













Diagnostic challenges and treatment strategies in the management of upper-tract urothelial carcinoma

Victor M. Schuettfort^{1,2} , Benjamin Pradere^{1,3} , Fahad Quhal^{1,4} , Hadi Mostafaei^{1,5} , Ekaterina Laukhtina^{1,6} , Keiichiro Mori^{1,7} , Reza Sari Motlagh¹ , Michael Rink² , David D'Andrea¹ , Mohammad Abufaraj^{1,8} , Pierre I. Karakiewicz⁹ , Shahrokh F. Shariat^{1,6,10-14} 

Cite this article as: Schuettfort VM, Pradere B, Quhal F, Mostafaei H, Laukhtina E, Mori K, et al. Diagnostic challenges and treatment strategies in the management of upper-tract urothelial carcinoma. Turk J Urol 2020; 47(Supp. 1): S33-S44.

ABSTRACT

Upper-tract urothelial carcinoma (UTUC) is a rare disease, posing many challenges for the treating physician due to the lack of strong evidence-based recommendations. However, novel molecular discoveries and a better understanding of the clinical behavior of the disease lead to a continuous evolution of therapeutic landscape in UTUC. The aim of the review is to provide a comprehensive update of the current diagnostic modalities and treatment strategies in UTUC with a special focus on recent developments and challenges. A comprehensive literature search including relevant articles up to August 2020 was performed using the MEDLINE/PubMed database. Despite several technological improvements, accurate staging and outcome prediction remain major challenges and hamper appropriate risk stratification. Kidney-sparing surgery can be offered in low risk UTUC; however, physician and patient must be aware of the high rate of recurrence and risk of progression due to tumor biology and understaging. The value and efficacy of intracavitary therapy in patients with UTUC remains unclear due to the lack of high-quality data. In high-risk diseases, radical nephroureterectomy with bladder cuff excision and template lymph node dissection is the standard of care. Perioperative systemic chemotherapy is today accepted as a novel standard for advanced cancers. In metastatic or unresectable disease, the therapeutic landscape is rapidly changing due to several novel agents, such as checkpoint inhibitors. While several diagnostic and treatment challenges remain, progress in endoscopic technology and molecular knowledge have ushered a new age in personalized management of UTUC. Novel accurate molecular and imaging biomarkers are, however, still needed to guide decision making as tissue acquisition remains suboptimal. Next generation sequencing and novel agents are promising to rapidly improve patient outcomes.

Keywords: Diagnostics; review; treatment; upper tract urothelial carcinoma; UTUC.

Introduction

Upper-tract urothelial carcinoma (UTUC) is a rare disease that accounts for only 5-10% of all cases of urothelial carcinoma (UC).^[1,2] Improved understanding of the genetic/epigenetic background has helped to distinguish UTUC from bladder cancer (BCa) on a molecular level, especially with respect to high prevalence of fibroblast growth factor receptor (FGFR)3 and HRAS alterations as well as APOBEC-induced mutagenesis.^[3-6] UTUC and BCa are indeed two different disease entities with differences in diagnostic and therapeutic challenges and opportunities.^[7] Nevertheless, due to limited data, many UTUC treatment strategies are still extrapolated from BCa.

With progress in molecular medicine such as next generation sequencing (NGS) and with the increasing diagnostic and treatment tools in our armamentarium, we are steadily moving towards the possibility of tailored treatments for UTUC based precision medicine concepts.^[8] The aim of this review is to provide a comprehensive update of the current diagnostic modalities and treatment strategies in UTUC with a special focus on recent developments and challenges.

Material and methods

A comprehensive literature search including relevant articles up to August 2020 was performed using the MEDLINE/PubMed data-

¹Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

²Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

³Department of Urology, University Hospital of Tours, Tours, France

⁴Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia

⁵Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

⁶Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia

⁷Department of Urology, The Jikei University School of Medicine, Tokyo, Japan

⁸Division of Urology, Department of Special Surgery, Jordan University Hospital, The University of Jordan, Amman, Jordan

⁹Cancer Prognostics and Health Outcomes Unit, Division of Urology, University of Montreal Health Center, Montreal, Canada

¹⁰Department of Urology, Weill Cornell Medical College, New York, New York, USA

¹¹Department of Urology, University of Texas Southwestern, Dallas, Texas, USA

¹²Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic

¹³Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria

¹⁴European Association of Urology Research Foundation, Arnhem, Netherlands

Submitted:
26.08.2020

Accepted:
03.09.2020

Available Online Date:
09.10.2020

Corresponding Author:
Shahrokh F. Shariat
E-mail:
shahrokh.shariat@meduniwien.ac.at

©Copyright 2021 by Turkish
Association of Urology

Available online at
www.turkishjournalofurology.com

base. Original articles, review articles, and editorials were included. Searches were limited to English language as well as studies in humans and in adults. To identify appropriate publications with respect to diagnostic challenges and treatment strategies in UTUC, the search terms urothelial carcinoma, upper tract urothelial carcinoma, transitional cell carcinoma, nephroureterectomy, ureteroscopy, renal pelvis, ureter, chemotherapy, immunotherapy, intracavitary therapy, FGFR3, imaging, and urine cytology were combined using a Boolean operator. Additionally, references of all included articles were reviewed to expand search results. Furthermore, the U.S. National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov) was searched for ongoing clinical trials associated with UTUC. The article selection process was performed by two reviewers. Disagreements were resolved by a third reviewer.

Evidence synthesis

Imaging

Multidetector computed tomography urography (MDCTU) has the highest diagnostic accuracy for UTUC (pooled sensitivity of 92% and pooled specificity of 95%)^[9] and is, therefore, recommended as first choice imaging technique. MRI urography (MRU) can be used if CT urography is contraindicated.^[10] However, the inaccuracy of MDCTU and MRU to identify patients with lymph node metastases remains a challenge. Recently, 18 F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) was reported to have a 82% sensitivity and 84% specificity for the detection of lymph node metastases in patients with UTUC, offering a potential novel diagnostic strategy for patient selection toward perioperative systemic treatment.^[11]

Biopsy sampling and endoscopic imaging

Ureteroscopy can give detailed information on tumor localization^[12,13], architecture^[14], focality^[15], and tumor size and is an essential step to establish the diagnosis of UTUC. However, tumor staging represents a diagnostic challenge, as pathological assessment of the depth of tumor infiltration remains inadequate due to the suboptimal tissue acquisition.^[16] In contrast, ureteroscopic biopsies are mostly useful

to determine tumor grade.^[17-19] They have been found to accurately predict final histologic grade even in low-volume specimens (grade concordance: 92.6% [95%CI: 82.4-98.0%]).^[17] Percutaneous biopsies, however, are deemed to bear a potential risk of tumor seeding. Nevertheless, a recent study reported that for pelvicalyceal tumors, percutaneous core-needle biopsy offered a 90% concordance with final pathology without any case of tumor seeding.^[20] Currently, more studies are needed to answer this question with accuracy.

Another challenging step in the diagnosis of UTUC is the visualization and interpretation of tumors during ureteroscopy. In the last decade, technical improvements, such as narrow-band imaging (NBI), photodynamic diagnosis (PDD), multimodal optical analysis or confocal laser endomicroscopy, have shown to improve visualization, especially with respect to carcinoma *in situ* (CIS).^[18,21-23] NBI increased tumor detection rates by 22.7% in comparison with white light ureteroscopy.^[24] Kata et al.^[25] reported an increase of sensitivity from 54% to 96% and specificity from 95% to 97% between white light and PDD ureteroscopy; however, this technology has currently not been explored for digital ureteroscopy, making the white light ureteroscopy control arm, in this study, suboptimal. Multimodal optical analysis and confocal endomicroscopy are also promising tools, especially with respect to staging, but are still under evaluation.

Cytology

Urine cytology has been found to perform poorly in prediction of muscle-invasive or high-grade disease in UTUC (sensitivity 56% for high-grade tumors, sensitivity of 62% muscle-invasive UTUC).^[19,26,27] However, adequately collected selective barbotage-cytology may improve its accuracy (up to 91% detection rate).^[28] The sensitivity of molecular markers, such as fluorescence in situ hybridization (FISH), NMPP-22, or ImmunoCyt, of voided urine ranges from 44% to 75%.^[29-32] Considering the selection bias of published studies and the high costs compared with urine cytology^[33], these tests are not recommended in clinical routine. The value of novel molecular test developed for urinary bladder cancer for the

Main Points:

- The optimal risk stratification in UTUC is obtained through the combination of biopsy tissue grade, imaging, and urine cytology.
- Standard treatment for non-metastatic high risk UTUC is radical nephroureterectomy with bladder cuff excision and template lymph node dissection.
- Kidney-sparing surgery can be performed in patients with a low-risk disease without compromising oncologic outcomes; however, physician and patient must be aware of the risk of understaging and strict adherence to follow-up schedule is required.
- In the future, identification of molecular drivers and novel agents, such as enfortumab, vedotin, and FGFR inhibitors, can enable targeted therapies while the development of novel molecular biomarkers can improve risk assessment and guide clinical decision making.

diagnosis and surveillance of UTUC needs to be tested in future trials.^[34]

Next generation sequencing

In the last couple of years, next-generation sequencing (NGS) has led to a better understanding of UTUC biology and promises to significantly change our clinical routine. For example, NGS can help identify UTUC patients who are at differentially higher risk of BCa recurrence, as these patients were found to frequently carry distinct molecular alterations (e.g., FGFR3, KDM6A, and CCND1).^[35,36] NGS could also be used to identify patients with TP53 mutations who are more likely to benefit from perioperative chemotherapy and/or immunotherapy.^[6,37] For the Lynch syndrome screening, NGS identified a higher frequency of alterations in top mutated genes (i.e., KMT2D, CREBBP, ARID1A, and SMARCA4) as well as some mutations that are nearly exclusively present in this population (i.e., CIC, FOXP1, NOTCH1, NOTCH3, and RB1).^[38-40] NGS can also determine the rate of microsatellite instability, which has been suggested to be a marker for responsiveness to immune checkpoint inhibitors.^[6]

In the future, identification of molecular drivers could enable the discovery of accurate novel biomarkers, improving risk stratification and guiding clinical decision making. However, further research and data are required to implement targeted NGS in clinical decision making, thereby improving current under- and overtreatment based on adequate reflection of each individual tumor's biologic and clinical behavior.

Risk stratification in UTUC

Appropriate risk stratification is of utmost importance to allow an adequate patient selection with respect to different therapeutic options. However, patients are currently solely risk stratified based on clinico-pathological features into low vs high-risk groups. EAU guidelines define low grade disease as tumor size <2 cm, low grade cytology + biopsy, unifocal disease, and non-invasive aspect on CT urography.^[10,14,15,19] Nevertheless, several other clinico-pathologic features as well as serum and tissue biomarkers have been associated with oncologic outcomes in UTUC (Table 1).^[14,15,41-55] Based on some of these variables, several different prognostic models have been created (Table 2).^[19,44,56-61] Most of these models focus on prediction of cancer-specific survival (CSS), recurrence-free survival (RFS), or non-organ confined disease; they demonstrated a relatively good predictive accuracy.^[57] Notably, the Yates nomogram underwent an external validation during which a similar accuracy was reproduced (71.8% for prediction of CSS).^[62] These models can guide identification of patients that would benefit from intensified postoperative surveillance or adjuvant systemic therapy. However, there are no validated predictive models for risk stratification that offer a

satisfactory degree accuracy with respect to the use of an intensified neoadjuvant treatment.^[63-65] Prospective studies and novel biomarkers are needed to reliably identify the patients who are likely to benefit from kidney sparing surgery (KSS), perioperative systemic therapy, and/or extended lymph node dissection.

Kidney Sparing Surgery

Traditionally, KSS was performed only in patients with an imperative indication. However, it has been shown that KSS can be performed in patients with low-risk disease without significantly compromising their oncologic outcomes.^[66-68] Endoscopic tumor ablation is the preferred method for low risk tumors. The evidence regarding safety and tumor seeding using a percutaneous approach is still low. Therefore, this approach should only be used in highly selected cases (i.e., larger low-risk tumor in the pelvic system).^[69] During clinical decision making regarding KSS, physician and patient must be aware of the risk of understaging, which could result in a higher risk of recurrence and progression, as well as the lack of strong evidence especially with respect to long term follow-up. Therefore, strict adherence to follow-up schedule is of paramount importance.^[70,71] Further studies that focus on improved patient selection and the combination with other treatment strategies, such as endocavitary therapy, are needed in order to improve the efficacy and safety of KSS.

Segmental ureterectomy

Segmental excision of the ureter has shown similar oncologic outcomes compared with RNU in low-grade disease and in selected patients with high-grade disease.^[66,68,72,73] In comparison with an endoscopic approach, it offers the advantage of providing a definitive pathological stage with a concurrent lymphadenectomy while still being less invasive and preserving kidney function. Simonato et al.^[74] reported 5-year RFS, OS and CSS rates of 82.2, 85.3 and 94.1%, respectively, for patients with pTa-T3 distal UTUC. Similar to radical nephroureterectomy (RNU), the entire bladder-cuff has to be removed in this setting. Ureteroureterostomy has been suggested for patients with non-invasive low-grade tumors of the proximal and/or middle ureter which cannot be treated via an endoscopic approach as well as for patients with high-grade disease for who a kidney preserving approach is imperative.^[75] A recent meta-analysis comprising 18 studies found no statistically significant difference was found between the segmental ureterectomy and radical nephroureterectomy (RNU) with respect to recurrence, bladder metastasis or CSS.^[76] However, the quality of the currently available evidence is poor as most studies are retrospective with small sample sizes and heterogeneous cohorts of patients. In summary, segmental ureterectomy may be performed in select patients, however, appropriate risk stratification and strict follow up are paramount.^[77]

Table 1. Prognostic features of clinical variables, serum biomarkers, and tissues biomarkers in upper-tract urothelial carcinoma

Clinical variables	Hazard ratio (95% CI) on univariable analyses)	Serum biomarkers	Hazard ratio (95% CI) on univariable analyses)	Tissue biomarkers	Hazard ratio (95% CI) on univariable analyses)
Lymphovascular invasion ^[43]	RFS: 3.8 (2.8–5.1) CSS: 4.6 (3.3–6.3)	Preoperative anemia [47]	RFS 1.89 (1.26-2.86, multivariable analyses) CSS: 2.04 (1.21-3.45, multivariable analyses)	Caveolin-1 [50]	RFS: 1.7 (1.2-2.6) CSM: 1.8 (1.2-2.7)
Tumor multifocality ^[15]	RFS: 1.43 (1.06-1.92, multivariable analyses, organ-confined patients) CSS: 1.46 (1.04-2.04, multivariable analyses, organ-confined patients)	Preoperative Thrombocytosis [48]	RFS: 1.32 (1.05-1.65) OS: 1.4 (1.16-1.69)	HER2 over-expression [51]	RFS: 1.66 (1.24-2.24) CSM: 1.81 (1.33-2.48) OS: 1.55 (1.21-1.99)
Tumor necrosis ^[41, 42]	RFS: 1.27 (1.02–1.6) CSS: 1.29 (1.004–1.65)	Neutrophil-to-lymphocytes ratio [49]	RFS: 1.60 (1.16–2.19 pooled HR) CSS: 1.73 (1.23–2.44, pooled HR) OS: 1.64 (1.23–2.17, pooled HR)	N-cadherin [52]	RFS: 1.44 (1.07–1.95)
Variant histology ^[44]	Micropapillary variant - RFS: 2.27 (1.25-4.79) Sarcomatoid variant - CSS: 16.8 (6.86-41.17)			Androgen receptor expression [53]	Cumulative RFS, CSS and OS did not differ by AR status, however, AR was detected nearly twice as often in tumors of the ureter than of the pelvicalyceal system (p = 0.005)
Smoking ^[45]	RFS: 1.66 (1.18–2.34) multivariable analyses, current smokers CSS: 1.54 (1.00–2.07) analyses, current smokers			Urokinase-type plasminogen activator [54]	RFS: 2.04 (1.21-3.43) CSS: 2.55 (1.44-4.52) OS: 1.59 (1.08-2.24) (in patients with organ-confined disease)
Extra nodal extension ^[46]	RFS: 2.0 (1.44–2.78) CSS: 1.97 (1.38–2.8)			Modified Glasgow prognostic score (combination of decreased plasma albumin and elevated CRP) [55]	RFS: mGPS1: HR 1.6 (1.34-1.91) mGPS2: HR 3.23 (2.04-5.12) CSS: mGPS1: 1.65 (1.37-1.99) mGPS2: 3.74 (2.33-6.01) OS mGPS1: 1.33 (1.14-1.55) mGPS2: 2.68 (1.71-4.18)
Tumor architecture ^[14]	RFS: 3.65(95CI: NA) CSS: 3.92 (95CI: NA)				

RFS: Recurrence-free survival; CSS: cancer-specific survival, 95%CI: 95% Confidence interval

Table 2. Predictive models for risk stratification in upper-tract urothelial carcinoma

Author	Purpose	Variables included	Accuracy
Zamboni et al. ^[44]	Prediction of non-organ confined disease	Tumor grade, tumor architecture + tumor location	NOC-UTUC: 76.6%
Favaretto et al. ^[19]	Prediction of muscle-invasive and non-organ confined disease	Local invasion on imaging + ureteroscopy high grade	≥pT2 disease: 71% NOC-UTUC: 70%
Petros et al. ^[56]	Prediction of high-risk non-organ-confined upper-tract urothelial carcinoma	Tumor grade, tumor architecture, clinical stage +hemoglobin	NOC-UTUC: 82%
Rouprêt et al. ^[57]	Prediction of CSS after radical nephroureterectomy	Age, tumor stage, lymph node involvement, tumor architecture + lymphovascular invasion	CSS: 80%
Cha et al. ^[58]	Prediction of RFS and CSS after radical nephroureterectomy	Prediction of RFS: Tumor stage, lymph node involvement, tumor architecture, lymphovascular invasion + concomitant CIS Prediction of CSS: Tumor stage, lymph node involvement, tumor architecture + lymphovascular invasion	RFS: 76.8% CSS: 81.5%
Yates et al. ^[59]	Prediction of CSS after radical nephroureterectomy	Tumor stage, lymph node involvement tumor grade, age + tumor location	CSS: 78%
Seisen et al. ^[60]	Prediction of CSS after radical nephroureterectomy in patients with localized and/or locally advanced disease	Age, tumor stage, tumor grade, tumor location, tumor architecture + lymphovascular invasion	CSS: 81%
Krabbe et al. ^[61]	RFS in patients with High grade disease	Age, tumor stage, lymph node involvement + tumor architecture	RFS: 77% (external validation cohort)

RFS: Recurrence-free survival; CSS: cancer-specific survival; NOC-UTUC: non-organ confined upper tract urothelial carcinoma

Endocavitary therapy

Current evidence on the benefit of adjuvant endocavitary therapy following KSS is mainly based on small retrospective series. A recently published meta-analysis of 27 articles included 438 patients. Foerster et al.^[78] found that the overall pooled estimates for recurrence in Ta-T1 disease was 40%, which is comparable to that of untreated patients. However, due to heterogeneity between studies and strong selection, the results of this meta-analysis should be interpreted with caution. In the attempt to improve the drug delivery in endocavitary treatment, a mitomycin-containing reverse thermal gel was developed. In the OLYMPUS trial, an open-label, single-arm, phase 3 trial which included patients with low-grade UTUC, this drug showed a complete response rate of 59% (95%CI: 47–71%). While this high rate is really promising, the study also reports a high rate of ureteric stenosis (44%), which is a major concern in the treatment of low-grade tumors. Furthermore, the median follow-up was only eleven months.^[79] Also, the high cost of the treatment has to be taken into consideration (\$21,376/dose i.e. a total amount of \$128,256 for only the 6 firsts instillations without maintenance treatment), as well as the fact that there is no data comparing the mitomycin gel with laser ablation alone. Therefore, it is unlikely that this treatment will find routine application in clinical practice yet. In summary, the value and efficacy of intracavitary therapy in pa-

tients with UTUC remains suboptimal, and more data is needed for it to be recommended by current international guidelines.

Radical nephroureterectomy

The standard treatment for non-metastatic high grade UTUC is radical nephroureterectomy (RNU) with bladder cuff excision and template lymph node dissection (LND).^[8,10,80] Due to the aggressiveness of the disease, definitive therapy should not be delayed^[81] and chronological age should not preclude RNU with curative intent.^[8,82,83] A recent meta-analysis comprising 9,221 patients found no significant differences between open or minimal-invasive RNU with respect to total complication rates (Odds ratio 1.22 [95% CI: 0.91-1.65] $p=0.19$), 5-year RFS (risk ratio 1.01 [95% CI: 0.92-1.10] $p=0.90$), 5-year CSS (risk ratio 1.04 [95% CI: 0.99-1.10] $p=0.12$), and 5-year overall survival (OS, risk ratio 1.08 [95% CI: 0.98-1.18] $p=0.11$).^[84] However, one randomized prospective trial reported significantly favorable CSS and metastasis-free survival in patients with advanced UTUC treated with open RNU compared to laparoscopic RNU (log rank test, $p=0.039$ and $p=0.004$, respectively).^[85] Several approaches for bladder cuff excision have been proposed. A large meta-analysis comprising 2,681 patients found no differences with respect to RFS, CSS, and OS; however, endoscopic dissection of the bladder-cuff seem to increase intravesical recurrence

(34.1%) in comparison with transvesical (21.4%) or extravesical bladder cuff excision (20.3%, $p=0.02$).^[63] In summary, minimal invasive RNU, therefore, appears to be a feasible option in patients with organ-confined disease^[86], but patient selection is of the utmost importance especially for advanced UTUC where open surgery remains recommended. Complete excision of the entire ipsilateral ureter is important, and an endoscopic approach is inferior to a trans- or extravesical removal.^[63]

Lymph node dissection

As the incidence of lymph node metastases in patients with $\geq pT2cN0$ UTUC ranges from 14.3% to 40%, lymph node dissection (LND) should be performed in all patients with high risk disease.^[64,87–89] A systematic review identified multiple studies that report a positive association between survival outcomes and LND for patients with UTUC of the renal pelvis.^[87] A recent meta-analysis comprising 7,516 patients demonstrated improved staging and prediction of survival through LND, however, results concerning a survival benefit were inconclusive due to an unbalanced patient distribution.^[90] The value of LND in patients with UTUC of the ureter remains unclear, as a prospective study showed no significant difference in terms of survival between LND and no LND in 48 patients with ureteral cancer $\geq pT2cN0M0$.^[91] As the appropriate extent of LND remains unclear, further prospective studies evaluating the impact of LND in different settings of UTUC are needed (e.g., NCT 02607709).

Intravesical recurrence

Up to 47% of the patients will eventually develop an intravesical recurrence after RNU.^[36] Two randomized controlled trials showed an absolute risk reduction (11% and 16.9%) and a relative risk reduction of (40% and 42.2%) without serious adverse events for the intravesical administration Mitomycin-C or Pirarubicin.^[92,93] These findings were confirmed by a large meta-analysis comprising 979 patients, which found a 41% relative risk reduction of bladder recurrence following a single dose postoperative intravesical chemotherapy.^[94] Based on this evidence, current guidelines recommend a single postoperative instillation of intravesical chemotherapy.^[10] However, optimal timing of administration remains unclear.^[95] The ongoing GEMINI Trial, which investigates the use of a single intraoperative intravesical instillation of gemcitabine at time of RNU (NCT 04398368) will hopefully add some information on this topic.

Perioperative chemotherapy

Retrospective series have shown conflicting results regarding oncologic outcomes in patients treated with adjuvant chemotherapy for locally advanced or lymph node positive UTUC.^[96–99] Recently, a randomized trial comparing adjuvant chemotherapy (AC) vs observation in patients with locally advanced disease (POUT trial), reported that the addition of platinum-based adjuvant chemotherapy after RNU significantly improved RFS (haz-

ard ratio 0.45 [95%CI 0.30–0.68] $p<0.001$).^[100] However, one must be aware of the limitation of the study, such as the short follow-up, the skewness in patient distribution despite randomization and the compound endpoint. Data on overall survival are still awaited.

A recently published meta-analysis comprising 15,378 patients found an improved survival in patients with locally advanced UTUC following both neoadjuvant chemotherapy (NAC) or AC.^[65] NAC was associated with high rates of pathological downstaging and complete response.^[65] As there is no comparative data on NAC vs AC available, the dilemma of choosing the superior treatment modality remains unresolved. NAC offers an early treatment of micrometastases, pathological downstaging, and potentially higher pre-nephrectomy GFR for administration of cisplatin-based chemotherapy, while AC offers a lower risk of overtreatment and a therefore lower unnecessary toxicity.^[101] There are several ongoing prospective studies that investigate the use of NAC vs. surgery alone (e.g., NCT 02412670, NCT 01663285 or NCT 02876861). Likewise, the URANUS trial is currently investigating the feasibility of NAC vs. AC (NCT 02969083). As of now, there is no data on the use of immunotherapy in a neoadjuvant or adjuvant setting in UTUC, but this therapeutic option is being investigated by the PURE-02 trial (neoadjuvant pembrolizumab preceding RNU for patients with localized high-risk UTUC, NCT02736266).

Systemic Chemotherapy – First-line treatment

Currently, systemic therapy regimens extrapolated from the BCa literature are based MVAC^[102,103] (Methotrexate, Vinblastine, Doxorubicin, Cisplatin) Gemcitabine with Cisplatin^[104] or Paclitaxel, Gemcitabine plus Cisplatin (PGC)^[105] as first line treatment in cisplatin-eligible patients. There are no prospective or comparative trials that have investigated the differential effect of these regimens in UTUC.

Immunotherapy based on pembrolizumab or atezolizumab is also approved as first-line treatment in cisplatin-unfit PD-L1 patients with unresectable or metastatic UTUC which are platinum-ineligible. In the KEYNOTE-052 trial, pembrolizumab achieved an overall objective response rate of 24% (38% for patients with a PD-L1-expression cutoff over 10%) and a six-month OS of 67% (95% CI 62–73). 16% of all patients included had treatment-related adverse events of grade 3 or worse.^[106] Irrespective of the PD-L1 status, atezolizumab showed a 23% objective response (9% complete response rate) and a median OS of 15.9 months (95% CI 10.4–not estimable).^[107] In cisplatin ineligible patients with a negative PD-L1 status, carboplatin + gemcitabine is the current standard of care, however, efficacy is not comparable to cisplatin based combinations.^[108,109]

Systemic Chemotherapy – Second-line treatment

Immunotherapies have become a standard of care for treatment of patients with disease progression following platinum-based combination chemotherapy for metastatic UTUC. However, all relevant studies focused on patients with advanced UC and only included a subset of patients with UTUC. In a phase III trial that compared the effect of pembrolizumab vs. the investigator's choice of paclitaxel, docetaxel, or vinflunine in patients with advanced UC that recurred or progressed after platinum-based chemotherapy, pembrolizumab significantly prolonged OS compared with the various chemotherapeutic agents (10.3 vs 7.4 months, $p=0.002$). Furthermore, the rate of grade ≥ 3 adverse effects was reduced (15% vs 49%).^[110] Contrary, in a randomized phase III trial that included 931 patients, atezolizumab showed no significant difference in OS (11.1 vs 10.6 months, $p=0.41$) in comparison with various chemotherapeutic agents. Atezolizumab was better tolerated than chemotherapy of choice, as it showed less grade ≥ 3 adverse effects (20% vs 43%).^[111] In addition to pembrolizumab and atezolizumab, nivolumab has also been FDA and EMA approved after showing a 19.6% objective response rate and OS of 8.7 months in a phase II single-arm study with 270 patients. These findings were irrespective of the PD-L1 expression status and nivolumab had also a favorable safety profile.^[112] In the Check Mate-032 trial (phase I/II trial testing different combinations of nivolumab alone/plus ipilimumab), the combination of nivolumab and ipilimumab showed an objective response of 38.0% and a median overall survival of 15.3 months (95%CI 10.1-27.6 months). Grade 3 or 4 treatment-related adverse events occurred with this combination in 39.1% of all patients.^[113] This trial suggests a potential benefit of immunotherapy combinations in this disease. Preliminary phase III data presented at the ASCO 2020 (JAVELIN Bladder 100 trial), showed that maintenance avelumab was able to improve OS compared to best supportive care (median OS 21.4 vs 14.3 months, $p<0.001$) in the setting of unresectable and metastatic UC after platinum-based first-line chemotherapy. With this plethora of new agents, further studies are now needed to identify the optimal immunotherapeutic and combination regimen in the UTUC population.

There is limited data on the efficacy of a second chemotherapeutic agent in the second-line treatment. Vinflunine showed in a randomized phase III trial only a modest survival benefit in comparison to best supportive care (median OS 6.9 vs 4.3 months, $p=0.04$).^[114] Vinflunine should therefore only be used as a second-line treatment, if immunotherapy or combination chemotherapy is not feasible. However, it still might be offered as third-line treatment for eligible patient with a desire for treatment.^[10]

Novel agents

FGFR3 has been found to be the most commonly mutated gene in both low grade (92%) and high-grade UTUC (60%).^[5] In

2018, the FDA approved erdafitinib, the first pan-FGFR inhibitor, for patients with locally advanced or metastatic UC that have progressed during or after platinum-based chemotherapy and whose tumors have susceptible mutations. In a phase II trial of 99 patients, erdafitinib showed an objective response rate of 40% and a complete response in 3%.^[115] However, tolerability seems inferior to immune check point inhibitors, as there was a high rate of grade ≥ 3 adverse events (46%) and 13% of the patients discontinued treatment.

In February 2020, the FDA also approved enfortumab vedotin plus pembrolizumab for cisplatin-ineligible patient as a first-line treatment for unresectable locally advanced or metastatic UC. Enfortumab vedotin is an antibody-drug conjugate that targets Nectin-4, a cell adhesion protein highly expressed in UC. In an as yet unpublished phase Ib/II clinical trial (NCT 03288545), the investigators report an impressive objective response rate of 73.3% (95%CI 58.1-85.4%) and a complete response rate of 15.6% (preliminary data presented at ASCO 2020). Currently, there is also an ongoing phase III that will compare the survival benefit of enfortumab vedotin in comparison to chemotherapy (EV-301 trial, status: accrual completed, results pending).

While all of these novel agents and the previously mentioned immunotherapies achieved promising results in the field of advanced or metastatic UC, their specific value in the UTUC patient population needs to be verified. Various further novel agents that might also improve patient outcome are currently being investigated, such as sitravatinib (tyrosine kinase inhibitor, NCT 03606174), eribulin mesylate (mitotic inhibitor, NCT 00365157), regorafenib (multi-kinase inhibitor, NCT 02459119), berzosertib (ATR kinase inhibitor, NCT 02567409) or infigratinib, and PRN1371 (further FGFR inhibitors, NCT 04197986 and NCT 02608125). With this increasing number of agents in our armamentarium, identifying reliable biomarkers that can guide clinical decision making will become a major challenge in the future. However, only this will allow physicians to offer tailored treatment in the era of precision medicine.

Conclusions

Despite several technological improvements, diagnosis and treatment of UTUC remains a challenge for the treating physician. Accurate staging and outcome prediction remain major challenges and hamper appropriate risk stratification. Similarly, the appropriate extent of lymph node dissection and surgical approach as well as the benefit of intracavitary remain unanswered clinical question. Novel biomarkers are needed to guide treatment decision and help physicians give the right treatment to the right patient at the right time. In the future, next generation sequencing and novel agents will improve patient outcomes through precision medicine/tailored medicine.

Peer-review: This manuscript was prepared by the invitation of the Editorial Board and its scientific evaluation was carried out by the Editorial Board.

Author Contributions: Concept – V.M.S., S.F.S.; Design – V.M.S., D.D'A., S.F.S.; Supervision – S.F.S.; Resources – V.M.S., D.D'A., B.P., S.F.S.; Materials – V.M.S., B.P., D.D'A., S.F.S.; Data Collection and/or Processing – V.M.S.; Analysis and/or Interpretation – V.M.S., B.P., F.Q., H.M., E.L., K.M., R.S.M., M.R., D.D'A., M.A., P.K., S.F.S.; Literature Search – V.M.S., D.D'A., B.P.; Writing Manuscript – V.M.S., B.P., F.Q., H.M., E.L., K.M., R.S.M., M.R., D.D'A., M.A., P.K., S.F.S.; Critical Review – B.P., F.Q., H.M., E.L., K.M., R.S.M., M.R., D.D'A., M.A., P.K., S.F.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: Victor Schuettfort is supported by the EUSP Scholarship of the European Association of Urology (EAU).

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424. [\[Crossref\]](#)
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7-30. [\[Crossref\]](#)
- Green DA, Rink M, Xylinas E, Matin SF, Stenzl A, Roupert M, et al. Urothelial carcinoma of the bladder and the upper tract: disparate twins. *J Urol* 2013;189:1214-21. [\[Crossref\]](#)
- Sfakianos JP, Cha EK, Iyer G, Scott SN, Zabor EC, Shah RH, et al. Genomic Characterization of Upper Tract Urothelial Carcinoma. *Eur Urol* 2015;68:970-7. [\[Crossref\]](#)
- Moss TJ, Qi Y, Xi L, Peng B, Kim TB, Ezzedine NE, et al. Comprehensive Genomic Characterization of Upper Tract Urothelial Carcinoma. *Eur Urol* 2017;72:641-9. [\[Crossref\]](#)
- Hassler MR, Bray F, Catto JWF, Grollman AP, Hartmann A, Margulis V, et al. Molecular Characterization of Upper Tract Urothelial Carcinoma in the Era of Next-generation Sequencing: A Systematic Review of the Current Literature. *Eur Urol* 2020;78:209-20. [\[Crossref\]](#)
- Rink M, Ehdaie B, Cha EK, Green DA, Karakiewicz PI, Babjuk M, et al. Stage-specific impact of tumor location on oncologic outcomes in patients with upper and lower tract urothelial carcinoma following radical surgery. *Eur Urol* 2012;62:677-84. [\[Crossref\]](#)
- Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupert M, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. *Eur Urol* 2012;62:100-14. [\[Crossref\]](#)
- Janisch F, Shariat SF, Baltzer P, Fajkovic H, Kimura S, Iwata T, et al. Diagnostic performance of multidetector computed tomographic (MDCTU) in upper tract urothelial carcinoma (UTUC): a systematic review and meta-analysis. *World J Urol* 2020;38:1165-75. [\[Crossref\]](#)
- Rouprêt M, Babjuk M, Burger M, Compérat E, Cowan N, Gontero P, et al. Upper Urinary Tract Urothelial Cell Carcinoma, EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam. 2020. EAU Guidelines Office, Arnhem, The Netherlands.
- Voskuilen CS, Schweitzer D, Jensen JB, Nielsen AM, Joniau S, Muilwijk T, et al. Diagnostic Value of (18)F-fluorodeoxyglucose Positron Emission Tomography with Computed Tomography for Lymph Node Staging in Patients with Upper Tract Urothelial Carcinoma. *Eur Urol Oncol* 2020;3:73-9. [\[Crossref\]](#)
- Raman JD, Ng CK, Scherr DS, Margulis V, Lotan Y, Bensalah K, 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. [\[Crossref\]](#)
- Favaretto RL, Shariat SF, Chade DC, Godoy G, Adamy A, Kaag M, 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. [\[Crossref\]](#)
- Remzi M, Haitel A, Margulis V, Karakiewicz P, Montorsi F, Kikuchi E, 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. [\[Crossref\]](#)
- Chromiecki TF, Cha EK, Fajkovic H, Margulis V, Novara G, Scherr DS, et al. The impact of tumor multifocality on outcomes in patients treated with radical nephroureterectomy. *Eur Urol* 2012;61:245-53. [\[Crossref\]](#)
- Mathieu R, Bensalah K, Lucca I, Mbeutcha A, Roupert M, Shariat SF. Upper urinary tract disease: what we know today and unmet needs. *Transl Androl Urol* 2015;4:261-72.
- Rojas CP, Castle SM, Llanos CA, Santos Cortes JA, Bird V, Rodriguez S, et al. Low biopsy volume in ureteroscopy does not affect tumor biopsy grading in upper tract urothelial carcinoma. *Urol Oncol* 2013;31:1696-700. [\[Crossref\]](#)
- Territo A, Foerster B, Shariat SF, Roupert M, Gaya JM, Palou J, et al. Diagnosis and kidney-sparing treatments for upper tract urothelial carcinoma: state of the art. *Minerva Urol Nefrol* 2018;70:242-51.
- Favaretto RL, Shariat SF, Savage C, Godoy G, Chade DC, Kaag M, et al. Combining imaging and ureteroscopy variables in a pre-operative 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. [\[Crossref\]](#)
- Joseph JP, Potretzke TA, Packiam V, Sharma V, Toussi A, Miest TS, et al. Percutaneous Image-guided Core Needle Biopsy for Upper Tract Urothelial Carcinoma. *Urology* 2020;135:95-100. [\[Crossref\]](#)
- Bus MT, de Bruin DM, Faber DJ, Kamphuis GM, Zondervan PJ, Laguna Pes MP, et al. Optical diagnostics for upper urinary tract urothelial cancer: technology, thresholds, and clinical applications. *J Endourol* 2015;29:113-23. [\[Crossref\]](#)
- Pradere B, Poulon F, Comperat E, Lucas IT, Bazin D, Doizi S, et al. Two-photon optical imaging, spectral and fluorescence lifetime analysis to discriminate urothelial carcinoma grades. *J Biophotonics* 2018;11:e201800065. [\[Crossref\]](#)
- Keller EX, Doizi S, Villa L, Traxer O. Which flexible ureteroscope is the best for upper tract urothelial carcinoma treatment? *World J Urol* 2019;37:2325-33. [\[Crossref\]](#)

24. Traxer O, Geavlete B, de Medina SG, Sibony M, Al-Qahtani SM. Narrow-band imaging digital flexible ureteroscopy in detection of upper urinary tract transitional-cell carcinoma: initial experience. *J Endourol* 2011;25:19-23. [\[Crossref\]](#)
25. Kata SG, Aboumarzouk OM, Zreik A, Somani B, Ahmad S, Nabi G, et al. Photodynamic diagnostic ureterorenoscopy: A valuable tool in the detection of upper urinary tract tumour. *Photodiagnosis Photodyn Ther* 2016;13:255-60. [\[Crossref\]](#)
26. Messer J, Shariat SF, Brien JC, Herman MP, Ng CK, Scherr DS, et al. Urinary cytology has a poor performance for predicting invasive or high-grade upper-tract urothelial carcinoma. *BJU Int* 2011;108:701-5. [\[Crossref\]](#)
27. Karakiewicz PI, Benayoun S, Zippe C, Lüdecke G, Boman H, Sanchez-Carbayo M, et al. Institutional variability in the accuracy of urinary cytology for predicting recurrence of transitional cell carcinoma of the bladder. *BJU Int* 2006;97:997-1001. [\[Crossref\]](#)
28. Malm C, Grahm A, Jaremkó G, Tribukait B, Brehmer M. Diagnostic accuracy of upper tract urothelial carcinoma: how samples are collected matters. *Scand J Urol* 2017;51:137-45. [\[Crossref\]](#)
29. 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. [\[Crossref\]](#)
30. Lodde M, Mian C, Wiener H, Haitel A, Pycha A, Marberger M. Detection of upper urinary tract transitional cell carcinoma with ImmunoCyt: a preliminary report. *Urology* 2001;58:362-6. [\[Crossref\]](#)
31. Marín-Aguilera M, Mengual L, Ribal MJ, Musquera M, Ars E, Villavicencio H, 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. [\[Crossref\]](#)
32. Coskuner E, Cevik I, Ozkan A, Dillioglulugil O, Akdas A. In the cystoscopic follow-up of non-muscle-invasive transitional cell carcinoma, NMP-22 works for high grades, but unreliable in low grades and upper urinary tract tumors. *Int Urol Nephrol*.2012;44:793-8. [\[Crossref\]](#)
33. Gayed BA, Seideman C, Lotan Y. Cost-effectiveness of fluorescence in situ hybridization in patients with atypical cytology for the detection of urothelial carcinoma. *J Urol* 2013;190:1181-6. [\[Crossref\]](#)
34. D'Andrea D, Soria F, Zehetmayer S, Gust KM, Korn S, Witjes JA, et al. Diagnostic accuracy, clinical utility and influence on decision-making of a methylation urine biomarker test in the surveillance of non-muscle-invasive bladder cancer. *BJU Int* 2019;123:959-67. [\[Crossref\]](#)
35. Audenet F, Isharwal S, Cha EK, Donoghue MTA, Drill EN, Ostrovnya I, et al. Clonal Relatedness and Mutational Differences between Upper Tract and Bladder Urothelial Carcinoma. *Clin Cancer Res* 2019;25:967-76. [\[Crossref\]](#)
36. Seisen T, Granger B, Colin P, Léon P, Utard G, Renard-Penna R, et al. A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. *Eur Urol* 2015;67:1122-33. [\[Crossref\]](#)
37. Shariat SF, Chade DC, Karakiewicz PI, Ashfaq R, Isbarn H, Fradet Y, et al. Combination of multiple molecular markers can improve prognostication in patients with locally advanced and lymph node positive bladder cancer. *J Urol* 2010;183:68-75. [\[Crossref\]](#)
38. Metcalfe MJ, Petros FG, Rao P, Mork ME, Xiao L, Broaddus RR, et al. Universal Point of Care Testing for Lynch Syndrome in Patients with Upper Tract Urothelial Carcinoma. *J Urol* 2018;199:60-5. [\[Crossref\]](#)
39. Pradere B, Lotan Y, Roupert M. Lynch syndrome in upper tract urothelial carcinoma: significance, screening, and surveillance. *Curr Opin Urol* 2017;27:48-55. [\[Crossref\]](#)
40. Donahu TF, Bagrodia A, Audenet F, Donoghue MTA, Cha EK, Sfakianos JP, et al. Genomic Characterization of Upper-Tract Urothelial Carcinoma in Patients With Lynch Syndrome. *JCO Precis Oncol* 2018;PO.17.00143.
41. Zigeuner R, Shariat SF, Margulis V, Karakiewicz PI, Roscigno M, Weizer A, 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. [\[Crossref\]](#)
42. Seitz C, Gupta A, Shariat SF, Matsumoto K, Kassouf W, Walton TJ, 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. [\[Crossref\]](#)
43. Novara G, Matsumoto K, Kassouf W, Walton TJ, Fritsche HM, Bastian PJ, 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. [\[Crossref\]](#)
44. Zamboni S, Foerster B, Abufaraj M, Seisen T, Roupert M, Colin P, et al. Incidence and survival outcomes in patients with upper urinary tract urothelial carcinoma diagnosed with variant histology and treated with nephroureterectomy. *BJU Int* 2019;124:738-45. [\[Crossref\]](#)
45. Rink M, Xylinas E, Margulis V, Cha EK, Ehdaie B, Raman JD, et al. Impact of smoking on oncologic outcomes of upper tract urothelial carcinoma after radical nephroureterectomy. *Eur Urol* 2013;63:1082-90. [\[Crossref\]](#)
46. Fajkovic H, Cha EK, Jeldres C, Donner G, Chromecki TF, Margulis V, et al. Prognostic value of extranodal extension and other lymph node parameters in patients with upper tract urothelial carcinoma. *J Urol* 2012;187:845-51. [\[Crossref\]](#)
47. Rink M, Sharifi N, Fritsche HM, Aziz A, Miller F, Kluth LA, et al. Impact of preoperative anemia on oncologic outcomes of upper tract urothelial carcinoma treated with radical nephroureterectomy. *J Urol* 2014;191:316-22. [\[Crossref\]](#)
48. Foerster B, Moschini M, Abufaraj M, Soria F, Gust KM, Roupert M, et al. Predictive and Prognostic Value of Preoperative Thrombocytosis in Upper Tract Urothelial Carcinoma. *Clin Genitourin Cancer* 2017;15:e1039-e45. [\[Crossref\]](#)
49. Vartolomei MD, Kimura S, Ferro M, Vartolomei L, Foerster B, Abufaraj M, et al. Is neutrophil-to-lymphocytes ratio a clinical relevant preoperative biomarker in upper tract urothelial carcinoma? A meta-analysis of 4385 patients. *World J Urol* 2018;36:1019-29. [\[Crossref\]](#)
50. D'Andrea D, Moschini M, Foerster B, Abufaraj M, Margulis V, Karam J, et al. Caveolin-1 Expression in Upper Tract Urothelial Carcinoma. *Eur Urol Focus* 2019;5:97-103. [\[Crossref\]](#)
51. Soria F, Moschini M, Haitel A, Wirth GJ, Karam JA, Wood CG, et al. HER2 overexpression is associated with worse outcomes in patients with upper tract urothelial carcinoma (UTUC). *World J Urol* 2017;35:251-9. [\[Crossref\]](#)

52. Abufaraj M, Moschini M, Soria F, Gust K, Ozsoy M, Mathieu R, et al. Prognostic role of expression of N-cadherin in patients with upper tract urothelial carcinoma: a multi-institutional study. *World J Urol* 2017;35:1073-80. [\[Crossref\]](#)
53. Wirth GJ, Haitel A, Moschini M, Soria F, Klatte T, Hassler MR, et al. Androgen receptor expression is associated with adverse pathological features in ureteral but not in pelvicalyceal urothelial carcinomas of the upper urinary tract. *World J Urol* 2017;35:943-9. [\[Crossref\]](#)
54. Abufaraj M, Kimura S, Haitel A, Iwata T, Isleem U, D'Andrea D, et al. The expression of urokinase-type plasminogen activator system in upper tract urothelial carcinoma and its prognostic value after radical nephroureterectomy. *Urol Oncol* 2020;38:685.e17-e25. [\[Crossref\]](#)
55. Soria F, Giordano A, D'Andrea D, Moschini M, Roupert M, Margulis V, et al. Prognostic value of the systemic inflammation modified Glasgow prognostic score in patients with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy: Results from a large multicenter international collaboration. *Urol Oncol* 2020;38:602.e11- e19. [\[Crossref\]](#)
56. Petros FG, Qiao W, Singla N, Clinton TN, Robyak H, Raman JD, et al. Preoperative multiplex nomogram for prediction of high-risk nonorgan-confined upper-tract urothelial carcinoma. *Urol Oncol* 2019;37:292.e1- e9. [\[Crossref\]](#)
57. Roupert M, Hupertan V, Seisen T, Colin P, Xylinas E, Yates DR, et al. Prediction of cancer specific survival after radical nephroureterectomy for upper tract urothelial carcinoma: development of an optimized postoperative nomogram using decision curve analysis. *J Urol* 2013;189:1662-9. [\[Crossref\]](#)
58. Cha EK, Shariat SF, Kormaksson M, Novara G, Chromecki TF, Scherr DS, et al. Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. *Eur Urol* 2012;61:818-25. [\[Crossref\]](#)
59. Yates DR, Hupertan V, Colin P, Ouazzane A, Descazeaud A, Long JA, et al. Cancer-specific survival after radical nephroureterectomy for upper urinary tract urothelial carcinoma: proposal and multi-institutional validation of a post-operative nomogram. *Br J Cancer* 2012;106:1083-8. [\[Crossref\]](#)
60. Seisen T, Colin P, Hupertan V, Yates DR, Xylinas E, Nison L, et al. Postoperative nomogram to predict cancer-specific survival after radical nephroureterectomy in patients with localised and/or locally advanced upper tract urothelial carcinoma without metastasis. *BJU Int* 2014;114:733-40. [\[Crossref\]](#)
61. Krabbe LM, Eminaga O, Shariat SF, Hutchinson RC, Lotan Y, Sagalowsky AI, et al. Postoperative Nomogram for Relapse-Free Survival in Patients with High Grade Upper Tract Urothelial Carcinoma. *J Urol* 2017;197:580-9. [\[Crossref\]](#)
62. Ku JH, Moon KC, Jung JH, Jeong SH, Kwak C, Kim HH. External validation of an online nomogram in patients undergoing radical nephroureterectomy for upper urinary tract urothelial carcinoma. *Br J Cancer* 2013;109:1130-6. [\[Crossref\]](#)
63. Xylinas E, Rink M, Cha EK, Clozel T, Lee RK, Fajkovic H, et al. Impact of distal ureter management on oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma. *Eur Urol* 2014;65:210-7. [\[Crossref\]](#)
64. Roscigno M, Brausi M, Heidenreich A, Lotan Y, Margulis V, Shariat SF, et al. Lymphadenectomy at the time of nephroureterectomy for upper tract urothelial cancer. *Eur Urol* 2011;60:776-83. [\[Crossref\]](#)
65. Quhal F, Mori K, Sari Motlagh R, Laukhtina E, Pradere B, Roupert M, et al. Efficacy of neoadjuvant and adjuvant chemotherapy for localized and locally advanced upper tract urothelial carcinoma: a systematic review and meta-analysis. *Int J Clin Oncol* 2020;25:1037-54. [\[Crossref\]](#)
66. Seisen T, Peyronnet B, Dominguez-Escrig JL, Bruins HM, Yuan CY, Babjuk M, et al. Oncologic Outcomes of Kidney-sparing Surgery Versus Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Systematic Review by the EAU Non-muscle Invasive Bladder Cancer Guidelines Panel. *Eur Urol* 2016;70:1052-68. [\[Crossref\]](#)
67. Mandalapu RS, Remzi M, de Reijke TM, Margulis V, Palou J, Kapoor A, et al. Update of the ICUD-SIU consultation on upper tract urothelial carcinoma 2016: treatment of low-risk upper tract urothelial carcinoma. *World J Urol* 2017;35:355-65. [\[Crossref\]](#)
68. Verges DP, Lallas CD, Hubosky SG, Bagley DH, Jr. Endoscopic Treatment of Upper Tract Urothelial Carcinoma. *Curr Urol Rep* 2017;18:31. [\[Crossref\]](#)
69. Cutress ML, Stewart GD, Zakikhani P, Phipps S, Thomas BG, Tolley DA. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. *BJU Int* 2012;110:614-28. [\[Crossref\]](#)
70. Villa L, Cloutier J, Letendre J, Ploumidis A, Salonia A, Cornu JN, et al. Early repeated ureteroscopy within 6-8 weeks after a primary endoscopic treatment in patients with upper tract urothelial cell carcinoma: preliminary findings. *World J Urol* 2016;34:1201-6. [\[Crossref\]](#)
71. Wang JK, Tollefson MK, Krambeck AE, Trost LW, Thompson RH. High rate of pathologic upgrading at nephroureterectomy for upper tract urothelial carcinoma. *Urology* 2012;79:615-9. [\[Crossref\]](#)
72. Huang Z, Zhang X, Zhang X, Li Q, Liu S, Yu L, et al. Segmental Ureterectomy is Acceptable for High-risk Ureteral Carcinoma Comparing to Radical Nephroureterectomy. *J Invest Surg* 2019;32:746-53. [\[Crossref\]](#)
73. Lughezzani G, Jeldres C, Isbarn H, Sun M, Shariat SF, Alasker A, 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. [\[Crossref\]](#)
74. Simonato A, Varca V, Gregori A, Benelli A, Ennas M, Lissiani A, et al. Elective segmental ureterectomy for transitional cell carcinoma of the ureter: long-term follow-up in a series of 73 patients. *BJU Int* 2012;110:E744-9. [\[Crossref\]](#)
75. Xylinas E, Roupert M, Shariat SF. Segmental ureterectomy for upper tract urothelial carcinoma: two procedures with different indications. *Urol Oncol* 2013;31:1841-3. [\[Crossref\]](#)
76. Veccia A, Antonelli A, Checcucci E, Falagario U, Carrieri G, Guruli G, et al. Segmental Ureterectomy for Upper Tract Urothelial Carcinoma: A Systematic Review and Meta-analysis of Comparative Studies. *Clin Genitourin Cancer* 2020;18:e10-e20. [\[Crossref\]](#)
77. Lucca I, Klatte T, Roupert M, Shariat SF. Kidney-sparing surgery for upper tract urothelial cancer. *Curr Opin Urol* 2015;25:100-4. [\[Crossref\]](#)

78. Foerster B, D'Andrea D, Abufaraj M, Broenimann S, Karakiewicz PI, Roupriet M, et al. Endocavitary treatment for upper tract urothelial carcinoma: A meta-analysis of the current literature. *Urol Oncol* 2019;37:430-6. [\[Crossref\]](#)
79. Kleinmann N, Pierorazio P, Gore J, Shabsigh A, Hu B, Chamie K, et al. Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial. *Lancet Oncol* 2020;21:776-85. [\[Crossref\]](#)
80. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer* 2009;115:1224-33. [\[Crossref\]](#)
81. Waldert M, Karakiewicz PI, Raman JD, Remzi M, Isbarn H, Lotan Y, et al. A delay in radical nephroureterectomy can lead to upstaging. *BJU Int* 2010;105:812-7. [\[Crossref\]](#)
82. Shariat SF, Godoy G, Lotan Y, Droller M, Karakiewicz PI, Raman JD, et al. Advanced patient age is associated with inferior cancer-specific survival after radical nephroureterectomy. *BJU Int* 2010;105:1672-7. [\[Crossref\]](#)
83. Chromecki TF, Ehdaie B, Novara G, Pummer K, Zigeuner R, Seitz C, et al. Chronological age is not an independent predictor of clinical outcomes after radical nephroureterectomy. *World J Urol* 2011;29:473-80. [\[Crossref\]](#)
84. Liu F, Guo W, Zhou X, Ding Y, Ma Y, Hou Y, et al. Laparoscopic versus open nephroureterectomy for upper urinary tract urothelial carcinoma: A systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e11954. [\[Crossref\]](#)
85. Simone G, Papalia R, Guaglianone S, Ferriero M, Leonardo C, Forastiere E, et al. Laparoscopic versus open nephroureterectomy: perioperative and oncologic outcomes from a randomised prospective study. *Eur Urol* 2009;56:520-6. [\[Crossref\]](#)
86. Favaretto RL, Shariat SF, Chade DC, Godoy G, Kaag M, Cronin AM, 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. [\[Crossref\]](#)
87. Dominguez-Escrig JL, Peyronnet B, Seisen T, Bruins HM, Yuan CY, Babjuk M, et al. Potential Benefit of Lymph Node Dissection During Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Systematic Review by the European Association of Urology Guidelines Panel on Non-muscle-invasive Bladder Cancer. *Eur Urol Focus* 2019;5:224-41. [\[Crossref\]](#)
88. Lughezzani G, Jeldres C, Isbarn H, Shariat SF, Sun M, Pharand D, et al. A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. *Urology* 2010;75:118-24. [\[Crossref\]](#)
89. Roscigno M, Shariat SF, Margulis V, Karakiewicz P, Remzi M, Kikuchi E, 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;56:512-8. [\[Crossref\]](#)
90. Guo R, Zhu Y, Xiong G, Li X, Zhang K, Zhou L. Role of lymph node dissection in the management of upper tract urothelial carcinomas: a meta-analysis. *BMC Urol* 2018;18:24. [\[Crossref\]](#)
91. Kondo T, Hara I, Takagi T, Kodama Y, Hashimoto Y, Kobayashi H, et al. Template-based lymphadenectomy in urothelial carcinoma of the renal pelvis: a prospective study. *Int J Urol* 2014;21:453-9. [\[Crossref\]](#)
92. O'Brien T, Ray E, Singh R, Coker B, Beard R. 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. [\[Crossref\]](#)
93. Ito A, Shintaku I, Satoh M, Ioritani N, Aizawa M, Tochigi T, et al. Prospective Randomized Phase II Trial of a Single Early Intravesical Instillation of Pirarubicin (THP) in the Prevention of Bladder Recurrence After Nephroureterectomy for Upper Urinary Tract Urothelial Carcinoma: The THP Monotherapy Study Group Trial. *J Clin Oncol* 2013;31:1422-7. [\[Crossref\]](#)
94. Fang D, Li XS, Xiong GY, Yao L, He ZS, Zhou LQ. Prophylactic intravesical chemotherapy to prevent bladder tumors after nephroureterectomy for primary upper urinary tract urothelial carcinomas: a systematic review and meta-analysis. *Urol Int* 2013;91:291-6. [\[Crossref\]](#)
95. Wu P, Zhu G, Wei D, Liu S, Walsh K, Li D, et al. Prophylactic intravesical chemotherapy decreases bladder tumor recurrence after nephroureterectomy for primary upper tract urothelial carcinoma: A systematic review and meta-analysis. *J Buon* 2015;20:1229-38.
96. Seisen T, Krasnow RE, Bellmunt J, Roupriet M, Leow JJ, Lipsitz SR, et al. Effectiveness of Adjuvant Chemotherapy After Radical Nephroureterectomy for Locally Advanced and/or Positive Regional Lymph Node Upper Tract Urothelial Carcinoma. *J Clin Oncol* 2017;35:852-60. [\[Crossref\]](#)
97. Necchi A, Lo Vullo S, Mariani L, Moschini M, Hendricksen K, Rink M, et al. Adjuvant chemotherapy after radical nephroureterectomy does not improve survival in patients with upper tract urothelial carcinoma: a joint study by the European Association of Urology-Young Academic Urologists and the Upper Tract Urothelial Carcinoma Collaboration. *BJU Int* 2018;121:252-9. [\[Crossref\]](#)
98. Hellenthal NJ, Shariat SF, Margulis V, Karakiewicz PI, Roscigno M, Bolenz C, 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. [\[Crossref\]](#)
99. Lucca I, Kassouf W, Kapoor A, Fairey A, Rendon RA, Izawa JJ, et al. The role of adjuvant chemotherapy for lymph node-positive upper tract urothelial carcinoma following radical nephroureterectomy: a retrospective study. *BJU Int* 2015;116:72-8. [\[Crossref\]](#)
100. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet* 2020;395:1268-77. [\[Crossref\]](#)
101. Xylinas E, Rink M, Margulis V, Clozel T, Lee RK, Comploj E, et al. Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephroureterectomy. *BJU Int* 2013;112:453-61. [\[Crossref\]](#)
102. Sternberg CN, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989;64:2448-58. [\[Crossref\]](#)

103. Sternberg CN, de Mulder P, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer* 2006;42:50-4. [\[Crossref\]](#)
104. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068-77. [\[Crossref\]](#)
105. Bellmunt J, von der Maase H, Mead GM, Skoneczna I, De Santis M, Daugaard G, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. *J Clin Oncol* 2012;30:1107-13. [\[Crossref\]](#)
106. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2017;18:1483-92. [\[Crossref\]](#)
107. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet* 2017;389:67-76. [\[Crossref\]](#)
108. De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol* 2012;30:191-9. [\[Crossref\]](#)
109. Galsky MD, Chen GJ, Oh WK, Bellmunt J, Roth BJ, Petrioli R, et al. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. *Ann Oncol* 2012;23:406-10. [\[Crossref\]](#)
110. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med* 2017;376:1015-26. [\[Crossref\]](#)
111. Powles T, Duran I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2018;391:748-57. [\[Crossref\]](#)
112. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017;18:312-22. [\[Crossref\]](#)
113. Sharma P, Siefker-Radtke A, de Braud F, Basso U, Calvo E, Bono P, et al. Nivolumab Alone and With Ipilimumab in Previously Treated Metastatic Urothelial Carcinoma: CheckMate 032 Nivolumab 1 mg/kg Plus Ipilimumab 3 mg/kg Expansion Cohort Results. *J Clin Oncol* 2019;37:1608-16. [\[Crossref\]](#)
114. Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;27:4454-61. [\[Crossref\]](#)
115. Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E, et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med* 2019;381:338-48. [\[Crossref\]](#)