Upper urinary tract urothelial carcinoma: what have we learned in the last 4 years?

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***Abstract*:** In the last 4 years many studies have been published on the topic of upper urinary tract urothelial carcinoma (UTUC). This is a recent review of the available literature of the last 3 years. A systematic Medline/PubMed search on UTUC including limits for clinical trials and randomized, controlled trials was performed for English-language articles using the keywords 'upper urinary tract carcinoma', 'nephroureterectomy', 'laparoscopic', 'ureteroscopy', 'percutaneous', 'renal pelvis', 'ureter' and their combinations from January 2008 to December 2010. Additional selected reports from 2007 were included. Case reports and non-English literature were excluded. Publications were mostly retrospective, including some large, multicentre studies from the Upper Tract Urothelial Carcinoma Collaboration (UTUCC). The authors of this article are members of the UTUCC. Altogether, 92 original articles dealing with UTUC were identified and summarized. The vast majority of the available literature has a low level of evidence (level IV), although many multicentre studies tried to overcome the problem of low numbers by pooling data. It was concluded that in the last 3 years our knowledge regarding UTUC has increased dramatically, although new study concepts allowing us to increase the level of evidence are needed.

***Keywords*:** upper tract urothelial carcinoma, nephroureterectomy, laparoscopic, endoscopic, ureter, renal pelvis

Introduction

Upper urinary tract urothelial carcinoma (UTUC) comprises approximately 10% of renal neoplasms and around 5% of urothelial carcinomas [Oosterlinck *et al*. 2004; Munoz and Ellison, 2000]. Minimally invasive organ-sparing endoscopic procedures have shown favourable survival data in select patients with small, low-grade tumours. These methods, however, are troublesome because of high recurrence rates requiring regular endoscopic evaluation of the affected upper urinary tract [Zigeuner and Pummer, 2008]. Consequently, radical nephroureterectomy (RNU) with excision of an ipsilateral bladder cuff remains the gold standard for treatment [Margulis *et al*. 2009; Zigeuner and Pummer, 2008; Oosterlinck *et al*. 2004].

After RNU in clinically nonmetastatic disease, a significant proportion of patients will experience disease recurrence and subsequently die from metastatic UTUC. While the benefit of (neo)adjuvant therapies remains to be proven [Koppie *et al*. 2008; Zigeuner and Pummer, 2008], identification of patients at high risk of failure with RNU alone is important for accurate prognostication, patient counselling, and design of clinical trials using integrated multimodal therapy.

To date, however, most of our clinical decision making is based on tumour stage and grade [Langner *et al*. 2006]. The accuracy of these two parameters alone is, however, suboptimal for accurate prognostication/prediction. Owing to the relative sparseness of UTUC, identification, testing and validation of additional prognostic parameters has been limited to relatively small single-centre studies. To circumvent these limitations, several institutes and authors, including the authors of the present study, have created a large international collaboration group called the Upper Tract Urothelial Carcinoma Collaboration (UTUCC). The combined efforts and experience of 22 centres worldwide in the UTUCC has led to a multitude of studies investigating the natural history, prognostic factors and clinical outcomes of UTUC. In this article

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we review the recent findings from this and other groups in UTUCC.

Material and Methods

A systematic Medline/PubMed search on upper tract urothelial carcinoma review including limits for clinical trials and randomized controlled trials was performed for English language articles using the keywords 'upper urinary tract carcinoma', 'nephroureterectomy', 'laparoscopic', 'ureteroscopy', 'percutaneous', 'renal pelvis', 'ureter' and their combinations from January 2008 to December 2010. Additional selected reports from 2007 were included. Case reports or non-English literature were excluded. Publications were mostly retrospective, including some large, multicentre studies from the Upper Tract Urothelial Carcinoma Collaboration (UTUCC). The authors of this article are members of the UTUCC. Altogether 92 original articles dealing with UTUC were identified and summarized.

Results

Prognosticators

Tumour architecture. Remzi and colleagues found that papillary tumour architecture was an independent prognosticator in patients treated with RNU ($n = 1363$) for both recurrence rate and cancer-specific survival (CSS). It was also stated that papillary tumour architecture might be surrogate marker for endoscopic treatment of UTUC [Remzi *et al.* 2009]. Similar results were found by another group [Fritsche *et al.* 2011].

Preoperative hydronephrosis. In patients with bladder cancer, the presence of hydronephrosis at the time of diagnosis is associated with poorer outcomes [Divrik *et al.* 2007]. Ng and colleagues investigated the impact on UTUC and found that hydronephrosis was a predictor of nonorgan-confined disease on final pathology (hazard ratio [HR] 3.7, $p < 0.01$), was independently associated with cancer metastasis (HR 8.2, $p = 0.02$) and cancer-specific death (HR 12.1, $p = 0.03$) [Ng *et al.* 2011]. Similarly, Brien and colleagues described preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology as markers for advanced UTUC [Brien *et al.* 2010].

Tumour necrosis. Tumour necrosis is an independent predictor in clear cell renal carcinoma and is part of the Mayo Clinic Stage, Size, Grade, and Necrosis (SSIGN) Score [Leibovic *et al.* 2005]. Two international studies of the UTUCC [Seitz *et al.* 2010; Zigeuner *et al.* 2009] and one single-centre study [Simone *et al.* 2008] evaluated the impact of tumour necrosis on recurrence and survival after RNU. Zigeuner and colleagues described extensive tumour necrosis in 364 patients (25.5%). Tumour necrosis was associated with advanced tumour stage, high tumour grade, sessile architecture, lymphovascular invasion (LVI), concomitant carcinoma *in situ* and lymph node metastasis (all $p < 0.0001$). Extensive tumour necrosis was independently associated with disease recurrence and survival after adjusting for the effects of pathologic stage, grade, LVI and lymph node status ($p = 0.037$ and $p = 0.046$, respectively). The addition of extensive tumour necrosis to a base model comprising standard pathologic predictors marginally improved its predictive accuracy for both cancer-specific recurrence and CSS (1.4% for both). Although Seitz and colleagues also revealed a significant association between tumour necrosis and high grade, lymph node metastasis, LVI, sessile tumour architecture and concomitant carcinoma *in situ*, tumour necrosis was not an independent predictor for recurrence (HR 1.1, $p = 0.49$) or cancer-specific mortality (CSM) (HR 1.1, $p = 0.51$) in 754 patients. Thus, no final conclusion can be drawn for tumour necrosis as an independent prognosticator for UTUC.

Age. Shariat and colleagues showed in multivariable analyses that being older was associated with decreased all-cause (>60 years) and CSS (>80 years) after controlling for the effects of standard pathological features ($p \leq 0.006$). However, the addition of age did not improve the predictive accuracy of a base model that included standard pathological features for prediction of disease recurrence. Interestingly, even elderly patients had effective local disease control with RNU. Therefore, elderly patients should not be denied potentially curative RNU [Shariat *et al.* 2009].

Gender differences

The majority of patients with UTUC are male. Fernandez and colleagues and Shariat and colleagues found no difference in histopathologic features and outcomes between men and women treated with RNU for UTUC [Shariat *et al.* 2011; Fernandet *et al.* 2009]. In contrast, Lughezzani and colleagues found, based on a

Surveillance, Epidemiology, and End Results (SEER) database, that females were more likely to have more advanced pathologic T stage and higher tumour grade at RNU than males [Lughezzani *et al.* 2010b]. After accounting for other-course mortality, stage, grade, and noncancer characteristics, gender no longer affects CSM. Relative to males, females had a higher proportion of pT3 UTUC (43.1% *versus* 39%; $p = 0.02$) and a higher proportion of grade III/IV UTUC (63.8% *versus* 59.8%; $p = 0.04$) at RNU. The female gender represented an independent predictor of pT3 UTUC at nephroureterectomy (HR 1.15, $p = 0.03$).

Male gender was independently associated with higher intravesical recurrence rates in a large Japanese trial after laparoscopic (L)-RNU, after hand-assisted RNU [Kamihira *et al.* 2009] and also in a Taiwanese trial [Huang *et al.* 2009].

Tumour location

A study from UTUCC investigated the predictive value of tumour location (ureter *versus* renal pelvis) in a large cohort of patients ($n = 1249$). There was no difference in the probability of disease recurrence (HR 1.22, $p = 0.133$) or cancer death (HR 1.23, $p = 0.25$) between ureteral and renal pelvic tumours [Raman *et al.* 2010]. Isbarn and colleagues presented similar results [Isbarn *et al.* 2009]. Relative to ureteral tumours, renal pelvis tumours were of higher stage (T3/T4 disease 38.4% *versus* 57.9%, $p = 0.001$) and had a higher rate of lymph node metastases (6.0% *versus* 9.8%, $p = 0.003$) at nephroureterectomy. The respective 5-year CSM-free survival estimates were 81.0% *versus* 75.5% ($p = 0.007$). However, after multivariable adjustment tumour location failed to reach independent predictor status of CSM ($p = 0.8$). In contrast a Taiwanese study showed that UTUC of the ureter had worse outcomes compared with renal pelvis UTUC [Tan *et al.* 2008].

Time to surgery

Two contradictory studies were published in the last 3 years. First Waldert and colleagues showed in a subgroup of patients ($n = 90$, 48.1%) who had muscle-invasive disease (≥pT2) that delay from diagnosis to RNU was associated with advanced stage ($p = 0.030$), higher grade ($p = 0.014$), infiltrative tumour architecture ($p = 0.044$), LVI ($p = 0.034$), disease recurrence ($p = 0.02$) and CSM ($p = 0.03$) [Waldert *et al.* 2009]. The other study showed no difference in survival between patients undergoing early *versus* delayed extirpative surgery for UTUC [Sundi *et al.* 2011]. Thus, further prospective studies are needed to have a deeper insight of this important issue.

New diagnostic tools for UTUC

Nomogram. A nomogram including tumour grade, architecture and location of the tumour achieved 76.6% accuracy in predicting nonorgan-confined UTUC and can be used for designing clinical trials, selecting patients for preoperative systemic therapy and guiding the extent of concomitant lymph node dissection (LND) at RNU [Margulis *et al.* 2010].

Fluorescence in situ hybridization. Prediction by fluorescence *in situ* hybridization (FISH) assay was significantly higher than that for the corresponding urine cytology (76.7% *versus* 36%, respectively, $p = 0.0056$) in prediction of UTUC in 30 consecutive patients with UTUC and 19 healthy controls. Specificities for FISH and cytology were 94.7% and 100%, respectively ($p =$ ns). The positive and negative predictive values for FISH were 95.8% and 72%, whereas for cytology they were 100% and 54%, respectively [Marin-Aguilera *et al.* 2007]. The detection of molecular abnormalities by FISH is becoming more popular for UTUC early detection and surveillance, but results are still preliminary [Mian *et al.* 2010; Luo *et al.* 2009b]. UroVysion® is a multitarget FISH system containing probes specific for the centromeres of chromosomes 3, 7, and 17 and for the p16 locus at 9p21. The sensitivity of FISH for the identification of UTUC parallels its performance in bladder cancer [Herman *et al.* 2008]. Results from recent studies have shown that FISH was an important adjunct in the detection of UTUC, with a sensitivity of 76.6–100% and a specificity of 97.4–100% [Mian *et al.* 2010; Akkad *et al.* 2007; Nieder *et al.* 2007; Fromont *et al.* 2005]. However, the preponderance of low-grade, recurrent disease in the population undergoing surveillance and minimally invasive therapy for UTUC may limit its usefulness [Johannes *et al.* 2010; Chen and Grasso, 2008; Nieder *et al.* 2007]. In a recent, well-designed, retrospective study, the sensitivity of FISH was 54% and its specificity was 78% [Mian *et al.* 2010]. Taken together, FISH is becoming a new adjunct in the early detection and management of UTUC, especially in cases of clinical suspicion with negative or equivocal

cytology. Invasive sampling methods with washing or brushing cytology may improve the detection by FISH [Mian *et al.* 2010].

Role of lymphadenectomy

LVI was an independent predictor of poor outcome in a large multicentre trial ($n = 1453$) [Kikuchi *et al.* 2009] and in single-centre series ($n = 76$, $n = 136$, $n = 271$) [Kim *et al.* 2010; Bolenz *et al.* 2008; Chung *et al.* 2008].

Busby and colleagues compared LND during laparoscopic and open (O)-RNU and found no difference between the techniques [Busby *et al.* 2008]; however, performing LND is surgeon dependent [Secin *et al.* 2007] and even the templates suggested by Kondo and colleagues for LND depending on the tumour location, the necessity, the number and the size are still unclear [Kondo *et al.* 2010]. LND seems to also have an impact on node-positive patients [Bolenz *et al.* 2009]. In another study, 76 out of 293 patients developed disease relapse. Regional lymph node recurrence was the most common site (34 patients). On multivariate analyses that adjusted for the effect of tumour stage and tumour grade, pNx (skipping LND) was an adverse factor not only for locoregional recurrence, but also for distant relapse. Immunohistochemistry identified micrometastases in seven (14%) of 51 patients [Abe *et al.* 2010]. However in the study by Lughezzani and colleagues analysing 2824 patients from the SEER database, LND showed no benefit in patients with N0 status compared with Nx status. [Lughezzani *et al.* 2010a]. In addition, Roscigno and colleagues addressed CSM rates according to lymph node status at RNU for UTUC ($n = 1130$) [Roscigno *et al.* 2009]. They suggested that LND should be performed in patients with suspected T2–4 stages, to improve the prediction of the natural history of surgically treated UTUC and to use this information for possible adjuvant chemotherapy.

Thus, the majority of recent studies suggest an impact of LND, especially in advanced stages, although it is still unclear how to define the right patient, the right LND template and the extent of LND.

Role of technique during RNU

Outcomes. In the last 3 years many studies [Walton *et al.* 2011; Favaretto *et al.* 2010; Capitanio *et al.* 2009; Greco *et al.* 2009; Waldert *et al.* 2009; Hemal *et al.* 2008; Li *et al.* 2008; Terakawa *et al.* 2008] compared the results of O-RNU and L-RNU. Short-term oncologic data on L-RNU are comparable to O-RNU. Since L-RNU was selectively performed in favourable-risk patients, we cannot state with certainty that O-RNU and L-RNU have the same oncologic efficacy in poor-risk patients. Long-term follow-up data and morbidity data are necessary before LNU can be considered as the standard of care in patients with muscle-invasive or high-grade UTUC. A study from the Cleveland Clinic including 100 L-RNU had the longest follow-up until today (median 7 years). Oncological results were comparable to O-RNU [Berger *et al.* 2008].

However, in the only low-powered randomized trial by Simone and colleagues it was shown that L-RNU had similar results to O-RNU in organ-confined disease only, whereas it was inferior in advanced disease [Simone *et al.* 2009]. When matched for pT3 and high-grade tumours, CSS and metastases-free survival were significantly different between the two groups in favour of O-RNU ($p = 0.039$ and $p = 0.004$, respectively, for pT3 tumours; $p = 0.078$ and $p = 0.014$, respectively, for high-grade tumours). A major drawback of this study was the low number of patients with only 13 and 12 pT3 patients in the O-RNU and L-RNU group, respectively.

In all studies L-RNU was associated with less blood loss and the advantages of laparoscopy compared with open surgery [Walton *et al.* 2011; Favaretto *et al.* 2010; Capitanio *et al.* 2009; Waldert *et al.* 2009; Hemal *et al.* 2008; Li *et al.* 2008; Terakawa *et al.* 2008; Schatteman *et al.* 2007]

Technical changes. A gasless hand-assisted retroperitoneoscopic nephroureterectomy (HARNU) without hand-ports was introduced [Luo *et al.* 2009a]. Experiences with robot-assisted L-RNU with and without repositioning of the patient have also been reported in nine patients [Hu *et al.* 2008].

Of course L-RNU can be performed with a robot [Eandi *et al.* 2010] or with a hand-assisted port. However, in a large Japanese trial, hand-assisted L-RNU was independently associated with higher intravesical recurrence rates [Kamihira

et al. 2009]. In contrast, Chung and colleagues described no differences in bladder recurrences after hand-assisted RNU and O-RNU (19% *versus* 32%, $p = 0.56$) [Chung *et al.* 2009].

Bladder cuff. Discussions about the optimal approach for the bladder cuff during L-RNU are ongoing. Ghazi and colleagues described their pure laparoscopic technique in eight patients using an additional 5-mm trocar. The distal ureter is mobilized with dissection of the medial umbilical ligament and the bladder is opened to resect the bladder cuff including the whole orifice [Ghazi *et al.* 2010]. Another approach without opening the urinary tract using a bulldog clamp at the orifice has been described by Cho and colleagues [Cho *et al.* 2010]. Hora and colleagues compared his new antegrade mini-invasive nephroureterectomy (AMNUE; $n = 12$) with O-RNU ($n = 7$), L-RNU with open ureterectomy ($n = 8$) and complete laparoscopic nephroureterectomy ($n = 8$). He found AMNUE to be fast, safe and easy, lowering the risk of possible spillage during L-RNU. The main disadvantage of AMNUE was the need to reposition the patient [Hora *et al.* 2009]. Another approach uses a pneumovesicum introducing trocars into the bladder for endoscopic bladder cuff excision [Guzzo *et al.* 2008], and another description for the management of the distal ureter included circumscribed resection of the ureteric orifice with a bladder cuff using a Collins knife and a ligation of the ureteric stump via cystoscope to avoid urine spillage from the upper tract [Agarwal *et al.* 2008]. Mueller and colleagues described a modification of the Pluck technique injecting ureteral fibrin sealant before using the Collins knife to dissect the orifice until the extravesical fat [Mueller *et al.* 2010].

A comparison of three different techniques including intravesical incision, extravesical incision, and transurethral incision showed no differences regarding bladder recurrence (23.5%, 24.0% and 17.6%, respectively; $p = 0.485$), local retroperitoneal recurrence (7.4%, 7.8% and 5.5%, respectively; $p = 0.798$), contralateral recurrence (4.9%, 3.9% and 2.2%, respectively; $p = 0.632$) and distant metastasis (7.4%, 10.4% and 5.5%, respectively; $p = 0.564$) in 301 patients. There were no differences in recurrence-free and CSS among the three groups ($p = 0.680$ and $p = 0.502$, respectively) [Li *et al.* 2010].

As seen by the number of publications dealing with the technique of bladder cuff resection during L-RNU this is still an unsolved problem, however, bladder cuff excision during RNU remains standard [Lughezzani *et al.* 2010c]. This standard is in up to 25.8% of patients neglected who had undergone incomplete ureteral resection at the time of RNU [Abouassaly *et al.* 2010].

To obtain the optimal outcome after RNU, especially after L-RNU, the following precautions must be taken:

a. avoid opening of the urinary tract;
b. avoid direct contact to the tumour with instruments or hands;
c. do not use mocellation and extract the entire specimen *en bloc* in an organ bag.

Predictors of survival and recurrence after RNU

See Table 1 for a description of predictors of survival and recurrence after RNU.

Concomitant carcinoma *in situ* and tumour size were predictors for bladder cancer recurrence [Pieras *et al.* 2010]. In a series 196 patients bladder recurrence was lower in patients who received mitomycin C or epirubicin compared with those who did not received anything (29.0%, 25.9% and 41.3%, respectively) [Wu *et al.* 2010].

Novara and colleagues found that only history of bladder cancer before RNU was an independent risk factor for metachronous recurrence which was found in 6% of patients ($n = 234$) [Novara *et al.* 2009]. Youssef and colleagues underlined the prognostic impact of previous bladder cancer. In their study, patients with positive bladder cancer Carcinoma *in situ* (CIS) history had greater risk of recurrence and death from UTUC after RNU [Youssef *et al.* 2011].

Outcomes after endoscopic organ-sparing management

RNU is the standard treatment for UTUC. Alternative management is considered, because preserving the renal function and/or reducing morbidity of the treatment while having excellent oncological results is attractive. Alternative treatment can be sufficient in selected patients, especially in those with small, low-grade UTUC.

Table 1. Selected studies showing independent predictors for 5-year cancer-specific survival (CSS) after treatment of upper urinary tract urothelial carcinoma (UTUC) with radical nephroureterectomy (RNU).

Study	Number of patients (mean age years)	Independent predictors on multivariate analyses [Hazard ratio]	5-year CSS	Mean follow up (months)
[Novara *et al.* 2007] (multicentre, 3 centres)	269 (68)	Prior bladder cancer [1.743]	76%	34
		Prior muscle-invasive bladder cancer [4.687]		
		Multifocality [2.971]		
		Pathologic stage [3.346]		
		N-Stage [2.978]		
[Margulis *et al.* 2009] (multicentre, 12 centres)	1363 (70)	Stage T2 [2.811]	73%	51
		T3 [5.168]		
		T4 [11.04]		
		N-Stage [1.713]		
		Grade (high *versus* low) [1.745]		
		Lymphovascular invasion [1.370]		
		Tumour architecture papillary/sessile [1.532]		
[Li *et al.* 2009] (single centre)	145 (65)	Stage T3 [9.479]	75%	—
		T4 [62.79]		
		Severe chronic kidney disease [7.089]		

Ishikawa and colleagues underlined that diagnostic ureteroscopy was no risk factor for intravesical recurrence and survival in UTUC patients [Ishikawa *et al.* 2010]. Diagnostic ureteroscopy with cytology and biopsies to determine tumour grade as a surrogate marker for the aggressiveness of the underlying tumour should be performed in the case of endoscopic treatment [Williams *et al.* 2008]. Large size, broad base and nonpapillary pattern favour tumour invasiveness. If necessary, biopsies can be done with flexible instruments or percutaneously. In a Dutch study, an increasing time trend was found for endoscopic treatment [Cauberg *et al.* 2009].

Lucas and colleagues compared 27 low-grade (median follow up of 29 months) and 12 high-grade (median follow up of 53 months) tumours treated endoscopically with 21 low-grade (median follow up of 38 months) and 56 tumours treated immediately with RNU (median follow up of 49 months). Seven patients treated endoscopically had stage or grade progression and had delayed nephroureterectomy. The mean CSS at 5 years in patients with low-grade disease was equally good for conservative treatment and immediate nephroureterectomy, ($86.2 \pm 9.1\%$ *versus* $87.4 \pm 8.4\%$, $p = 0.909$). Ten out of the 12 high-grade tumours had an imperative indication for endoscopic treatment and four required delayed nephroureterectomy. The 5-year CSS for the conservative and immediate nephroureterectomy groups were $68.6 \pm 8.6\%$ *versus* $75.0 \pm 8.1\%$, $p = 0.528$ [Lucas *et al.* 2008]. Similarities were reported by several other authors [Gadzinski *et al.* 2010; Dragicevic *et al.* 2009]. However, at least one recurrence is very common (up to 86%) [Gradzinski *et al.* 2010] and close surveillance including invasive procedures (ureteroscopy) are necessary. One tool to ablate UTUC is the use of a laser. A Japanese group reported their experience using the neodymium–YAG and/or holmium laser in 15 patients and the local recurrence rate was 33%. Six patients developed 13 bladder cancer recurrences. The authors stated that this kind of approach is also feasible in selected patients with low-grade disease and normal contralateral kidney [Tada *et al.* 2010]. Thompson and colleagues from the Mayo Clinic underline this statement describing their experience in 22 patients treated endoscopically for UTUC in patients with a normal contralateral kidney [Thompson *et al.* 2008].

With experience, good results can be also achieved with flexible ureteroscopy only. Cornu and colleagues after a median follow up of 30 months (range 12–66 months) reported a recurrence in 21 out of 35 patients (60%). The median survival rate without recurrence was 10 months (95% CI 5–22). Four patients underwent nephroureterectomy during follow up and none of the patients died of disease progression [Cornu *et al.* 2010].

Irwin and colleagues described percutaneous treatment in complex situations: (a) tumour size >2.5 cm ($n = 8$); (b) preoperative creatinine level >3.0 mg/dl ($n = 3$); or (c) anatomic variant (cystectomy/urinary diversion [$n = 2$]; autotransplanted kidney [$n = 1$]; ipsilateral partial nephrectomy [$n = 1$]; distal ureterectomy [$n = 1$]). These were compared with noncomplex patients ($n = 23$). After a median follow up of 36 months, no differences were seen in CSS ($p = 0.98$), recurrence-free survival ($p = 0.39$) and complication rates [Irwin *et al.* 2010]. However, seeding of the percutaneous track with urothelial cancer cells can occur with catastrophic consequences.

Role of segmental ureterectomy and others, rather than endoscopic organ-sparing surgery

Jeldres and colleagues showed by analysing SEER data that segmental ureterectomy ($n = 569$) compared with RNU ($n = 1222$) showed 5-year CSM-free rates for segmental ureterectomy *versus* nephroureterectomy with bladder cuff removal of 86.6% *versus* 82.2%, respectively [Jeldres *et al.* 2010]. Thus, segmental resection does not appear to undermine cancer control compared with RNU. However, it is imperative that the results of population-based data analysis be interpreted with caution.

Steffens and colleagues reported in four out of 978 patients a partial nephrectomy and autotransplantation with pyelovesicostomy in solitary kidneys. All patients received mitomycin or bacille Calmette–Guérin instillation therapy after surgery. There were no recurrences or deaths and kidney function was stable [Steffens *et al.* 2007].

Guidelines on UTUC [Roupret *et al.* 2011] stated the following indications for endoscopic treatment:

a. unifocal tumour;
b. small tumour;
c. low-grade tumours (cytology or biopsy);
d. no evidence of an infiltrative lesion on computed tomography;
e. understanding the close follow up.

Segmental ureteral resection with wide margins provides adequate pathologic specimens for definitive staging and grade analysis while also preserving the ipsilateral kidney. Segmental resection is possible for the treatment of low- and high-risk tumours of the distal ureter. It is necessary, however, to ensure that the area of tissue around the tumour is not invaded. This approach can be recommended [Roupret *et al.* 2011] in imperative cases or in low-grade and low-stage tumours. The choice of technique depends on the facilities and skills available and anatomic locations.

Impact of radical nephroureterectomy on kidney function

Recent data showed an association between chronic kidney disease and cardiovascular morbidity and mortality after radical treatment of cortical renal tumours leaving a single renal unit [Huang *et al.* 2006; Go *et al.* 2004]. This can be translated also in the radical treatment of UTUC. Kaag and colleagues showed that the estimated glomerular filtration rate (eGFR) is significantly diminished after RNU particularly in the elderly. Preoperatively only about 50% (80%) and postoperatively only about 20% (55%) of all patients who underwent RNU had eGFR ≥60 ml/min per 1.73 cm^2 (≥45 ml/min per 1.73 cm^2), respectively [Kaag *et al.* 2010].

Similar results in a different context (perioperative cisplatin-based chemotherapy [CBC]) were found in another study: median age was 72 years and median preoperative eGFR was 59 ml/min/1.73 m^2. Before nephroureterectomy, only 48% of patients were eligible to receive CBC and this decreased to 22% postoperatively ($p < 0.001$). In the 144 patients with pT2–pT4 and/or pN1–pN3 disease who are suitable to receive CBC, these proportions were 40% and 24%, respectively ($p < 0.009$) [Lane *et al.* 2010].

Role of metastasectomy in UTUC

In selected patients metastasectomy can be advantageous, however it is rarely performed. In a large German retrospective study in 15

different uro-oncological centres between 1991 and 2008, only 44 patients with distant metastases of the bladder or upper urinary tract underwent complete resection of all detectable metastases and were analysed. Resected metastatic sites were the following: retroperitoneal lymph nodes (56.8%), distant lymph nodes (11.3%), lung (18.2%), bone (4.5%), adrenal gland (2.3%), brain (2.3%), small intestine (2.3%) and skin (2.3%). Systemic chemotherapy was administered in 35 of 44 patients (79.5%) before and/or after metastasectomy surgery. Median survival from initial diagnosis of metastases and subsequent resection was as follows: overall survival, 35 months and 27 months; CSS, 38 months and 34 months; and progression-free survival, 19 months and 15 months. Overall 5-year survival from metastasectomy for the entire cohort was 28%. Seventeen patients were still alive without progression at a median follow up of 8 months. Seven patients without disease progression survived for >2 years and remained free from tumour progression at a median follow up of 63 months. No significant prognostic factors could be determined due to the limited patient numbers [Lehmann *et al*. 2009].

Chemotherapy followed by retroperitoneal LND for isolated retroperitoneal recurrence after nephroureterectomy for upper UTUC was feasible and safe treatment that may be potentially therapeutic in selected patients [Childs *et al*. 2010].

Combining sound clinical judgment with expert surgical skill, up to a third of patients with metastatic urothelial cancers may survive their disease with aggressive surgery integrated with effective chemotherapy [Matin *et al*. 2010; Hellenthal *et al*. 2009; Herr, 2009].

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Conflict of interest statement

All authors state no conflict of interest.

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