

# Upper urinary tract urothelial carcinoma with loco-regional nodal metastases: insights from the Upper Tract Urothelial Carcinoma Collaboration

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## OBJECTIVE

- To describe a multicentre experience with preoperative platinum-based chemotherapy before radical nephroureterectomy (RNU) in patients with upper tract urothelial carcinoma (UTUC) with loco-regional nodal metastases.

## PATIENTS AND METHODS

- We identified 313 patients from the UTUC Collaboration (over 1200 patients), who underwent RNU with concomitant retroperitoneal lymph node dissection between 1990 and 2007 and met the inclusion criteria for one of three groups.
- Group 1 comprised patients who received chemotherapy before RNU because of biopsy-proven loco-regional nodal metastases.
- Group 2 consisted of patients who underwent primary RNU and were found to have metastatic nodal disease on final pathological review (node-positive).

## What's known on the subject? and What does the study add?

Neoadjuvant chemotherapy offers survival benefits for patients with urothelial carcinoma of the bladder. However, it is still underutilized in the 'biologically similar' upper tract urothelial carcinoma. Systemic chemotherapy in a neoadjuvant setting is a more attractive option, as loss of renal function after nephrectomy can complicate the administration of adjuvant chemotherapy. We found that preoperative systemic therapy followed by aggressive surgical debulking is a promising treatment strategy for upper tract urothelial carcinoma patients with known or at risk of loco-regional nodal metastasis.

- Group 3 comprised a comparative cohort of patients treated with primary RNU for invasive or locally advanced (pT2/pT4) node-negative (NO) UTUC.
- Meanwhile, group 2 had significantly lower disease-free and cancer-specific survival rates compared with group 3 ( $P < 0.001$  and  $P < 0.001$ , respectively) and compared with group 1 ( $P = 0.04$  and  $P = 0.06$ , respectively).

## RESULTS

- Groups 1, 2 and 3 included 18, 120 and 175 patients, respectively. The 5-year disease-free survival rates were 49%, 30% and 64%, whereas the 5-year cancer-specific survival rates were 44%, 36% and 69% in groups 1, 2 and 3, respectively.
- In group 1, on final pathological evaluation, nine patients were pN0, six patients were pT0 and five patients had pT0N0 disease. Kaplan–Meier survival analyses showed similar recurrence and survival rates in group 1 compared with group 3 ( $P = 0.14$  and  $P = 0.06$ , respectively).

## CONCLUSIONS

- Preoperative chemotherapy followed by aggressive surgical consolidation may yield favourable oncological outcomes in patients with UTUC with loco-regional nodal metastases.
- These data support further evaluation of neoadjuvant systemic therapy in patients at risk for locally advanced UTUC.

## KEYWORDS

urothelial carcinoma, chemotherapy, lymph node metastases

## INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) is relatively rare, accounting for approximately 5% of genitourinary malignancies, although recent data suggest that the incidence is increasing [1,2]. Radical nephroureterectomy (RNU) with excision of an ipsilateral bladder cuff via a laparoscopic or open approach remains the standard treatment in patients with invasive UTUC and a functional contralateral kidney. Although surgical techniques have improved, locally advanced UTUC still has a poor prognosis and systemic recurrences are common [2–4].

Unfortunately, with the rarity of the disease and historical difficulties in gathering patients with urothelial carcinoma for clinical trials, there are very few direct data providing clinical guidance on the optimal management of patients diagnosed with locally advanced UTUC. Small series show measurable response rates, specifically in patients treated with chemotherapy for metastatic or unresectable UTUC [5]. The loss of renal function that occurs with nephrectomy can complicate the administration of appropriate systemic chemotherapy in an adjuvant setting. Uncertainties regarding the survival benefit gained from chemotherapy combined with inadequacy of clinical staging are additional contributing factors that have led to the under-use of neoadjuvant chemotherapy for UTUC. However, analogous to the experience with urothelial carcinoma of the bladder (UCB), where administration of neoadjuvant cisplatin-based combination chemotherapy translated into a tangible survival advantage [6], it is argued that preoperative systemic chemotherapy should be used in patients with locally advanced UTUC [6,7].

Patients with UTUC and loco-regional nodal metastatic disease represent a challenging cohort of patients, with no randomized trials to guide their optimal management. Using a multi-institutional database of patients treated for UTUC, we evaluated the oncological outcomes in patients with UTUC and loco-regional nodal metastases treated with preoperative systemic therapy followed by aggressive surgical consolidation with RNU. Oncological outcomes were compared with node-positive patients treated with immediate RNU and with node negative (NO) patients with locally advanced UTUC managed with immediate surgery.

## PATIENTS AND METHODS

We used a database comprising patients from the UTUC Collaboration, this patient cohort has been described in detail elsewhere [3]. After combining the data sets from the enrolled centres, a database containing more than 1200 patients who underwent RNU with ipsilateral bladder cuff resection between 1987 and 2007 was generated. We identified 313 patients who met the criteria for one of three groups. Group 1 comprised patients who had clinical evidence of positive loco-regional nodal metastases, confirmed by biopsy. These patients received preoperative chemotherapy followed by RNU. Group 2 consisted of patients who underwent primary RNU and were found to have metastatic nodal disease on final pathological review. Group 3 comprised a comparative cohort of patients treated with primary RNU for (pT2–T4N0) UTUC. Selection criteria required adequate pathological staging with standard, rather than limited, lymph node dissection during RNU. Adequate pathological nodal staging was defined as removal of the para-aortic, paracaval, or interaortocaval nodes from the renal hilum to the inferior mesenteric artery for renal pelvis and proximal ureteral tumours. For mid- and lower ureteral tumours, lymph node dissection was performed from the renal hilum to the bifurcation of the common iliac artery and ipsilateral pelvic nodes, respectively. The standardization of lymph node dissection was impossible because of the multicentre and retrospective study design. As a result of inadequate regional lymphadenectomy (as reported by individual contributing centres), 223 patients were excluded from further analysis.

All surgical specimens were processed according to standard pathological procedures, and all slides were re-reviewed by genitourinary pathologists according to prospectively defined uniform criteria. All pathologists were blinded to clinical outcomes. Tumours were staged according to the American Joint Committee on Cancer – Union International Contre le Cancer (AJCC–UICC) Tumor-Node-Metastasis (TNM) classification 2002 [8]. Tumour grading was assessed according to the 1998 WHO/International Society of Urologic Pathology (ISUP) consensus classification [9]. In addition, all specimens were evaluated for tumour location, pattern of tumour growth (papillary vs sessile), presence of lymphovascular

invasion, tumour necrosis, and concomitant carcinoma *in situ*.

Follow up was performed according to institutional protocols. Patients were generally followed every 3 months for the first year after RNU and every 6 months from the second year. Follow up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest CT or MRI were taken when clinically indicated.

Statistical analysis was performed with SPSS version 17 (SPSS, Chicago, IL, USA). Bladder recurrences were not considered in the analysis of disease-free survival rate. Disease-free survival and cancer-specific survival were estimated using the Kaplan–Meier survival analysis. Disease recurrence was defined as local failure in the nephroureterectomy bed, regional lymph nodes, or distant metastasis after RNU for UTUC. The period of disease-free survival was defined as the time between the date of RNU and the development of local recurrence or distant metastasis. Censored survival values represent patients who were alive without clinical evidence of disease at the last follow-up. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. The period of cancer-specific survival was defined as the time between the date of RNU and death due to cancer. Statistical differences were determined by the log-rank test. All reported *P* values are two-sided and significance was set at <0.05.

## RESULTS

Table 1 describes clinical characteristics of the patients according to the study grouping. Preoperative systemic chemotherapy regimens consisted of gemcitabine/cisplatin in 14 patients, methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) in four patients. The patients in group 1 received two to nine preoperative chemotherapy cycles (median six cycles). Three of the 18 patients in this group, received additional adjuvant chemotherapy. Patients in groups 2 and 3 were managed with initial RNU (with open technique in 87%

**TABLE 1** Clinical characteristics of 313 patients managed for advanced upper urinary tract urothelial carcinoma, according to treatment group

	Group 1 Preoperative chemotherapy before RNU (N+)	Group 2 RNU (N+)	Group 3 RNU (NO)	Total number of patients
Total, n (%)	18 (5.8)	120 (38.3)	175 (55.9)	313 (100)
Gender, n (%)				
Female	9 (50)	78 (65)	117 (67)	204 (65)
Male	9 (50)	42 (35)	58 (33)	109 (35)
Age, years				
Mean + SD	68 ± 8	68 ± 12	67 ± 11	68 ± 11
Range	52–80	27–90	31–97	27–97
ECOG, n (%)				
0	10 (55.5)	79 (66)	111 (63)	200 (64)
1	7 (39)	35 (29)	61 (35)	103 (33)
2	1 (5.5)	6 (5)	3 (2)	10 (3)
Previous bladder UC diagnosis, n (%)				
Absent	10 (55.5)	94 (78)	140 (80)	244 (78)
Present	8 (44.5)	26 (22)	35 (20)	69 (22)
Surgical technique, n (%)				
Open	17 (94.5)	104 (87)	150 (86)	271 (86.5)
Laparoscopic	1 (5.5)	16 (13)	25 (14)	42 (13.5)
Chemotherapy, n (%)				
Neoadjuvant	18 (100)	0	0	18 (6)
Adjuvant	3 (17)	52 (43)	33 (19)	88 (24)
Outcome, n (%)				
Recurrence	8 (44)	78 (65)	59 (34)	145 (46)
Death due to cancer	7 (39)	66 (55)	48 (27)	121 (39)

ECOG, Eastern Cooperative Oncology Group; N+, node-positive; NO, node-negative; RNU, radical nephroureterectomy; UC, urothelial carcinoma.

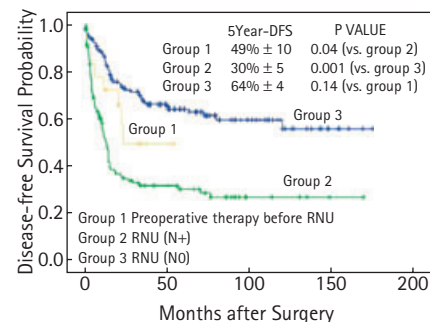
and 86% of cases, respectively) followed by adjuvant chemotherapy in 43% and 19% of patients, respectively. Adjuvant chemotherapy regimens consisted of MVAC in 60%, gemcitabine/cisplatin in 20% and other platinum-based regimens in the remaining 20% of patients. On average, three cycles of adjuvant chemotherapy were administered (range one to six). Adjuvant systemic therapies were more likely to be used in younger patients as well as in patients with pathological features of advanced disease (pN1+, pT4Nany, pT3Nany). Table 2 describes the pathological characteristics in each group. In group 1, nine patients were pN0, six patients were pT0 and five patients had pT0N0 disease on final pathological evaluation.

Figures 1 and 2 compare the probability of disease-free and cancer-specific survival among the study groups. The 5-year disease-

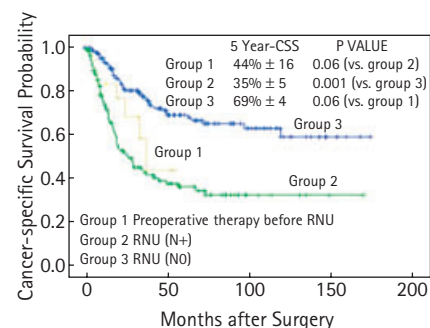
free survival rates were 49%, 30% and 64%, and the 5-year cancer-specific survival rates were 44%, 36% and 69% in groups 1, 2 and 3, respectively. Kaplan–Meier survival analyses showed similar recurrence and survival rates in group 1 compared with group 3 ( $P = 0.14$  and  $P = 0.06$ , respectively). Meanwhile, group 2 had significantly lower disease-free survival and cancer-specific survival rates compared with group 3 ( $P < 0.001$  and  $P < 0.001$ , respectively) and compared with group 1 ( $P = 0.04$  and  $P = 0.06$ , respectively). Patients with no residual disease at RNU (pT0pN0) showed 83% 5-year cancer-specific survival, compared with 31% for patients with residual disease (pTany/pNany) ( $P = 0.092$ ).

On multivariable Cox proportional hazards regression analysis, only pT stage ( $P < 0.001$ ) and lymphovascular invasion ( $P = 0.003$ ) were independent predictors of CSS.

**FIG. 1.** Disease-free survival after radical nephroureterectomy in 313 patients managed for advanced upper urinary tract urothelial carcinoma, according to treatment group.



**FIG. 2.** Cancer-specific survival after radical nephroureterectomy in 313 patients managed for advanced upper urinary tract urothelial carcinoma, according to treatment group.



## DISCUSSION

UTUC and UCB share similar histological, biological, as well as molecular oncogenic characteristics and show comparable oncological outcomes when adjusted for tumour stage and grade [6,7]. Previous studies have shown a survival advantage in patients with UCB managed with neoadjuvant cisplatin-based combination chemotherapy before cystectomy [6,10]. Can this survival advantage be extrapolated to appropriately selected patients with UTUC? Unfortunately, conclusive data to support the use of neoadjuvant chemotherapy before RNU for UTUC are lacking. Moreover, unlike in UCB, clinical staging of patients with UTUC is of limited use, presenting additional difficulties in accurate selection of patients for neoadjuvant systemic therapy before RNU. Specifically, unlike in UCB, the depth of tumour invasion and primary tumour stage

**TABLE 2** Pathological characteristics of 313 patients managed for advanced upper urinary tract urothelial carcinoma, according to treatment group

	Group 1 Preoperative chemotherapy before RNU (N+)	Group 2 RNU (N+)	Group 3 RNU (NO)	Total number of patients
Total, n (%)	18 (5.8)	120 (38.3)	175 (55.9)	313 (100)
Side, n (%)				
Right	7 (39)	47 (39)	82 (47)	136 (43.5)
Left	11 (61)	73 (61)	93 (53)	177 (56.5)
Index tumour location, n (%)				
Renal pelvis	15 (83.5)	87 (72.5)	108 (62)	210 (67)
Ureter	1 (5.5)	31 (26)	63 (36)	95 (30)
Uretero-enteric anastomosis	2 (11)	2 (1.5)	4 (2)	8 (3)
Tumour architecture, n (%)				
Papillary	3 (17)	53 (44)	115 (66)	171 (55)
Sessile	15 (83)	67 (56)	60 (34)	142 (45)
Tumour grade, n (%)				
Low	2 (11)	3 (2.5)	40 (23)	45 (14.5)
High	16 (89)	117 (97.5)	135 (77)	268 (85.5)
Pathological T stage, n (%)				
T0	6 (33)	0 (0)	0 (0)	6 (2)
T1	0 (0)	6 (5)	0 (0)	6 (2)
T2	3 (17)	19 (16)	61 (35)	83 (26)
T3	7 (39)	66 (55)	108 (62)	181 (58)
T4	2 (11)	29 (24)	6 (8)	37 (12)
Concomitant CIS, n (%)				
Absent	11 (61)	70 (58)	116 (66)	197 (63)
Present	7 (39)	50 (42)	59 (34)	37 (37)
Necrosis, n (%)				
Absent	10 (55.5)	53 (44)	115 (66)	178 (57)
Present	8 (44.5)	67 (56)	60 (34)	135 (43)
N stage, n (%)				
0	9 (50)	0 (0)	175 (100)	184 (59)
1	4 (22)	94 (78)	0 (0)	98 (31)
2	5 (28)	26 (22)	0 (0)	31 (10)
Mean no. of removed LNs (range)	13 (1–35)	6 (1–41)	7 (1–27)	7 (1–41)
Mean no. of positive LNs (range)	1 (0–10)	3 (1–22)	0 (0)	1 (0–22)
LVI, n (%)				
Absent	11 (61)	35 (29)	106 (61)	152 (48.5)
Present	7 (39)	85 (71)	69 (39)	161 (51.5)

CIS, carcinoma in situ; LN, lymph nodes; LVI, lymphovascular invasion; N+, node-positive; NO, node-negative; RNU, radical nephroureterectomy.

are difficult to ascertain with delicate endoscopic instruments designed for the upper urinary tract. In an ongoing Phase II clinical trial of neoadjuvant systemic therapy for UTUC, all patients with high-grade UTUC are offered systemic chemotherapy before surgery, because of the high correlation between high tumour grade and advanced pathological stage [11]. Alternatively, we have recently developed a preoperative nomogram, using grade, architecture and location of the

tumour to predict the probability of non-organ-confined UTUC [12]. If validated prospectively, this tool can be used for selection of patients to receive systemic therapy before RNU.

The results of this study suggest that favourable oncological outcomes can be achieved in patients with UTUC and loco-regional nodal metastases treated with preoperative systemic therapy followed by

aggressive surgical consolidation with RNU. This is shown by a significant rate of complete pathological responses achieved in both primary tumours and lymph nodes, as well as by the favourable survival observed in node-positive patients treated with preoperative chemotherapy before consolidative RNU, compared with node-positive patients treated with initial surgery. Ultimately, the safety and efficacy of such an approach should be evaluated in the context of a prospective clinical trial [11].

In UCB, the advantages of neoadjuvant chemotherapy include timely treatment of systemic micrometastatic disease; significant rates of complete pathological responses in the bladder and decrease in positive surgical margins [1]. In UTUC, several unique disease features lend additional rationale for the use of neoadjuvant, rather than the adjuvant, chemotherapy in these patients. The loss of renal function that occurs with RNU can significantly complicate administration of appropriate adjuvant chemotherapy after surgery, especially in the elderly patient population, who are likely to have a multitude of associated comorbidities. Hence, the additional advantages of administering chemotherapy before RNU include better treatment tolerance and the ability to deliver higher treatment doses than in the adjuvant setting [7]. Despite concerns about increased surgical morbidity after preoperative chemotherapy, the data in patients with UCB have not supported this idea [13,14]. Proposed benefits of preoperative chemotherapy have to be carefully balanced against the risks of overtreatment and delay of potentially curative surgical intervention. Isolated clinical pathological parameters, such as tumour stage and grade, are not adequate for accurate assessment of the true disease burden so integrative staging tools, similar to a recently developed preoperative nomogram for prediction of non-organ-confined UTUC can guide patient selection for neoadjuvant chemotherapy [12].

Unfortunately, our data suggest that systemic chemotherapy continues to be underutilized in patients with UTUC, with <50% of node-positive patients receiving chemotherapy before or after RNU. The reasons for this underutilization remain unclear, but probably include physician practice patterns, unwillingness by patients to undergo chemotherapy, and significant deterioration of renal function after RNU.

Based on our findings, as well as on experience gained from the management of patients with advanced UCB, preoperative platinum-based chemotherapy should be prospectively explored and incorporated into treatment algorithms of patients with advanced UTUC. We believe that an aggressive strategy with preoperative chemotherapy followed by RNU including meticulous lymph node dissection [15–17] may improve the outcome of these patients.

The data presented here are descriptive and exploratory, and several limitations of this study merit further discussion. First, are the limitations inherent to the retrospective study design, which undoubtedly translate into a significant selection bias and a disproportionately small number of patients in the preoperative chemotherapy group. Moreover, the number of patients treated with preoperative chemotherapy that could undergo subsequent RNU because of disease progression or declining performance status is not known. In addition, the true number of patients with clinically positive regional lymphadenopathy who did not undergo diagnostic biopsy and were managed with chemotherapy and surgery is not known. Finally, the patients with UTUC who were included in this study were managed by multiple surgeons who used different surgical techniques and templates of lymph node dissection. However, there was no established standard of care with regard to the performance and the extent of lymph node dissection during RNU at the time of study [18]. We believe that, with the rarity of UTUC, a retrospective study design, in which rigorous clinical and pathological review of patient data from multiple high-volume cancer centres is implemented, provides valuable clinical information, and serves as an important link into thoughtful prospective clinical trial design.

Preoperative systemic therapy followed by aggressive surgical consolidation may afford favourable oncological outcomes in patients with UTUC with loco-regional nodal metastases. This approach represents a promising treatment strategy for patients with UTUC with known loco-regional nodal metastasis or for those at risk of such metastases and should be explored in prospective protocols.

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## CONFLICT OF INTEREST

None declared.

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**Abbreviations:** **UTUC**, Upper urinary tract urothelial carcinoma; **RNU**, radical nephroureterectomy; **UCB**, urothelial carcinoma of the bladder; **MVAC**, methotrexate, vinblastine, doxorubicin and cisplatin.