

Why are upper tract urothelial carcinoma two different diseases?

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Abstract: In the last few years growing evidence highlighted the differences between upper tract urothelial carcinoma (UTUC) and urothelial bladder carcinoma (UBC) which cannot be explained solely by their different anatomical location. The aim of this review was to summarize current progress in UTUC research and to underline the differences and similarities between UTUC and UBC by focusing on epidemiology, etiology, staging and risk factors as well as on surgical and medical management. UBC and UTUC sharing common risk factors such as smoking and aromatic amines, while aristolochic acid exposure or familiar Lynch syndrome are rather specific for UTUC. The grading of UBC and UTUC are identical, but inherent from their different anatomical locations, there are some differences between their stage classifications. As an example, in contrast to UBC where a clear recommendation for pT3 subclassification exists, in UTUC current research aims to define an adequate subclassification for pelvic pT3 cases aiming to provide a better risk stratification. The primary treatment for both UBC and UTUC is surgery. Similarly to UBC, UTUC patients at high risk of disease progression are treated by radical surgery. However, because of the inaccurate preoperative or transurethral staging of UTUC, many radical nephroureterectomies are performed unnecessarily. Preoperative prediction of pathological stage or patients' prognosis may reduce this overtreatment by selecting patients for nephron-sparing surgery. To this end, predictive models combining histological and molecular features together with imaging data may be used. The antegrade or retrograde instillation of BCG or mitomycin C, as topical agents is feasible after conservative treatment of UTUC or for the treatment of CIS. However, the prognostic significance of lymph node positivity in UTUC seems to be similar to that of UBC, the therapeutic benefit of lymph node dissection (LND) in UTUC has not been firmly established yet. In addition, the number of lymph nodes to be removed and the sequence of lymphadenectomy also remain to be defined. Systemic neoadjuvant and adjuvant chemotherapies appear to have beneficial effect on UTUC survival, however, this has to be confirmed by large prospective studies. Due to the intensive research of the last few years, our knowledge on UTUC has been largely improved, but many questions remained to be answered. Further research on the molecular background of UTUC holds the potential to identify prognostic or predictive markers which, together with imaging and histologic data, may help to overcome the inaccuracy of ureterosopic endoscopy and may therefore help to improve therapeutic decision-making. Further, prospective studies should confirm the benefit of LND and adjuvant chemotherapy. Considering the low incidence of UTUC, conduction of such studies is difficult and may only be performed in a multicenter setting.

Keywords: Upper tract urothelial carcinoma (UTUC); epidemiology; staging; risk factors; predictive tools; chemotherapy

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Introduction

Urothelial carcinomas are the most common malignancies of the urinary tract and are among the most prevalent cancers worldwide. While the majority of urothelial carcinomas affect the urinary bladder, approximately ~5% of all cases are located in the upper urinary tract (1,2). Therefore, upper tract urothelial carcinoma (UTUC) has long been considered simply as a common carcinoma at a rare location. Both arising from the same tissue type, it is not surprising that upper tract urinary carcinoma share several similarities to urothelial bladder carcinoma (UBC). These similarities and its low incidence have determined the therapy of UTUC for a long time by simply adopting clinical decision making based on evidence originally gathered for UBC. In the last few years increasing body of evidence revealed the differences between UCB and UTUC including their etiology and both molecular and pathological characteristics. Therefore, it becomes increasingly evident that these two similar but distinct tumor entities require different diagnostic and therapeutic approaches. Accordingly, since 2011, the European Association of Urology submits guidelines specifically addressing the treatment of UTUC (3). The careful evaluation of their similarities and at the same time to be aware of their differences may help to further improve the management of UTUC. The aim of this review is to summarize our current knowledge on UTUC by pointing out both its similarities and differences to UBC.

Differences in epidemiology and risk factors

Urothelium is the highly specific epithelial lining of the urinary tract which includes the renal pelvis, ureters, bladder and urethra. Malignant transformation of the urothelium is frequent making urothelial carcinoma for the fourth most common tumor (1). UTUC represents a small subgroup of all urothelial carcinomas and accounts for about only 2 cases per 100,000 people each year (2).

The UTUC and UBC show an obvious difference regarding their gender disparity; while UBC occurs 3-4 times more commonly in men than in women, this ratio is 2:1 for men in UTUC (4,5). Furthermore, UBC is diagnosed at more progressed stages and has an inferior survival in women compared to men, however in contrast, no such differences were observed in UTUC (5,6). These differences may probably be explained by their anatomical location, embryological development and hormonal milieu (7).

UBC and UTUC share some common risk-factors. Similarly to UBC, smokers are at 2.5- to 7-fold elevated risk to develop UTUC compared to nonsmokers (8,9). In addition, lifetime cigarette smoking increase the risk of both tumor recurrence and disease-related death by ~25% in UBC and by ~50% in UTUC patients, showing similarities and differences at the same time (10). As UBC and UTUC are urothelial carcinomas, it is not surprising that they are mutually associated as risk factors. However, it is more likely for UBC to develop after UTUC (22-47%) (11-13) than UTUC to develop after UBC (2-6%) (14,15). Further, common risk factors for both UBC and UTUC include phenacetin and occupational risk factors such as aromatic amines, benzidine and b-naphthalene (16).

Beside the above common risk factors, UTUC also has more specific ones. The uneven geographic and familiar distribution pattern of the incidence of UTUC led to the discovery of further important risk factors. Known endemic areas of UTUC include some regions of the Balkan and Taiwan. It has been observed that in some rural villages the endemic Balkan nephropathy is strongly associated with the diagnosis of UTUC elevating its local incidence rate up to 60-100 times. The etiology of this disease however, remained largely unknown for almost 5 decades until women in Belgium were diagnosed with end-stage nephropathy following the use of aristolochic acid containing Chinese herb remedy (17,18) Finally, ~50% of them developed UTUC. Aristolochic acid, as it also produced by *Aristolochia clematitis*—a plant abundantly growing and frequently mixing with wheat in the affected Balkan region—represented the link between the two endemic regions. Subsequent analyses revealed that aristolochic acid caused molecular changes including the formation of aristolactam-DNA adducts in the renal cortex and specific p53 mutations at codon 139 (A:T to T:A) were present in most of these endemic patients (19). Taiwan is a further endemic region of UTUC with the world's highest reported incidence rates (20). Also here, the use of aristolochic acid containing Chinese herbs may be accused for the increased incidence of UTUC (20). A further, however, less clear association between the “black foot disease” and UTUC may also be involved in the increased risk of UTUC in Taiwan. Black foot disease is a vasculitis caused by environmental exposure to arsenic pollution of water and its endemic areas overlap with those of UTUC (21,22).

In addition to environmental risk factors, hereditary genetic alterations may also be involved in the tumorigenesis

of UTUC. Approximately 10–20% of all UTUCs have a hereditary background. It is well established that the incidence of UTUC is 8–25 fold higher in Lynch syndrome (also known as hereditary non-polyposis colorectal carcinoma; HNPCC) (23,24). The *hMLH1* and *hMSH2* are the most commonly damaged genes in Lynch syndrome. If both alleles of one of these genes are affected by mutation, deletion or epigenetic silencing, the mismatch-repair (MMR) function is blocked resulting in the accumulation of damaged genes ultimately leading to cancer formation with colorectal (type I) and sometimes also extra-colonic location such as ovary or upper urinary tract (type II) (24). For urothelial cancers of hereditary origin, the *bMSH2* mutations are more prevalent as those of *bMLH1* (25). To classify UTUC into hereditary and sporadic group the European Guidelines recommend to perform molecular analysis for UTUC patients susceptible for hereditary background based on four criteria: (I) UTUC diagnosis before the age of 60 years; (II) personal history of HNPCC-spectrum cancer; (III) at least one first-degree relative diagnosed with HNPCC under the age of 50 years; or (IV) two first-degree relatives with known HNPCC (without age restriction) (3). The molecular analysis aims to detect loss of MMR function by using immunostaining of MMR genes (*bMLH1*, *bMSH2*), DNA sequencing and microsatellite instability analysis. The loss of MMR function is associated with the resistance against chemotherapeutic agents with DNA-damaging effect (cisplatin, 5-fluorouracil, doxorubicin etc.) (26). The most frequently used radical surgical treatment of UTUC leads to the loss of kidney function that strongly limits the use of chemotherapies. Therefore, the prediction, of which patient will benefit from chemotherapy, is even more important in UTUC than in UBC.

Differences in staging

The diagnostic procedures for UTUC and UBC, using cystoscopy and cytology are similar with some important differences. Urine cytology is less sensitive for UTUC as for UBC, however, a positive cytology with a negative cystoscopy finding is strongly suggestive of UTUC (3). Nevertheless, for definitive diagnosis a positive biopsy is required. Flexible ureteroscopy is used for the visualization and sampling of UTUC. As the lamina muscularis of ureter is thick, ureteroscopic biopsies rarely contain muscle, limiting the accuracy of stage evaluation (11). This anatomical and technical limitation of ureteroscopic sampling is probably

responsible for the higher frequency of upgrading and upstaging in UTUC (27–30) compared to UBC (31–33). In a retrospective study Smith *et al.* performed repeated biopsy after a median of 6 weeks of initial UTUC biopsy and described upstaging (from non-invasive to invasive) in 32%, while upgrading (from low grade to high grade) was observed only in 14% of patients (27). Furthermore, in contrast to UBC, tumor grade in UTUC highly correlates with stage. About 68–100% of UTUC patients with G1 tumors have a tumor stage of \leq pT1, while 62–100% of patients with G3 tumors have a \geq pT2 finding (34). Because of the inaccurate ureteroscopic staging of UTUC and the stronger correlation between grade and pathological tumor stage, it is not surprising that grade contains more relevant pathological information as tumor stage. In accordance, UTUC grade more accurately predicts survival at initial biopsy as tumor stage (35).

Various preoperative models have been constructed to predict pathological tumor stage of ureteroscopic staging. Most of these models include imaging data, biopsy staging/grading and/or cytology findings in various combinations (36–40) (Table 1). These analyses showed that the combination of selected, preoperatively available data may help to overcome the limited accuracy of ureteroscopic staging.

In contrast to UBC currently there is no recommended subclassification for pT3 pelvicalyceal UTUC. This led several authors to propose additional criteria for subclassification of pT3 tumors aiming to reach a more accurate risk-stratification (41–49) (Table 2). Most of the suggested criteria used various cut-offs based on the extent of tumors infiltration into the renal parenchyma and/or perirenal fat. The main limit for the first studies of this topic is that they are focusing on one single stage group with a specific location of a rare disease, necessarily limiting case numbers (14,15). Sassa (Nagoya) divided tumors to those invading the renal medulla *vs.* cortex, Shariat (Cornell) classified pT3 cases into microscopically *vs.* macroscopically renal invasive groups, while Park (Asan) categorized cases according to their invasion into renal parenchyma *vs.* pelvic adiposa (44,46,47). All three authors found their subclassifications prognostic for disease-specific survival (DSS) (46,47). In a subsequent study, Park *et al.* (43) analyzed these three proposed subclassifications in 250 pT3 pelvicalyceal UTUC cases to compare their prognostic value for recurrence-free survival (RFS) and CSS. However, all of these models proved to be prognostic, when predictive accuracy was analyzed by the Harell's c-index

Table 1 Predictive models

Predictive models	N	Included variables	Category	End-point	Accuracy	End-point	Accuracy
Favaretto <i>et al.</i> 2012 (37)	274	Ureteroscopy	High grade	pT2+	70%	NOCD	71%
		Ureteroscopy	Location				
		Hydronephrosis	Present/absent				
		Invasion on imaging	Present/absent				
Margulis <i>et al.</i> 2010 (38)	659	Ureteroscopy	High grade	NOCD	77%	-	-
		Architecture	Papillary/sessile				
		Location	Renal pelvis/ureter				
Brien <i>et al.</i> 2010 (36)	172	Hydronephrosis	Present/absent	pT2+	90%	NOCD	75%
		Ureteroscopy	High grade				
		Urinary cytology	Positive/negative				
Chen <i>et al.</i> 2013 (39)	693	Gender	Male/female	pT2+	79%	-	-
		Architecture	Papillary/sessile				
		Multifocality	Present/absent				
		Location	Ureter/pelvis				
		Grade	G1/G2/G3				
		Hydronephrosis	Present/absent				
Green <i>et al.</i> 2012 (40)	201	TURBT stage	Ta, Tis/T1/T2	pT3+	83%	-	-
		TURBT LVI	Present/absent				
		Abnormal imaging	Present/absent				

NOCD, non-organ confined disease; pT2+, muscle invasive disease; LVI, lymphovascular invasion.

only the Cornell subclassification (47) attained statistical significance (43).

Computer tomography urography (CTU) with at least one image series in the excretory phase (10–15 min) after the administration of contrast medium is the standard imaging technique for the detection and staging of UTUC (3). Its sensitivity for UTUC detection was reported to be between 67% and 100%, while its specificity was found to be between 93% and 99% (50,51). Furthermore, its accuracy for UTUC staging was lower; 59% and 88% (52,53). Hydronephrosis and enlarged lymph nodes may also be observed on CTU images and are associated with poor patients' prognosis (54). Magnetic resonance urography (MRU) shows a wide variability regarding its accuracy in UTUC staging, therefore it is recommended for those patients who are not eligible for CTU (3). The continuously improving imaging techniques hold the potential to overcome the limitations of biopsy in UTUC (55). Endoluminal

ultrasound (56), optical coherence tomography (55), confocal laser endomicroscopy (57), multiparametric MRI (58), ¹¹C choline PET/CT (59), narrow band imaging (60) and high definition ureteroscopy were assessed for their diagnostic and/or staging performance in UTUC in preliminary studies with limited patient numbers.

Differences in surgical treatment

Endoscopic management

Ureteroscopic resection of UTUC is limited to highly selected cases (3,34) and flexible ureteroscope is preferred over the semirigid one. Understaging and undergrading represent a significant risk when performing endoscopic surgery for UTUC (3). On the other hand, the high number of pT_a cases at radical nephroureterectomy (RNU) with low risk of progression suggests that some patients

Table 2 The prognostic value of different subclassifications for pT3 pelvicalyceal upper urinary tract carcinomas

Study	Total number	Criterion	Category	N	Prognosis (5 year)	
					RFS (%)	DSS (%)
Fujimoto <i>et al.</i> 1995 (41)	21	Renal parenchymal inv.	Intraductal inv.	10	–	100
			Microscopic inv.	5	–	~82
			Extensive*	6	–	35
Komatsu <i>et al.</i> 1997 (42)	17	Type of inv.	Renal parenchyma	6	–	100
			Peripelvic and/or periureteral fat	11	–	~25
Yoshimura <i>et al.</i> 2002 (49)	70	Renal parenchymal inv.	Non-extensive	48	–	77
			Extensive*	22	–	25
Wu <i>et al.</i> 2007 (48)	72	Type of inv.	Superficial	18	~89	~88
			Peripelvic fat	10	~74	~76
			Extensive*	25	~46	~42
			Periureteral fat	19	~39	~18
Sassa <i>et al.</i> 2012 (46)	96	Renal parenchymal inv.	Renal medulla only	32	–	~85
			Renal cortex and/or peripelvic fat	64	–	~37
Shariat <i>et al.</i> 2012 (47)	266	Renal parenchymal inv.	Microscopic level	146	~63	~65
			Macroscopic level*	120	~42	~50
Roscigno <i>et al.</i> 2012 (45)	284	Renal parenchymal inv.	Microscopic level	148	~64	~66
			Macroscopic level	136	~55	~61
Park <i>et al.</i> 2014 (44)	44	Type of inv.	Renal parenchyma	13	85	92
			Peripelvic fat	31	61	82
Park <i>et al.</i> 2014 (43)	250	Renal parenchymal inv. (Sassa - Nagoya)	Renal medulla only	100	~75	~83
			Renal cortex and/or peripelvic fat	150	~49	~64
	250	Renal parenchymal inv. (Shariat - Cornell)	Microscopic level	65	~80	~90
			Macroscopic level*	185	~50	~65
	250	Type of inv. (Park - Asan)	Renal parenchyma	122	~68	~82
			Peripelvic fat	128	~50	~62

*, invasion >5 mm from basement membrane. inv, invasion; DSS, disease-specific survival; RFS, recurrence-free survival.

would benefit from a ureter preserving treatment strategy. Improvement in risk-stratification together with the widespread use of flexible ureterorenoscopy made this treatment option available for patients with low-risk UTUC who are consenting to undergo strict surveillance (3,34,61,62).

Organ preservative surgery

Open nephron-sparing surgery for UTUC is mostly

performed in imperative indication in patients with renal insufficiency, solitary kidney or synchronous bilateral tumors (63). Maier *et al.* evaluated the largest series of 55 patients undergoing nephron-sparing surgery in a multicenter protocol. They reported ~70% RFS and OS rate at a mean follow-up of over 40 months (64).

Organ preserving procedure for noninvasive low-grade tumors with proximal or mid-ureter location can be recommended, for those cases which cannot be

endoscopically managed. Partial ureteral resection should be performed with wide margins to provide adequate specimens for pathological evaluation while preserving the ipsilateral kidney (3).

In patients with high-grade or invasive tumors partial ureter resection and anastomosis can be performed if renal-sparing surgery is an imperative indication when renal function preservation is the preferred goal.

Open radical surgery

For high-risk UTUC similar to UBC open radical surgery is the standard of care. However, the management of lymph nodes regarding both extent and templates are much more controversial for UTUC patients (63,65,66).

In contrast to well-established benefit of lymph node dissection (LND) during radical cystectomy, the role of LND during RNU is less obvious and therefore its performance is at the discretion of the surgeon. Only limited data are available on the impact of LND on clinical outcomes of UTUC patients. Komatsu *et al.* (42) analyzed 36 patients who underwent complete RNU and LND concluded that LND may offer a therapeutic advantage for selected patients with lymphatic metastasis. Furthermore, LND may help to select patients for adjuvant chemotherapy if an effective regimen is established. Miyake and coworkers (67) evaluated 72 patients who underwent RNU with or without LND for primary UTUC. They found therapeutic advantage for patients who underwent LND, especially when lymph vessel invasion was absent.

Brausi and coworkers compared the RFS and DSS in pT2-pT4 UTUC patients who underwent RNU with or without retroperitoneal LND. They found significantly better survival for patients who received LND compared to those who not. They advocated that an extended LND could be curative in patients with advanced UTUC. However, they considered neither the number of removed lymph nodes nor the template of LND (68). Similar results were found by Roscigno *et al.* (69) examined the role of LND on RFS and DSS in a series of 132 pT2-pT4, RNU-treated UTUC patients. The 95 patients who received LND in addition to RNU had a significant better RFS and DSS compared to those who were managed with RNU without LND. About 27% (26/95) of patients had nodal metastases in the LND group. Similar lymph node positivity rates (~28%) were found by Secin *et al.* in a further LND series (70). They also showed that CT has only a limited accuracy in the prediction of positive lymph

nodes (70). Further studies and a recent meta-analysis consequently found LND to provide a survival benefit only in muscle-invasive UTUC (71,72). Overall, the presence of lymph node metastasis seems to have a similar impact on survival in UTUC as in UBC patients.

Further important questions are the number of lymph nodes to be necessarily removed for accurate staging and also the sequence of LND. Roscigno found that the excision of at least 8 lymph nodes provides an independent prognostic benefit for patients and a 75% probability to find one or more positive nodes. However, this study did not consider the template of LND (73). Kondo *et al.*, in a study on 42 node positive UTUC patients, proposed a LND template based on the location of the primary tumor (74). They proposed a more extended LND when the tumor is located to the right renal pelvis or the upper two-thirds of the ureter. In a following study, they further extended their recommendation also to interaortocaval nodes (75). Using this updated recommendation the same group in a prospective study with 77 N+M0 cases, recently demonstrated significant longer DSS and OS for patients with muscle-invasive UTUC who underwent template-based LND compared to those without LND. Template-based LND proved to be an independent prognostic factor in the subgroup of UTUC with renal pelvic location but not for tumors with ureteral involvement (75). In a recent study, Matin *et al.* (76) retrospectively analyzing 77 N+M0 UTUC patients confirmed that the lymphatic spread of UTUC is strongly determined by the anatomical location of the primary tumor and suggested similar LND-template as Kondo (74). Other authors also recommended to include the presacral lymph nodes in the regional lymph node template (77). Taken together, similar LND templates with only small differences have been proposed by independent studies, however, multicenter prospective analyses are still lacking to provide high grade evidence for their benefit.

Laparoscopic surgery

The number RNUs performed by laparoscopic surgery is increasing. The few available data on the long-term oncological outcomes with this surgical technique are encouraging (16). There are even more options for laparoscopic techniques than in open procedure, from hand assisted to the robotic-assisted, retroperitoneal to transperitoneal ways. The outcomes with these approaches mostly depend on the surgeon's experience (17,18). One of the major concerns with laparoscopic RNU is the limited

ability to adequately perform LND. As a consequence LND is far less frequently performed when RNU is done laparoscopically compared to open RNU (78).

Differences in medical treatment

The role of peri-operative chemotherapy is important in the treatment of UBC and UTUC. The key problem of medical treatment of UTUC is that it mainly derived from experiences initially made on bladder cancer. For both locations the discussion should be divided for superficial/non-muscle invasive and advanced/muscle invasive groups. In non-muscle invasive bladder cancer intravesical chemotherapy and immunotherapy are essential components of standard care to avoid recurrence and progression (79). More than one-third of endoscopically treated UTUCs will recur. Other authors reported up to 70% recurrence rate in the upper tract after kidney sparing surgery (80). To reduce recurrence adjuvant immunotherapy or chemotherapy can be used.

The methods to achieve appropriate concentrations of immuno/chemotherapy agents during instillation in UTUC are difficult. Infusion through a percutaneous nephrostomy tube, retrograde ureteral catheter or retrograde reflux from the bladder with an indwelling double-J stent is all acceptable methods for the instillation. The aim of the treatment is a continued exposure of urothelium to the local agent while maintaining a low-pressure system that is free of infection (63). For the antegrade instillation a nephrostomy should be inserted for the whole period of adjuvant treatment, which impairs the patients' quality of life. The intrarenal pressure should keep below 25 cmH₂O during antegrade filling. The main criticism of percutaneous instillation is the risk of tumor recurrence through seeding of cancer cells at the puncture site. However, it seems only to be a theoretical risk since seeding after adjuvant percutaneous therapy has not been reported yet in the literature (81). Retrograde instillation of topical agent using an indwelling double-J stent is advised to start with a cystogram performed in Trendelenburg position in order to determine the volume necessary to reach appropriate retrograde reflux from the bladder (82). According to Yossepowitch *et al.*, only 59% of patients had reflux after cystography in the presence of a double-J stent (83). The major concern with ureteric stents is the increased risk of mucosa injury and the possibility of ureteric obstruction that will lead to a subsequent pyelovenous influx during instillation. With a perfect instillation technique the topical

agent should remain at the tumor site for a sufficient period to cause a satisfactory antitumor effect, with a relative short duration of exposure.

Some types of intravesical therapies used to treat UBC can also be used for UTUC. Several chemotherapeutic and immunomodulatory agents have been tested in the upper tract: BCG, mitomycin C, epirubicin, thiotepa, BCG/interferon (84). The most common agents instilled are BCG or mitomycin C (85). Eastham *et al.* examined the use of mitomycin C after endoscopic resection of superficial UTUC. Systemic side effects were not seen with mitomycin C perfusion. Five out of seven patients had no evidence of the disease (86). According to Martínez-Piñeiro *et al.*, the recurrence rate of UTUC treated by endourological approach decrease from 24% to 12.5% with adjuvant BCG instillation and to 14% with adjuvant mitomycin C instillation (87). In a retrospective analysis, Thalmann *et al.* found no tumor seeding along the nephrostomy tract and BCG therapy did not alter renal function. The authors concluded that BCG therapy of papillary UTUC does not prevent recurrence or progression but might prevent high risk patients from dialysis. However, BCG did provide cure in approximately 50% in CIS of the upper urinary tract (88). Katz *et al.* reported their results with BCG and interferon- α 2B therapy using a retrograde instillation for UTUC. Eight patients (80%) demonstrated a complete response to therapy, and 2 had a partial response without any side effects or complications (89). Giannarini *et al.* showed 40% recurrence and 5% progression rate when treating CIS in the upper urinary tract and no encouraging results for Ta/T1 lesions with the same method (90). Similarly, Rastinehad *et al.* showed no significant benefit with adjuvant BCG perfusion in Ta/T1 tumors (81). Jabbour *et al.* found lower recurrence rate in grade 1 tumors treated with BCG (14%) compared to the control, non BCG group (50%) (91). According to Kojima *et al.* topical instillation of BCG can be used with curative intent in CIS, as the authors concluded that BCG therapy was as effective as RNU in the long-term outcomes (92). Topical instillations of the upper urinary tract appear to be safe as the major complications like BCG dissemination and secondary urosepsis are relatively rare. Renal function was not impaired after instillations of BCG or mitomycin C, preserving patients' quality of life (93).

In muscle-invasive UBC intravenous chemotherapy is important in the standard of care. Data from a randomized phase III study demonstrated a survival advantage for neoadjuvant cisplatin-based combination chemotherapy in UBC (94). According to consensus opinion patients with

pT3–4 disease or lymph node involvement likely benefit from adjuvant chemotherapy (63). Because of the low incidence of advanced UTUC, neoadjuvant and adjuvant chemotherapy settings are based on experience from UBC. There are two major components in the decision making for these patients. First, the loss of renal function that occurs with RNU can alter the administration of appropriate postoperative cisplatin-based chemotherapy. Before nephrectomy only 49% of patients have a GFR that allows cisplatin based chemotherapy and this decreases to 19% after nephrectomy. Second, before neoadjuvant chemotherapy patients are just clinically staged and there is a risk for upstaging or downstaging on final pathologic evaluation.

The goal of neoadjuvant chemotherapy is to cure subclinical metastases and decrease the size of primary tumor. Patients tolerate much better chemotherapy before surgery and higher doses can be delivered for them, but neoadjuvant chemotherapy may have a negative effect on the non-responder patients due to the delayed surgery. Igawa *et al.* showed an 53% overall response rate of using cisplatin-based neoadjuvant chemotherapy (MVAC, MEC, MVEC) in locally advanced UTUC (95). Matin *et al.* reported significantly higher pathologic downstaging and 14% complete response with neoadjuvant chemotherapy in high grade UTUC patients (96). Porten *et al.* showed significant improvement in OS and DSS with neoadjuvant chemotherapy compared to RNU alone (97).

On the other hand, adjuvant chemotherapy appears to have a limited role in advanced UTUC treatment. Adjuvant chemotherapy can achieve a recurrence-free rate $\leq 50\%$ (98). Lee *et al.* reported no significant differences in RFS and DSS between adjuvant chemotherapy and control groups for pT3N0M0 UTUC patients (99). Soga *et al.* published significantly lower recurrence rate in the adjuvant MVAC chemotherapy UTUC patients, compared to the control group (100). Kwak *et al.* demonstrated the therapeutic benefit of adjuvant chemotherapy in invasive but non-metastatic UTUC patients, where the RFS rate was higher in the chemotherapy group (101). Hellenthal *et al.* showed a retrospective data analysis of T3–4 and/or node positive, non-metastatic UTUC patients. There was no significant difference in OS or DSS between adjuvant chemotherapy and control group (102). Thus specific clinical characteristics of each individual patient (renal function, comorbidities, tumor location, grade, stage and molecular markers) should take into account at the decision making. Recent studies suggested that adjuvant chemotherapy may provide benefit only for high risk patients

with pT3–4 UTUC and lymph node involvement (103). Further prospective trials are needed to assess the role of perioperative chemotherapy in advanced UTUC and also studies with concurrent chemoradiotherapy are eagerly awaited.

Conclusions

UTUC and UBC are two different tumor entities with many important similarities. These similarities on the one hand providing advantages, as some diagnostic and treatment methods can be adapted more easily from UBC, but on the other hand, disregarding the characteristic differences between UTUC and UBC may result in treatment failure.

Current research gained more insight into the characteristics of UTUC providing more detailed information for optimal treatment-decision. Multiple predicting models may help to overcome the inaccuracy of ureteroscopic staging which represents one of the major problems of UTUC management. A more accurate preoperative risk stratification may help to select patients for kidney-sparing surgery. Further collaborative clinical studies are urgently needed to evaluate the benefit of LND and chemotherapy in UTUC.

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Footnote

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