

Upper Tract Urothelial Carcinomas: Prognostic Factors and Outcomes in Patients With Non–Lymph Node Distant Metastasis

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Abstract

Metastatic UTUC is an aggressive disease. 45 patients with distant metastasis were analysed at the time of initiating chemotherapy in a risk score that includes anemia and receipt of cisplatin helping stratify overall survival patients for future clinical trials.

Background: Upper tract urothelial carcinomas (UTUCs) are increasingly recognized as separate malignancies. Additional insight into clinical outcomes and key prognostic factors are needed. **Objectives:** To detail outcomes of patients with UTUCs recurring after radical nephroureterectomy (RNU) and to determine a risk score that predicts outcomes of patients with non–lymph node distant metastasis. **Design, Setting, and Participants:** Chart review of all patients who had an extraurothelial recurrence after RNU for UTUC at Dana-Farber Cancer Institute between 2009 and 2014. **Outcome Measurements and Statistical Analysis:** Median overall survival defined as time from chemotherapy for distant relapse to death. Prognostic relevance of performance status, hemoglobin, and receipt of cisplatin were assessed by Cox regression model. **Results and Limitations:** A total of 102 patients were identified, 57 of whom had non–lymph node distant metastases at relapse; 45 received chemotherapy. Median follow-up was 29.8 months; median overall survival was 14.7 months. Objective response rate to any chemotherapy in the first-line setting was only 22%. Hemoglobin > 11 g/dL and receipt of cisplatin was associated with numerically longer median survival but did not reach statistical significance in univariate and multivariate analysis. Prognostic risk score scale including hemoglobin < 11 g/dL and receipt of cisplatin was inversely associated with survival, with scores of 0, 1, and 2 leading to median survival of 19.0, 14.9, and 7.2 months ($P = .38$), respectively. **Conclusions:** Advanced UTUC portends a poor prognosis, and most patients cannot receive cisplatin-based chemotherapy. A risk score that includes anemia and receipt of cisplatin helps stratify patients with distant metastasis for inclusion into eventual clinical trials. More studies are needed to validate these findings. **Patient Summary:** Metastatic UTUC is an aggressive disease, where anemia and ineligibility to receive cisplatin are adverse features associated with shorter survival.

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Introduction

Pyelocaliceal and ureteral tumors are rare malignancies accounting for approximately 5% to 10% of all urothelial carcinomas.¹ These tumors, defined as upper tract urothelial carcinomas (UTUCs), compared to urothelial bladder carcinoma, are

increasingly recognized as biologically distinct aggressive malignancies.² Historically, localized UTUCs were associated with up to 60% of invasive disease at diagnosis, and up to 28% of these patients experienced recurrence after radical nephroureterectomy (RNU).³ Lymph node (LN) and distant metastases are frequently

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observed at the time of diagnosis, with the respective incidences estimated to be approximately 36% and 9%.⁴

Patients with advanced UTUCs differ from patients with urothelial bladder carcinoma at the clinical, genetic, and molecular level. These patients are generally older, and many previously underwent RNU,⁵ which can compromise their eligibility to receive cisplatin-containing chemotherapy.⁶ UTUCs are also known to have a higher prevalence of microsatellite instability⁷ and a different genomic landscape.^{8,9} Collectively, these particularities may alter the natural history of these malignancies, key prognostic factors, and selection of systemic therapy for advanced UTUCs compared to urothelial bladder carcinoma.

In view of the lack of prospective data on patients with advanced UTUCs, clinicians have extended the treatment and management principles learned from metastatic urothelial carcinoma to UTUCs. To date, most of the effort invested in identifying new prognostic factors in UTUCs has been concentrated into the pre- and post-RNU space,¹⁰ but little is known about patients with established metastatic disease. In urothelial bladder carcinoma, performance status and visceral metastasis are established prognostic factors in the first-line treatment of patients with platinum-sensitive disease,¹¹ whereas hemoglobin levels ≤ 10 g/dL have prognostic value in second-line chemotherapy.¹² However, it is unclear if these factors also predict outcomes in patients with advanced UTUCs.

We thus performed a single-institution retrospective study to explore clinical outcomes and prognostic factors for patients with UTUC who experienced metastatic non-LN disease recurrence after RNU.

Methods

Patients

This study was approved by our institutional review board before data collection. We identified all patients treated with a RNU and bladder cuff excision between January 2009 and December 2014 at Dana-Farber Cancer Institute/Brigham and Women's Hospital (Boston, MA). Chart review was performed; patients with non-metastatic UTUC who underwent RNU and who subsequently experienced relapse were included. A subset of patient with non-LN distant metastases and treated with chemotherapy was created to identify prognostic factors. Patients with intravesical recurrence and those who did not receive chemotherapy at relapse were not included in the analysis.

Data Extraction

Data extracted for patients in our study included the following: perioperative baseline characteristics and performance status; tumor location; pathologic tumor, node, metastasis classification system stage; tumor grade; presence of carcinoma-in-situ and lymphovascular invasion; surgical approach; LN dissection status; receipt of perioperative chemotherapy; and start date. In addition, we extracted the type of chemotherapy provided at relapse, hemoglobin levels, location of metastasis, date of relapse, and date of death.

Risk Score

In the subgroup of patients with distant metastasis, we investigated the association between 3 established prognostic factors in bladder cancer and survival: hemoglobin level, performance status,

and receipt of cisplatin. Prechemotherapy continuous and categorical data were dichotomized as follows: hemoglobin (< 11 g/dL or > 11 g/dL), performance status (< 1 or ≥ 1), and receipt of cisplatin-based chemotherapy (yes or no). However, the attempt to include factors such as albumin was not considered because albumin level data were not available for several patients. Time from prior chemotherapy prognostic factor was not considered because this has been described in second-line treatment setting. Overall survival was measured from the date of the first chemotherapy for recurrent disease to date of death or last follow-up.

Statistical Analysis

Patient and clinical characteristics were summarized as numbers and percentages for categorical variables, and as medians with interquartile ranges for continuous variables. The Kaplan-Meier method was used to estimate the overall median survival, and the association between the prognostic factors and survival was summarized by the Cox proportional hazards regression model. All statistical computations were performed by SAS 9.2 (SAS Institute, Cary, NC). Statistical significance was assumed for 2-sided $P \leq .05$.

Results

A total of 102 patients met the cohort's inclusion criteria, of whom 57 (56%) had visceral distant metastasis, and 45 patients initiated chemotherapy for metastatic disease. Patient characteristics are presented in Table 1. Eighty-nine percent of the cohort had invasive disease on their pathology specimen, and among those who had a LN dissection, more than a third had nodal involvement. Thirty percent of patients (31 of 102) received perioperative chemotherapy consisting of platinum-based regimens.

At the time of analysis, the median follow-up was 46 months, and the median time to relapse was 29.8 months. The most common sites of distant metastasis were lungs ($n = 27$; 47%), liver ($n = 22$; 38%), bone ($n = 16$; 28%), and brain ($n = 4$; 7%).

Distant Recurrence

Most patients with distant metastases (45 of 57) were treated with chemotherapy; 2 were treated with metastasectomy and 6 with radiotherapy, and 4 received best supportive care only. Those who did not receive chemotherapy at relapse were not included in the analysis. There were 8 (14%) such patients who fulfilled this criterion, which was the result of early disease progression with a quick deterioration in performance status. Because only limited information was available, we decided to exclude these patients from analysis.

At the time of initiating chemotherapy, the median age was 67 years (range, 58-75 years), the median hemoglobin level was 11.7 g/dL, and most patients had a performance status of 0 or 1. Fourteen patients received cisplatin-containing chemotherapy, whereas carboplatin backbone chemotherapy and nonplatinum regimens were used in 23 (51%) and 8 (18%), respectively. Complete prechemotherapy baseline characteristics are presented in (Table 2).

Complete response to any first-line chemotherapy occurred in 2 patients (4%), partial response in 8 (18%), and stable disease in 17 (38%). At the time of analysis, the median follow-up time from first chemotherapy onward was 31 months (range, 1-44 months), and 35 deaths had occurred. The median overall survival was 14.9 months (95% confidence interval, 10.2-19.6).

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