Late Recurrence after Radical Cystectomy: Patterns, Risk Factors and Outcomes

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Abbreviations and Acronyms

CSS = cancer specific survival

ECOG = Eastern Cooperative Oncology Group

LR = late recurrence

RC = radical cystectomy

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Purpose: We evaluated the outcome in patients with late recurrence of urothelial carcinoma after radical cystectomy.

Materials and Methods: We identified 2,091 patients who underwent radical cystectomy at our institution between 1980 and 2006. Survival was estimated using the Kaplan-Meier method and compared based on recurrence timing (less than 5 years vs 5 or greater) and location (urothelial vs nonurothelial) using the log rank test. Cox proportional hazard regression models were used to evaluate variables associated with late recurrence and death from bladder cancer.

Results: Median postoperative followup was 16.6 years. Late recurrence was identified in 82 patients (3.9%). On multivariate analysis younger age ($p = 0.0008$), nonmuscle invasive disease ($p = 0.01$) and prostatic urethral involvement ($p < 0.0001$) were significantly associated with an increased risk of late recurrence. Five-year post-recurrence cancer specific survival was significantly worse after recurrence within 5 years from radical cystectomy vs after late recurrence (17% vs 37%, $p = 0.001$). Patients with nonurothelial late recurrence had adverse 5-year cancer specific survival compared to those with urothelial late recurrence (19% vs 67%, $p < 0.0001$). On multivariate analysis younger patient age (HR 1.01, $p = 0.003$), muscle invasive disease (HR 1.31, $p < 0.0001$) and nonurothelial recurrence site (HR 2.76, $p < 0.0001$) but not time to recurrence ($p = 0.38$) were associated with a significantly increased risk of death from bladder cancer following recurrence after radical cystectomy.

Conclusions: Late recurrence is uncommon after radical cystectomy. Younger patient age, nonmuscle invasive disease and prostatic urethral involvement were associated with a significantly increased risk of late recurrence. Interestingly, time to recurrence was not associated with a subsequent risk of patient death.

Key Words: kidney, carcinoma, cystectomy, neoplasm recurrence, urothelium

In 2013 an estimated 72,570 new cases of bladder cancer were diagnosed in the United States and an estimated 15,210 patients died of this disease.[1] RC with pelvic lymph node dissection remains the gold standard treatment for muscle invasive and high risk nonmuscle invasive tumors.[2,3] Nevertheless, up to 50% of patients experience disease recurrence after RC.[4–8] Most recurrences develop in the first 2 or 3 years after surgery and outcomes in such patients are well characterized.[9,10] However, limited data exist on late

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(ie greater than 5 years postoperatively) relapse of disease after RC.[4,11] As such, predictors and outcomes in patients who experience urothelial carcinoma LR continue to be defined.[4,11] Characterizing recurrence patterns after RC is critical for patient counseling and developing evidence-based surveillance guidelines. Indeed, time to recurrence was previously found to be associated with outcomes in patients who experience disease relapse after RC.[9,10]

We evaluated the incidence and clinicopathological variables associated with LR following RC. We also investigated factors associated with survival after recurrence, including the importance of time to disease recurrence.

MATERIALS AND METHODS

After receiving institutional review board approval we reviewed the cystectomy registry at our institution and identified 2,091 patients with bladder cancer treated with RC between 1980 and 2006. RC with lymphadenectomy was performed by various surgeons at our institution during the study period using standard techniques. Given the time span of patients included, the extent of lymph node dissection varied. It currently extends from the mid common iliac artery proximally to Cooper ligament distally, laterally to the genitofemoral nerve and inferiorly to the internal iliac vessels.

Clinicopathological variables recorded included patient age, gender, ECOG performance status, tobacco use, surgical margin status, pathological tumor stage, lymph node involvement, urinary diversion type, receipt of perioperative (neoadjuvant/adjuvant) chemotherapy, and cancer recurrence time and location. Tumors were staged according to the 2010 American Joint Committee on Cancer/UICC TNM classification, 7th edition.[12] Cancer recurrence was categorized by location as occurring in the remnant urothelium (urethra and/or upper urinary tract) vs a nonurothelial site (lymph node and visceral/soft tissue). Early recurrence was defined as recurrence less than 5 years after surgery while late recurrence was defined as recurrence 5 or more years after RC.

Due to the retrospective nature of this study postoperative surveillance was not standardized. However, at our institution followup after RC has generally been recommended quarterly for the first 2 years postoperatively, semiannually for the next 2 years and annually thereafter in patients without evidence of recurrent disease. Oncological evaluation includes history, physical examination, urine cytology and imaging of the chest/abdomen/pelvis. Stomal cytology plus urethral wash cytology in patients with cutaneous urinary diversion or voided cytology in those with orthotopic diversion were done at least annually. Recurrence was confirmed by pathology findings and/or based on imaging findings in all patients classified with tumor recurrence. To evaluate survival end points we identified vital status from death certificates or physician correspondence. For patients followed elsewhere our institutional cystectomy registry monitors outcomes annually by correspondence with the patient and local treating physician.

Post-recurrence CSS was estimated as time from recurrence to death from bladder cancer using the Kaplan-Meier method. It was compared with the log rank test based on recurrence timing and location. Cox proportional hazard regression models were used to evaluate variables associated with LR in patients treated with RC and assess factors associated with subsequent cancer specific mortality in those with disease recurrence after RC. All tests were 2-sided with $p \leq 0.05$ considered statistically significant. Statistical analysis was done with SAS®.

RESULTS

Of 2,091 patients treated with RC disease recurred postoperatively in 832 (39.8%), including 82 (3.9%) with LR. Median overall time to recurrence was 1 year (IQR 0.48, 2.34). The supplementary table lists clinicopathological demographics for all patients with recurrence stratified by time to recurrence (http://jurology.com/). Compared to patients with early recurrence those with LR were significantly younger at surgery ($p = 0.002$) with a higher likelihood of prostatic urethral involvement by tumor ($p = 0.007$) and lower pathological disease stage ($p < 0.0001$). The rate of symptoms at presentation with recurrence was similar in patients with LR and early recurrence (64.6% and 70.3%, respectively, $p = 0.29$).

In regard to recurrence site recurrence in the remnant urothelium was more common in the setting of LR than early recurrence (47.4% vs 25.3%, $p = 0.002$, table 1). Patients with recurrence in the remnant urothelium were more likely to be male (87% vs 80%, $p = 0.03$) with less frequent locally advanced (pT3/4) tumor stage (13% vs 56%) and less frequent lymph node invasion (8% vs 26%, each $p < 0.0001$). They less commonly had lymphovascular invasion in the RC specimen than those with recurrence at another site (8% vs 32%, $p < 0.0001$, table 2). Also, patients with recurrence in the remnant urothelium were more likely to have prostatic urethral involvement at RC ($p < 0.0001$).

We then evaluated factors associated with LR in the 2,091 patients who underwent RC. On multivariate analysis younger patient age at surgery

Table 1. *Recurrence site in patients with early and late recurrence*

	No. Early (%)	No. Late (%)*
Total pts	750	82
Site:		
Abdominopelvic	134 (24.2)	15 (26.3)
Urothelial	140 (25.3)	27 (47.4)
Thoracic	140 (25.3)	10 (17.5)
Bone	130 (23.5)	5 (8.8)
Brain	10 (1.8)	0

* $p = 0.002$ vs early recurrence.