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TOPIC PAPER

Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC)

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Abstract
Purpose Upper-tract urothelial carcinoma (UTUC) is a relatively uncommon disease with limited available evidence on specific topics. The purpose of this article was to review the previous literature to summarize the current knowledge about UTUC epidemiology, diagnosis, preoperative evaluation and prognostic assessment.
Methods Using MEDLINE, a non-systematic review was performed including articles between January 2000 and February 2016. English language original articles, reviews and editorials were selected based on their clinical relevance.
Results UTUC accounts for 5–10 % of all urothelial cancers, with an increasing incidence. UTUC and bladder cancer share some common risk factors, even if they are two different entities regarding practical, biological and clinical characteristics. Aristolochic acid plays an important role in UTUC pathogenesis in certain regions. It is further estimated that approximately 10 % of UTUC are part of the hereditary non-polyposis colorectal cancer spectrum disease. UTUC diagnosis remains mainly based on imaging and endoscopy, but development of new technologies is rapidly changing the diagnosis algorithm. To help the decision-making process regarding surgical treatment, extent of lymphadenectomy and selection of neoadjuvant systemic therapies, predictive tools based on preoperative patient and tumor characteristics have been developed.

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Conclusions Awareness regarding epidemiology, diagnosis, preoperative evaluation and prognostic assessment changes is essential to correctly diagnose and manage UTUC patients, thereby potentially improving their outcomes.

Keywords UTUC · Epidemiology · Risk factor · Diagnosis · New technologies · Predictive tools · Prognosis

Introduction

Knowledge of upper-tract urothelial carcinoma (UTUC) epidemiology and risk factors is essential to improve early diagnosis and to promote prevention strategies. The ongoing development of new technologies holds the promise of improving UTUC diagnosis and management. The application of preoperative predictive tools is of fundamental importance to guide the optimal treatment choice. The necessity of our report is born out of the realization that urothelial cancer of the upper and lower (bladder cancer) tracts is similar yet different because of differences in biological, practical and anatomical features [1].

Evidence acquisition

A non-systematic MEDLINE/PubMed© literature search was performed with different combinations of terms as "UTUC," "upper tract tumor," "upper urinary tract," upper tract urothelial carcinoma," "upper tract transitional cell carcinoma," "epidemiology," "risk factor," "diagnosis," "endoscopy," "imaging," "predictive tools" and "prognosis." Time period included articles between January 2000 and February 2016. Original articles, reviews and editorials were selected based on their clinical relevance. Cited references from selected articles were analyzed to find and include significant papers previously excluded from our search, including several articles published before 2000.

Evidence synthesis

Epidemiology

UTUC refers to any malignancies that arise from the urothelial lining of the urinary tract, from the calyceal system to the distal ureter. It is a relatively uncommon entity, accounting for 5–7 % of all renal tumors and 5–10 % of all urothelial tumors, with an estimated annual incidence of 1–2 cases per 100,000 [2]. This rate seems to be rising in the last decades as the result of an improved diagnosis, a combination of improved imaging/endoscopic techniques, and an improved bladder cancer survival. Similarly, the mean age at diagnosis increased over the last three decades from 68 to 73 years [3].

UTUC is more common in men than in women with a male-to-female ratio of 2:1 [4]. This ratio is more balanced compared to the 4:1 differential in urothelial carcinoma of the bladder (UCB). Moreover, while females are more likely to harbor advanced tumor stages and worse prognosis in UCB, this is not the case in UTUC [5].

Due to the low prevalence of the disease, specific epidemiologic data about the role of racial differences in UTUC development are missing. Patients with Asian ethnicity seem to present with more advanced and higher-grade diseases compared to other ethnicities [6]. However, stage for stage, there seems to be no difference between ethnicities. This could be explained with differences in genetic and epigenetic factors such as environmental and occupational exposures, lifestyle choices as well as socioeconomic factors.

At diagnosis, renal pelvis location is twice more common than the ureter [7]. Data from radical nephroureterectomy (RNU) series reveal an increase in aggressive disease in the last years, resulting in a high proportion of locally advanced (60 %) and high-grade (70 %) tumors, which may be due to increased use of nephron-sparing approaches for low-grade tumors [8]. Nowadays, the rate of known metastatic disease at presentation is around 7 %. Multifocal tumors are found to be present in around 10–20 % of new UTUC diagnosis, and a concomitant UCB is found in approximately 20 % of cases [9]. The presence of concomitant carcinoma in situ (CIS) of the upper tract varies between 11 and 36 %, depending on the series [10].

Risk factors

In Western countries, the most common risk factors are tobacco and aromatic amines exposure. Smoking increases the relative risk of developing UTUC from 2.5 to 7 times [11], depending on the number of years of exposure, the number of cigarettes smoked everyday and the variability in individual susceptibility based on intrinsic ability to repair oxidative damage. The risk of developing UTUC appears to be twice more common for patients who smoke more than 40 cigarettes per day compared to those who smoke less than 20 cigarettes per day. A reduction of 60–70 % of relative risk has been shown in former smokers after having been 10 years smoke-free [12]. Smoking seems to be a significant risk factor for an earlier diagnosis of UTUC, with an anticipation of approximately 5 years for current smokers compared to non-smokers. Moreover, smoking has been associated with an increased risk of disease recurrence and cancer-specific mortality in patients treated with RNU for UTUC [13]. There was a dose relationship with heavy

long-term smokers doing worse, and furthermore, those smokers who had over 10 years of smoking cessation had no higher risk than non-smokers. Finally, it has to be noted that the impact of smoking on UTUC outcomes seems to be gender specific. Actually, female who are current and heavy long-term smokers have worse survival outcomes than their male counterparts [14].

The second main risk factor for UTUC in Western countries is occupational exposure to diesel fumes and aromatic amines. Benzidine and β-naphthylamine are two aromatic amines used in the past in various industries for dyes, textiles, rubbers and chemicals [11]. The relative risk of developing UTUC after the exposure to aromatic amines is 8.3, with an average duration of exposure of 7 years and a latency period of approximately 20 years [15]. Occupational exposure to these carcinogens has dramatically diminished in recent years, thanks to the widespread adoption of adequate safety measures.

Nowadays, UTUCs related to the consumption of phenacetin have almost completely disappeared, after the ban of this drug occurred 40 years ago. This drug, used for years in analgesic preparations, induced carcinogenesis by causing papillary necrosis and end-stage renal failure [16]. This inflammatory process represented a risk factor for UTUC development. Other analgesics such as paracetamol have not been related to UTUC.

One of the major discoveries of the last decade has been the proof of the causal relationship between aristolochic acid and UTUC development. Aristolochic acid is a plant extract derived from *Aristolochia fangchi* and *Aristolochia clematis*, which are endemic in the Balkans [11]. These plants were usually ingested as ingredients of Chinese and other traditional herbal remedies or with the consumption of bread contaminated by Aristolochia seeds. Aristolochic acid is the causal agent of Balkan endemic nephropathy and Chinese herbs nephropathy, now considered the same entity. This end-stage renal disease is in part the consequence of a specific mutation of p53 gene, caused by a derivative of aristolochic acid. Patients with Balkan endemic/Chinese herbs nephropathy are at significantly increased risk of developing UTUC. Indeed, this explains the dramatically higher incidence of UTUC in geographic hotspots such as Taiwan, where UTUC represents 20–25 % of all urothelial tumors [17].

Familial/hereditary UTUC accounts for 10–20 % of all UTUCs and is closely linked to hereditary non-polyposis colorectal carcinoma (HNPCC) [18]. In fact, UTUC represents the third most frequent extra-colonic cancer in HNPCC syndrome [19]: Patients at risk have an approximately 22-fold increased relative risk of developing UTUC, compared to the general population. That is why some guidelines and experts recommend that all patients with UTUC should be screened for HNPCC spectrum disease through a short interview and should undergo DNA sequencing if they fulfill all the criteria for HNPCC. These include age at diagnosis <60 years or a personal history of HNPCC spectrum cancer or one first-degree relative <50 years with HNPCC spectrum cancer or two first-degree relatives with HNPCC spectrum cancer [20]. If DNA sequencing confirms the diagnosis of HNPCC syndrome, patients should undergo a clinical evaluation for other HNPCC-related cancers [19], a close follow-up and a familial genetic counseling.

Other risk factors for UTUC development are the blackfoot disease, a vasculitis thought to be caused by chronic exposure to arsenic pollution of water and the exposure to specific iatrogenic factors such as cyclophosphamide and ifosfamide [11].

Finally, differences in genetic susceptibility to specific carcinogens could play a role in UTUC development. Rouprêt et al. [21] found that a specific polymorphism located at the T allele of chromosome 8q24, as previously shown in UCB, constitutes a risk factor for UTUC and is associated with features of biological and clinical tumor aggressiveness. Sasaki et al. [22] suggested that some DNA repair gene polymorphisms may serve as prognostic factors.

Symptoms and clinical presentation

Symptoms other than hematuria are associated with more advanced disease states. Localized UTUCs are mainly silent, diminishing the chance of early diagnosis. Raman et al. [23], reviewing data of 650 patients with localized UTUC, found that 33 % of patients had incidental diagnosis, 61 % presented with local symptoms and 6 % presented with systemic symptoms. Principal symptoms of UTUC are macrohematuria or microhematuria, followed by flank pain [24]. The latter is usually caused by the presence of hydronephrosis (HN). Systemic symptoms such as anorexia, weight loss, fever, night sweats and fatigue are uncommon and usually associated with advanced/metastatic disease [24].

Diagnosis

UTUC diagnosis is based on a combination of laboratory, imaging and endoscopic modalities. Diagnostic tools are often also the key factors to establish risk stratification and therapeutic management.

Urine cytology and FISH

Positive urine cytology can be suggestive of UTUC when cystoscopy is negative and CIS of bladder and prostatic urethra has been ruled out [20]. Voided urine cytology performances are worse for UTUC than for UCB. Actually,

sensitivity of selective cytology in UTUC varies from 43 and 78 %, depending on the case mix in the population [25, 26]. Positive urine cytology is suggestive of high-grade/invasive UTUC. Messer et al., reviewing urinary cytology results from 326 patients with UTUC, found an overall sensitivity and positive predictive value for high grade (56 and 54 %, respectively) and muscle-invasive disease (62 and 44 %, respectively) [27]. A significant improvement in cytology performance was observed when restricting the analysis to patients with selective positive urinary cytology. Because of its low sensitivity, it is strongly recommended to collect urine samples in situ before injection of contrast medium for retrograde pyelography.

Since fluorescence in situ hybridization (FISH) has been shown to increase the sensitivity of cytology in the detection of early UCB, it has been proposed also in the diagnosis of UTUC. FISH was able to increase the sensitivity of urine cytology (52 vs 38 % for cytology and FISH combined and cytology alone, respectively) but, at the same time, it diminished the specificity (from 89 % for cytology alone to 77 % for combined) [28]. Fernandez et al. [29] tested the role of FISH in patients with UTUC who previously underwent radical cystectomy for UCB. Without UCB confounding, sensitivity, specificity and positive predictive value of FISH and cytology were 86, 87, 23 and 80, 86, 11 %, respectively. Unless prospective trials show otherwise, FISH can be omitted in the routine clinical practice as it does not improve diagnostic accuracy.

Imaging

The highest imaging accuracy for the diagnosis of UTUC is provided by multidetector computed tomography (MDCT) urography [20]. Therefore, it currently represents the standard imaging technique for UTUC replacing intravenous pyelography (IVP). A recent meta-analysis regarding performance of MDCT in patients presenting with hematuria showed a pooled sensitivity of 96 % and a pooled specificity of 99 % for UTUC diagnosis [30]. It has to be stressed that for UTUC diagnosis, it is mandatory to perform and evaluate the excretory phase. Actually, nephrographic and excretory phases have to be considered complementary. MDCT has also shown to be able to correctly predict final pathologic stage in a high percentage of cases. MDCT correctly staged organ-confined disease in 97 % of cases and T3–T4 disease in 67 % [31]. Overall, MDCT was accurate in predicting pathologic stage in 88 % of patients. Moreover, MDCT offers good sensitivity (87.5 %) and specificity (98 %) in the detection of lymph-node involvement [32].

Contraindications for MDCT are mainly related to iodinate contrast material. In these patients, magnetic resonance (MR) urography represents a valid alternative. Takahashi et al. [33] found that MR urography with nephrographic and excretory phases was able to detect 74 % of UTUCs smaller than 2 cm. However, the accuracy of MR urography seems slightly inferior to that of MDCT, and therefore, MR is generally performed only when MDCT is contraindicated. Moreover, it has to be reminded that gadolinium contrast material used in MR is associated with the development of nephrogenic systemic fibrosis in patients with severe renal failure (estimated glomerular filtration rate below 30 ml/min).

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is not frequently used or recommended for UTUC. Recently, the ability of FDG-PET/CT in detecting metastasis in UTUC patients has been tested [34]. In this setting, its diagnostic accuracy was significantly superior to that of MDCT with a sensitivity rate of 85 % compared to 50 %. Despite these first encouraging results, further studies are needed to assess the role of FDG-PET/CT in UTUC management.

Endoscopy

The introduction of flexible ureteroscopy (URS) has dramatically changed the preoperative evaluation of UTUC, allowing exploration of the entire upper urinary tract and the ability to biopsy the tumor. Moreover, it is an essential tool for obtaining the necessary information to guide clinical risk stratification as well as deliver therapy. When URS is performed routinely, it reduced UTUC misdiagnosis from 15.5 to 2.1 %, compared to MDCT [35]. By allowing direct visualization of the lesion and tumor biopsies, it increases the opportunity to retain the kidney if the tumor has appropriate stage, grade and size. URS also allows assessment of the tumor architecture, location and focality. This information is useful to determine the individual risk profile and, therefore, to safely select patients for kidney-sparing approaches [20].

Ureteroscopically obtained biopsy correctly determines tumor grade in the majority of cases. Clements et al. [36] assessed UTUC grade in 238 patients who underwent ureteroscopic biopsies and final surgical resection of the tumor. High ureteroscopic biopsy grade, but not stage, was associated with adverse tumor pathology at the RNU specimen (high grade and muscle-invasive disease, both $p < 0.001$). Meanwhile, in a study of 54 patients, Rojas et al. [37] showed a high concordance of tumor grade (93 %) between ureteroscopic biopsies and final RNU pathology, while stage concordance was significantly lower (43 %). Interestingly, biopsy volume did not affect the assessment of grade and stage. Upgrading and upstaging are observed in up to 28 and 32 % of cases, respectively, when re-biopsies are performed 6 weeks after initial ureteroscopy [38].

Moreover, when conservative treatment was planned, re-biopsies after 6–8 weeks detected a cancer rate of 51.2 %, thereby lowering disease recurrence and progression rates significantly [39].

Diagnostic URS seems to increase the risk of developing intravesical recurrence but not distant recurrence, metastasis or death. Sung et al. [40] evaluated 630 patients with UTUC treated with RNU. Of these, 282 patients underwent URS before RNU. Five-year intravesical recurrence rate was significantly higher in patients who had previous diagnostic URS (63.6 vs 42.6 %, $p < 0.001$). Lee et al. [41] found that the intravesical recurrence rate was significantly greater when the median interval between URS and RNU was 5 days compared to patients in which the URS was performed immediately before RNU or not performed at all.

Conversely, diagnostic URS does not affect survival outcomes. Nison et al. [42] found no difference in distant recurrence-free, cancer-specific and overall survival rates when comparing patients who underwent diagnostic URS before RNU to those who did not, regardless of the time to radical surgery.

In conclusion, diagnostic URS is useful and has to be performed to ensure diagnostic certainty. In addition, it allows improved selection of patients for the right treatment and is the optimal method for treating the tumor with a kidney-sparing approach as may be indication for low-grade tumors, and patients with renal insufficiency, or a solitary kidney. Moreover, if kidney-sparing treatment is selected, an intense endoscopic surveillance strategy has to be planned.

New technologies

In order to improve staging and risk stratification by imaging and to compensate for the paucity of current pathologic information obtained by biopsies, new modalities of sample acquisition and diagnostic evaluation have been developed.

Kleinmann et al. [43] showed that flat wire basket was superior to cup biopsy forceps in obtaining a successful diagnostic tissue (94 vs 63 %, $p < 0.001$). Moreover, among positive biopsies, specific grade was determined in 93 and 80 % of cases with baskets and forceps, respectively. The use of access sheath during ureteroscopic biopsies facilitated the acquisition of multiple specimens adequate for histopathologic evaluation. Biopsies obtained through an access sheath were highly predictive of tumor grade in RNU specimens.

Narrow-band imaging (NBI) has shown to be a feasible procedure in the diagnosis of UTUC. It improves the endoscopic visualization of the tumor, providing a detailed description of lesion characteristics and improved UTUC detection rate by 22.7 % compared to white-light URS [44]. Although these results are encouraging, further evaluation of the technique is required.

Experience with photodynamic diagnosis (PDD) in the upper tract is limited. Kata et al. [45] showed that PDD enhanced the visualization of flat lesion such as CIS compared to white-light URS. The sensitivity and the detection rate were significantly improved with PDD. However, due to the tangential vision provided by the acute angle of ureterorenoscopes, there is an increased risk of false positives, both for PDD and for NBI.

Optical coherence tomography (OCT) is a high-resolution imaging technology analogous to ultrasound, but it uses backscattered light instead of reflected sound waves. This technique is applicable through the working channel of flexible, semirigid and rigid ureterorenoscopes. In a recent pilot study, OCT has been performed in 8 patients with UTUC [46]. In 7 patients OCT staging was in accordance with final histology, while in one patient tumor thickness transcended OCT imaging depth range, and therefore, invasiveness findings were inconclusive.

Another promising technique developed in order to improve UTUC staging is represented by high-frequency endoluminal ultrasound (ELUS). It consisted of a mechanically rotating transducer that allows placement over a guide wire and provides radial images with depth range between 1 and 6 cm. A pilot study in 15 patients showed a positive predictive value of 66.7 % and a negative predictive value of 100 % for prediction of final tumor staging [47].

Confocal laser endomicroscopy (CLE) enables real-time in vivo microscopy of mucosal surfaces during standard endoscopy with the aim of obtaining "in vivo optical biopsies." The probe is 0.85 mm in diameter and can be inserted through the working channel of standard ureterorenoscopes. A pilot study in 14 patients demonstrated the feasibility of this method and reported tumor features similar to those obtained for lower tract neoplasms, including papillary structure, fibrovascular stalks and pleomorphisms [48].

For all the presented techniques, more research has to be conducted before their adoption in UTUC management. All techniques might be useful in specific clinical settings and could be integrated to improve diagnostic accuracy of conventional URS.

Preoperative prognostic factors

Preoperative predictive models have been developed to improve outcomes prediction and to guide clinical decision making. As staging remains too inaccurate in UTUC, preoperative prognostic factors are used to risk-stratify patients into low risk and high risk with the goal of guiding therapeutic and management choices.

Patient characteristics

Advanced age at diagnosis is associated with decreased overall and cancer-specific survivals after RNU [49]. This might be due to increased biological aggressiveness of tumor cells and to a decrease in the host's defense mechanisms. However, patients should not be withheld a potentially curative surgical treatment only because of their chronological age.

Differently from UCB, gender is no longer considered a prognostic factor in UTUC [5], while the role of racial differences remains controversial [6].

Smoking is associated with increased risk of disease recurrence and mortality after RNU. Rink et al. [13] found that current smoking status, smoking ≥20 cigarettes per day and cumulative smoking exposure ≥20 years were associated with advanced disease ($p \leq 0.004$), disease recurrence ($p \leq 0.01$) and cancer-specific mortality ($p \leq 0.05$). Moreover, in this study, patients who quit smoking ≥10 years had the same risk as never smokers. Smoking is also significantly associated with intravesical recurrence after RNU [50]. As before, current and heavy long-term smokers have the highest risk of developing intravesical recurrence and smoking cessation for >10 years before RNU seems to reduce these probabilities. Interestingly, the impact of smoking on UTUC outcomes seems to be gender specific. Actually, female smokers had worse outcomes than their male counterparts [14]. All these aspects underline the importance of educational and informational anti-smoking campaigns and the need of developing gender-specific cessation programs. Moreover, the diagnosis is the teachable moment and the urologist the best vessel to set the initiative for smoking cessation.

Tumor characteristics

The presence of preoperative HN is associated with features of aggressive disease and predicts advanced pathologic stage at RNU and poor survival outcomes. In a multicenter cohort of 408 patients with UTUC [51], preoperative HN was an independent predictor of muscle-invasive (HR 7.4, $p < 0.001$), non-organ-confined (HR 5.5, $p < 0.001$) and high pathologic grade (HR 1.6, $p = 0.03$) disease. Moreover, the degree of HN can serve as a surrogate for advanced disease and predicts disease recurrence and cancer-specific mortality [52].

UTUC location is predictive of tumor staging but does not affect patient prognosis. A study of 2824 patients treated with RNU found that renal pelvis tumors were more likely to have higher stage (T3/T4 disease 58 vs 38 %, $p < 0.001$) and had a higher rate of lymph-node metastases (10 vs 6 %, $p = 0.003$) compared to ureteral tumors [53]. These results were successively externally validated in two large, retrospective studies [7, 54].

Tumor multifocality is associated with high tumor stage and grade, lymph-node metastasis, disease progression and cancer-specific mortality in patients with organ-confined UTUC [55].

Tumor architecture is another clinical factor obtained through URS. Sessile growth pattern is associated with features of biological and clinical tumor aggressiveness such as high grade, stage and the presence of lymph-node metastasis [56]. More importantly, it is an independent predictor of disease recurrence and cancer-specific mortality.

The prognostic value of imaging and histological variables such as grading and staging has been previously discussed.

Preoperative prognostic models

Combining imaging and ureteroscopic variables could help improve the accuracy in predicting muscle-invasive and non-organ-confined disease and help in the decision making regarding surgical approach, extent of lymphadenectomy and selection for neoadjuvant systemic therapy. Brien et al. [57] evaluated whether the combination of preoperative HN, ureteroscopic biopsy grade and urinary cytology could improve the prediction of advanced UTUC. Combining all these variables incrementally improved the predictive value of the model, reaching a positive predictive value of 89 % and a negative predictive value of 73 % when all the variables were abnormal. Interestingly, when all the three tests were normal, the negative predictive value for muscle-invasive and non-organ-confined disease was 100 %. Favaretto et al. [58] showed that adding additional imaging features such as local invasion on MDCT improved further the accuracy for predicting muscle-invasive and non-organ-confined disease. A predictive model combining imaging information and ureteroscopic grade reached an accuracy of 71 % for predicting advanced disease. Margulis et al. [59] developed a nomogram based on URS grade, architecture and location to predict non-organ-confined disease at RNU with an accuracy of 77 %. Finally, in order to identify patients that would be appropriately treated with a kidney-sparing approach, Roupret et al. [60] proposed a risk stratification based on smoking habit, previous UCB, focality, size, location, preoperative HN, imaging signs of invasiveness, high-grade cytology and high-grade ureteroscopic biopsy. Those patients at high risk of more advanced disease may serve as ideal candidates for neoadjuvant chemotherapy. There is a current cooperative group trial assessing the utility of neoadjuvant chemotherapy for patients with high-grade UTUC (ECOG).

Conclusions

1. UTUC is a relatively uncommon entity, but it represents 5–10 % of all urothelial tumors and its incidence is increasing.
2. UTUC and UCB are similar in biology and share some risk factors such as smoking and occupational exposure. However, they represent different entities because of anatomical and practical differences.
3. Aristolochic acid exposure and HNPCC spectrum disease represent important risk factors for UTUC development.
4. UTUC diagnosis is mainly based on imaging and endoscopy. MDCT and ureteroscopic biopsies represent standard procedures for UTUC diagnosis and treatment allocation.
5. New technologies focused on improving UTUC detection and sample acquisition are in continuous development.
6. URS grade is accurate, but a re-URS is necessary if a kidney-sparing approach is planned.
7. Preoperative patient and tumor characteristics are useful to stratify patients into low and high risks, thereby guiding treatment choice regarding surgical treatment, extent of lymphadenectomy and selection for neoadjuvant systemic therapy.

Authors' contribution Thalmann GN and Shariat SF were involved in protocol/project development; Soria F, Shariat SF, Lerner SP, Fritsche H, Rink M, Kassouf W, Spiess PE, Lotan Y, Ye D, Fernández MI, Kikuchi E, Chade DC, Babjuk M, Grollman AP and Thalmann GN were involved in data collection or management; Soria F, Shariat SF, Thalmann GN, Data analysis; Soria F, Shariat SF and Thalmann GN wrote the manuscript; Soria F, Shariat SF, Lerner SP, Fritsche H, Rink M, Kassouf W, Spiess PE, Lotan Y, Ye D, Fernández MI, Kikuchi E, Chade DC, Babjuk M, Grollman AP and Thalmann GN wrote and edited the manuscript.

Compliance with ethical standards

Conflict of interest I certify that all conflicts of interest including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript are the following: Shahrokh Shariat owns or co-owns the following patents: Methods to determine prognosis after therapy for prostate cancer. Granted 2002-09-06. Methods to determine prognosis after therapy for bladder cancer. Granted 2003-06-19. Prognostic methods for patients with prostatic disease. Granted 2004-08-05. Soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma. Granted 2010-07-20. He is advisory board member of Astellas, Cepheid, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanofi, Wolff. He is speaker for Astellas, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanochemia, Sanofi, Wolff.

Ethical standards This study was conducted according to the Declaration of Helsinki.

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