



## Predictors of recurrence and patterns of failure among patients treated with nephroureterectomy for upper tract urothelial carcinoma



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### ABSTRACT

**Purpose:** Recurrence rates following nephroureterectomy (NU) for upper tract urothelial carcinoma (UTUC) remain high. As such, adjuvant therapy directed at high risk sites may improve long term outcomes. We describe patterns and predictors of UTUC recurrence according to patient, disease and treatment-related factors.

**Methods and materials:** We reviewed the records of 113 patients treated with NU for UTUC at our institution between 2006 and 2013. Time to locoregional (LR), intravesical (IV), distant recurrence and death were described using the Kaplan–Meier method and compared using the log rank statistic. Cox Proportional Hazards analyses were performed to evaluate the adjusted hazard for LR/IV and LR recurrence.

**Results:** Advanced T stage (T3/4) was present in 41 (36%) patients, 10 (9%) were node-positive and 21 (19%) showed evidence of lymphovascular space invasion (LVSI). Median overall survival and time to any recurrence was 54.6 and 20.7 months, respectively. Disease recurrence was observed in 48 (42%) patients. The location of failure was intravesical in 27 (24%), locoregional in 22 (19%) and distant in 20 (18%). Three-year LR/IV and distant failure rates were 38.7% and 22.2%, respectively. Three-year LR failure was 4.6% in pTa-2 vs. 25.8% in T3–T4 disease. Multivariate analysis identified history of prior bladder disease as a significant predictor of LR/IV recurrence.

**Conclusions:** In this study we demonstrate LR/IV recurrence as the predominant pattern of failure in UTUC patients treated with nephroureterectomy. This systematic description of recurrence patterns and associated factors will guide further investigation of adjuvant therapy to minimize the treatment failures defined herein.

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### 1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) has been reported in rates of approximately two cases per 100,000 person-years with 5-year overall survival of 20–75% over the last 40 years [1]. The current guidelines for treatment of UTUC include radical nephroureterectomy, with resection of the bladder cuff and lymph node dissection in the case of invasive disease [2]. While the role of chemotherapy in UTUC is not yet clear, recent studies have described a survival benefit with neoadjuvant and adjuvant chemotherapy and currently ongoing trials are expected to further

define its utility [3–5]. Drawing on treatment paradigms for lower tract urothelial carcinoma, platinum-based regimens are used most commonly and may improve survival [6]. Additionally, postoperative intravesical therapy may reduce the rate of bladder recurrence after nephroureterectomy [7]. Adjuvant chemoradiation with cisplatin may be considered to improve disease-free and overall survival in patients with locally advanced or node-positive disease, although distant failure has predominated and previous studies of adjuvant radiotherapy have not shown a significant survival benefit [8–10]. Recent studies have shown improvements in locoregional (LR) and intravesical (IV) recurrence-free survival as well as overall survival with adjuvant radiotherapy to the tumor bed, regional lymph nodes, course of ureter ± bladder irradiation in patients with locally advanced disease [11,12].

Many single- and multi-institutional studies have demonstrated a number of prognostic variables for tumor recurrence and patient survival, including stage, grade, multifocality, synchronous

*Abbreviations:* NU, Nephroureterectomy; UTC, urothelial carcinoma; UTUC, upper tract urothelial carcinoma; LR, locoregional; IV, intravesical; LVSI, lymphovascular space invasion; CIS, carcinoma in situ

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bladder tumor, concurrent carcinoma in situ (CIS), lymph node involvement, and lymphovascular space invasion (LVSI) [13–22]. In this single-institution study, we evaluate our experience with this rare disease treated with a variety of surgical approaches over a relatively short period of time. The above variables and additional patient, disease, and therapeutic factors were analyzed and detailed time-to-event analyses were performed with regard to patterns of disease recurrence and patient survival. The focus of this study is to identify patients who are at high risk of recurrence and therefore may be best served by adjuvant therapy to potential regions at risk (such as the tumor bed, regional lymph nodes, and the bladder) or directed toward clinical trials following their resection.

## 2. Materials and methods

### 2.1. Patient population

In this study, we reviewed a prospectively maintained, IRB-approved database of patients treated with nephroureterectomy for UTUC at our institution between 2006 and 2013. This review was conducted with IRB approval. Patient age, tumor size, prior bladder UTC, pathologic T stage, nodal status, concurrent CIS, LVSI, resection margins, surgical approach, lymphadenectomy, bladder cuff resection, adjuvant chemotherapy and/or radiotherapy were analyzed as potential predictors of locoregional and intravesical recurrence.

### 2.2. Treatment paradigm

All patients underwent nephroureterectomy with curative intent. Nephroureterectomy was performed by multiple surgeons throughout the duration of the study period with surgeon preference and experience dictating surgical technique. Surgical management of the distal ureter included removal of a bladder cuff with complete distal ureteral resection including the intramural ureter and the ipsilateral ureteral orifice being removed en bloc, except when not technically possible. In cases of laparoscopic removal, a small Gibson incision was made for bladder cuff excision and specimen extraction. Robotic nephroureterectomy was performed as published previously [23].

Lymphadenectomy in patients with localized disease was performed at the surgeon's discretion and consisted of a retroperitoneal node dissection with removal of all lymphatic tissue surrounding the IVC for right sided tumors and the aorta with the peri-caval tissue for left sided specimens. All patients with imaging suggestive of lymphadenopathy had a lymph node dissection. Chemotherapy and radiotherapy were given in select patients based on physician discretion. Following extirpative surgery patients were followed with cystoscopy every 3 months for 2 years; this interval increased to 4 months at 3 years and then to 6 months at 5 years. Abdominal axial imaging via computerized tomography with IV contrast was given to those without renal impairment at least biannual for 3 years following their procedure and then annually thereafter. Chest radiography was obtained at those times as well. Patients with chronic kidney disease had ultrasonographic or magnetic resonance imaging at these intervals.

### 2.3. Outcomes

Locoregional recurrence was defined as any disease recurrence in the ipsilateral bladder cuff, ureteral stump, renal pelvis, surgical field, or regional nodal chains (renal hilar, paracaval, para-aortic, retroperitoneal, iliac, or periureteral) as defined by our interpretation of historic clinical or radiographic findings. Intravesical

recurrence represented any urothelial carcinoma of the bladder diagnosed after nephroureterectomy. Distant metastasis represented spread of disease to anatomic regions outside the genitourinary tract or adjacent nodal regions. Overall survival was defined as the all-cause freedom from mortality from the time of nephroureterectomy. Recurrence-free survival represented the length of time from nephroureterectomy to the time of the first instance of cancer recurrence.

### 2.4. Statistical analysis

Descriptive analyses of continuous data were summarized using the mean (range) and median (interquartile range) in the case of normal and non-normal distributions, respectively. Categorical data were described as frequencies. Continuous data were compared across groups with the *t*-test while categorical data are compared using either the Fisher's exact or Chi-Square test. All time-to-event data were described with Kaplan–Meier plots and differences across strata are tested using the log-rank test.

A univariate and multivariate cox proportional hazards analysis was performed to identify potential factors associated with LR and LR/IV recurrence. Interactions and adherence with the proportional hazards assumptions were tested for all potential combinations of covariates meeting a threshold *p*-value of 0.2 prior to inclusion in the multivariate model. All computations were carried out using SAS version 9.2 (SAS Institute, Cary, North Carolina, USA) and Microsoft Excel 2013.

## 3. Results

### 3.1. Patient and treatment characteristics

Patient characteristics are outlined in Table 1. Advanced T stage (T3/4) was present in 41 (36%) of patients, lymph node involvement was present in 10 (9%), lymphovascular space invasion (LVSI) in 21 (19%), and concurrent carcinoma in situ (CIS) in 21 (19%). Twenty-nine (26%) patients had a history of non-muscle-invasive bladder urothelial carcinoma (UTC), 11 of which had previously received at least one course of intravesical BCG. One hundred and thirteen patients received laparoscopic (42%), robotic (38%), or open (20%) nephroureterectomy (Table 2). Complete ureterectomy and resection of the bladder cuff were achieved in 91% and 78% of patients, respectively. The surgical margins were positive in 10%. Lymphadenectomy was performed for 45 (40%) patients and revealed N1 disease in 10 (9%). Twelve patients received chemotherapy, 9 of which were high-stage (pT3–T4) and 3 were node-positive. Chemotherapeutic regimens included gemcitabine and cisplatin (*n*=8), gemcitabine and paclitaxel (*n*=1), carboplatin and paclitaxel (*n*=1), paclitaxel alone (*n*=1) and unknown (*n*=1). Both patients that received radiotherapy were low pT stage and pN0. The variation in surgical techniques and operative extent across primary tumor location are reported in Supplemental Table 1 and the extent of tumor resection achieved by operative technique in Supplemental Table 2.

### 3.2. Clinical outcomes

Median follow-up was 39 months. Three-year overall survival and disease-free survival was 65.4% and 45.4%, respectively (Fig. 1a and b). In total, 48 (42%) patients experienced disease recurrence (Table 3). Seven (6%) patients failed locally, 6 of which were synchronous with either IV, regional, or distant failure. Four (4%) local failures occurred in the remnant ureter and 1 (1%) in each of the renal pelvis, surgical field, and bladder cuff. Intravesical failure occurred in 27 (24%) patients and was the initial site of failure in

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