World J Urol (2017) 35:1401–1407
DOI 10.1007/s00345-016-1995-z

INVITED REVIEW

Perioperative chemotherapy in upper tract urothelial carcinoma: a comprehensive review

Atiqullah Aziz[1] · Jakub Dobruch[2] · Kees Hendricksen[3] · Luis A. Kluth[1] · Andrea Necchi[4] · Aidan Noon[5] · Michael Rink[1] · Florian Roghmann[6] · Roland Seiler[7,8] · Paolo Gontero[9] · Wassim Kassouf[10] · Shahrokh F. Shariat[11] · Evanguelos Xylinas[12,13] · For the Young Academic Urologists Urothelial Carcinoma Group of the European Association of Urology

Received: 19 October 2016 / Accepted: 19 December 2016 / Published online: 10 January 2017

Abstract
Purpose To evaluate the role of neoadjuvant (NAC) and adjuvant chemotherapy (AC) in patients with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy (RNU).
Methods A comprehensive review of the current literature was performed searching for all studies investigating NAC and AC in UTUC in MEDLINE and https://clinicaltrials.gov, prior to April 2016. The following keywords were used: "ureteral neoplasms," "urothelium," "ureter," "upper tract urothelial," "chemotherapy," "adjuvant," "neoadjuvant" and relevant variants.
Results No randomized trials investigated the role of AC or NAC for UTUC. There was one prospective study with $n = 36$ patients investigating AC with carboplatin–paclitaxel. We included 14 retrospective studies (four in the NAC and ten in the AC setting), with a total of 694 patients receiving cisplatin-based or non-cisplatin-based AC after RNU and 1437 patients undergoing RNU alone. We found that the current literature, mainly based on retrospective studies, suggests significant overall and cancer-specific survival benefits for AC in UTUC. NAC appears promising, with favorable pathologic response rates up to 14%.
Conclusions Evidence is scarce for both NAC and AC use in UTUC. This comprehensive review suggests promising response rates for NAC and a survival benefit for patients treated with AC. Prospective randomized trials are needed to establish the role of AC and NAC in UTUC.

Keywords Upper urinary tract tumors · Urothelial carcinoma · Radical nephroureterectomy · Neoadjuvant chemotherapy · Adjuvant chemotherapy

✉ Evanguelos Xylinas
evanguelosxylinas@hotmail.com

[1] Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[2] Department of Urology, Centre of Postgraduate Medical Education, European Health Centre, Otwock, Poland

[3] Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands

[4] Department of Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[5] Department of Urology, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK

[6] Department of Urology, Marien Hospital Herne, Ruhr-University Bochum, Herne, Germany

[7] Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, Canada

[8] Department of Urology, University of Bern, Bern, Switzerland

[9] Division of Urology, Department of Surgical Sciences, San Giovanni Battista Hospital, University of Studies of Torino, Turin, Italy

[10] Department of Urology, McGill University Health Center, Montreal, QC, Canada

[11] Department of Urology, Medical University of Vienna, Vienna, Austria

[12] Department of Urology, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris Descartes University, 27, rue du Faubourg Saint Jacques, 75014 Paris, France

[13] INSERM U955 Eq07 Department of Urology, CHU Mondor, 51, avenue du Maréchal de Lattre de Tassigny, 94000 Créteil, France

Introduction

Despite recent improvements in perioperative management and increasing knowledge of the disease's natural history, most patients following radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC) with high-grade or locally advanced tumors still face a poor prognosis [1, 2]. More than a quarter of those with locally advanced disease and no less than a third with high-grade cancer harbor lymph node metastases at the time of surgery [3]. Patients who underwent RNU for UTUC are associated with 5-year recurrence-free (RFS) and cancer-specific survival (CSS) probabilities of 69 and 73%, respectively [1, 2]. Thus, additional systemic therapy, especially in patients with advanced disease, seems to be warranted to provide long-term cancer control.

Chemotherapy in UTUC is predominantly based on regimens that are utilized in urothelial carcinoma of the bladder (UCB) [4, 5]. However, there is a lack of a consensus regarding the administration of neoadjuvant (NAC) and adjuvant chemotherapy (AC) in UTUC [4–6]. In addition, response to chemotherapy might differ between patients with UTUC and UCB, underlining the fact that results from UCB cannot arbitrarily be applied to UTUC [7, 8]. Moreover, the timing of systemic therapies is of even more importance in UTUC, compared to UCB, as RNU can impair renal function and thus might lower the eligibility for adjuvant chemotherapy, at least cisplatin based [9, 10].

Given the rarity of the disease accounting for approximately 5% of all urothelial malignancies [11] and the scarcity of data on chemotherapy in UTUC, the aim of the present report was to review the current evidence regarding perioperative chemotherapy in UTUC.

Methods

From June 2015 to April 2016, we performed a comprehensive literature search of PubMed (MEDLINE) and https://clinicaltrials.gov to identify observational cohort studies and controlled trials performed. All studies examined the role of chemotherapy for UTUC. Non-english written studies were not included. Patients received AC, defined as administration three months after surgery without recurrence, after definitive surgical treatment with RNU, NAC before RNU, or RNU alone. Search terms included "ureteral neoplasms," "urothelium," "ureter," "upper tract urothelial," "chemotherapy," "adjuvant," "neoadjuvant" and relevant variants. Search results were independently reviewed by two authors (AA and EX). Full articles were retrieved for further qualitative review. Finally, 14 retrospective studies (four in the NAC and ten in the AC setting), with a total of 694 patients receiving cisplatin-based or non-cisplatin-based perioperative chemotherapy, and 1437 patients receiving RNU alone were thoroughly investigated.

Neoadjuvant chemotherapy

In UCB, NAC has agrade A recommendation for T2–T4a, cN0M0 patients before radical cystectomy in several guidelines [12]. In theory, NAC in UTUC comprises the eradication of micro-metastatic disease, pathological downstaging and cisplatin eligibility before RNU, and the possibility to deliver higher doses of the chemotherapy before RNU [13]. However, it has to be kept in mind that a delay in definitive surgical management might lead to disease progression in patients harboring chemotherapy-resistant tumors [14, 15].

Currently, there are four retrospective studies published in this setting (Table 1) [16–19]. The first study presented by Igawa et al. included 15 patients who were treated either with MVAC (methotrexate, vinblastine, adriamycin and cisplatin; $n = 5$), MEC (methotrexate, etoposide and cisplatin; $n = 4$), or MVEC (methotrexate, vinblastine, epirubicin and cisplatin; $n = 6$) before RNU. Their findings showed that a total of two (13%) subjects yielded a pathologic complete response as reflected by the lack of cancerous tissue in the specimen and six (40%) yielded a pathologic partial response, achieving an overall response rate of 53% (95% confidence interval 29–77%) [16].

Data from the M.D. Anderson Cancer Center (MDACC), including 43 UTUC patients receiving NAC, showed that pathologic downstaging was significantly higher in the NAC cohort when compared to a historical cohort of 107 UTUC patients undergoing initial RNU. Moreover, a total of 14% had a complete pathologic response to NAC [17], which underscores the findings by Igawa et al. [16]. An update of the MDACC data with a median overall survival of 78 months reported a 3- and 5-year cancer-specific survival of 77 and 67% for the NAC and the upfront RNU cohorts, respectively [18].

Youssef et al. presented data from the international UTUC Collaboration in 2011, including 18 UTUC patients who received NAC in a modified fashion due to histologically confirmed locoregional lymph node metastases. The authors showed a benefit of NAC in these patients with favorable 5-year RFS and CSS rates of 49 and 44%, respectively [19].

Given the lack of robust data in UTUC, the use of NAC in UTUC consequently remains lower than in UCB. To date, there is one prospective trial, which evaluates the impact of a platinum-based NAC with GC (NCT01261728) in high-risk UTUC on pathological response rate, time to disease progression, OS, safety and tolerability. Another

Table 1 Summary of the studies evaluating the benefit of neoadjuvant chemotherapy administration before radical nephroureterectomy for upper tract urothelial carcinoma

References	Design	Setting	*n*	Regimen	Outcomes			
					Response	5-year survival		
						RFS	CSS	OS
Igawa et al. [14]	Retrospective	cN0/+	15	MVAC ($n = 5$), MEC ($n = 4$), MVEC ($n = 6$)	13% CR; 40% PR	N/A	N/A	N/A
Matin et al. [15]	Retrospective	cN0/+	43	MVAC ($n = 19$, CGI ($n = 9$), GC ($n = 5$), other ($n = 4$)	14% CR, 32.6% PR% (52% < pT3N0)	N/A	N/A	N/A
			107	RNU alone	N/A		N/A	N/A
Youssef et al. [17]	Retrospective	cN+	18	GC ($n = 14$); MVAC ($n = 4$)	N/A	49%	44%	N/A
		pN+	120	RNU		30%	36%	N/A
		pT2-4 N0	175	RNU		64%	69%	N/A
Porten et al. [16]	Retrospective	cN0	31	Cisplatin-containing with standard or dose-dense MVAC, GC, or CGI ($n = 21$); high-dose IDG ($n = 3$); GPA ($n = 7$ with kidney-sparing therapy)	N/A	N/A	90.20%	80.20%
			81	RNU alone		N/A	57.60%	57.60%

MVAC methotrexate, vinblastine, adriamycin and cisplatin; *MEC* methotrexate, etoposide and cisplatin; *MVEC* methotrexate, vinblastine, epirubicin and cisplatin; *GC* gemcitabine and cisplatin; *CGI* cisplatin, gemcitabine, ifosfamide; *IDG* ifosfamide, doxorubicin, gemcitabine; *GPA* gemcitabine, paclitaxel, doxorubicin; *RNU* radical nephroureterectomy; *CR* complete response; *PR* partial response; *N/A* not available; *RFS* recurrence-free survival; *CSS* cancer-specific survival; *OS* overall survival

trial (NCT01663285) investigating the role of NAC with GC in UTUC was terminated due to poor accrual.

Adjuvant chemotherapy

In contrast to NAC, cisplatin-based AC surmounts the inaccuracies of clinical staging in UTUC and allows an adequate selection of patients at highest risk of an impaired survival following RNU based on the pathological analysis of the surgical specimen [20]. However, AC has significant risks of toxicity, especially in the setting of a reduced renal function after RNU [9]. To date, no randomized trial has evaluated the role of AC specifically for UTUC patients following RNU, presumably due to the rarity of the disease.

Several retrospective studies and one prospective trial (both UTUC and UCB included) investigated the role of AC in UTUC (Table 2) [21–31]. In 2006, Lee et al. [26] presented their retrospective data on a comparative analysis including 27 UTUC patients with pT3N0M0 following RNU, of whom 16 received AC with MVAC versus 11 who did not. After a median follow-up (FU) of 15 months, 31% of the AC group and 36% of the RNU alone group had a disease recurrence; however, no significant differences were seen between the two groups regarding 5-year RFS and CSS.

Kwak et al. [25] retrospectively evaluated 43 RNU patients with non-metastatic UTUC, of whom 32 were administered a minimum of four cycles of cisplatin-based AC (MVAC $n = 23$; GC $n = 7$, CISCA $n = 2$). At a median FU of 30.7 months, 37.5% ($n = 12$) of the AC group and 63.6% ($n = 7$) of the non-AC group experienced disease recurrence. The 5-year CSS rate in the AC group was 62.5%, while the corresponding rates in the non-AC group were 36.4%, respectively.

Soga et al. [28] analyzed 132 UTUC patients after RNU. A total of 46 patients with pT2-3N0M0 were divided into two arms with $n = 24$ receiving MVAC and $n = 22$ without administration of AC. Albeit the 5-year OS was 95.8% in the AC group versus 86.5% in the non-AC group, no statistical significance could be observed here ($p = 0.081$).

Kawashima et al. [23] evaluated 93 UTUC patients with pT3N0/xM0 following RNU. Platinum-based AC was administered in $n = 38$ patients versus $n = 55$ treated with RNU alone. The authors found a 5-year RFS of 74% in the AC group versus 57% in the RNU alone group. The 5-year CSS rate was 80.8% in the AC group and 64.4% in the non-AC group, respectively.

Kim et al. [24] analyzed their single-center series with 65 RNU patients with locally advanced UTUC (pT3/pT4 or pT1-2N1-3), of whom 36 patients received cisplatin-based AC and 29 patients RNU alone. The study group found that at a median FU of 34 months, the incidence of intravesical recurrence was significantly higher in patients who did not undergo AC with 41.4 versus 13.9% (HR 14.862, $p = 0.001$). The authors did not observe any statistically

Table 2 Summary of the studies evaluating the survival benefit of adjuvant chemotherapy administration after radical nephroureterectomy for upper tract urothelial carcinoma

References	Design	Inclusion criteria	*n*	Regimen	5-year survival		
					RFS	CSS	OS
Bamias et al. [20]	Prospective	pT2-4 or pN0/+	36	Paclitaxel/carboplatin	40.2%	N/A	52%
Lee et al. [25]	Retrospective	pT3N0	16	MVAC	68.2%	75.0%	N/A
			11	RNU alone	62.3%	70.7%	N/A
Kwak et al. [24]	Retrospective	pT2-3 and/or pN+	32	MVAC ($n = 23$), GC ($n = 7$), CISCA ($n = 2$)	N/A	62.5%	78.10%
			11	RNU alone		36.4%	36.40%
Soga et al. [27]	Retrospective	pT2-3N0	24	MVAC	N/A	N/A	95.80%
			22	RNU alone	N/A	N/A	86.50%
Hellenthal et al. [21]	Retrospective	pT3-4 and/or pN+	121	89% Cisplatin-based	N/A	45%	41%
			421	RNU alone		52%	43%
Kawashima et al. [22]	Retrospective	pT3N0	38	82% Cisplatin-based	74%	80.80%	N/A
			55	RNU alone	57%	64.40%	N/A
Vassilakopoulou et al. [28]	Retrospective	pT3-4 and/or pN+	140	CG ($n = 35$), CP ($n = 31$); CAG ($n = 23$); MVAC ($n = 19$); CMV ($n = 17$)	54%		43%
Kim et al. [23]	Retrospective	pT3/pT4 or pT1-2N1-3	36	GC ($n = 30$), MVAC ($n = 6$)	N/A	68%	N/A
			29	RNU alone	N/A	54%	N/A
Shirotake et al. [26]	Retrospective	High-risk: pT3-4, pN+, tumor grade 3, LVI	85	MVAC ($n = 46$), GC ($n = 31$), others ($n = 8$)	2-year RFS: MVAC 47.9%; GC: N/A;	2-year CSS: MVAC 71.6%; GC 52.5%	
			144	RNU alone	2-year RFS: 39.6%	2-year CSS: 59%	
Yafi et al. [29]	Retrospective	Any pT and pN	59	Unknown regimen		38%	37%
			249	RNU alone		52%	43%

MVAC methotrexate, vinblastine, adriamycin and cisplatin; *RNU* radical nephroureterectomy; *GC* gemcitabine and cisplatin; *CISCA* cisplatin, cyclophosphamide, doxorubicin; *CP* cisplatin, paclitaxel; *CAG* carboplatin, gemcitabine; *CMV* cisplatin, methotrexate, vinblastine; *RFS* recurrence-free survival; *CSS* cancer-specific survival; *OS* overall survival

significant benefit for AC in terms of 5-year CSS with 68% (AC) versus 54% (non-AC, $p = 0.47$).

Shirotake et al. [27] evaluated the impact of MVAC versus gemcitabine + cisplatin (GC) versus no administration of AC on 229 high-risk UTUC patients following RNU. High risk was defined as three or more of the variables observed: pathological stage T3-4, positive lymph node involvement, tumor grade 3 and presence of lymphovascular invasion. After a median FU of 32 months (IQR 16–62), the 1- and 2-year RFS rates in the MVAC group were 71.4 and 47.9%, respectively, and significantly higher than in the GC group (48.2% and not reached, $p = 0.022$) or those not treated with AC (53.4 and 39.6%, $p = 0.039$). Likewise, the 1- and 2-year CSS rates in the MVAC group were 87.0 and 71.6% and significantly higher than those in the GC group (82.7 and 52.5%, $p = 0.014$) or in those without administration of AC (73.8 and 59.0%, $p = 0.043$).

Data from the French Collaborative National Database on UTUC evaluated 627 high-risk patients with pT3/4 and/or pN+, of whom 22.6% ($n = 140$) were treated with AC [29]. Of those, 52.8% received cisplatin-based AC and roughly 40% were treated with carboplatin-based AC. There were no significant differences in 5-year CSS and OS rates between the groups.

The UTUC Collaboration group investigated 542 high-risk patients (pT3/4 and/or pN+), of whom 22% ($n = 121$) were administered AC (89% cisplatin based) from their database comprising 1390 UTUC patients [19]. A total of $n = 121$ (22%) received AC (89% cisplatin based). The collaboration group did not observe any statistically significant differences in AC versus non-AC regarding CSS with 45 versus 52% and OS 41 versus 43%, respectively [22].

In 2014, Yafi et al. [30] presented their findings from a database comprising 1029 UTUC patients of whom 5.7%

($n = 59$) were treated with AC following RNU. Based on an estimated glomerular filtration rate (eGFR) cutoff of 60 mL/min/1.73 m^2, 49% of all the patients in their cohort and 48% of the patients with ≥pT3 and/or pN+ would have been eligible for cisplatin-based chemotherapy preoperatively and only 18 and 21% of the patients, respectively, remained eligible after RNU. The eGFR in 75% of the AC arm was below 60. Moreover, AC did not have a beneficial impact on CSS (HR 0.775, $p = 0.45$) and OS (HR 0.695, $p = 0.41$) in multivariate analysis. Albeit patients treated with RNU alone showed favorable outcomes with a CSS of 52 versus 38% ($p = 0.88$), respectively, and OS of 43 versus 37% ($p = 0.20$), these numbers did not reach a statistical significance.

Lucca et al. [31] retrospectively analyzed data of 263 patients with LN-positive UTUC, who underwent full surgical resection. In all, 107 patients (41%) received three to six cycles of AC, while 156 (59.3%) were treated with RNU alone. UTUC-related mortality was evaluated using competing-risks regression models. In all pN+ patients, administration of AC had no significant impact on UTUC-related mortality. Further stratified analyses showed that only pN+ patients with pT3-4 disease benefited from AC. In this subgroup, AC reduced UTUC-related mortality by 34% ($p = 0.02$). The absolute difference in mortality was 10% after the first year and increased to 23% after 5 years. This subgroup of LN-positive patients could serve as target population for an AC prospective randomized trial.

To date, there is only one prospective phase II trial by the Hellenic Cooperative Oncology Group that has investigated the impact of four cycles of adjuvant paclitaxel and carboplatin in 36 UTUC patients with ≥pT2 and/or pN+ following RNU [21]. At a median FU of 40.6 months, the study group found a year–year RFS and OS of 40.2 and 52%, respectively.

Our comprehensive review highlights that survival after RNU was improved by the administration of AC as compared to surgery alone. Our findings underline the effect of AC including an accurate pathologic staging following RNU and the potential of eradicating any subclinical metastases [6]. Nevertheless, some of the studies reported a limited benefit for AC in terms of survival compared to RNU alone. However, these findings have to be interpreted with caution since the majority of the studies are retrospective and various chemotherapy regimens were employed. Most of the patients who were treated with AC were associated with adverse prognostic factors for survival following RNU for UTUC [6]. Furthermore, patients with node-positive disease were more likely to receive AC [22, 30]. In light of these limitations, the lack of distinct differences in survival outcome may underestimate the true efficacy of AC. Hence, the findings from the POUT trial (ISRCTN98387754), which randomizes UTUC patients following RNU in a platinum-based AC arm versus surveillance arm [32], are eagerly awaited.

Future directions

The blockade of the PD-L1–PD-1 pathway displays a new therapeutic agent in cancers with broad expression of PD-L1 resulting in overall survival benefits in non-small-cell lung cancer, melanoma and renal cell carcinoma [33–38]. With that being said, two investigations on the role of anti-PD-L1 immune checkpoint inhibitor in advanced and/or metastatic UCB have been initiated. Powles et al. reported the results of an expanded phase 1 trial with an adaptive design on the safety and activity of the anti-PD-L1 immune checkpoint inhibitor MPDL3280A in metastatic bladder cancer. After a median follow-up of 6 weeks, the overall response rate was 43% for a PD-L1 TIIC IHC score of 2/3 and 11% for a score of 0/1, respectively, in the 67 patients enrolled. Rosenberg et al. [39] recently presented their results from an international, multicenter, single-arm, phase 2 trial investigating the therapeutic role of the anti-PD-L1 immune checkpoint inhibitor atezolizumab in patients with locally advanced or metastatic UCB. The authors found that while the overall response rate was 10%, the administration of atezolizumab resulted in a significantly improved RECIST v1.1 objective response rate of 15% (95% CI 11–20, $p = 0.0058$). Moreover, higher objective response rates were observed in two of the PD-L1 expression immune cell groups (IC2/3: 27%, 95% CI 19–37, $p < 0.0001$; IC1/2/3: 18%, 95% CI 13–24, $p = 0.0004$). To date and to the best of our knowledge, no study has been published regarding the role of anti-PD-L1 immune checkpoint inhibitors and UTUC. Further trials here are urgently warranted and the results of the NCT02632409 (A Study of Nivolumab, Compared to Placebo, in Patients With Bladder or Upper Urinary Tract Cancer, Following Surgery to Remove the Cancer (CheckMate 274); open for accrual) eagerly waited.

Conclusion

Our comprehensive review regarding the role of perioperative chemotherapy in patients with UTUC showed that perioperative chemotherapy may portend a beneficial effect compared to surgery alone in patients with an UTUC having a high risk of relapse. Nevertheless, with respect to the limitations of the small amount of the currently available studies including selection bias and non-randomized retrospective design and the descriptive quality of the present review, no general recommendation can be given in regard to the administration of cisplatin-based AC in all UTUC

patients. Selection criteria are needed and will imply the definition of formally approved criteria to allow the inclusion of patients with UTUC in clinical trials of perioperative systemic therapy. In the absence of such information, we think that patients with distinct features for a high-risk UTUC (pT3/4 and/or pN+) and an adequate renal function after RNU might benefit from an AC regimen. Regarding NAC, the results are promising; however, further trials are needed to again identify the most suitable patients and validate its use in daily clinical practice. Neoadjuvant systemic therapy yields favorable pathologic outcomes and may be delivered in at least half of the cases before RNU, especially in light of the 20% loss of GFR after RNU which underlines the potential benefit of an NAC approach [9]. Although the results of trials devoted to NAC are promising, further studies are needed to underscore its use in daily clinical practice. The advent of immunotherapy showed beneficiary results in UCB; however, no conclusion can be drawn in UTUC due to the lack of data on the impact of anti-PD-L1 immune checkpoint inhibitors in UTUC.

Authors contribution AA, JD, KH, LAK, AN, AN, MR, FR, RS, PG, WK, SFS and EX contributed to protocol/project development, data collection, data analysis and manuscript writing/editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Roupret M, Babjuk M, Comperat E et al (2013) European guidelines on upper tract urothelial carcinomas: 2013 update. Eur Urol 63:1059–1071
2. Margulis V, Shariat SF, Matin SF et al (2009) Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer 115:1224–1233
3. Kondo T, Nakazawa H, Ito F, Hashimoto Y, Toma H, Tanabe K (2007) Primary site and incidence of lymph node metastases in urothelial carcinoma of upper urinary tract. Urology 69:265–269
4. Advanced Bladder Cancer Meta-analysis C (2005) Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 48:202–205 **(discussion 05-6)**
5. Leow JJ, Martin-Doyle W, Rajagopal PS et al (2014) Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 66:42–54
6. Leow JJ, Martin-Doyle W, Fay AP, Choueiri TK, Chang SL, Bellmunt J (2014) A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma. Eur Urol 66:529–541
7. Bellmunt J, Petrylak DP (2012) New therapeutic challenges in advanced bladder cancer. Semin Oncol 39:598–607
8. van Oers JM, Zwarthoff EC, Rehman I et al (2009) FGFR3 mutations indicate better survival in invasive upper urinary tract and bladder tumours. Eur Urol 55:650–657
9. Kaag MG, O'Malley RL, O'Malley P et al (2010) Changes in renal function following nephroureterectomy may affect the use of perioperative chemotherapy. Eur Urol 58:581–587
10. Xylinas E, Rink M, Margulis V et al (2013) Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy. BJU Int 112:453–461
11. Cordier J, Sonpavde G, Stief CG, Tilki D (2013) Oncologic outcomes obtained after neoadjuvant and adjuvant chemotherapy for the treatment of urothelial carcinomas of the upper urinary tract: a review. World J Urol 31:77–82
12. Stenzl A, Cowan NC, De Santis M et al (2011) Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. Eur Urol 59:1009–1018
13. Audenet F, Yates DR, Cussenot O, Roupret M (2013) The role of chemotherapy in the treatment of urothelial cell carcinoma of the upper urinary tract (UUT-UCC). Urol Oncol 31:407–413
14. Gayed BA, Thoreson GR, Margulis V (2013) The role of systemic chemotherapy in management of upper tract urothelial cancer. Curr Urol Rep 14:94–101
15. Waldert M, Karakiewicz PI, Raman JD et al (2010) A delay in radical nephroureterectomy can lead to upstaging. BJU Int 105:812–817
16. Igawa M, Urakami S, Shiina H et al (1995) Neoadjuvant chemotherapy for locally advanced urothelial cancer of the upper urinary tract. Urol Int 55:74–77
17. Matin SF, Margulis V, Kamat A et al (2010) Incidence of downstaging and complete remission after neoadjuvant chemotherapy for high-risk upper tract transitional cell carcinoma. Cancer 116:3127–3134
18. Porten S, Siefker-Radtke AO, Xiao L et al (2014) Neoadjuvant chemotherapy improves survival of patients with upper tract urothelial carcinoma. Cancer 120:1794–1799
19. Youssef RF, Shariat SF, Lotan Y et al (2011) Upper urinary tract urothelial carcinoma with loco-regional nodal metastases: insights from the Upper Tract Urothelial Carcinoma Collaboration. BJU Int 108:1286–1291
20. Gray PJ, Lin CC, Jemal A et al (2014) Clinical–pathologic stage discrepancy in bladder cancer patients treated with radical cystectomy: results from the national cancer data base. Int J Radiat Oncol Biol Phys 88:1048–1056
21. Bamias A, Deliveliotis C, Fountzilas G et al (2004) Adjuvant chemotherapy with paclitaxel and carboplatin in patients with advanced carcinoma of the upper urinary tract: a study by the Hellenic Cooperative Oncology Group. J Clin Oncol 22:2150–2154
22. Hellenthal NJ, Shariat SF, Margulis V et al (2009) Adjuvant chemotherapy for high risk upper tract urothelial carcinoma: results from the Upper Tract Urothelial Carcinoma Collaboration. J Urol 182:900–906
23. Kawashima A, Nakai Y, Nakayama M et al (2012) The result of adjuvant chemotherapy for localized pT3 upper urinary tract carcinoma in a multi-institutional study. World J Urol 30:701–706
24. Kim TS, Oh JH, Rhew HY (2013) The efficacy of adjuvant chemotherapy for locally advanced upper tract urothelial cell carcinoma. J Cancer 4:686–690
25. Kwak C, Lee SE, Jeong IG, Ku JH (2006) Adjuvant systemic chemotherapy in the treatment of patients with invasive transitional cell carcinoma of the upper urinary tract. Urology 68:53–57
26. Lee SE, Byun SS, Park YH, Chang IH, Kim YJ, Hong SK (2006) Adjuvant chemotherapy in the management of pT3N0M0

transitional cell carcinoma of the upper urinary tract. Urol Int 77:22–26
27. Shirotake S, Kikuchi E, Tanaka N et al (2015) Impact of an adjuvant chemotherapeutic regimen on the clinical outcome in high risk patients with upper tract urothelial carcinoma: a Japanese multi-institution experience. J Urol 193:1122–1128
28. Soga N, Arima K, Sugimura Y (2008) Adjuvant methotrexate, vinblastine, adriamycin, and cisplatin chemotherapy has potential to prevent recurrence of bladder tumors after surgical removal of upper urinary tract transitional cell carcinoma. Int J Urol 15:800–803
29. Vassilakopoulou M, de la Motte Rouge T, Colin P et al (2011) Outcomes after adjuvant chemotherapy in the treatment of high-risk urothelial carcinoma of the upper urinary tract (UUT-UC): results from a large multicenter collaborative study. Cancer 117:5500–5508
30. Yafi FA, Tanguay S, Rendon R et al (2014) Adjuvant chemotherapy for upper-tract urothelial carcinoma treated with nephroureterectomy: assessment of adequate renal function and influence on outcome. Urol Oncol 32:31.e17–31.e24
31. Lucca I, Kassouf W, Kapoor A et al (2015) The role of adjuvant chemotherapy for lymph node-positive upper tract urothelial carcinoma following radical nephroureterectomy: a retrospective study. BJU Int 116:72–78
32. Birtle AJ, Lewis R, Johnson M, Hall E, Group PTM (2012) Time to define an international standard of postoperative care for resected upper urinary tract transitional cell carcinoma (TCC)—opening of the peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (POUT) Trial. BJU Int 110:919–921
33. Inman BA, Sebo TJ, Frigola X et al (2007) PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. Cancer 109:1499–1505
34. Garon EB, Rizvi NA, Hui R et al (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372:2018–2028
35. Robert C, Long GV, Brady B et al (2015) Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372:320–330
36. Motzer RJ, Escudier B, McDermott DF et al (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373:1803–1813
37. Brown JA, Dorfman DM, Ma FR et al (2003) Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 170:1257–1266
38. Latchman Y, Wood CR, Chernova T et al (2001) PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2:261–268
39. Rosenberg JE, Hoffman-Censits J, Powles T et al (2016) Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 387:1909–1920