-up strategies in UTUC patients [4]. The aim of the current review was to provide an overview of the currently available prognostic factors for UTUC, focusing on clinical and pathologic characteristics, as well as on molecular markers.

2. Evidence acquisition

A systematic literature search was conducted using the PubMed, Scopus, and Embase databases to identify original articles, review articles, and editorials regarding prognostic factors in patients with UTUC. Keywords used for article retrieval included *("upper tract urothelial carcinoma" OR "upper urinary tract carcinoma") AND ("prognosis" or "prognostic factors" or "markers" or "survival").*

Overall, 626 articles published between 2000 and 2011 were retrieved with the consensus of all the authors. The choice to limit the search to articles published within this time frame was driven by the fact that several multi-institutional studies, as well as several studies in which an intermediate/long-term follow-up was available, were published only in very recent years. Of these articles, 139 articles were selected by the authors for the purpose of this review. Because of the paucity of randomized data, articles were selected for this review with regard to the following criteria: evolution of concepts, development and refinement of techniques, intermediate- and long-term clinical outcomes, sample size, use of multivariable statistical analyses, and relevance. Older studies were selectively included if historically relevant or if data in more recent publications were scant. It is noteworthy that although the authors chose the articles to be included based on the criteria mentioned, a selection bias may be operational given the paucity of randomized trials on the topic.

3. Evidence synthesis

3.1. *Preoperative/clinical factors (Table 1)*

3.1.1. *Patient gender*

UTUC is more common in men than in women. Two recent multi-institutional analyses did not show any differences in pathologic characteristics and cancer-control outcomes between men and women [5,6]. Conversely, in a population-based study, women were more likely to present with higher-stage and higher-grade UTUCs relative to men [7]. However, after accounting for these differences in a multivariable model, gender did not affect cancer-specific survival (CSS). Therefore, gender should not be considered as a predictor of survival in patients with UTUC.

3.1.2. *Patient age*

Using the Surveillance Epidemiology and End Results database, Lughezzani et al. observed that advanced patient age is an independent predictor of CSS after adjustment for several clinicopathologic characteristics [8]. Similarly, Shariat et al. and Chromecki et al. confirmed the role of age as a prognostic factor, with elderly patents having lower CSS and overall survival (OS) rates [9,10]. This finding could be attributed to changes in the biologic potential of the tumor, with UTUCs being more aggressive in elderly patients, as well as to differences in care patterns (eg, greater reluctance to perform radical surgery in these individuals). Based on these observations, advanced patient age should be considered a predictor of more aggressive disease and worse cancer-control outcomes in UTUC patients. However, age should not be an exclusion criterion, because most elderly patients treated with RNU showed low disease recurrence rates [10]. Further work is needed to improve our understanding of the reasons for worse UTUC outcomes in this growing segment of the population and to develop strategies to improve cancer care in the elderly.

3.1.3. *Patient race*

Although the incidence of UTUC appears to be increasing in most racial groups, likely because of earlier detection, survival in black non-Hispanic patients is poorer at 5 and

Table 1 – Summary of preoperative/clinical prognostic factors in patients with upper tract urothelial carcinoma

Markers	Comment	Level of evidence	References
Patient characteristics			
Age	Advanced age is an independent predictor of worse CSS, RFS, and OS.	3	5–7
Race	Black non-Hispanic patients have worse survival relative to other racial groups.	3	1
ECOG-PS	ECOG-PS ≥1 is an independent predictor of worse OS.	3	12
Obesity	Body mass index ≥30 is an independent predictor of worse CSS, RFS, and OS.	3	13
Smoking status	Smokers are more likely to be diagnosed with UTUC and have higher cancer-specific mortality and bladder recurrence rates.	3	14,15
Disease characteristics			
Tumor location	According to several studies, ureteral location is an independent predictor of worse cancer control outcomes. Conversely, other studies showed that after adjustment for tumor stage, tumor location is no longer a predictor of CSS.	3	16–23
Clinical grade	Higher clinical (biopsy-determined) grade is a predictor of advanced pathologic tumor stage.	3	24–26
Hydronephrosis	Presence of hydronephrosis is an independent predictor of lower progression-free and cancer-specific survival rates.	3	26,29–31
Symptoms	Systemic symptoms are associated with advanced tumor stage and grade.	3	32,33
Previous/synchronous bladder cancer	The presence of a previous or synchronous bladder cancer is an independent predictor of lower RFS and CSS rates.	3	20,34–37

CSS = cancer-specific survival; RFS = recurrence-free survival; OS = overall survival; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; UTUC = upper tract urothelial carcinoma.

10 yr compared with other racial groups [1]. Conversely, no differences in survival were observed when comparing European and Japanese patients [11].

3.1.4. *Eastern Cooperative Oncology Group performance status*

Eastern Cooperative Oncology Group performance status (ECOG-PS) has gained wide popularity as an integral part of the assessment of patients with UTUC. In a recent multi-institutional study, Martinez-Salamanca et al. showed that ECOG-PS was independently associated with higher perioperative mortality and worse OS rates, but not with worse recurrence-free survival (RFS) and CSS rates [12]. Therefore, although ECOG-PS may be used in the clinical decision-making process, further studies are needed to ascertain its additive prognostic role in UTUC patients.

3.1.5. *Obesity*

The prognostic role of obesity has been demonstrated for several malignancies, such as BCa, colorectal cancer, renal cell carcinoma, and prostate cancer. A recent multi-institutional study examined the relationship between body mass index and cancer-control outcomes in UTUC patients [13]. This study showed that obesity, defined as a body mass index ≥30, was related to worse RFS, CSS, and OS rates. This observation may be attributed to the fact that obese patients are more likely to have worse tumor characteristics. In addition, excess body fat was also associated with systemic inflammation and increased insulin-like growth factor-1 levels, which are strictly related to cell proliferation and apoptosis. Because this is the first evidence of this correlation, further studies are needed to confirm the role of obesity as a prognostic factor in UTUC patients.

3.1.6. *Smoking status*

Cigarette smoking represents an established risk factor for the development of UTUC. McLaughlin et al. observed a 3.1-fold higher risk of being diagnosed with UTUC in smokers, increasing to a 7.2-fold higher risk in long-term smokers [14]. More recently, Simsir et al. demonstrated that smokers had higher cancer-specific mortality and bladder recurrence rates [15]. However, since the authors did not provide a multivariable analysis, their findings need further validation after adjustment for several well-established prognostic factors.

3.1.7. *Tumor location*

The impact of tumor location (renal pelvis compared with ureter) on the prognosis of patients with UTUC is still a matter of debate. Several single-institutional studies demonstrated the independent predictor status of tumor location on CSS, with ureteral tumors showing a worse prognosis than renal pelvis tumors after adjustment for several pathologic variables [16]. Similarly, Zigeuner et al. showed that patients with ureteral tumors were more likely to develop subsequent BCa [17]. Park et al. confirmed the prognostic relevance of the ureteral location of the tumor only in patients with pT3 disease, suggesting that renal parenchyma may have a protective role in patients with a pT3 tumor of the renal pelvis [18]. These findings were confirmed by a recent multi-institutional French study, which demonstrated that tumor location in the ureter independently predicted worse survival outcomes in patients with UTUC [19]. On the contrary, several population-based and large multi-institutional studies did not confirm the independent prognostic impact of tumor location on survival, showing the same RFS and CSS estimates for renal pelvis and ureteral tumors after adjustment for several clinicopathologic parameters [20–23]. To conclude, the currently available retrospective studies do not permit a definitive conclusion regarding the impact of tumor location on UTUC prognosis. The overwhelming evidence suggests, however, that the prognostic effect of tumor location is dissipated when controlling for the effects of tumor stage. These conflicting findings underscore the need for a multicenter prospective

study evaluating the differences in survival between patients with renal pelvis tumors and ureteral tumors.

3.1.8. Clinical tumor grade and stage

Endoscopic evaluation and biopsy establish the definitive diagnosis of UTUC and help with its risk stratification. Clinical (or biopsy) tumor grade provides important information on which other factors may be built. Various studies have shown that biopsy grade is accurate and can predict pathologic findings [24–26]. Recently, Brien et al. showed that biopsy grade, combined with preoperative hydronephrosis and urine cytology, accurately predicted the presence of non–organ-confined UTUC [26]. However, biopsy grade may still be subject to a non-negligible rate of sampling error, particularly with larger tumors [27]. Unlike bladder urothelial carcinoma, the clinical staging of UTUC is notoriously difficult because biopsies that include underlying muscle are generally not possible due to the thinness of the muscularis and the delicate, small instrumentation used in ureteroscopy. In regard to clinical staging, Guarnizo and colleagues showed a 45% rate of upstaging with attempted clinical staging alone [25]. Imaging has poor predictive value except in the assessment of significant locoregional extension or the presence of metastasis [28]. In summary, although clinical tumor staging is generally unreliable except in advanced disease, biopsy tumor grading provides a fundamentally important variable that guides clinical management and risk allocation, and predicts recurrence and survival.

3.1.9. Hydronephrosis

Several studies explored the relationship between hydronephrosis at preoperative imaging, pathologic stage, and CSS in patients with UTUC. Cho et al. showed that the grade of hydronephrosis was associated with more advanced disease stage and worse survival in patients with ureteral tumors [29]. More recently, Brien et al. and Ito et al. confirmed the relationship between hydronephrosis and advanced pathologic stage both in ureteral and in renal pelvis tumors, suggesting that the pathogenesis of hydronephrosis in this setting may not be simply obstruction [26,30]. Finally, Ng et al. recently demonstrated that preoperative hydronephrosis was independently associated with cancer metastasis and CSS [31]. In conclusion, the presence of hydronephrosis at preoperative imaging represents a valuable predictive factor for advanced disease stage and survival in UTUC patients.

3.1.10. Symptoms

The presence of locoregional or systemic symptoms is an established prognostic factor in patients with renal cell carcinoma. Inman et al. observed that the presence of constitutional symptoms such as pain or weight loss was associated with a worse OS in patients with UTUC [32]. Similarly, Raman et al. showed a relationship between systemic symptoms (eg, weight loss, anorexia, bone pain) and the presence of higher-stage and higher-grade UTUC [33]. Conversely, no difference in survival was observed between asymptomatic patients and patients having local symptoms. In multivariable analyses, the presence of systemic symptoms did not achieve the independent predictor status for both RFS and CSS. Therefore, although symptoms appear to be related to OS and disease characteristics, further multi-institutional efforts are still needed to validate their role as predictors of cancer-control outcomes.

3.1.11. Previous/synchronous bladder cancer

Cancers of the upper urinary tract are considered part of a panurothelial phenomenon that can yield multifocal tumors and transcend from the lower to the upper collecting system. In a single-institutional study, Mullerad et al. demonstrated that a history of BCa had an adverse effect on the prognosis of patients with UTUC [34]. More specifically, the presence of a previous or synchronous BCa was an independent predictor of lower RFS and CSS rates. Similarly, in a multicenter European study, Novara et al. observed that prior BCa history and the presence of muscle-invasive BCa at RNU were independent predictors of worse CSS [35]. The prognostic impact of a previous or synchronous bladder tumor was further confirmed by a single-institutional Taiwanese study and by a multi-institutional Japanese study [20,36]. In addition, Tran et al. demonstrated that patients who had any ureteral involvement with a prior radical cystectomy remained at high risk for the recurrence of UTUC [37]. In conclusion, the presence of a BCa history should always be evaluated in patients with UTUC, because they may be considered for more aggressive treatment and a closer follow-up schedule.

3.2. Intraoperative/surgical factors

3.2.1. Delayed surgery

A delay of radical cystectomy is considered to have a negative prognostic impact in patients with BCa. Boorjian et al. were the first to investigate the impact of delay of RNU in patients with UTUC who were endoscopically treated compared with patients who underwent an upfront RNU [38]. In their study, no differences in cancer-control outcomes were observed between patients who underwent upfront RNU and those who underwent an RNU after ureteroscopic biopsy or laser tumor ablation. However, this cohort was highly selected based on the inclusion criteria for endoscopic management. More recently, these findings were confirmed by Sundi et al, who did not observe any difference in survival between patients undergoing early ($<$3 mo) or delayed extirpative surgery for UTUC [39].

Conversely, Waldert et al. investigated the prognostic impact of the time interval between diagnosis and radical treatment of UTUC [40]. The authors showed that a longer interval from diagnosis of UTUC to RNU was associated with aggressive pathologic features, such as more advanced stage, higher tumor grade, and lymphovascular invasion (LVI). In addition, the authors showed that in patients with muscle-invasive disease, a longer ($\geq$3-mo) interval to radical surgery was associated with lower RFS and CSS estimates. Based on these findings, further studies are needed to address the question of whether a delay to radical

surgery has an impact on the prognosis of patients with UTUC. However, in the absence of further data to the contrary, we would recommend that patients be brought to the operating room expeditiously for definitive surgical therapy.

3.2.2. Type of surgery: open versus laparoscopic approach

Open RNU (ORNU) with excision of a bladder cuff is considered the gold standard treatment of UTUC regardless of the location of the tumor in the urinary tract [2]. In recent years, laparoscopic RNU (LRNU) has emerged as a minimally invasive alternative to ORNU, with advantages in terms of lower blood loss, shorter length of hospital stay, and shorter convalescence. Several single- and multi-institutional retrospective studies showed equivalence in cancer-control outcomes between ORNU and LRNU in well-selected patients [41–44]. A recent single-institutional randomized study confirmed these findings, showing no differences in metastasis-free survival and CSS between the ORNU and LRNU in patients with organ-confined UTUC [45]. On the contrary, according to the same authors, patients with locally advanced (pT3) or high-grade tumors appeared to benefit from an open approach. The results of this randomized study underscore the need for proper patient selection to warrant the most appropriate surgical approach according to the characteristics of the disease.

In conclusion, when performed by laparoscopically experienced surgeons, LRNU appears to be an oncologically effective alternative to ORNU in patients with organ-confined disease. Conversely, ORNU may be considered in patients with locoregional disease at preoperative clinical staging or by surgeons without adequate laparoscopic experience.

3.2.3. Management of the bladder cuff: open versus endoscopic techniques

The excision of the distal part of the ureter and of its orifice is usually performed at RNU, because this part of the urinary tract is at high risk for disease recurrence. However, recent data suggest that up to a fourth of patients may undergo incomplete ureterectomy [46]. Different techniques for the management of the distal ureter have been proposed, including open and endoscopic approaches, whose main advantage consists of a shorter operative time. Several retrospective studies compared these different techniques [47–52]. Among the endoscopic approaches, the pluck technique had at least five reported cases of local recurrence or tumor seeding [53], and the stripping technique showed a higher rate of intravesical disease recurrence [47]. Conversely, all other endoscopic techniques showed similar cancer-control outcomes in comparison with a formal open bladder-cuff excision. Finally, several investigators showed that stapling of the bladder cuff was associated with a higher risk of positive margins and recurrence [48,52,54]. However, it is noteworthy that these observations were mostly based on small retrospective studies.

In conclusion, a bladder-cuff removal at RNU has to be considered the gold standard treatment of UTUC regardless of tumor stage and location. Although several alternative techniques have been described, open surgery should be considered the gold standard technique for the excision of the bladder cuff.

3.2.4. Lymph node dissection and invasion

Lymph node dissection (LND) is not routinely performed during RNU because it is still unclear whether that procedure provides a survival benefit. Although some studies reported comparable survival rates between patients without lymph node invasion (LNI) after LND and patients who did not undergo LND, there is also evidence that, at least in patients with locally advanced disease (pT2–T4), performing an LND may result in a survival benefit [55–57]. In a single-institution study, Kondo et al. showed a direct relationship between the extent of LND and CSS [58]. More recently, the same authors showed that the completeness of LND was prognostically more important than the absolute number of lymph nodes removed [59]. In a recent multi-institutional study, Roscigno et al. also observed a relationship between the number of lymph nodes removed and CSS in patients with node-negative UTUC. Specifically, the authors suggested a cut-off value of eight lymph nodes to be removed to achieve a survival benefit [60,61].

To conclude, the benefit of LND at RNU has been shown for locally advanced tumor stages and should be considered in all such cases [62]. In addition, LND has been suggested to be curative in cases of limited nodal invasion and should be performed in patients with clinically positive regional nodal disease in the absence of distant metastases. Thus, the performance of LND per se seems to be prognostically beneficial. However, better designed prospective trials are still needed to standardize the indications for LND and to determine which lymph nodes should be removed according to different tumor locations within the urinary tract. Precise templates need to be established for each tumor location.

3.3. Postoperative/pathologic factors (Table 2)

3.3.1. Pathologic tumor stage

Pathologic tumor stage represents the cornerstone for classifying the prognosis of patients with UTUC in the postoperative setting. As with other malignancies, UTUC patients with higher pathologic stages are expected to have less favorable prognoses, with increasing metastatic potential of the disease. To date, several single-institutional, multi-institutional, and population-based studies have confirmed the prognostic value of pathologic stage in patients with UTUC [8,16,18,20,34–36,63–68]. According to these studies, the 5-yr CSS rates decrease from >90% in patients with pTa/pT1 disease to <20% in patients with pT4 UTUC. In conclusion, pathologic tumor stage represents the best-established predictor of survival in patients with UTUC and should always be considered in the preoperative and postoperative counseling of these patients and in the determination of the intensity of postoperative surveillance.

3.3.2. Pathologic tumor grade

Tumor grade represents a well-established predictor of cancer-related outcomes in patients with UTUC because it is

Table 2 – Summary of postoperative/pathologic prognostic factors in patients with upper tract urothelial carcinoma

Markers	Comment	Level of evidence	References
Disease characteristics			
Pathologic tumor stage	Advanced pT stage is an independent predictor of worse cancer control outcomes.	3	8,16,18–20,34–36,63–68
Pathologic tumor grade	Higher tumor grade is an independent predictor of lower CSS rates. Both the 1973 and the 2004 WHO classifications of tumor grade independently predict cancer control outcomes.	3	8,18,20,32,35,64,66,67
Concomitant CIS	Concomitant CIS is associated with advanced tumor stage and grade and is an independent predictor of lower RFS and CSS rates.	3	71–74
LNI	The presence of LNI is an independent predictor of lower CSS rates.	3	8,18,20,35,56,67,68,75,76
Tumor multifocality	The presence of multifocal tumors is an independent predictor of lower CSS rates.	3	19,20,35,64,77,78
Tumor architecture	A sessile growth pattern is an independent predictor of lower progression-free survival, RFS, and CSS rates.	3	77,79–81
Tumor size	Larger tumor size is an independent predictor of lower progression-free survival and RFS rates.	3	71,82
LVI	The presence of LVI is associated with advanced tumor stage/grade and is an independent predictor of lower RFS and CSS rates.	3	83–87
Tumor necrosis	According to several studies, the presence of extensive tumor necrosis is associated with advanced tumor stage and is an independent predictor of lower RFS and CSS rates. A recent multi-institutional study did not confirm the prognostic role of tumor necrosis after adjustment for tumor stage and other tumor characteristics.	3	82,88–91

CSS = cancer-specific survival; WHO = World Health Organization; CIS = carcinoma in situ; RFS = recurrence-free survival; LNI = lymph node invasion; LVI = lymphovascular invasion.

strictly related to cancer aggressiveness and tumor stage. Until 2004, the most commonly used classification was the 1973 World Health Organization (WHO) classification, which distinguished among three grades (G1, G2, and G3) [69]. Several investigators confirmed the independent predictor status of the three-tiered grade classification when predicting survival [8,18,20,32,35,64]. The 2004 WHO classification distinguishes among three groups of noninvasive tumors: papillary urothelial neoplasia of low malignant potential, low-grade carcinomas, and high-grade carcinomas [70]. Several studies also validated the prognostic role of this newer classification [36,66,67]. In conclusion, tumor grade represents a powerful predictor of cancer-control outcomes in patients with UTUC and should always be taken into account in the preoperative and postoperative counseling of these patients.

3.3.3. *Concomitant carcinoma in situ*

Concomitant carcinoma in situ (CIS) of the upper urinary tract represents a rare entity that is considered to be associated with increased disease recurrence and progression rates. In a single-institutional study, Pieras et al. observed that the presence of concomitant CIS after RNU was associated with an increased risk of bladder tumor recurrence [71]. Similarly, in a multi-institutional setting, Wheat et al. demonstrated the prognostic relevance of concomitant CIS for both RFS and CSS in patients with organ-confined UTUC [72]. More recently, Otto et al. showed that concomitant CIS was associated with more advanced tumor stage and grade and confirmed its independent predictor status when predicting both RFS and CSS [73]. It is interesting to note that this study also showed that a previous history of bladder CIS was an independent prognostic factor for survival in UTUC patients treated with RNU. This finding was also confirmed by Youssef et al. in a recent multi-institutional study [74]. Therefore, the presence of a concomitant CIS should always be evaluated in patients with UTUC, because they may require more aggressive surveillance regimens and strategies utilizing topical therapies.

3.3.4. *Lymph node invasion*

The presence of LNI is universally considered an important prognostic factor, because LNI indicates the metastatic spread of a tumor to its regional lymph nodes. Largely depending on the stage of the primary tumor, between 20% and 40% of patients with UTUC are found to harbor lymph node metastases [58]. Several studies demonstrated the independent prognostic value of LNI in UTUC [8,18,20,35,56,67,68,75]. All these studies showed an important detrimental effect of LNI on CSS, with a 5-yr survival rate of approximately 30% in patients with lymph node metastases. In a recent study, Bolenz et al. showed that as in BCa, lymph node density could stratify the survival of patients with lymph node–positive UTUC [76]. Specifically, patients with a lymph node density $\geq$30% were at higher risk of disease recurrence and mortality. In conclusion, LNI is an important prognostic factor in patients with UTUC. Efforts are still needed to standardize the indications and lymphadenectomy templates in these patients.

3.3.5. *Tumor multifocality*

Multifocal tumors are defined as those tumors with two or more distinct locations within the urinary tract. When reported pathologically, tumor multifocality can be seen in $>$30% of cases [64]. Keeley et al. first reported multifocality as a prognostic factor with a negative impact on RFS [77].

Subsequent studies by Novara et al. and Brown et al. confirmed the prognostic role of tumor multifocality in UTUC patients [35,64]. Specifically, individuals with a multifocal UTUC showed a threefold higher risk of cancer-specific mortality relative to patients without tumor multifocality. More recently, the independent predictive value of tumor multifocality on CSS was confirmed by a multi-institutional French study and a multi-institutional Japanese study [19,20]. Similarly, using a large multi-institutional database, Chromecki et al. showed that tumor multifocality was an independent predictor of survival in patients with organ-confined UTUC [78]. Based on this evidence, tumor multifocality should be routinely determined and reported by pathologists.

3.3.6. Tumor architecture

As for BCa, different patterns of invasion reported at final pathology may significantly affect the survival of patients with UTUC. Several studies have investigated the prognostic impact of tumor architecture (sessile compared with papillary) on the survival of patients with UTUC. The first evidence that a sessile invasion pattern was associated with metastasis-free survival was provided by Langner et al. in 2006 [79]. Subsequently, three multi-institutional worldwide studies confirmed that a sessile growth pattern was associated with more aggressive disease and is an independent predictor of RFS and CSS [67,80,81]. These findings suggest that tumor architecture should always be mentioned during the endoscopic evaluation of UTUC, as well as in pathology reports, because it represents a valuable prognostic factor in UTUC patients in both the preoperative and postoperative settings.

3.3.7. Tumor size

Tumor size is an established predictor of cancer-related outcomes in several malignancies. Simone et al. investigated the relationship between tumor diameter and metastasis-free survival in patients with UTUC [82]. In their study, no metastases were noted in patients presenting with a tumor diameter $<$3 cm, whereas patients with a tumor diameter $\geq$3 cm had a 5-yr estimated metastasis-free survival of 67%. Similarly, Pieras et al. observed that patients with a tumor diameter $>$4 cm had a higher risk of developing a bladder tumor recurrence [71]. Because both these studies relied on a small population, larger multi-institutional studies are needed to confirm the prognostic role of tumor size in UTUC patients.

3.3.8. Lymphovascular invasion

Lymphatic vessels serve as the primary pathway for metastatic tumor cell spread in many types of cancer. As such, LVI is an essential step in the systemic dissemination of cancer cells and may be associated with the presence of micrometastases. Consequently, the presence of LVI may help identify patients without lymph node involvement who are at increased risk of cancer recurrence and mortality despite radical surgery. Several single-center studies have shown that LVI was associated with higher tumor stage and grade [83–85]. In addition, these studies have shown that LVI independently predicted worse RFS and CSS rates. These findings were confirmed by two independent international multi-institutional studies, which demonstrated that LVI was associated with established features of biologically aggressive UTUC, such as advanced stage, high tumor grade, metastasis to lymph nodes, sessile tumor architecture, tumor necrosis, and concomitant CIS [86,87]. In addition, these studies validated the independent status of LVI for predicting both RFS and CSS. Based on these data, LVI status should always be included in the pathologic report of RNU specimens, and patients with LVI should be considered in the future update of the TNM staging system for UTUC.

3.3.9. Tumor necrosis

Tumor necrosis is a well-established predictor of cancer aggressiveness in several malignancies. Two single-institutional studies by Simone et al. and Langner et al. showed that extensive tumor necrosis (defined as $>$10% of the tumor area) was an independent predictor of worse metastasis-free survival and RFS in UTUC patients [82,88]. Similarly, Lee et al. demonstrated that the presence of tumor necrosis independently predicted CSS [89]. These findings were validated by a multi-institutional worldwide study, in which extensive tumor necrosis was found to be associated with many aggressive features, such as advanced tumor stage, high-tumor grade, sessile architecture, LVI, concomitant CIS, and LNI [90]. In addition, extensive tumor necrosis was an independent predictor of RFS and CSS. However, in a recent multicenter international study, tumor necrosis did not achieve independent predictor status when predicting survival [91]. Because of these contradictory findings, the prognostic role of tumor necrosis in UTUC patients needs further confirmation in larger well-designed multi-institutional studies.

3.3.10. Positive surgical margins

The presence of positive surgical margins (PSMs) is reported in $\leq$8.5% of RNU cases and strictly depends on the management of the bladder cuff. According to two single-institutional studies, the presence of PSMs was associated with higher rates of disease recurrence in the bladder but not mortality after adjusting for the effects of standard clinicopathologic features [46,63].

3.3.11. Neoadjuvant and adjuvant therapies

As for BCa, several platinum-based chemotherapy schemes have been proposed for UTUC. Neoadjuvant chemotherapy capitalizes on the patient's maximal renal reserve to deliver optimal doses of chemotherapy, because data show that most patients are precluded from chemotherapy after nephroureterectomy as a result of worsening renal function [92]. Recently, Matin et al. demonstrated that the use of neoadjuvant chemotherapy in patients with high-risk UTUC resulted in a significant rate of downstaging and a 14% complete remission rate [93]. Youssef et al. showed a survival benefit of neoadjuvant chemotherapy in patients with locoregional LNI from UTUC, providing additional evidence supporting the role of neoadjuvant therapies in patients with locally advanced disease [74].

In addition, several studies explored the impact of adjuvant chemotherapy in patients with UTUC. In 2004, a preliminary single-institutional study first reported the feasibility of a platinum-based adjuvant therapy in patients with advanced UTUC [94]. Subsequently, two small retrospective studies showed the independent predictor status of adjuvant chemotherapy when predicting CSS and intravesical recurrence [95,96]. These findings were not confirmed by two recent retrospective multi-institutional studies, in which the administration of adjuvant chemotherapy did not result in a survival benefit in patients with high-risk UTUC [97,98]. These controversial findings underscore the need for prospective studies to enroll patients with high-risk UTUC in clinical trials investigating the impact of neoadjuvant chemotherapy and adjuvant chemotherapy on CSS and RFS. In regard to adjuvant topical therapy to prevent bladder recurrence, a recent prospective multicenter randomized clinical trial published by the British Association of Urological Surgeons Section of Oncology was highly informative [99]. This study deserves particular attention, as it represents the first randomized trial addressing the role of adjuvant therapy in patients with UTUC. According to this study, the incidence of bladder tumor recurrence in the first year after RNU was significantly reduced (absolute and relative risk reduction: 11% and 40%, respectively; number needed to treat: nine) with a single postoperative dose of intravesical chemotherapy.

3.4. Molecular markers (Table 3)

3.4.1. Tissue-based markers

In recent years, clinicians have focused their research on biomarkers associated with biologically aggressive disease and the prognosis of patients with UTUC. Several studies investigated the prognostic impact of various tissue-based markers that are related to cellular processes such as cell adhesion, angiogenesis, cell proliferation, and apoptosis. However, because of the rarity of the disease, the main limitations shared by these studies were their retrospective nature and their small sample size.

Rey et al. were the first to investigate the prognostic role of proteins involved in cell-cycle regulation in 83 patients with UTUC [100]. The authors showed that the overexpression of p53 was significantly associated with tumor aggressiveness and patient survival, even after adjustment for several patient and disease characteristics. More recently, the impact of p53 on survival was investigated by a Japanese single-center study ($n = 66$) and a European single-center study ($n = 53$) [101,102]. According to these studies, while p53 was a predictor of survival in univariable analyses, it did not emerge as an independent prognostic factor after adjustment for other clinical and pathologic characteristics.

The overexpression of Ki-67, a protein involved in cell proliferation, was found to be associated with advanced tumor stage and higher grade and to be an independent predictor of survival in a Japanese study of 107 patients with UTUC [103]. In addition, by evaluating 38 patients diagnosed with UTUC, Joung et al. demonstrated that Ki-67 overexpression was an independent predictor of synchronous and metachronous BCa development [104].

Epidermal growth factor receptor (EGFR) is strictly related to cell growth, proliferation, and differentiation. Leibl et al. evaluated the clinicopathologic significance of EGFR in 268 patients with UTUC [105]. According to this study, the overexpression of EGFR was found to be associated with advanced UTUC and metaplastic differentiation but not with CSS in multivariable analysis. Similarly, two markers involved with cell differentiation—namely, uroplakin III and Snail—were shown to correlate with RFS and CSS in two relatively small retrospective studies ($n = 71$ and $n = 150$), even after adjustment for several established prognostic factors [106,107].

Several apoptosis-related markers have also been investigated in patients with UTUC. The overexpression of survivin and Bcl-2, although associated with higher tumor grade and stage, was not associated with patient survival, according to a retrospective study by Nakanishi et al. consisting of 103 patients [108]. Conversely, in a more recent study, Jeong et al. demonstrated the independent predictor status of survivin when predicting disease-specific survival in 112 UTUC patients [109]. Similarly, Nakanishi et al. demonstrated that an elevated expression of telomerase mRNA component was a prognostic marker of RFS and OS in both univariable and multivariable analysis [110].

Angiogenesis is essential for human tumor growth. Increased levels of hypoxia-inducible factor 1α were found to be associated with both RFS and CSS by two single-institutional Japanese studies ($n = 127$ and $n = 98$), even after adjustment for several clinicopathologic variables [111,112]. Similarly, an increased expression of metalloproteinases was shown to correlate with cancer aggressiveness and to be an independent predictor of prognosis in two studies by Inoue et al. ($n = 55$ and by Miyata et al. ($n = 91$) [113,114].

The prognostic value of molecules involved in cell adhesion was also evaluated by several investigators. A lower expression of E-cadherin was shown to be associated with higher tumor stage and grade by Nakanishi et al. [115]. This finding was confirmed by a Japanese study ($n = 55$) and a European study ($n = 62$) that confirmed the independent predictor status of E-cadherin when predicting RFS and CSS [113,116]. Similarly, two single-institutional studies demonstrated that loss of normal membrane β-catenin expression and lower expression of parvin-β were independent predictors of CSS in 70 and 129 UTUC patients, respectively [117,118]. Finally, the expression of the mucin-like adhesion molecule CD24 was also found to be associated with several aggressive histopathologic features but not with patient outcomes in multivariable analysis [119].

In conclusion, several investigators have evaluated the prognostic value of tissue-based markers. Multi-institutional efforts are still needed to confirm the results of these studies and to determine the usefulness of these markers in the clinical decision-making process.

Table 3 – Summary of the molecular markers in upper tract urothelial carcinoma patients

Markers	Function	Detection	Comment	Level of evidence	References
Tissue-based					
p53	Cell-cycle regulation	Immunohistochemistry	Overexpression is associated with advanced T stage and higher tumor grade.	3	100–102
Ki-67	Cell proliferation	Immunohistochemistry	Overexpression is associated with advanced T stage and higher tumor grade. It is an independent predictor of synchronous/ metachronous bladder cancer.	3	103,104
EGFR	Cell proliferation and differentiation	Immunohistochemistry	Overexpression is associated with advanced disease and metaplastic differentiation.	3	105
Uroplakin III	Cell differentiation	Immunohistochemistry	Loss of expression is associated with advanced disease. It is an independent predictor of lower CSS rates.	3	106
Snail	Cell differentiation	Immunohistochemistry	Overexpression is associated with advanced T stage and higher tumor grade. It is an independent predictor of lower RFS and CSS rates.	3	107
Bcl-2	Apoptosis	Immunohistochemistry	Overexpression is associated with advanced T stage and higher tumor grade.	3	108
Survivin	Apoptosis	Immunohistochemistry	Overexpression is associated with advanced T stage and higher tumor grade. It is an independent predictor of lower CSS rates.	3	108,109
Telomerase mRNA	Maintaining DNA integrity	In situ hybridization	Overexpression is an independent marker for lower FRS and OS rates.	3	110
HIF-1α	Angiogenesis	Immunohistochemistry	Overexpression is an independent marker for lower RFS and OS rates.	3	111,112
Metalloproteinases	Angiogenesis	Immunohistochemistry	Overexpression is associated with advanced T stage. It is an independent predictor of lower CSS rates.	3	113,114
E-cadherin	Cell adhesion	Immunohistochemistry	Lower levels are associated with advanced disease and are an independent predictor of lower progression-free survival, RFS, and CSS rates.	3	113,115,116
β-Catenin	Cell adhesion	Immunohistochemistry	Loss of normal expression is an independent marker for lower progression-free survival and CSS rates.	3	117
Parvin-β	Cell adhesion	Immunohistochemistry	Lower expression is an independent marker for lower CSS rates.	3	118
CD24	Cell adhesion	Immunohistochemistry	Expression is associated with advanced T stage and higher grade.	3	119
Blood-based					
C-reactive protein	Inflammatory response	ELISA	Elevated levels are independently associated with lower RFS and CSS rates.	3	120
Leukocytes	Inflammatory response	Cytometry	Elevated levels are independently associated with lower RFS and CSS rates.	3	121
Alkaline phosphatase	Hydrolase enzyme	Spectrophotometry	Elevated levels are independently associated with lower RFS and CSS rates.	3	121
CYFRA 21-1	Cell structural integrity	ELISA	Elevated levels are independently associated with lower OS rates.	3	122
Genetic					
Microsatellite instability	Defect in DNA repair process	PCR	Microsatellite instability is an independent marker for lower CSS rates.	3	124
Promoter hypermethylation	Repression of gene transcription	PCR	Promoter hypermethylation is associated with advanced disease and is an independent marker for lower progression-free survival rates.	3	125
FGFR-3	Cell proliferation and differentiation	PCR	Mutations in the *FGFR* gene are associated with milder disease and better survival.	3	126
Urine					
Chromosomal alterations	Defect in DNA repair process	FISH	Chromosomal alterations increase sensitivity and specificity for UTUC detection.	3	129–135

EGFR = epidermal growth factor receptor; CSS = cancer-specific survival; RFS = recurrence-free survival; OS = overall survival; HIF-1α = hypoxia-inducible factor 1α; ELISA = enzyme-linked immunosorbent assay; PCR = polymerase chain reaction; *FGFR-3* = fibroblast growth factor receptor 3; FISH = fluorescence in situ hybridization; UTUC = upper tract urothelial carcinoma.

3.4.2. *Blood-based markers*

Only a few blood-based markers have been investigated in UTUC patients, and none of them are available for the prediction of survival. Increased levels of C-reactive protein were shown to predict RFS and CSS in a single-institutional retrospective study of 130 surgically treated UTUC patients [120]. Similarly, Lehmann et al. showed that elevated white blood cell count and high alkaline phosphatase levels were

independent predictors of CSS in 145 consecutive patients with urothelial carcinoma of the ureter who underwent segmental ureterectomy or nephroureterectomy [121]. More recently, a small single-institutional study ($n = 45$) demonstrated that increased levels of cytokeratin 19 fragments (CYFRA 21–1) independently predicted OS in UTUC patients [122]. In conclusion, little evidence is currently available supporting the role of blood-based markers as predictors of clinical outcomes in patients with UTUC. All the currently available studies are based on small retrospective single-institutional series, underscoring the need for multi-institutional efforts aimed at determining blood-based predictors of prognosis in patients with UTUC.

3.4.3. Genetic markers

Microsatellite instability (MSI) is defined as the presence of ubiquitous mutations in microsatellite DNA sequences and has been found to be associated with hereditary non-polyposis colorectal cancer, as well as with many sporadic human cancers. The presence of MSI has also been demonstrated in UTUC patients [123]. To date, only a single-institutional study by Roupret et al. demonstrated the independent predictor status of MSI on OS in 80 patients with invasive (stage pT2 or worse) UTUC [124].

Promoter hypermethylation is an important pathway for the repression of gene transcription in human cancers. Catto et al. demonstrated that hypermethylation was associated with advanced tumor stage and confirmed its role as an independent predictor of progression-free survival in a relatively large cohort of UTUC patients ($n = 280$) [125].

Fibroblast growth factor receptor 3 is expressed in normal urothelium. Recently, van Oers et al. demonstrated that mutations of this gene were associated with low-stage tumors and a milder disease course in UTUC [126]. In addition, the authors showed that these mutations indicated better prognosis in patients with invasive UTUC, even after adjustment for several established predictors of survival.

In conclusion, few studies have investigated the prognostic role of genetic markers in UTUC patients. Further evidence is needed to confirm the findings of these studies and eventually promote the use of these markers in clinical practice.

3.4.4. Urinary markers

Positive urine cytology is highly suggestive of UTUC when cystoscopy is normal and if CIS of the bladder or prostatic urethra has been excluded [2]. Skolarikos et al. and Williams et al. showed that positive exfoliated cell cytology increased the accuracy of biopsy grade in determining the presence of advanced-stage and advanced-grade UTUC [127,128]. More recently, a single-institutional study of 172 UTUC patients by Brien et al. showed that positive cytology was frequently associated with muscle-invasive and non–organ-confined disease and therefore may be helpful for preoperatively predicting tumor stage [26].

Fluorescence in situ hybridization (FISH) is a cytogenetic technique used to detect molecular abnormalities associated with cancers. The use of FISH analysis in voided urine for the early detection and screening of UTUC patients is becoming progressively more popular. Preliminary studies demonstrated that FISH had a higher sensitivity than urine cytology in determining the presence of UTUC (52–76% for FISH compared with 26–36% for urine cytology) [129,130]. More recently, several studies showed that FISH was more sensitive than urine cytology (85–100% compared with 21–24%, respectively) for the detection of UTUC [131,132]. In addition, Xu et al. showed that the combination of urine cytology and the FISH test (cyto-FISH) may be useful for further improving the sensitivity of the FISH test alone (sensitivity: 86% compared with 79%, respectively) in the detection of both invasive and noninvasive tumors [133]. Conversely, several authors have questioned the usefulness of FISH for the surveillance of patients with UTUC [129,134]. After cystectomy and diversion, both cytology and FISH had high false-positive rates and appeared to be most useful only for their negative predictive value [135]. In conclusion, the FISH test is a valuable tool for the detection of UTUC, as it significantly increases the sensitivity of standard cytology. Conversely, because of its high false-positive rates, FISH appears to have a limited value in the surveillance of these patients and should be omitted from surveillance strategies.

3.5. Prediction tools

3.5.1. Prediction of non–organ-confined disease

Traditionally, clinical decisions are based on the physician's clinical experience and ability to predict the individual patient's risk level. However, the physician's risk estimates are frequently biased because of both subjective and objective confounders. In addition, current imaging techniques are poor at determining pathologic stage except when disease is significantly advanced. As a consequence, predictive and prognostic tools based on various statistical techniques have been developed to provide clinicians with more accurate estimates of the outcome of interest for the individual patient.

Prediction of pathologic stage would be extremely valuable for proper risk allocation and patient preoperative counseling, as well as for selecting candidates for neoadjuvant systemic therapy and guiding the extent of LND at RNU. Clinical biopsy grade by itself is an important predictor, because biopsy low grade is associated with a >90% chance of pathologic low-stage disease, whereas biopsy high grade is associated with a 66% chance of pathologic high stage [24,77]. The addition of tumor architecture and other clinically available factors may improve these predictions. Margulis et al. developed a nomogram for the prediction of non–organ-confined UTUC based on readily available preoperative clinical and pathologic parameters, namely, tumor grade, architecture, and location [131,136]. Their prediction tool showed good calibration and a 76.7% accuracy. Similarly, Favaretto et al. developed a preoperative model for predicting the presence of muscle-invasive and non–organ-confined disease based on local invasion at imaging and ureteroscopy grade [137]. Their nomogram showed an accuracy of 71% and 70% in predicting the presence of muscle-invasive and non–organ-confined disease, respectively. External

validation of these tools is needed before their implementation in clinical practice.

3.5.2. Prediction of cancer-specific mortality and perioperative mortality after surgery

The prediction of cancer-specific mortality represents an important end point for the risk stratification of patients with UTUC. Jeldres et al. developed a nomogram based on age, pT stage, pN stage, and tumor grade for predicting UTUC-related events 5 yr after RNU. The model was externally validated showing an accuracy of 75.4% [138]. The same authors developed a tool for predicting perioperative (90-d) mortality after RNU, which showed 73.4% accuracy [139]. However, these tools were based on a North American cancer registry and still await external validation in different patient populations.

4. Conclusions

Clinical predictive factors represent a major deficiency in the ability to accurately risk stratify patients prior to definitive therapy. Prospective studies validating the role of these factors and investigating new molecular markers are urgently needed to assist clinicians in the decision-making process. In the absence of any imaging findings suggestive of very advanced stage, five clinical factors can be used for risk stratification: age, tumor architecture, cytology, biopsy tumor grade, and presence of hydronephrosis. These five factors appear currently to be the most reliable and readily available variables that can be used for such assessment and determination of kidney-sparing, surgical-only, or multimodality therapies. Tissue and urinary markers hold promise in improving the clinical prediction of invasiveness, recurrence, and survival, and their further development is eagerly awaited. Pathologic predictive factors such as tumor stage, grade, CIS, LVI, and LNI may be more accurate prognosticators of recurrence and survival than clinical factors, but such information is available usually only after the patient has lost a significant amount of renal reserve, possibly precluding the ability to receive adequate platinum-based chemotherapy if poor features exist. The research of the last 5 yr has helped us gain great insight into the biology and clinical behavior of UTUC. The integrated cooperation among experts from multiple disciplines is promising to help us translate this knowledge into better care and improved outcomes for our patients with UTUC.

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Acquisition of data: Lughezzani.
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References

[1] Raman JD, Messer J, Sielatycki JA, Hollenbeak CS. Incidence and survival of patients with carcinoma of the ureter and renal pelvis in the USA, 1973–2005. BJU Int 2011;107:1059–64.
[2] Rouprêt M, Zigeuner R, Palou J, et al. European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. Eur Urol 2011;59:584–94.
[3] NCCN guidelines. Clinical guidelines in oncology. Bladder cancer, version 2.2012. National Comprehensive Cancer Network Web site. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
[4] Chromecki TF, Bensalah K, Remzi M, et al. Prognostic factors for upper urinary tract urothelial carcinoma. Nat Rev Urol 2011;8:440–7.
[5] Fernandez MI, Shariat SF, Margulis V, et al. Evidence-based sex-related outcomes after radical nephroureterectomy for upper tract urothelial carcinoma: results of large multicenter study. Urology 2009;73:142–6.
[6] Shariat SF, Favaretto RL, Gupta A, et al. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol 2011;29:457–63.
[7] 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;75:321–7.
[8] Lughezzani G, Jeldres C, Isbarn H, et al. Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: a population-based study of 2299 patients. Eur J Cancer 2009;45:3291–7.
[9] Shariat SF, Godoy G, Lotan Y, et al. Advanced patient age is associated with inferior cancer-specific survival after radical nephroureterectomy. BJU Int 2010;105:1672–7.
[10] Chromecki TF, Ehdaie B, Novara G, et al. Chronological age is not an independent predictor of clinical outcomes after radical nephroureterectomy. World J Urol 2011;29:473–80.
[11] Matsumoto K, Novara G, Gupta A, et al. Racial differences in the outcome of patients with urothelial carcinoma of the upper urinary tract: an international study. BJU Int 2011;108:304–9.
[12] Martinez-Salamanca JI, Shariat SF, Rodriguez JC, et al. Prognostic role of ECOG performance status in patients with urothelial carcinoma of the upper urinary tract: an international study. BJU Int 2012;109:1155–61.
[13] Ehdaie B, Chromecki TF, Lee RK, et al. Obesity adversely impacts disease specific outcomes in patients with upper tract urothelial carcinoma. J Urol 2011;186:66–72.
[14] McLaughlin JK, Silverman DT, Hsing AW, et al. Cigarette smoking and cancers of the renal pelvis and ureter. Cancer Res 1992;52:254–7.
[15] Simsir A, Sarsik B, Cureklibatir I, Sen S, Gunaydin G, Cal C. Prognostic factors for upper urinary tract urothelial carcinomas: stage, grade, and smoking status. Int Urol Nephrol 2011;43:1039–45.

[16] 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;176:48–52.
[17] Zigeuner RE, Hutterer G, Chromecki T, Rehak P, Langner C. Bladder tumour development after urothelial carcinoma of the upper urinary tract is related to primary tumour location. BJU Int 2006;98:1181–6.
[18] Park J, Ha SH, Min GE, et al. The protective role of renal parenchyma as a barrier to local tumor spread of upper tract transitional cell carcinoma and its impact on patient survival. J Urol 2009;182: 894–9.
[19] Ouzzane A, Colin P, Xylinas E, et al. Ureteral and multifocal tumours have worse prognosis than renal pelvic tumours in urothelial carcinoma of the upper urinary tract treated by nephroureterectomy. Eur Urol 2011;60:1258–65.
[20] Kamihira O, Hattori R, Yamaguchi A, et al. Laparoscopic radical nephroureterectomy: a multicenter analysis in Japan. Eur Urol 2009;55:1397–409.
[21] 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;182:2177–81.
[22] Favaretto RL, Shariat SF, Chade DC, et al. The effect of tumor location on prognosis in patients treated with radical nephroureterectomy at Memorial Sloan-Kettering Cancer Center. Eur Urol 2010;58:574–80.
[23] 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;57:1072–9.
[24] Brown GA, Matin SF, Busby JE, et al. Ability of clinical grade to predict final pathologic stage in upper urinary tract transitional cell carcinoma: implications for therapy. Urology 2007;70:252–6.
[25] Guarnizo E, Pavlovich CP, Seiba M, Carlson DL, Vaughan Jr ED, Sosa RE. Ureteroscopic biopsy of upper tract urothelial carcinoma: improved diagnostic accuracy and histopathological considerations using a multi-biopsy approach. J Urol 2000;163:52–5.
[26] 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;184:69–73.
[27] Smith AK, Stephenson AJ, Lane BR, et al. Inadequacy of biopsy for diagnosis of upper tract urothelial carcinoma: implications for conservative management. Urology 2011;78:82–6.
[28] Scolieri MJ, Paik ML, Brown SL, Resnick MI. Limitations of computed tomography in the preoperative staging of upper tract urothelial carcinoma. Urology 2000;56:930–4.
[29] 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;70:662–6.
[30] Ito Y, Kikuchi E, Tanaka N, et al. Preoperative hydronephrosis grade independently predicts worse pathological outcomes in patients undergoing nephroureterectomy for upper tract urothelial carcinoma. J Urol 2011;185:1621–6.
[31] 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;29:27–32.
[32] Inman BA, Tran VT, Fradet Y, Lacombe L. Carcinoma of the upper urinary tract: predictors of survival and competing causes of mortality. Cancer 2009;115:2853–62.
[33] 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 2011;29:716–23.
[34] Mullerad M, Russo P, Golijanin D, et al. Bladder cancer as a prognostic factor for upper tract transitional cell carcinoma. J Urol 2004;172:2177–81.
[35] Novara G, De Marco V, Gottardo F, Dalpiaz O, 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;110:1715–22.
[36] 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;182:451–8, discussion 458.
[37] Tran W, Serio AM, Raj GV, et al. Longitudinal risk of upper tract recurrence following radical cystectomy for urothelial cancer and the potential implications for long-term surveillance. J Urol 2008;179:96–100.
[38] Boorjian S, Ng C, Munver R, et al. Impact of delay to nephroureterectomy for patients undergoing ureteroscopic biopsy and laser tumor ablation of upper tract transitional cell carcinoma. Urology 2005;66:283–7.
[39] Sundi D, Svatek RS, Margulis V, et al. Upper tract urothelial carcinoma: impact of time to surgery. Urol Oncol 2012;30:266–72.
[40] Waldert M, Karakiewicz PI, Raman JD, et al. A delay in radical nephroureterectomy can lead to upstaging. BJU Int 2010;105: 812–7.
[41] Roupret M, Hupertan V, Sanderson KM, et al. Oncologic control after open or laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: a single center experience. Urology 2007;69:656–61.
[42] 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;56:1–9.
[43] Favaretto RL, Shariat SF, Chade DC, 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;58: 645–51.
[44] Walton TJ, Novara G, Matsumoto K, et al. Oncological outcomes after laparoscopic and open radical nephroureterectomy: results from an international cohort. BJU Int 2011;108:406–12.
[45] Simone G, Papalia R, Guaglianone S, et al. Laparoscopic versus open nephroureterectomy: perioperative and oncologic outcomes from a randomised prospective study. Eur Urol 2009;56:520–6.
[46] Aboussaly R, Alibhai SM, Shah N, Timilshina N, Fleshner N, Finelli A. Troubling outcomes from population-level analysis of surgery for upper tract urothelial carcinoma. Urology 2010;76:895–901.
[47] Saika T, Nishiguchi J, Tsushima T, et al. Comparative study of ureteral stripping versus open ureterectomy for nephroureterectomy in patients with transitional carcinoma of the renal pelvis. Urology 2004;63:848–52.
[48] Matin SF, Gill IS. Recurrence and survival following laparoscopic radical nephroureterectomy with various forms of bladder cuff control. J Urol 2005;173:395–400.
[49] Walton TJ, Sherwood BT, Parkinson RJ, et al. Comparative outcomes following endoscopic ureteral detachment and formal bladder cuff excision in open nephroureterectomy for upper urinary tract transitional cell carcinoma. J Urol 2009;181:532–9.
[50] Lughezzani G, Sun M, Perrotte P, et al. Should bladder cuff excision remain the standard of care at nephroureterectomy in patients with urothelial carcinoma of the renal pelvis? A population-based study. Eur Urol 2010;57:956–62.
[51] Phe V, Cussenot O, Bitker MO, Roupret M. Does the surgical technique for management of the distal ureter influence the outcome after nephroureterectomy? BJU Int 2011;108:130–8.
[52] Brown JA, Strup SE, Chenven E, Bagley D, Gomella LG. Hand-assisted laparoscopic nephroureterectomy: analysis of distal

ureterectomy technique, margin status, and surgical outcomes. Urology 2005;66:1192–6.
[53] Matin SF. Radical laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: current status. BJU Int 2005;95:68–74.
[54] Romero FR, Schaeffer EM, Muntener M, Trock B, Kavoussi LR, Jarrett TW. Oncologic outcomes of extravesical stapling of distal ureter in laparoscopic nephroureterectomy. J Endourol 2007;21:1025–7.
[55] Brausi MA, Gavioli M, De Luca G, et al. Retroperitoneal lymph node dissection (RPLD) in conjunction with nephroureterectomy in the treatment of infiltrative transitional cell carcinoma (TCC) of the upper urinary tract: impact on survival. Eur Urol 2007;52:1414–20.
[56] 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;181:2482–9.
[57] Burger M, Shariat SF, Fritsche HM, et al. No overt influence of lymphadenectomy on cancer-specific survival in organ-confined versus locally advanced upper urinary tract urothelial carcinoma undergoing radical nephroureterectomy: a retrospective international, multi-institutional study. World J Urol 2011;29:465–72.
[58] Kondo T, Nakazawa H, Ito F, Hashimoto Y, Toma H, Tanabe K. Impact of the extent of regional lymphadenectomy on the survival of patients with urothelial carcinoma of the upper urinary tract. J Urol 2007;178:1212–7, discussion 1217.
[59] Kondo T, Hashimoto Y, Kobayashi H, et al. Template-based lymphadenectomy in urothelial carcinoma of the upper urinary tract: impact on patient survival. Int J Urol 2010;17:848–54.
[60] 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;74:1070–4.
[61] 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;56:512–9.
[62] Roscigno M, Brausi M, Heidenreich A, et al. Lymphadenectomy at the time of nephroureterectomy for upper tract urothelial cancer. Eur Urol 2011;60:776–83.
[63] Bolenz C, Fernandez MI, Trojan L, et al. Lymphovascular invasion and pathologic tumor stage are significant outcome predictors for patients with upper tract urothelial carcinoma. Urology 2008;72:364–9.
[64] Brown GA, Busby JE, Wood CG, et al. Nephroureterectomy for treating upper urinary tract transitional cell carcinoma: time to change the treatment paradigm? BJU Int 2006;98:1176–80.
[65] Langner C, Hutterer G, Chromecki T, Winkelmayer I, Rehak P, Zigeuner R. pT classification, grade, and vascular invasion as prognostic indicators in urothelial carcinoma of the upper urinary tract. Mod Pathol 2006;19:272–9.
[66] Li C-C, Chang T-H, Wu W-J, et al. Significant predictive factors for prognosis of primary upper urinary tract cancer after radical nephroureterectomy in Taiwanese patients. Eur Urol 2008;54:1127–35.
[67] Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer 2009;115:1224–33.
[68] Rabbani F, Perrotti M, Russo P, Herr HW. Upper-tract tumors after an initial diagnosis of bladder cancer: argument for long-term surveillance. J Clin Oncol 2001;19:94–100.
[69] 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;45:257–66.
[70] Sauter G, Algaba F, Amin MB, et al. Noninvasive urothelial neoplasias: WHO classification of noninvasive papillary urothelial tumors. In: Eble JN, Epstein JI, Sesterhenn I, editors. World Health Organization classification of tumors: pathology and genetics of tumors of the urinary system and male genital organs. Lyon, France: IARCC Press; 2004. p. 110–23.
[71] 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;106:1319–23.
[72] Wheat JC, Weizer AZ, Wolf Jr JS, et al. Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ confined urothelial carcinoma following radical nephroureterectomy. Urol Oncol 2012;30:252–8.
[73] 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;29:487–94.
[74] Youssef RF, Shariat SF, Lotan Y, et al. Prognostic effect of urinary bladder carcinoma in situ on clinical outcome of subsequent upper tract urothelial carcinoma. Urology 2011;77:861–6.
[75] Lughezzani G, Jeldres C, Isbarn H, et al. A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. Urology 2010;75:118–24.
[76] 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;103:302–6.
[77] Keeley Jr FX, Kulp DA, Bibbo M, McCue PA, Bagley DH. Diagnostic accuracy of ureteroscopic biopsy in upper tract transitional cell carcinoma. J Urol 1997;157:33–7.
[78] Chromecki TF, Cha EK, Fajkovic H, et al. The impact of tumor multifocality on outcomes in patients treated with radical nephroureterectomy. Eur Urol 2012;61:245–53.
[79] 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;448:604–11.
[80] 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;103:307–11.
[81] Fritsche HM, Novara G, Burger M, et al. Macroscopic sessile tumor architecture is a pathologic feature of biologically aggressive upper tract urothelial carcinoma. Urol Oncol. In press. http://dx.doi.org/10.1016/j.urolonc.2010.07.010.
[82] 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;103:1052–7.
[83] 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;103:1040–6.
[84] Kikuchi E, Horiguchi Y, Nakashima J, et al. Lymphovascular invasion independently predicts increased disease specific survival in patients with transitional cell carcinoma of the upper urinary tract. J Urol 2005;174:2120–3, discussion 2124.
[85] Lin WC, Hu FC, Chung SD, Chueh SC, Pu YS, Huang KH. The role of lymphovascular invasion in predicting the prognosis of clinically localized upper tract urothelial carcinoma (pT1-3cN0M0). J Urol 2008;180:879–84, discussion 884–5.
[86] 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;27:612–8.
[87] 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;57:1064–71.
[88] 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;176:910–3, discussion 913–4.
[89] Lee SE, Hong SK, Han BK, et al. Prognostic significance of tumor necrosis in primary transitional cell carcinoma of upper urinary tract. Jpn J Clin Oncol 2007;37:49–55.
[90] Zigeuner R, Shariat SF, 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;57:575–81.
[91] Seitz C, Gupta A, Shariat SF, 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;184:1895–900.
[92] Lane BR, Smith AK, Larson BT, et al. Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. Cancer 2010;116:2967–73.
[93] Matin SF, Margulis V, Kamat A, et al. Incidence of downstaging and complete remission after neoadjuvant chemotherapy for high-risk upper tract transitional cell carcinoma. Cancer 2010;116:3127–34.
[94] Bamias A, Deliveliotis C, Fountzilas G, et al. Adjuvant chemotherapy with paclitaxel and carboplatin in patients with advanced carcinoma of the upper urinary tract: a study by the Hellenic Cooperative Oncology Group. J Clin Oncol 2004;22:2150–4.
[95] Kwak C, Lee SE, Jeong IG, Ku JH. Adjuvant systemic chemotherapy in the treatment of patients with invasive transitional cell carcinoma of the upper urinary tract. Urology 2006;68:53–7.
[96] Soga N, Arima K, Sugimura Y. Adjuvant methotrexate, vinblastine, adriamycin, and cisplatin chemotherapy has potential to prevent recurrence of bladder tumors after surgical removal of upper urinary tract transitional cell carcinoma. Int J Urol 2008;15:800–3.
[97] Hellenthal NJ, Shariat SF, Margulis V, et al. Adjuvant chemotherapy for high risk upper tract urothelial carcinoma: results from the Upper Tract Urothelial Carcinoma Collaboration. J Urol 2009; 182:900–6.
[98] Vassilakopoulou M, de la Motte Rouge T, Colin P, et al. Outcomes after adjuvant chemotherapy in the treatment of high-risk urothelial carcinoma of the upper urinary tract (UUT-UC): results from a large multicenter collaborative study. Cancer 2011;117:5500–8.
[99] O'Brien T, Ray E, Singh R, Coker B, Beard R, British Association of Urological Surgeons Section of Oncology. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C trial). Eur Urol 2011;60:703–10.
[100] Rey A, Lara PC, Redondo E, Valdes E, Apolinario R. Overexpression of p53 in transitional cell carcinoma of the renal pelvis and ureter: relation to tumor proliferation and survival. Cancer 1997;79: 2178–85.
[101] Hashimoto H, Sue Y, Saga Y, Tokumitsu M, Yachiku S. Roles of p53 and MDM2 in tumor proliferation and determination of the prognosis of transitional cell carcinoma of the renal pelvis and ureter. Int J Urol 2000;7:457–63.
[102] Zigeuner R, Tsybrovskyy O, Ratschek M, Rehak P, Lipsky K, Langner C. Prognostic impact of p63 and p53 expression in upper urinary tract transitional cell carcinoma. Urology 2004;63:1079–83.
[103] Jeon HG, Jeong IG, Bae J, et al. Expression of Ki-67 and COX-2 in patients with upper urinary tract urothelial carcinoma. Urology 2010;76:513 e7–12.
[104] Joung JY, Yang SO, Jeong IG, et al. Identification of immunohistochemical factors that predict the synchronous or metachronous development of bladder tumors in patients with upper urinary tract tumors. Urol Int 2008;81:306–11.
[105] Leibl S, Zigeuner R, Hutterer G, Chromecki T, Rehak P, Langner C. EGFR expression in urothelial carcinoma of the upper urinary tract is associated with disease progression and metaplastic morphology. APMIS 2008;116:27–32.
[106] Ohtsuka Y, Kawakami S, Fujii Y, et al. Loss of uroplakin III expression is associated with a poor prognosis in patients with urothelial carcinoma of the upper urinary tract. BJU Int 2006;97: 1322–6.
[107] Kosaka T, Kikuchi E, Mikami S, et al. Expression of Snail in upper urinary tract urothelial carcinoma: prognostic significance and implications for tumor invasion. Clin Cancer Res 2010;16:5814–23.
[108] Nakanishi K, Tominaga S, Hiroi S, et al. Expression of survivin does not predict survival in patients with transitional cell carcinoma of the upper urinary tract. Virchows Arch 2002;441:559–63.
[109] Jeong IG, Kim SH, Jeon HG, et al. Prognostic value of apoptosis-related markers in urothelial cancer of the upper urinary tract. Hum Pathol 2009;40:668–77.
[110] Nakanishi K, Kawai T, Hiroi S, et al. Expression of telomerase mRNA component (hTR) in transitional cell carcinoma of the upper urinary tract. Cancer 1999;86:2109–16.
[111] Nakanishi K, Hiroi S, Tominaga S, et al. Expression of hypoxia-inducible factor-1alpha protein predicts survival in patients with transitional cell carcinoma of the upper urinary tract. Clin Cancer Res 2005;11:2583–90.
[112] Ke HL, Wei YC, Yang SF, et al. Overexpression of hypoxia-inducible factor-1alpha predicts an unfavorable outcome in urothelial carcinoma of the upper urinary tract. Int J Urol 2008;15:200–5.
[113] Inoue K, Kamada M, Slaton JW, et al. The prognostic value of angiogenesis and metastasis-related genes for progression of transitional cell carcinoma of the renal pelvis and ureter. Clin Cancer Res 2002;8:1863–70.
[114] Miyata Y, Kanda S, Nomata K, Hayashida Y, Kanetake H. Expression of metalloproteinase-2, metalloproteinase-9, and tissue inhibitor of metalloproteinase-1 in transitional cell carcinoma of upper urinary tract: correlation with tumor stage and survival. Urology 2004;63: 602–8.
[115] Nakanishi K, Kawai T, Torikata C, Aurues T, Ikeda T. E-cadherin expression in upper-urinary-tract carcinoma. Int J Cancer 1997; 74:446–9.
[116] Fromont G, Rouprêt 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;48:764–70.
[117] Izquierdo L, Truan D, Petit A, Gutierrez R, Mallofre C, Alcaraz A. Adhesion molecules alpha, beta and gamma-catenin as prognostic factors of tumour progression in upper urinary tract urothelial tumours: the role of AKT-P/GSK-3beta/beta-catenin pathway. BJU Int 2009;104:100–6.
[118] Wu CF, Ng KF, Chen CS, et al. Expression of parvin-beta is a prognostic factor for patients with urothelial cell carcinoma of the upper urinary tract. Br J Cancer 2010;103:852–60.
[119] Winkler A, Zigeuner R, Rehak P, Hutterer G, Chromecki T, Langner C. CD24 expression in urothelial carcinoma of the upper urinary tract correlates with tumour progression. Virchows Arch 2007;450: 59–64.
[120] Saito K, Kawakami S, Ohtsuka Y, et al. The impact of preoperative serum C-reactive protein on the prognosis of patients with upper urinary tract urothelial carcinoma treated surgically. BJU Int 2007; 100:269–73.
[121] Lehmann J, Suttmann H, Kovač I, et al. Transitional cell carcinoma of the ureter: prognostic factors influencing progression and survival. Eur Urol 2007;51:1281–8.

[122] Suyama T, Nakajima K, Kanbe S, Tanaka N, Hara H, Ishii N. Prognostic significance of preoperative serum CYFRA 21-1 in patients with upper urinary tract urothelial carcinoma. Int J Urol 2011;18:43–7.
[123] Roupret M, Catto J, Coulet F, et al. Microsatellite instability as indicator of MSH2 gene mutation in patients with upper urinary tract transitional cell carcinoma. J Med Genet 2004;41:e91.
[124] Roupret M, Fromont G, Azzouzi AR, et al. Microsatellite instability as predictor of survival in patients with invasive upper urinary tract transitional cell carcinoma. Urology 2005;65:1233–7.
[125] Catto JW, Azzouzi AR, Rehman I, et al. Promoter hypermethylation is associated with tumor location, stage, and subsequent progression in transitional cell carcinoma. J Clin Oncol 2005;23:2903–10.
[126] van Oers JMM, Zwarthoff EC, Rehman I, et al. *FGFR3* mutations indicate better survival in invasive upper urinary tract and bladder tumours. Eur Urol 2009;55:650–8.
[127] Skolarikos A, Griffiths TR, Powell PH, Thomas DJ, Neal DE, Kelly JD. Cytologic analysis of ureteral washings is informative in patients with grade 2 upper tract TCC considering endoscopic treatment. Urology 2003;61:1146–50.
[128] Williams SK, Denton KJ, Minervini A, et al. Correlation of upper-tract cytology, retrograde pyelography, ureteroscopic appearance, and ureteroscopic biopsy with histologic examination of upper-tract transitional cell carcinoma. J Endourol 2008;22:71–6.
[129] Chen AA, Grasso M. Is there a role for FISH in the management and surveillance of patients with upper tract transitional-cell carcinoma? J Endourol 2008;22:1371–4.
[130] Marín-Aguilera M, Mengual L, Ribal MJ, et al. Utility of fluorescence *in situ* hybridization as a non-invasive technique in the diagnosis of upper urinary tract urothelial carcinoma. Eur Urol 2007;51:409–15, discussion 415.
[131] Luo B, Li W, Deng CH, et al. Utility of fluorescence in situ hybridization in the diagnosis of upper urinary tract urothelial carcinoma. Cancer Genet Cytogenet 2009;189:93–7.
[132] Mian C, Mazzoleni G, Vikoler S, et al. Fluorescence in situ hybridisation in the diagnosis of upper urinary tract tumours. Eur Urol 2010;58:288–92.
[133] Xu C, Zeng Q, Hou J, et al. Utility of a modality combining FISH and cytology in upper tract urothelial carcinoma detection in voided urine samples of Chinese patients. Urology 2011;77:636–41.
[134] Johannes JR, Nelson E, Bibbo M, Bagley DH. Voided urine fluorescence in situ hybridization testing for upper tract urothelial carcinoma surveillance. J Urol 2010;184:879–82.
[135] Fernandez MI, Parikh S, Grossman HB, et al. The role of FISH and cytology in upper urinary tract surveillance after radical cystectomy for bladder cancer. Urol Oncol. In press. http://dx.doi.org/10.1016/j.urolonc.2010.08.006
[136] 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;184:453–8.
[137] Favaretto RL, Shariat SF, Savage C, et al. Combining imaging and ureteroscopy variables in a preoperative multivariable model for prediction of muscle-invasive and non-organ confined disease in patients with upper tract urothelial carcinoma. BJU Int 2012;109:77–82.
[138] Jeldres C, Sun M, Lughezzani G, et al. Highly predictive survival nomogram after upper urinary tract urothelial carcinoma. Cancer 2010;116:3774–84.
[139] Jeldres C, Sun M, Isbarn H, et al. A population-based assessment of perioperative mortality after nephroureterectomy for upper-tract urothelial carcinoma. Urology 2010;75:315–20.