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# Extraurothelial recurrence after radical nephroureterectomy: preoperative predictors and survival

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**Abstract**
*Objective* To identify the preoperative predictors of extraurothelial recurrence (EUR) after radical nephroureterectomy (RNU) in patients with upper tract urothelial carcinoma (UTUC).
*Methods* A single-center series of 238 consecutive patients who were treated with RNU for UTUC was evaluated. Recurrence-free probabilities and cancer-specific survival (CSS) were estimated using the Kaplan–Meier method. Multivariate Cox proportional hazards regression models were used to evaluate the association between various clinicopathological factors and EUR.
*Results* The median time to EUR was 17.6 months (range 3–73 months). EUR-free survival rates at 1, 3, 5, and 7 years were 87.8, 75.2, 73.5, and 72.6 %, respectively. In multivariate Cox regression analyses, tumor stage (HR 27.4; 95 % CI 7.83–95.8; $p = 0.0001$) and lymphovascular invasion (LVI) (HR 1.53; 95 % CI 1.22–3.12; $p = 0.01$) were independently associated with EUR. In patients with EUR, 5-year CSS estimate was 29.2 %. Tumor stage (HR 14.3; 95 % CI 4.55–45.2; $p < 0.001$) and EUR (HR 2.7; 95 % CI 1.54–4.73; $p = 0.001$) were the only independent predictors associated with worse CSS.
*Conclusions* EUR significantly affected the prognosis in patients with UTUC managed by RNU. Patient with EUR had a greater probability of having higher tumor stages, higher tumor grades, and positive LVI. Tumor stage and LVI were independently associated with a worse EUR-free survival.

**Keywords** Extraurothelial recurrence · Radical nephroureterectomy · Survival · Upper urinary tract urothelial carcinoma

## Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon disease, accounting for 5 % of all urothelial carcinomas with an incidence of two cases per 100,000 person-years [1]. Radical nephroureterectomy (RNU) constitutes the gold standard treatment for individuals with bulky, invasive, and/or high-grade UTUC [2]. However, despite definitive surgery, UTUC remains a malignancy with a high potential for local and distant recurrence, with reported recurrence rates of 22–66 % [3, 4].

Such outcomes indicate the importance of choosing adequate treatment plans and proper adjuvant therapy strategies for patients with higher risks of failure. Currently, no randomized trials that have investigated the role of adjuvant chemotherapy for UTUC exist. A recent meta-analysis showed that cisplatin-based adjuvant chemotherapy for UTUC was beneficial in terms of overall survival and disease-specific survival [5].

A multivariate analysis of patients with organ-confined UTUC treated by RNU showed cancer-specific mortality

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and progression-free survival to be significantly influenced by age, pathologic stage, lymphovascular invasion (LVI), and tumor multifocality [6]. Lymph node involvement at the time of RNU could be a reliable prognostic factor for metastatic relapse, but there is a lack of standardization in performing surgical lymph node removal in UTUCs, and the debate is ongoing around the appropriate area of dissection for the lymphadenectomy. Identification of prognostic factors allows the definition of high-risk groups of patients for whom specific therapy may be necessary.

The present study aimed to identify the preoperative predictors of extraurothelial recurrence (EUR) after RNU in patients with UTUC.

## Patients and methods

A total of 317 patients with UTUC, who had undergone RNU between January 1999 and December 2013, were selected from the database. Patients who had undergone a previous or concurrent cystectomy, neoadjuvant chemotherapy, or had distant metastasis at diagnosis were excluded from the study. Patients for whom LVI status was not mentioned in the initial pathological report were also excluded from the study. In total, 238 patients (mean age 66.5 years, range 36–88) were then available for evaluation. Hospital medical records from these 238 patients were retrospectively reviewed to assess the significance of several clinicopathologic factors stratified by EUR (Table 1).

Tumors were staged according to the TNM classification [7] and graded using the 1998 WHO classification [8]. Tumor location was defined as either renal pelvic or ureteral based on the location of the dominant tumor. The dominant lesion was defined as that with the highest pathological tumor stage (pT). For multifocal tumors at the same stage, the higher grade was selected for main tumor location. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any upper urinary tract location. No immunohistochemistry techniques were used to determine the presence of LVI.

Cisplatin-based adjuvant chemotherapy was administered to some patients with pathologically confirmed lymph node metastasis (LNM) or with muscle-invasive disease (48 patients). Local recurrence and metastasis were considered to be EUR. Routine follow-up consisted of physical examination and cystoscopy every 3 months during the first year and every 6–12 months thereafter. Chest radiography, abdominal ultrasonography, computed tomography, and excretory urography were performed annually, depending on the clinical stage of the cancer in the upper urinary tract. Most patients who were identified as having died from UTUC had progressive, widely disseminated metastases at the time of death.

**Table 1** Characteristics of 238 patients with UTUC managed by RNU stratified by extraurothelial recurrence

| Characteristic | No. of patients (%) | Extraurothelial recurrence | | |
|---|---|---|---|---|
| | | Yes (%) | No (%) | *p** value |
| All | 238 | 65 | 173 | – |
| Age (years), mean ± SD | 66.5 ± 8.9 | 67.1 ± 8.8 | 66.2 ± 9.1 | 0.23† |
| Sex | | | | 0.57 |
| Male | 132 (55.4) | 38 (58.5) | 94 (54.3) | |
| Female | 106 (44.6) | 27 (41.5) | 79 (45.7) | |
| Anemia at diagnosis | | | | 0.15 |
| Yes | 73 (30.6) | 23 (35.4) | 50 (28.9) | |
| No | 164 (69.4) | 41 (64.6) | 123 (71.1) | |
| History of BC | | | | 0.16 |
| Yes | 58 (24.4) | 20 (30.7) | 38 (22.0) | |
| No | 180 (75.6) | 45 (69.3) | 135 (78.0) | |
| Concomitant BC | | | | 0.52 |
| Yes | 45 (18.9) | 14 (21.5) | 31 (17.9) | |
| No | 193 (81.1) | 51 (78.5) | 142 (82.1) | |
| Tumor location | | | | 0.21 |
| Renal pelvis | 142 (59.6) | 43 (66.1) | 99 (57.2) | |
| Ureter | 96 (40.4) | 22 (33.9) | 74 (42.8) | |
| Tumor focality | | | | 0.76 |
| Unifocal | 161 (67.6) | 43 (66.1) | 118 (68.2) | |
| Multifocal | 77 (32.4) | 22 (33.9) | 55 (31.8) | |
| Tumor size | | | | 0.55 |
| ≤3 cm | 99 (41.6) | 25 (38.5) | 74 (42.8) | |
| >3 cm | 139 (58.4) | 40 (61.5) | 99 (57.2) | |
| Tumor grade | | | | 0.001 |
| G1 or G2 | 118 (49.6) | 21 (32.3) | 97 (56.1) | |
| G3 | 120 (50.4) | 44 (67.7) | 76 (43.9) | |
| Tumor stage | | | | 0.001 |
| pT2 or less | 95 (39.9) | 3 (4.6) | 92 (53.2) | |
| pT3 or greater | 143 (60.1) | 62 (95.4) | 81 (46.8) | |
| Lymph node metastasis | | | | 0.01 |
| pNx | 189 (79.4) | 46 (70.8) | 143 (82.6) | |
| pN0 | 36 (15.1) | 11 (16.9) | 25 (14.4) | |
| pN+ | 13 (5.5) | 8 (12.3) | 5 (3.0) | |
| LVI | | | | 0.035 |
| Positive | 154 (35.3) | 16 (24.6) | 68 (39.3) | |
| Negative | 84 (64.7) | 49 (75.4) | 105 (60.7) | |

* *p* value for Chi-square test

† *p* value for an unpaired *t* test

The initial treatment of all patients was open RNU. Lymph node dissection (LND) was performed in 49 patients, while 189 patients did not receive LND (pNx).

Whether LND would be performed or not as well as the extent of LND when performed were determined by each surgeon during surgery. Mainly LND were performed in patient with palpably or visibly (intraoperatively or radiographically) suspicious lymph nodes.

Demographic and clinicopathological factors were analyzed using the Chi-square test or an unpaired *t* test. Recurrence-free probabilities and cancer-specific survival were estimated using the Kaplan–Meier method, and the log-rank test was used for the statistical differences. We defined the time of surgery as time zero. Univariate and multivariate Cox proportional hazards regression models were used to evaluate the association between various clinicopathological factors and EUR, as well as cancer-specific mortality after surgery. In all tests, $p < 0.05$ (two-sided) was considered statistically significant. All statistical analyses were performed using SPSS© (version 17).

## Results

### Clinical and pathologic data

The patients' demographic, clinical, and pathological profiles are listed in Table 1. The median follow-up after surgery was 34.5 months (range 1–154 months). Of the 238 patients included in the present study, 65 (27.3 %) patients had EUR. From the patients with EUR, 58.3 % had initial recurrence in lymph nodes, 35.5 % had recurrence in distant organs, and 6.2 % had recurrence in local area.

Patient with EUR had a greater probability (43.3 vs. 30.7 %) of having higher tumor stages ($p = 0.001$) and higher tumor grades (36.6 vs. 29.1), which was statistically significant ($p = 0.001$). Lymphovascular invasion ($p = 0.03$) was also associated with EUR.

### Predictors of EUR

In univariate Cox regression analyses, tumor grade (HR 2.03; 95 % CI 1.21–3.42; $p = 0.008$), tumor stage (HR 22.6; 95 % CI 7.01–72.7; $p = 0.001$), and LVI (HR 1.85; 95 % CI 1.05–3.25; $p = 0.03$) were associated with EUR (Table 2). In multivariate Cox regression analyses (Table 2), tumor stage (HR 27.4; 95 % CI 7.83–95.8; $p = 0.0001$) and LVI (HR 1.53; 95 % CI 1.22–3.12; $p = 0.01$) were independently associated with EUR.

The median time to EUR was 17.6 months (range 3–73 months). EUR-free survival rates at 1, 3, 5, and 7 years were 87.8, 75.2, 73.5, and 72.6 %, respectively (Fig. 1). The EUR-free survival rates were significantly lower in patients with higher tumor stages (pT3 or greater, $p = 0.001$, log-rank) and higher tumor grades (G > 2, $p = 0.006$, log-rank). Also, EUR-free survival rates were lower in patients with LVI ($p = 0.03$, log-rank).

### Outcomes of patients with EUR

The 5-year cancer-specific survival (CSS) estimate was 71 %. However, in patients with EUR, 5-year CSS estimate was 29.2 %. In multivariate Cox regression analyses, tumor stage (HR 14.3; 95 % CI 4.55–45.2; $p < 0.001$) and EUR (HR 2.7; 95 % CI 1.54–4.73; $p = 0.001$) were the only independent predictors associated with worse CSS. The CSS in patients with EUR was significantly lower compared with those without EUR ($p < 0.001$, log-rank, mean CSS for patients with EUR 37.5 ± 4.8 months vs. mean CSS for patients without EUR 119.9 ± 7.1 months).

**Table 2** Univariate and multivariate Cox regression models predicting EUR in 238 patients after RNU

| Variable | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95 % CI | *p* | HR | 95 % CI | *p* |
| Sex (male vs. female) | 0.84 | 0.51–1.37 | 0.48 | 0.83 | 0.49–1.39 | 0.49 |
| Age (years) (≤60 vs. >60) | 1.65 | 0.86–3.16 | 0.13 | 1.42 | 0.71–2.82 | 0.32 |
| Anemia at diagnosis (Hgb < 115 g/l) | 0.83 | 0.50–1.38 | 0.48 | 0.94 | 0.55–1.61 | 0.83 |
| History of BC (no vs. yes) | 1.54 | 0.91–2.61 | 0.11 | 0.93 | 0.48–1.81 | 0.84 |
| Concomitant BC (no vs. yes) | 1.32 | 0.73–2.39 | 0.36 | 0.98 | 0.46–2.09 | 0.97 |
| Tumor location (renal pelvis vs. ureter) | 0.75 | 0.45–1.25 | 0.26 | 1.21 | 0.66–2.23 | 0.54 |
| Tumor focality (unifocal vs. multifocal) | 1.12 | 0.67–1.87 | 0.67 | 1.1 | 0.63–2.29 | 0.58 |
| Tumor size (≤3 cm vs. >3 cm) | 1.32 | 0.80–2.18 | 0.27 | 0.94 | 0.53–1.65 | 0.83 |
| Tumor grade (G1 or G2 vs. G3) | 2.03 | 1.21–3.42 | 0.008 | 0.84 | 0.47–1.49 | 0.55 |
| Tumor stage (pT2 or less vs. pT3 or greater) | 22.6 | 7.01–72.7 | 0.001 | 27.4 | 7.83–95.8 | 0.000 |
| Lymphovascular invasion (negative vs. positive) | 1.85 | 1.05–3.25 | 0.03 | 1.53 | 1.22–3.12 | 0.01 |

*p* values are for the log-rank test

*BEN* Balkan endemic nephropathy, *BC* bladder cancer, *CI* confidence interval, *HR* hazard ratio

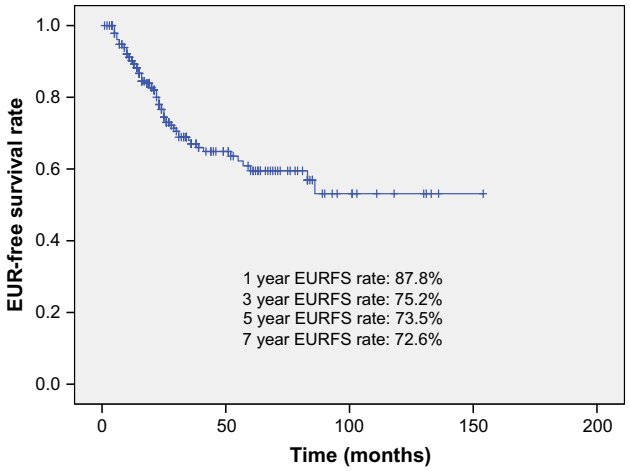


**Fig. 1** Kaplan–Meier curve for the EUR-free survival of 238 patients after RNU

Also, overall survival in patients with EUR was significantly lower compared with those without EUR ($p < 0.001$, log-rank, mean overall survival for patients with EUR 33.1 ± 3.6 months vs. mean overall survival for patients without EUR 99.8 ± 7.1 months).

Lymph node dissection was performed in 21 % of patients. Lymph node metastases after LND are shown in 26 % of patients.

## Discussion

To contribute to the ongoing discussions of UTUC predictive factors for recurrence, we analyzed the preoperative predictors of EUR after RNU. Pathological T stage, LVI, and C-reactive protein levels are documented as major prognostic factors for recurrence of UTUC [9–11]. In our study, the factors associated with a higher risk of EUR were pT3 or greater tumor stage and higher tumor grade (G3). In multivariate analysis, only tumor stage and LVI were independently associated with a worse oncologic outcome. LVI is the primary and essential step in the systemic dissemination of cancer cells [12]. Several studies have shown an association between the presence of LVI on the bladder biopsy specimen and extravesical disease at the time of cystectomy [13, 14]. Only a few publications have suggested that LVI has a negative impact on UTUC survival and have advocated the use of this factor to predict urothelial recurrence and metastatic spread [15–18]. We noted that EUR-free survival rates were significantly lower in patients with LVI.

In the present study, adjuvant cisplatin-based combination chemotherapy was only administered in patients with disease pT3 or pT4 and/or nodal involvement. Urothelial tumors are chemo-sensitive particularly to cisplatin-based regimens [19]. Recently, Raman et al. [20] showed a 15 % improvement in CSS for high-risk RNU patients who received adjuvant chemotherapy compared with those who did not. Kwak et al. [21] noted that the use of adjuvant chemotherapy and nodal status were associated with overall survival following UTUC surgery. Bamias et al. [22] prospectively studied a cohort of 36 patients who received adjuvant chemotherapy following UTUC surgery and reported a reduction in metastatic recurrences, although there was no difference in survival at 5 years. The use of adjuvant chemotherapy in the treatment of UTUC remains largely limited due to the decline in renal function following RNU.

The French Collaborative National Database on UTUC did not find any significant benefit in patient outcomes despite the use of adjuvant chemotherapy [23]. Only about 22 % of high-risk patients with a pathologic stage ≥pT3N0 and/or N+ and/or M+ disease received adjuvant chemotherapy, with only 50 % treated with a cisplatin-based regimen. The 5-year overall and CSS rates were 43 and 60 %, respectively, with no difference in outcomes compared with the group who did not receive adjuvant chemotherapy. It is again notable that patients offered adjuvant chemotherapy had a higher pathologic stage and a higher-grade disease. To date, there have been no randomized trials confirming the efficacy of postoperative chemotherapy or radiotherapy in patients with UTUC.

The 5-year cancer-specific survival for all patients was 70.1 % and for patients with EUR was 29.2 %. Overall survival in patients with EUR was significantly lower compared with those without EUR. In accordance with previous studies, tumor stage and EUR were the only independent predictors associated with worse CSS [3, 24]. Use of prognostic factors might help identify patients who could benefit from intensified therapy and monitoring. For example, prognostic factors could be used to identify patients for whom neoadjuvant or adjuvant chemotherapy is likely to be beneficial. Inclusion criteria for clinical trials based upon such prognostic factors might ensure an adequately selected study population to demonstrate a benefit for experimental therapies.

There are several limitations to the current study. First, it is inherently limited by biases associated with its retrospective design. Our results are subject to the inherent biases associated with high-volume tertiary care centers. Adjuvant treatments administered to patients with pT3 or pT4 disease could induce a bias, but these patients had the worst outcomes. In this cohort of patients, none had received neoadjuvant chemotherapy, which can be limitation of the study. In addition, patients were not randomized to receive LND or not, and the extent of LND was decided by each surgeon. Despite these limitations, our study has strengths,

such as a centralized pathologic review and standardized follow-up.

## Conclusions

EUR significantly affected the prognosis in patients with UTUC managed by RNU. Patient with EUR had a greater probability of having higher tumor stages, higher tumor grades, and positive LVI. Tumor stage and LVI were independently associated with a worse EUR-free survival. When a lymphadenectomy has not been achieved, the reporting of LVI status is crucial to identify those patients who are at higher risk of metastatic relapse. Tumor stage and EUR were the only independent predictors associated with worse CSS.

Determining prognostic factors of EUR can aid in the decision making in relation to management of patients with UTUC, consideration of adjuvant therapy, and selection of patients who would benefit from inclusion into clinical trials.

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

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