Prognostic Risk Stratification of Patients with Urothelial Carcinoma of the Bladder with Recurrence After Radical Cystectomy

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Purpose: We identify clinicopathological variables predicting overall survival in patients with recurrent bladder urothelial carcinoma after radical cystectomy.

Materials and Methods: We retrospectively collected data on 114 patients treated with radical cystectomy for bladder urothelial carcinoma who subsequently had remote metastasis and/or local recurrence. The Kaplan-Meier method with the log rank test and multivariate Cox regression models were used to address overall survival after recurrence.

Results : During followup 99 of the 114 patients died. Median survival in the 114 patients was 11.2 months. One and 3-year overall survival rates were 48.0% and 12.1%, respectively. On multivariate analysis independent predictors of poorer overall survival included less than 1 year to recurrence, symptoms at recurrence, 2 or more metastatic organs at recurrence, high serum C-reactive protein, high lactate dehydrogenase, no post-recurrence platinum based chemotherapy and no metastasectomy. Based on the 4 variables (time to recurrence, symptoms, number of metastatic organs and C-reactive protein), we constructed a risk model predicting post-recurrence overall survival that classified patients into 3 groups with significantly different overall survival ($p < 0.0001$).

Conclusions: Our data confirm that recurrent urothelial carcinoma after radical cystectomy is a highly aggressive, lethal disease. Seven clinicopathological factors were identified that predicted post-recurrence overall survival. Our risk model based on the 4 variables could be useful to provide relevant prognostic information to patients and physicians, and better stratify patients in clinical trials.

Key Words: urinary bladder; urinary bladder neoplasms; neoplasm recurrence, local; prognosis; risk

Abbreviations and Acronyms

CRP = C-reactive protein
GC = gemcitabine and cisplatin
LDH = lactate dehydrogenase
LN = lymph node
MST = median survival time
MVAC = methotrexate, vinblastine, doxorubicin and cisplatin
OS = overall survival
RC = radical cystectomy
TTR = time to recurrence
UC = urothelial carcinoma

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RADICAL cystectomy with pelvic LN dissection is standard treatment for muscle invasive and high risk, non-muscle invasive bladder cancer.[1] Despite advances in surgical technique and patient selection, the risk of disease recurrence remains high with reported 5-year recurrence-free survival and OS rates after RC of 48% to 68% and 57% to 66%, respectively.[2–6] Several clinicopathological factors affecting the clinical outcome of patients who undergo RC were identified, including age, pathological stage, nodal status, lymphovascular invasion, surgical margin status, adjuvant chemotherapy and smoking history.[2–6] However, few groups have examined the

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clinical outcome of patients in whom recurrence develops after RC.

Volkmer et al reported that 1 and 2-year OS rates after recurrence were 18% to 20% and 8% to 10%, respectively.[7] However, they focused on the significance of routine followup after cystectomy and did not propose any prognostic factors. Mitra et al reported a median post-recurrence OS of 5.59 months and noted that pathological stage, urinary diversion type, LN density, TTR, recurrence site and post-recurrence chemotherapy were associated with survival.[8] However, their cohort comprised patients who underwent surgery between 1971 and 2005. Thus, they might not represent a contemporary population. In fact, the percentage of patients who underwent MVAC or GC chemotherapy was as low as 15.9% in that series. Furthermore, laboratory data on recurrence were not examined to predict the prognosis. Thus, the variable clinical course of patients with recurrence after RC has not been fully described. To our knowledge clinicopathological factors that can stratify the risk of death in such patients remain to be elucidated.

We elucidated clinicopathological variables for predicting the outcome in patients with bladder UC in whom recurrence developed after RC.

MATERIALS AND METHODS

Patient Population

We retrospectively reviewed the medical records of patients who underwent RC and pelvic LN dissection for bladder cancer with curative intent at National Cancer Center Hospital between January 1990 and December 2010. Patients in whom remote metastasis and/or local recurrence of UC developed during post-cystectomy followup were identified. Recurrence in the preserved urothelium, ie the upper urinary tract and retained urethra, was considered a new primary tumor and these patients were not included in the study population. Patients were also excluded if they had pure nonurothelial cancer histologically (ie squamous cell carcinoma, adenocarcinoma or small cell carcinoma), remote metastases at surgery, or synchronous or metachronous urethral or invasive upper urinary tract cancer. On this basis, 114 patients were included in our study, which was approved by the institutional review board.

All cystectomy specimens were subjected to routine pathological examination. Two pathologists (EA and YK) examined the specimens microscopically. Primary tumors and LNs were restaged based on the 2009 UICC TNM system.[9]

All patients were followed routinely after surgery every 3 months in year 1, at 3 to 6-month intervals in years 2 and 3, every 6 months in years 4 and 5, and annually thereafter. Followup included physical examination, a serum biochemical profile, urine cytology, chest x-ray or computerized tomography and abdominopelvic computerized tomography. Bone scintigraphy was performed as clinically indicated.

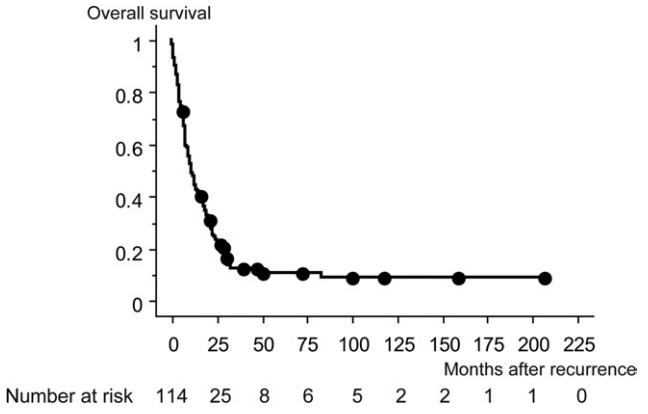

Figure 1. Kaplan-Meier analysis of OS in 114 patients

Statistical Analysis

The primary outcome was OS, defined as the interval from the date of documented recurrence to the date of death or censoring at the date of last followup. Survival distributions were estimated using the Kaplan-Meier method. Associations between OS and potential prognostic factors were assessed using the log rank test on univariate analysis. The multivariate Cox proportional hazards model was used to estimate independent relationships between OS and variables significant ($p < 0.05$) on univariate analysis. The final model was based on variables with $p < 0.05$. After prognostic factors were identified and the final model was formed, a risk group variable was created by counting the number of unfavorable features present in each patient with $p < 0.05$ considered significant. Statistical analyses were performed with JMP®, version 9.0.0.

RESULTS

The 92 male and 22 female patients had a median age of 67 years (range 32 to 84) at recurrence. Of the 114 patients 99 died during followup, mostly of progression of metastases. Median followup after recurrence was 11.0 months (range 0.2 to 206.7) in all patients and 47.3 months (range 6.1 to 206.7) in the 15 survivors at final followup. One and 3-year OS rates in the 114 patients overall was 48.0% and 12.1%, respectively, and median MST was 11.2 months (95% CI 7.7–15.2) (fig. 1).

Tables 1 and 2 list the results of univariate analyses to determine the contribution of each clinicopathological factor and biochemical feature to OS. Clinical features associated with an adverse prognosis included patient age at surgery, age at recurrence, TTR calculated from the date of RC to the date of documented recurrence, presence of symptoms at recurrence, recurrence site, number of metastatic organs at recurrence, presence of bone