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Review – Urothelial Cancer

Urothelial Carcinoma of the Upper Urinary Tract: Surgical Approach and Prognostic Factors

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Abstract

Objectives: Open radical nephroureterectomy (O-RNU) has been the gold standard for the treatment of upper urinary tract urothelial carcinoma (UUT-UC) for decades. With the advances in laparoscopic techniques and endourologic procedures, this concept has been increasingly challenged. Oncologic outcome prediction is mainly based on stage and grade. With progress in medical treatment, adjuvant therapies may gain importance in the future. This review assesses the values of the variety of available treatments as well as prognostic factors that may become relevant regarding patient selection for future adjuvant treatment trials.

Methods: We performed a systematic literature research using MEDLINE with emphasis on open surgical, laparoscopic, and endourologic (ureteroscopic or percutaneous) techniques and prognostic contents.

Results: Overall, no evidence level 1 information from prospective randomised trials is available for treatment of UUT-UC. Laparoscopic radical nephroureterectomy (L-RNU) is increasingly challenging open surgery. Currently, L-RNU should be reserved for low-stage, low-grade tumours. Ureteroscopy and percutaneous nephron-sparing techniques show favourable survival data but high local recurrence rates.

Regarding prognosis, estimation of outcome still relies mainly on stage and grade because no additional parameters have been introduced in a routine clinical setting.

Conclusions: O-RNU still represents the gold standard for the treatment of UUT-UC. The laparoscopic approach is not yet standard of care and should be reserved for low-stage, low-grade tumours. Endourologic nephron-sparing treatments are still experimental in elective indications due to high local recurrence rates. For prognosis, no parameters in addition to stage and grade have been standardised.

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1. Introduction

Upper urinary tract urothelial carcinoma (UUT-UC) is a relatively uncommon disease and accounts for about 5% of all urothelial tumours and 5–10% of all renal tumours, respectively [1].

UUT-UC is located more commonly in the renal pelvis than in the ureter with a ratio of 3:1 [1,2] and occurs more frequently in men with a male-to-female ratio of 3:2 for tumours in the renal pelvis and 2:1 for a ureteral location [3]. The incidence of bilateral UUT-UC ranges from 2% to 8% [1,4]. Although development of UUT-UC after primary diagnosis of bladder cancer is a rare event, occurring in only 2–4% of patients with bladder cancer [5], the development of secondary bladder cancer after primary UUT-UC is about 10-fold more frequent with a risk of 20–50% [2,6–8].

Open radical nephroureterectomy (O-RNU) with excision of a bladder cuff has been the gold standard of treatment for UUT-UC since its description by Albarran in 1909 [9]. Recently, this concept has been challenged due to the development of more advanced techniques for diagnosis, surgery, and follow-up. Minimally invasive procedures are gaining acceptance either with regard to laparoscopic RNU (L-RNU) instead of the open approach or, if nephron-sparing treatment options are intended, by ureteroscopy or a percutaneous approach.

Several authors have reported on single-centre series of >100 patients [2,4,7,8,10–23], including only three single-centre series of >200 patients [7,18,20]. However, sample sizes in all other studies are mainly well below 100. Consequently, no prospective trials have ever been performed for UUT-UC and therefore no evidence level 1 data are available for treatment recommendations.

Prognosis of UUT-UC has been mainly related to tumour stage and grade [12,18,24]. Like bladder cancer, UUT-UC can be subclassified into non–muscle invasive-(NMI) or muscle-invasive (MI) disease. This subdivision has not been widely used yet but may be of practical value in the UUT. Compared to bladder cancer, UUT-UC is diagnosed more frequently at advanced stages. In the majority of the series, tumour stages at diagnosis have been described as pT2 or higher in almost half the patients [2,7,12,18,25]. Survival is essentially influenced by stage: 5-yr survival rates range from about 90% in stages pTa/pT1 and decrease to <5% in N+ or M1 disease [2,7,12,18,20,25,26].

Both neoadjuvant and adjuvant chemotherapy regimens have exhibited some benefit in patients with advanced bladder cancer treated by radical cystectomy [27–29]. Similar data for UUT-UC are currently lacking. However, if prospective trials are intended in the future, the definition of prognostic indicators or, ideally, nomograms enabling a precise patient selection for neoadjuvant or adjuvant therapies are needed.

This review article focuses on the current status of surgical treatment options and shows an overview of the published prognostic factors for patients affected by UUT-UC.

2. Materials and methods

A MEDLINE research was performed with special emphasis on surgical procedures and prognostic factors using combinations of the following terms: urothelial cancer, transitional cell cancer, upper urinary tract, renal pelvis, ureter, surgery, nephroureterectomy, laparoscopy, endourology, percutaneous, ureteroscopy, prognosis, outcome, prognostic factors, and survival. Articles were selected depending on date of publication, quality of the study, and relevance for the presented review. Basically articles were considered from 1995 onwards. Older studies were included selectively if historically relevant or in case of scanty data in more recent publications. The total number of articles reviewed is reported in each of the following sections. In the section summaries, evidence levels are also given.

3. Surgical treatment

3.1. *Open surgery*

3.1.1. *O-RNU*

This section is based on 125 articles dealing with open nephroureterectomy. For almost a century, O-RNU has been the gold standard for treatment of UUT-UC. The indication for radical removal of the whole UUT, even in tumours confined to the renal pelvis, is a tumour recurrence rate of up to 58% in the remaining distal ureter if left in place [1,2,26,30,31]. Nephrectomy should include perinephric fat and Gerota's fascia just as for radical nephrectomy for renal cell carcinoma [31]. In a prospective, but not randomised study, Johansson et al compared intrafascial and perifascial nephrectomy for UUT-UC and found a significant prognostic advantage for the latter subgroup [32]. The procedure can be performed with either one incision, in this case usually via a transperitoneal approach, or with two incisions via a flank approach combined with a lower abdominal incision (Gibson, Pfannenstiel, or median) for the distal ureter and the bladder cuff. Lacking prospective data there is no evidence that one approach is superior to the other. Whatever approach is preferred, the integrity of the collecting system during RNU is crucial to prevent tumour cell spillage. An alternative to spare the second incision

is ureteral stripping in combination with either transurethral resection or dissection of the ureteral orifice [1,11,33–35]. However, the advantage of sparing a second incision has to be balanced against the potential risk of tumour cell seeding due to an open ending distal ureter. No data comparing survival or recurrence rates for these methods are available.

Oncologic outcomes after O-RNU have been reported in a couple of larger series. The results of the largest single-centre series have been published by Hall et al ($n = 252$) [7], Krogh et al ($n = 198$) [2], Secin et al ($n = 252$) [20], and our institution ($n = 239$ patients) [18]. Related to tumour stage, Hall et al reported 5-yr disease-free survival rates of 100% for pTa, 91.7% for pT1, 72.6% for pT2, 40.5% for pT3, and 0% for pT4 tumours, respectively. Our own data confirmed the results of Hall et al. With regard to tumour grade, we found a big difference between low-grade disease (5-yr metastasis-free survival 85%) and high-grade disease (5-yr metastasis-free survival 32%) [18]. Secin et al reported on a series of 252 patients undergoing O-RNU. The overall 5- and 10-yr cancer-specific survival (CSS) probabilities were 61% and 53%, respectively [20]. Series reporting 5-yr disease-specific survival (DSS) rates are listed in Table 1.

For MI disease, RNU undoubtedly represents the treatment of choice. In NMI disease, however, it may be an over-treatment. Whereas high tumour grade can be reliably assessed by cytology, the level of invasion can be obtained only by biopsy and may still be underestimated.

In summary, no doubt O-RNU represents a definitive local treatment. However, it may result in over-treatment in patients with low-stage and low-grade tumours. The level of evidence for O-RNU is 2a.

3.1.2. *Lymph node dissection*

Overall, 25 articles dealing with lymph node dissection (LND) in UUT-UC were evaluated. Regional lymph nodes are frequently involved by UUT-UC and represent the most common metastatic site [31]. Generally, patients with lymph node metastases have a poor outcome [31,32,36,37]. As yet, no valid data regarding indications for and extent of LND for UUT-UC are available. Compared with other cancer entities, this question has been evaluated relatively rarely in the literature. Kondo et al [19] retrospectively evaluated the incidence and primary site of lymph node involvement in 181 patients with UUT-UC. They found nodal metastases in 23%. Primary sites were related to tumour locations. For tumours in the right pelvis, primary metastatic sites were renal hilar, paracaval, and retrocaval nodes. For tumours located in the upper two thirds of the right ureter, primary sites were retrocaval and interaortocaval. On the left side, tumours in the pelvis mainly spread to left hilar and para-aortic nodes, whereas tumours in the upper two thirds of the left ureter tended to metastasise into para-aortic nodes. Tumours in the lower thirds of each side metastasised into pelvic lymph nodes below the aortic bifurcation [19]. Based on these data, a systematic LND would require a wide field especially in patients with multifocal disease extending across the whole length of the ureter. The same group recently published survival data on 169 patients undergoing surgery for clinically nonmetastatic urothelial cancer and concluded that extent of LND significantly improved survival in patients with pT3 tumours undergoing complete LND [38]. Secin et al [20] performed a retrospective study in 252 patients undergoing surgery for UUT-UC. Some LND was performed in every second patient, but the procedure was not standardised, and indication and

Table 1 – Selection of open radical nephroureterectomy series reporting 5-yr DSS rates

Author [reference]	No. of patients	5-yr DSS
Lehmann [4]	145	96% (pTa) – 29% (pT4)
Hall [7]	252	100% (pTa) – 41% (pT3)
Corrado [10]	124	80% (pTa) – 16% (pT4)
Kikuchi [15]	173	85% (L–) – 40% (L+)
Miyata [16]	125	90% (L–) – 50% (L+)
Kondo [19]	181	85% (N0) – 16% (N+)
Secin [20]	252	61%
Munoz [25]	9072	95% (in situ) – 17% (distant disease)
Racioppi [30]	100	70%
Chung [63]	36	86%
Park [94]	86	83%
Novara [96]	269	76%

DSS = disease-specific survival; L– = no lymphovascular invasion; L+ = presence of lymphovascular invasion; N0 = no nodal metastases; N+ = presence of nodal metastases.

extent were dependent on the surgeon. However, in this large sample, a clear association between preoperative imaging, pT classification, and grade could be found; from a preoperative viewpoint, only enlarged nodes on computed tomography (CT) were a significant predictor of node-positive disease. Postoperatively, in NMI disease the incidence of node metastases was 0–4%, and in low-grade disease it was 0%. In contrast, 92% and 100% of node-positive tumours were found in pT3–4 and high-grade tumours, respectively [20].

Two other retrospective series concluded that LND may provide some benefit in selected patients. Miyake et al found a prognostic advantage for patients undergoing LND and no evidence of lymph vessel invasion [37]. Because this parameter is known after pathology only, these data are not helpful for the indication of a node dissection at the time of surgery. Komatsu et al performed LND in all of their 36 patients and reported a 5-yr cause-specific survival rate for node-positive patients of 21%. These, however, represent only two patients [36]. The most recent retrospective study by Brausi included 82 patients with muscle-invasive UUT-UC undergoing mostly RNU. Consequently, no data on positive nodes in NMI disease are available. Almost 50% of the patients had LND in a nonrandomised fashion. They found a remarkable difference in survival of 21.2 versus 52.5 mo in favour of the LND group. Performing LND was an independent predictor of improved survival [39].

In summary, data regarding LND in UUT-UC surgery are scanty, obtained only from retrospective series and, therefore, inconclusive. The largest series provides no indication for LND in NMI and low-grade disease, but due to the high incidence of positive nodes in pT3 disease, LND is strongly recommended if MI disease is suspected and enlarged nodes are present on preoperative imaging. The level of evidence for LND is 2b. Thus, a prospective randomised trial evaluating the prognostic impact of LND compared to a control group is needed. This trial can be performed only in a multicentre fashion to provide sufficient statistical power and would require stratification for tumour location within the collecting system (pelvis, proximal, or distal ureter as well as multifocal), clinical stage, side, size, and clinical node status on preoperative imaging.

3.1.3. *Open surgical nephron-sparing procedures*

Twenty-five articles mentioning open nephron-sparing procedures in UUT-UC were found. In patients with solitary kidneys, nephron-sparing open surgery for UUT-UC has been reported to provide favourable outcomes in selected cases. Leitenberger et al reported data on 13 patients with ureteral cancer treated by segmental ureteral resection and either end-to-end anastomosis or ureterocystoneostomy. Only the four patients with invasive cancers had recurrences, whereas no recurrence was noted in the nine patients with noninvasive ureteral tumours [40]. Maier et al presented a multicentre series of 55 patients undergoing nephron-sparing procedures. After a mean follow-up of >40 mo, almost 70% of patients were alive and free from recurrence. Recurrence rates were similar for tumours in the pelvis and the upper or the lower ureter. Of note, 24 patients underwent surgery with an elective indication for nephron sparing and only 2 had recurrence [41]. The largest single-centre series of nephron-sparing surgery for ureteral tumours was published by Lehmann et al [4]. Of 145 patients with ureteral tumours, 51 underwent segmental ureterectomy. In this selected population, the 10-yr progression-free survival rate was 80%, and ipsilateral tumour recurrence was noted in 10%. After adjusting for stage, outcomes were similar for patients undergoing RNU or segmental ureterectomy. However, the majority of patients undergoing partial ureterectomy had NMI disease; MI cancers were found in only 17 cases. Therefore, no conclusive recommendations can be obtained regarding indication of partial ureterectomy in MI disease [4].

In summary, nephron-sparing surgery seems to provide a favourable outcome in selected patients with localised NMI tumours. Regarding MI disease, data are too scarce for recommendations (level of evidence: 2b). However, with the advances of endourologic organ-preserving techniques, the role of open surgical nephron-sparing procedures can be expected to be of minor importance in the future.

3.2. *Laparoscopy*

This section was based on 236 articles regarding laparoscopic nephroureterectomy.

3.2.1. *Laparoscopic techniques*

L-RNU was first reported by Clayman et al in 1991 [42]. Compared to open surgery, advantages of laparoscopy have been reported as shorter hospital stay, decreased postoperative pain, and earlier return to normal activities [43–51].

As for open surgery, the laparoscopic approach can be transperitoneal or retroperitoneal. Initially, the laparoscopic procedures were hampered by long operative times, which have led to the development of hand-assisted laparoscopic nephrour-

eterectomy (HAL-RNU) to decrease operating times [52]. With increasing experience, however, operating times declined and are usually not longer than those for open surgery [45,47]. One technical point of concern has been the management of the distal ureter and the bladder cuff. A variety of options have been reported: the pluck technique with transurethral resection of the ureteral orifice originally described to facilitate open surgery and spare a second incision [33,53]; cystoscopic circumferential incision of the ureteral orifice [54,55]; transvesical laparoscopy with dissection of the orifice [56]; an endoscopic GIA stapler [57]; or an open approach as for O-RNU to retrieve the specimen and get access to the distal ureter and bladder wall. The open approach has the advantage of maintaining the integrity of the ureter and avoiding tumour cell spillage, whereas the pluck techniques have been associated with an increased risk of recurrence [58]. Again, no prospective comparative data are available. In a retrospective international multicentre study by El Fettouh et al, several approaches were used depending on the centre. In this study of 116 patients no differences regarding recurrence were noted [59].

The indication for the laparoscopic approach should be based on the surgeon's experience and preoperative imaging. In case of clinically NMI disease, laparoscopy is certainly an option. No clear criteria have been established for suspected MI. Complete intact specimen retrieval without tumour damage must be ensured. Thus, Rassweiler et al recommended open surgery for clinical T3 tumours or enlarged nodes [50]. As mentioned previously, the role of LND in UUT-UC has not yet been fully elucidated. This is especially true for the laparoscopic approach, where data regarding LND are scarce. No comparative data regarding the yield of nodes after open or laparoscopic LND are available. Most urologic surgeons are more experienced with open than laparoscopic retroperitoneal LND. Thus, if LND is intended in locally advanced disease, the open approach should be preferred and considered as gold standard in these cases.

3.2.2. *Laparoscopy: oncologic outcomes*

Since the first report of L-RNU [42], a major concern has been the oncologic safety of this procedure. Compared to open surgery, an increased risk of tumour cell spillage due to elevated pressure and lack of tactile control has been presumed. However, to date only 11 port-site metastases have been reported in the literature [50,60–62]. All cases have in common that either no organ bag was used for specimen retrieval or the bag was torn. Quite a few studies, albeit retrospective, have compared oncologic outcomes after O-RNU and L-RNU. In an excellent review article from 2004, Rassweiler reported no differences between the methods regarding local recurrence, bladder recurrence, or distant metastases [50]. More recent single-centre series have confirmed these findings [17,21,62–67]. Many laparoscopic series, however, are hampered by small sample size and short follow-up. Currently eight studies with 5-yr survival data are available [17,21,45,50,63,64,66,67]. Bariol published a series with a median follow-up of 7 yr and showed 5-yr metastases-free survival rates of 72% (L-RNU) and 82% (O-RNU), respectively. The difference was not statistically significant, but the study contained only 26 patients having laparoscopic surgery [66]. The 5-yr CSS rates in other series range from 56% to 90%, probably due to different patient selection criteria, which make series hardly comparable. Details regarding outcomes are listed in Table 2. The series by Muntener et al contained 80% high-grade tumours, resulting in 5-yr CSS of 68% [67]. Roupret et al reported 5-yr CSS of 63% in high-grade tumours [64]. At present it is speculative if results by open surgery might have been different. However, in case of high-grade tumours confirmed by cytology and biopsy, laparoscopy should be advocated cautiously and performed only in experienced high-volume centres.

Table 2 – Series of laparoscopic nephroureterectomies reporting 5-yr DSS rates

Author [reference]	No. of patients	5-yr DSS	Bladder recurrence
McNeill [45]	25	56%	28%
Bariol [66]	26	72%	28%
Rassweiler [50]	23	81%	35%
Hattori [17]	89	81%	22%
Chung [63]	39	90%	44%
Hsueh [21]	66	92% (pT1) – 80% (pT3)	20%
Muntener [67]	39	68%	55%
Roupret [64]	20	89% (low grade), 63% (high grade)	10%

DSS = disease-specific survival.

The basic requirement for laparoscopic surgery in malignant diseases is to maintain oncologic rules and duplicate open surgical principles. As yet no prospective data comparing open and laparoscopic techniques are available. It is still too early to state that L-RNU is or will be the new gold standard for treatment of UUT-UC. However, there is at least no evidence from the published data that L-RNU is inferior to open surgery with regard to oncologic outcome provided that the integrity of the collecting system is maintained and the specimen is retrieved within an intact organ bag. To prove the non-inferiority of laparoscopy compared with open surgery regarding outcome, multicentre prospective trials including the issue of LND are needed. Once these data are available, laparoscopy might have the potential to replace open surgery as a standard of care for treatment of UUT-UC. Currently, laparoscopy should be indicated in low-grade, NMI, or clinically localised MI disease with no evidence of node enlargement on preoperative imaging. The highest level of evidence for L-RNU is 2a.

3.3. *Endourologic nephron-sparing techniques*

Endourologic procedures were originally developed to treat UUT-UC in patients with solitary kidneys, impaired renal function, or bilateral disease. Favourable results of conservative treatments have encouraged several centres to perform these procedures also in patients with normal, functioning contralateral kidneys. The endoscopic approach can be ureteroscopic or percutaneous.

3.3.1. *Ureteroscopy*

We found 128 articles on ureteroscopic management of UUT-UC. The first series were performed using rigid ureteroscopes and electrocautery for fulguration or tumour resection or both. With advances in technical equipment, semirigid or flexible ureteroscopes are more widely used today. For ablation of tumours holmium or neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers are most frequently used [31].

The advantages of a conservative endoscopic treatment are preservation of renal function, avoiding possible over-treatment in noninvasive disease, decrease of morbidity, and shorter hospital stay. These clear benefits of minimal invasiveness must be balanced against a variety of concerns. It is usually not possible to treat larger tumours, at least not in one session. Consequently, ureteroscopy is limited to tumours of $<$1.5 cm in diameter [49,60]. Tumours in the renal calices are not always reliably accessible, especially in the lower calyces. Moreover, there is always a risk of under-staging or under-grading, especially in multifocal disease, because small-sized modern ureteroscopes permit only limited tissue sampling. Oncologic outcome data show favourable results with respect to disease-specific survival, which has been reported from 81% to 100% and reflects selection of patients with good prognoses. On the other hand, local ipsilateral recurrence rates have been described from 25% up to 93% in these series [60,68–77]. Table 3 presents details.

In contrast, patients undergoing conservative treatment with imperative indication have a mark-

Table 3 – Outcomes of endourologic (ureteroscopic, percutaneous, or both) tumour resection/ablation with respect to local recurrence and DSS

Author [reference]	Approach	No. of patients	Recurrence	DSS	Follow-up, mo
Elliott [68]	URS	44	39%	86%	60
Martinez-Pineiro [69]	URS+PC	40	25%	86%	31
Keeley [70]	URS	28	29%	100%	35
Chen [71]	URS	23	65%	100%	35
Elliott [72]	URS	21	38%	70%	73
Deligne [73]	URS+PC	61	32%	84%	40
Daneshmand [74]	URS+PC	30	93%	97%	31
Suh [75]	URS+PC	35	88%	100%	21
Johnson [76]	URS	35	68%	100%	32
Roupret [77]	URS+PC	42	37% (URS), 31% (PC)	81% (URS), 80% (PC)	52 (URS), 58 (PC)
Jarrett [80]	PC	34	33%	87%	56
Patel [81]	PC	26	23%	91%	45
Clark [82]	PC	17	33%	83%	21
Goel [84]	PC	24	55%	69%	64
Palou [85]	PC	34	41%	94%	51
Roupret [86]	PC	24	33%	79%	62

DSS = disease-specific survival; URS = ureteroscopy; PC = percutaneous.

edly poorer outcome with 5-yr CSS rates of only 49% [78]. Similarly, in patients with a history of bladder cancer a 5-yr CSS rate of 71% and an upper tract recurrence rate of 61% at 6 mo have been reported [79]. Level of evidence is 2b.

3.3.2. *Percutaneous approach*

Percutaneous treatment of UT-UC was reported in 124 articles. The percutaneous approach permits treatment of pelvic tumours >1.5 cm and also proximal ureteral tumours not suitable for ureteroscopic treatment. The advantages of the percutaneous access are better visualisation due to larger instruments. The major disadvantage compared to ureteroscopy is opening of the collecting system for access. Thus, tumour cell seeding along the access tract is a point of concern, which, however, has been reported only twice [60].

Outcome data are comparable to ureteroscopic series with disease-specific survival rates ranging from 69% to 94% and local recurrence rates from 23% to 88% [75,77,80–86]. Table 3 presents details.

In summary, both endoscopic approaches are afflicted with a high risk of local recurrence and the possibility of under-staging due to insufficient tissue sampling from tumour bases. Thus, despite selecting patients for presumed NMI and low-grade disease, cancer-specific mortality does exist. Consequently, endoscopic nephron-sparing techniques are advocated only in NMI low-grade tumours as confirmed by imaging, cytology, and biopsy, but they are not indicated for suspected MI disease [1]. Postoperatively, regular follow-up with endoscopic evaluation of the affected upper urinary tract is mandatory [60,83]. Because ureteroscopic surveillance is more invasive than cystoscopy after bladder cancer, perfect patient compliance for close follow-up must be ensured before indicating conservative treatment options. Level of evidence is 2b.

4. Prognostic factors

This section on prognostic factors was based on 381 articles. UUT-UC is generally considered an aggressive disease because tumours are usually more advanced and more poorly differentiated at first diagnosis than bladder tumours [87]. Along with continuing progress of medical treatment for advanced cancers, identification of high-risk patients who might be candidates for either neoadjuvant or adjuvant treatment trials is essential. At present, data regarding adjuvant chemotherapy in locally advanced UUT-UC are scarce. Some small, nonrandomised series are available. Kwak et al reported on 32 patients receiving cisplatinum-based chemotherapy compared with 11 patients without chemotherapy. Based on multivariate analysis, they concluded that chemotherapy improved survival [88]. Czito et al published data on a series of 31 patients undergoing adjuvant radiotherapy following surgery. Nine patients subsequently received adjuvant chemotherapy without randomisation, resulting in an improvement of 5-yr DSS from 67% to 76% [89]. Kobayashi et al indicated adjuvant chemotherapy with methotrexate, vinblastine, Adriamycin, cisplatin (M-VAC) or methotrexate, vinblastine, epirubicin, cisplatin (M-VEC) in 33 patients with positive nodes, including only 13 with UUT-UC. Twenty patients received insufficient or no chemotherapy. The 5-yr survival rate was 31% in the M-VAC/M-VEC group versus 0% in the other groups. Data on the patients with UUT-UC were not reported separately [90]. Lee et al administered adjuvant chemotherapy in 16 of 27 patients with pT3N0M0 disease. In contrast to other reports, no impact on prognosis was noted [91]. Bamias et al evaluated 36 patients undergoing adjuvant chemotherapy without controls; the 5-yr survival rate was 52% [92]. Currently, based on these small series, there is no evidence for neoadjuvant or adjuvant treatment in UUT-UC.

Most authors evaluating prognostic factors after surgery for UUT-UC reported stage and grade as major indicators of outcome [2,7,12,18,24]. Clear outcome differences between NMI and MI disease have been reported. The prognostic impact of tumour location has been discussed but is controversial. Some authors found a poorer prognosis for ureteral compared with pelvic cancers after adjusting for stage [93–95], which could not be confirmed by others [2,30,87], including our own series [18]. Van der Poel et al even reported an opposite effect [14]. Recently, Novara et al reported tumour multifocality and the presence or history of bladder cancer as independent prognostic factors in a database of 269 patients from three centres [96].

Vascular invasion has been reported as another parameter of prognostic impact. In our own series, vascular invasion was a stronger predictor for metastatic disease than tumour grade in multivariate analysis [18]. Comparable data have been reported by Kikuchi [15], Hong [97], and Wu [98]. Lymphangiogenesis rather than vascular tumour invasion has been reported a prognostic indicator by Miyata [16].

pT3 cancers have been reported to represent a heterogenous group of patients with regard to outcome. In our own series, we found a remarkable

Table 4 – Prognostic factors with independent unfavourable impact on outcome by multivariate analysis in addition to stage and grade

Author [reference]	No. of patients	Prognostic factor
Langner [18]	190	Vascular invasion (lymphatic + venous)
Akdogan [95]	72	Ureteral location
van der Poel [14]	149	Proximal ureteral location
Kikuchi [15]	173	Lymphovascular invasion
Novara [96]	269	Tumour multifocality; previous or concomitant bladder cancer
Hong [97]	86	Lymphovascular invasion
Wu [98]	72	Vascular invasion, tumour location
Miyata [16]	125	Intratumour lymphatic vessels
Langner [99]	190	Extensive tumour necrosis
Langner [100]	190	Infiltrative invasion pattern
Saito [23]	130	Preoperative C-reactive protein level

difference between microscopic parenchymal tumour invasion compared to macroscopic parenchymal or peripelvic fat invasion with 5-yr metastasis-free survival rates of 92% versus 8% [18]. These results were confirmed by Wu et al, who reported that patients with only superficial parenchymal invasion had a better outcome than other pT3 subgroups [98].

Additional clinicopathologic predictors described in our own series included extensive tumour necrosis [99] and infiltrative pattern of invasion, whereas squamous or glandular differentiation lacked an independent impact [100].

The only routinely obtained serum parameter with prognostic impact in UUT-UC that has been systematically evaluated is C-reactive protein (CRP). Saito et al retrospectively analysed 130 patients and found that an elevated CRP level preoperatively was an independent predictor of poor survival [23]. Studies reporting on independent prognostic factors are listed in Table 4. The level of evidence regarding prognostic factors is 2b.

5. Conclusions

UUT-UC is an aggressive disease that can be cured by surgery in early stages. With regard to treatment, no prospective randomised trials are available. Laparoscopic nephroureterectomy has been reported to provide oncologic outcomes comparable to open surgery together with decreased morbidity in some series but less favourable outcomes in high-grade tumours. In the absence of randomised trials, open and laparoscopic series are hardly comparable due to differences in patient selection. Currently, laparoscopy should be reserved for low-grade, NMI or limited MI disease in experienced high-volume centres. Nephron-sparing procedures, nowadays usually performed endoscopically with tumour ablation, have shown favourable outcomes in selected patients with NMI low-grade tumours. These procedures, however, show high local recurrence rates and must, therefore, be considered experimental in elective indications.

Regarding prognosis, stage and grade are still the only established predictors, although a variety of promising clinicopathologic parameters have been published. As yet none of these parameters has been established as a standard prognostic indicator, mainly because of limited sample sizes and lack of validation by others. However, adjuvant treatment may be available in the future, and in that case, reliable estimation of individual prognosis will be of major importance. Prognostic models that have been established for other cancer entities are not available for UUT-UC. Thus, a pooled analysis of data obtained from a number of larger volume centres and creation of a prognostic model are recommended.

Conflicts of interest

The authors have nothing to disclose.

References

[1] Oosterlinck W, Solsona E, van der Meijden APM, et al. EAU guidelines on diagnosis and treatment of upper urinary tract transitional cell carcinoma. Eur Urol 2004;46:147–54.

[2] Krogh J, Kvist E, Rye B. Transitional cell carcinoma of the upper urinary tract: prognostic variables and postoperative recurrences. Br J Urol 1991;67:32–6.

[3] Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43–66.

[4] Lehmann J, Suttmann H, Kovac I, et al. Transitional cell carcinoma of the ureter: prognostic factors influencing progression and survival. Eur Urol 2007;51:1281–8.

[5] Sanderson KM, Cai J, Miranda G, Skinner DG, Stein JP. Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1,069 patients with 10-year followup. J Urol 2007;177:2088–94.
[6] Zigeuner RE, Hutterer G, Chromecki T, Rehak P, Langner C. Bladder tumour development after urothelial carcinoma of the upper urinary tract is related to primary tumour location. BJU Int 2006;98:1181–6.
[7] Hall MC, Womack S, Sagalowsky AI, Carmody T, Erickstad MD, Roehrborn CG. Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. Urology 1998;52:594–601.
[8] Kang CH, Yu TJ, Hsieh HH, et al. The development of bladder tumors and contralateral upper urinary tract tumors after primary transitional cell carcinoma of the upper urinary tract. Cancer 2003;98:1620–6.
[9] Albarran J. Medecine operatoire des voies urinaires. Paris: Masson et Cie; 1909.
[10] Corrado F, Ferri C, Mannini D, et al. Transitional cell carcinoma of the upper urinary tract: evaluation of prognostic factors by histopathology and flow cytometric analysis. J Urol 1991;145:1159–63.
[11] Salvador-Bayarri J, Rodríguez-Villamil L, Imperatore V, Palou Redorta J, Villavicencio-Mavrich H, Vicente-Rodríguez J. Bladder neoplasms after nephroureterectomy: does the surgery of the lower ureter, transurethral resection or open surgery, influence the evolution? Eur Urol 2002;41:30–3.
[12] Olgac S, Mazumdar M, Dalbagni G, Reuter VE. Urothelial carcinoma of the renal pelvis: a clinicopathologic study of 130 cases. Am J Surg Pathol 2004;28:1545–52.
[13] Boorjian S, Ng C, Munver R, et al. Impact of delay to nephroureterectomy for patients undergoing ureteroscopic biopsy and laser tumor ablation of upper tract transitional cell carcinoma. Urology 2005;66:283–7.
[14] van der Poel HG, Antonini N, van Tinteren H, Horenblas S. Upper urinary tract cancer: location is correlated with prognosis. Eur Urol 2005;48:438–44.
[15] Kikuchi E, Horiguchi Y, Nakashima J, et al. Lymphovascular invasion independently predicts increased disease specific survival in patients with transitional cell carcinoma of the upper urinary tract. J Urol 2005;174:2120–3.
[16] Miyata Y, Kanda S, Ohba K, et al. Tumor lymphangiogenesis in transitional cell carcinoma of the upper urinary tract: association with clinicopathological features and prognosis. J Urol 2006;176:348–53.
[17] Hattori R, Yoshino Y, Gotoh M, Katoh M, Kamihira O, Ono Y. Laparoscopic nephroureterectomy for transitional cell carcinoma of renal pelvis and ureter: Nagoya experience. Urology 2006;67:701–5.
[18] Langner C, Hutterer G, Chromecki T, Winkelmayer I, Rehak P, Zigeuner R. pT classification, grade, and vascular invasion as prognostic indicators in urothelial carcinoma of the upper urinary tract. Mod Pathol 2006;19:272–9.
[19] Kondo T, Nakazawa H, Ito F, Hashimoto Y, Toma H, Tanabe K. Primary site and incidence of lymph node metastases in urothelial carcinoma of upper urinary tract. Urology 2007;69:265–9.
[20] Secin FP, Koppie TM, Salamanca JI, et al. Evaluation of regional lymph node dissection in patients with upper urinary tract urothelial cancer. Int J Urol 2007;14:26–32.
[21] Hsueh TY, Huang YH, Chiu AW, Huan SK, Lee YH. Survival analysis in patients with upper urinary tract transitional cell carcinoma: a comparison between open and hand-assisted laparoscopic nephroureterectomy. BJU Int 2007;99:632–6.
[22] Dragicevic D, Djokic M, Pekmezovic T, et al. Survival of patients with transitional cell carcinoma of the ureter and renal pelvis in Balkan endemic nephropathy and non-endemic areas of Serbia. BJU Int 2007;99:1357–62.
[23] Saito K, Kawakami S, Ohtsuka Y, et al. The impact of preoperative serum C-reactive protein on the prognosis of patients with upper urinary tract urothelial carcinoma treated surgically. BJU Int 2007;100:269–73.
[24] Holmäng S, Johansson SL. Urothelial carcinoma of the upper urinary tract: comparison between the WHO/ISUP 1998 consensus classification and WHO 1999 classification system. Urology 2005;66:274–8.
[25] Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. J Urol 2000;164:1523–5.
[26] Huben RP, Mounzer AM, Murphy GP. Tumor grade and stage as prognostic variables in upper tract urothelial tumors. Cancer 1988;62:2016–20.
[27] Pectasides D, Pectasides M, Nikolaou M. Adjuvant and neoadjuvant chemotherapy in muscle invasive bladder cancer: literature review. Eur Urol 2005;48:60–8.
[28] Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:202–6.
[29] Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:189–201.
[30] Racioppi M, D'Addessi A, Alcini A, Destito A, Alcini E. Clinical review of 100 consecutive surgically treated patients with upper urinary tract transitional tumours. Br J Urol 1997;80:707–11.
[31] Arancibia MF, Bolenz C, Michel MS, Keeley Jr FX, Alken P. The modern management of upper tract urothelial cancer: surgical treatment. BJU Int 2007;99:978–81.
[32] Johansson S, Wahlqvist L. A prognostic study of urothelial renal pelvic tumors: comparison between the prognosis of patients treated with intrafascial nephrectomy and perifascial nephroureterectomy. Cancer 1979;43:2525–31.
[33] Palou J, Caparros J, Orsola A, Xavier B, Vicente J. Transurethral resection of the intramural ureter as the first step of nephroureterectomy. J Urol 1995;154:43–4.

[34] Roth S, van Ahlen H, Semjonow A, Hertle L. Modified ureteral stripping as an alternative to open surgical ureterectomy. J Urol 1996;155:1568–71.
[35] Laguna MP, de la Rosette JJ. The endoscopic approach to the distal ureter in nephroureterectomy for upper urinary tract tumor. J Urol 2001;166:2017–22.
[36] Komatsu H, Tanabe N, Kubodera S, Maezawa H, Ueno A. The role of lymphadenectomy in the treatment of transitional cell carcinoma of the upper urinary tract. J Urol 1997;157:1622–4.
[37] Miyake H, Hara I, Gohji K, Arakawa S, Kamidono S. The significance of lymphadenectomy in transitional cell carcinoma of the upper urinary tract. Br J Urol 1998; 82:494–8.
[38] Kondo T, Nakazawa H, Ito F, Hashimoto Y, Toma H, Tanabe K. Impact of the extent of regional lymphadenectomy on the survival of patients with urothelial carcinoma of the upper urinary tract. J Urol 2007;178:1212–7.
[39] Brausi MA, Gavioli M, De Luca G, et al. Retroperitoneal lymph node dissection (RPLD) in conjunction with nephroureterectomy in the treatment of infiltrative transitional cell carcinoma (TCC) of the upper urinary tract: impact on survival. Eur Urol 2007;52:1414–20.
[40] Leitenberger A, Beyer A, Altwein JE. Organ-sparing treatment for ureteral carcinoma? Eur Urol 1996;29:272–8.
[41] Maier U, Mertl G, Pummer K, et al. Organ-preserving surgery in patients with urothelial tumors of the upper urinary tract. Eur Urol 1990;18:197–200.
[42] Clayman RV, Kavoussi LR, Figenshau RS, Chandhoke PS, Albala DM. Laparoscopic nephroureterectomy: initial clinical case report. J Laparoendosc Surg 1991;1:343–9.
[43] McNeill A, Oakley N, Tolley DA, Gill IS. Laparoscopic nephroureterectomy for upper tract transitional cell carcinoma: a critical appraisal. BJU Int 2004;94:259–63.
[44] Matin SF. Radical laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: current status. BJU Int 2005;95(Suppl 2):68–74.
[45] McNeill SA, Chrisofos M, Tolley DA. The long-term outcome after laparoscopic nephroureterectomy: a comparison with open nephroureterectomy. BJU Int 2000; 86:619–23.
[46] Shalhav AL, Dunn MD, Portis AJ, Elbahnasy AM, McDougall EM, Clayman RV. Laparoscopic nephroureterectomy for upper tract transitional cell cancer: the Washington University experience. J Urol 2000;163:1100–4.
[47] Gill IS, Sung GT, Hobart MG, et al. Laparoscopic radical nephroureterectomy for upper tract transitional cell carcinoma: the Cleveland Clinic experience. J Urol 2000; 164:1513–22.
[48] Matsui Y, Ohara H, Ichioka K, et al. Retroperitoneoscopy-assisted total nephroureterectomy for upper urinary tract transitional cell carcinoma. Urology 2002;60:1010–5.
[49] Soderdahl DW, Fabrizio MD, Rahman NU, Jarrett TW, Bagley DH. Endoscopic treatment of upper tract transitional cell carcinoma. Urol Oncol 2005;23:114–22.
[50] Rassweiler JJ, Schulze M, Marrero R, Frede T, Palou Redorta J, Bassi P. Laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: is it better than open surgery? Eur Urol 2004;46:690–7.
[51] Tsujihata M, Nonomura N, Tsujimura A, Yoshimura K, Miyagawa Y, Okuyama A. Laparoscopic nephroureterectomy for upper tract transitional cell carcinoma: comparison of laparoscopic and open surgery. Eur Urol 2006;49:332–6.
[52] Landman J, Lev RY, Bhayani S, et al. Comparison of hand assisted and standard laparoscopic radical nephroureterectomy for the management of localized transitional cell carcinoma. J Urol 2002;167:2387–91.
[53] Ubrig B, Boenig M, Waldner M, Roth S. Transurethral approach to the distal ureter in nephroureterectomy: transurethral extraction vs. ''pluck'' technique with long-term follow-up. Eur Urol 2004;46:741–7.
[54] Kurzer E, Leveillee RJ, Bird VG. Combining hand assisted laparoscopic nephroureterectomy with cystoscopic circumferential excision of the distal ureter without primary closure of the bladder cuff—is it safe? J Urol 2006;175:63–7.
[55] Vardi IY, Stern JA, Gonzalez CM, Kimm SY, Nadler RB. Novel technique for management of distal ureter and en block resection of bladder cuff during hand-assisted laparoscopic nephroureterectomy. Urology 2006;67: 89–92.
[56] Gill IS, Soble JJ, Miller SD, Sung GT. A novel technique for management of the en bloc bladder cuff and distal ureter during laparoscopic nephroureterectomy. J Urol 1999;161:430–4.
[57] Tsivian A, Benjamin S, Sidi AA. A sealed laparoscopic nephroureterectomy: a new technique. Eur Urol 2007; 52:1015–9.
[58] Steinberg JR, Matin SF. Laparoscopic radical nephroureterectomy: dilemma of the distal ureter. Curr Opin Urol 2004;14:61–5.
[59] El Fettouh HA, Rassweiler JJ, Schulze M, et al. Laparoscopic radical nephroureterectomy: results of an international multicenter study. Eur Urol 2002;42:447–52.
[60] Argyropoulos AN, Tolley DA. Upper urinary tract transitional cell carcinoma: current treatment overview of minimally invasive approaches. BJU Int 2007;99: 982–7.
[61] Schatteman P, Chatzopoulos C, Assenmacher C, et al. Laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: results of a Belgian retrospective multicentre survey. Eur Urol 2007;51: 1633–8.
[62] Manabe D, Saika T, Ebara S, et al. Comparative study of oncologic outcome of laparoscopic nephroureterectomy and standard nephroureterectomy for upper urinary tract transitional cell carcinoma. Urology 2007;69:457–61.
[63] Chung SD, Chueh SC, Lai MK, et al. Long-term outcome of hand-assisted laparoscopic radical nephroureterectomy for upper-tract urothelial carcinoma: comparison with open surgery. J Endourol 2007;21:595–9.
[64] Roupret M, Hupertan V, Sanderson KM, et al. Oncologic control after open or laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: a single center experience. Urology 2007;69:656–61.
[65] Okegawa T, Odagane A, Ide H, Horie S, Nutahara K, Higashihara E. Oncological outcome of retroperitoneo-

scopic nephroureterectomy for upper urinary tract transitional cell carcinoma. Int J Urol 2006;13:493–7.
[66] Bariol SV, Stewart GD, McNeill SA, Tolley DA. Oncological control following laparoscopic nephroureterectomy: 7-year outcome. J Urol 2004;172:1805–8.
[67] Muntener M, Nielsen ME, Romero FR, et al. Long-term oncologic outcome after laparoscopic radical nephroureterectomy for upper tract transitional cell carcinoma. Eur Urol 2007;51:1639–44.
[68] Elliott DS, Blute ML, Patterson DE, Bergstralh EJ, Segura JW. Long-term follow-up of endoscopically treated upper urinary tract transitional cell carcinoma. Urology 1996;47:819–25.
[69] Martinez-Pineiro JA, Garcia Matres MJ, Martinez-Pineiro L. Endourological treatment of upper tract urothelial carcinomas: analysis of a series of 59 tumors. J Urol 1996;156:377–85.
[70] Keeley Jr FX, Bibbo M, Bagley DH. Ureteroscopic treatment and surveillance of upper urinary tract transitional cell carcinoma. J Urol 1997;157:1560–5.
[71] Chen GL, Bagley DH. Ureteroscopic management of upper tract transitional cell carcinoma in patients with normal contralateral kidneys. J Urol 2000;164:1173–6.
[72] Elliott DS, Segura JW, Lightner D, Patterson DE, Blute ML. Is nephroureterectomy necessary in all cases of upper tract transitional cell carcinoma? Long-term results of conservative endourologic management of upper tract transitional cell carcinoma in individuals with a normal contralateral kidney. Urology 2001;58:174–8.
[73] Deligne E, Colombel M, Badet L, et al. Conservative management of upper urinary tract tumors. Eur Urol 2002;42:43–8.
[74] Daneshmand S, Quek ML, Huffman JL. Endoscopic management of upper urinary tract transitional cell carcinoma: long-term experience. Cancer 2003;98:55–60.
[75] Suh RS, Faerber GJ, Wolf Jr JS. Predictive factors for applicability and success with endoscopic treatment of upper tract urothelial carcinoma. J Urol 2003;170:2209–16.
[76] Johnson GB, Fraiman M, Grasso M. Broadening experience with the retrograde endoscopic management of upper urinary tract urothelial malignancies. BJU Int 2005;95(Suppl 2):110–3.
[77] Roupret M, Hupertan V, Traxer O, et al. Comparison of open nephroureterectomy and ureteroscopic and percutaneous management of upper urinary tract transitional cell carcinoma. Urology 2006;67:1181–7.
[78] Krambeck AE, Thompson RH, Lohse CM, Patterson DE, Elliott DS, Blute ML. Imperative indications for conservative management of upper tract transitional cell carcinoma. J Urol 2007;178:792–6.
[79] Krambeck AE, Thompson RH, Lohse CM, et al. Endoscopic management of upper tract urothelial carcinoma in patients with a history of bladder urothelial carcinoma. J Urol 2007;177:1721–6.
[80] Jarrett TW, Sweetser PM, Weiss GH, Smith AD. Percutaneous management of transitional cell carcinoma of the renal collecting system: 9-year experience. J Urol 1995; 154:1629–35.
[81] Patel A, Soonawalla P, Shepherd SF, Dearnaley DP, Kellett MJ, Woodhouse CR. Long-term outcome after percutaneous treatment of transitional cell carcinoma of the renal pelvis. J Urol 1996;155:868–74.
[82] Clark PE, Streem SB, Geisinger MA. 13-year experience with percutaneous management of upper tract transitional cell carcinoma. J Urol 1999;161:772–5.
[83] Jabbour ME, Smith AD. Primary percutaneous approach to upper urinary tract transitional cell carcinoma. Urol Clin North Am 2000;27:739–50.
[84] Goel MC, Mahendra V, Roberts JG. Percutaneous management of renal pelvic urothelial tumors: long-term followup. J Urol 2003;169:925–9.
[85] Palou J, Piovesan LF, Huguet J, Salvador J, Vicente J, Villavicencio H. Percutaneous nephroscopic management of upper urinary tract transitional cell carcinoma: recurrence and long-term followup. J Urol 2004;172:66–9.
[86] Rouprêt M, Traxer O, Tligui M, et al. Upper urinary tract transitional cell carcinoma: recurrence rate after percutaneous endoscopic resection. Eur Urol 2007;51:709–14.
[87] Catto JW, Yates DR, Rehman I, et al. Behavior of urothelial carcinoma with respect to anatomical location. J Urol 2007;177:1715–20.
[88] Kwak C, Lee SE, Jeong IG, Ku JH. Adjuvant systemic chemotherapy in the treatment of patients with invasive transitional cell carcinoma of the upper urinary tract. Urology 2006;68:53–7.
[89] Czito B, Zietman A, Kaufman D, Skowronski U, Shipley W. Adjuvant radiotherapy with and without concurrent chemotherapy for locally advanced transitional cell carcinoma of the renal pelvis and ureter. J Urol 2004; 172:1271–5.
[90] Kobayashi H, Obata K. Results of adjuvant chemotherapy for invasive urothelial cancer with lymph-node metastasis. Cancer Chemother Pharmacol 1994;35(Suppl):S14–7.
[91] Lee SE, Byun SS, Park YH, Chang IH, Kim YJ, Hong SK. Adjuvant chemotherapy in the management of pT3N0M0 transitional cell carcinoma of the upper urinary tract. Urol Int 2006;77:22–6.
[92] Bamias A, Deliveliotis Ch, Fountzilas G, et al. 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 2004;22:2150–4.
[93] Ozsahin M, Zouhair A, Villà S, et al. Prognostic factors in urothelial renal pelvis and ureter tumours: a multicentre Rare Cancer Network study. Eur J Cancer 1999;35:738–43.
[94] Park S, Hong B, Kim CS, Ahn H. The impact of tumor location on prognosis of transitional cell carcinoma of the upper urinary tract. J Urol 2004;171:621–5.
[95] Akdogan B, Dogan HS, Eskicorapci SY, Sahin A, Erkan I, Ozen H. Prognostic significance of bladder tumor history and tumor location in upper tract transitional cell carcinoma. J Urol 2006;176:48–52.
[96] Novara G, De Marco V, Gottardo F, et al. Independent predictors of cancer-specific survival in transitional cell carcinoma of the upper urinary tract: multi-institutional dataset from 3 European centers. Cancer 2007;110: 1715–22.

[97] Hong B, Park S, Hong JH, Kim CS, Ro JY, Ahn H. Prognostic value of lymphovascular invasion in transitional cell carcinoma of upper urinary tract. Urology 2005;65: 692–6.

[98] Wu CF, Pang ST, Chen CS, Chuang CK, Chen Y, Lin PY. The impact factors on prognosis of patients with pT3 upper urinary tract transitional cell carcinoma. J Urol 2007;178:446–50.

[99] Langner C, Hutterer G, Chromecki T, Leibl S, Rehak P, Zigeuner R. Tumor necrosis as prognostic indicator in transitional cell carcinoma of the upper urinary tract. J Urol 2006;176:910–3.

[100] Langner C, Hutterer G, Chromecki T, Rehak P, Zigeuner R. Patterns of invasion and histological growth as prognostic indicators in urothelial carcinoma of the upper urinary tract. Virchows Arch 2006;448:604–11.