



Patterns and prognostic significance of clinical recurrences after radical cystectomy for bladder cancer: A 20-year single center experience

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Accepted 11 February 2016

Available online 18 February 2016

Abstract

Objective: Patients treated with radical cystectomy (RC) due to bladder cancer (BCa) face high risk of clinical recurrence. The aim of our study was to describe recurrence patterns and characteristics related to survival in patients treated with RC due to BCa.

Methods: Years 1992–2012 of a prospectively maintained institutional RC registry were queried for clinical localized urothelial BCa patients. Clinical recurrences were categorized as local, distant or secondary urothelial recurrences. Kaplan Meier analysis assessed time to cancer specific mortality (CSM). Multivariable Cox regression models were constructed to predict recurrence and CSM after recurrence.

Results: Data from 1110 patients with urothelial non-metastatic BCa at RC were analyzed with 7.5 years of median follow up. Overall, 324 patients experienced recurrence and 200 (61.7%) were single site recurrence. The locations were: 43 local (22 cystectomy bed and 21 pelvic lymph node dissection template), 138 distant (36 lung, 19 liver, 52 bone, 17 extra pelvic LN, 7 peritoneal, 4 brain and 3 others) and 19 secondary urothelial carcinoma (11 upper urinary tract, 8 urethra). Significant independent predictors of overall recurrence were pathological stage pT3/T4 vs. pT0–2, pathological N positive status and positive surgical margin. Median overall survival after recurrence was 18 months. At multivariate analysis, pathological T3 (Hazard ratio [HR]: 1.62), T4 (HR: 1.58), interval from RC to recurrence (HR: 0.92) and distant (HR: 2.57) recurrences were independently associated with CSM (all $p < 0.05$).

Conclusions: Overall, one out of three patients treated with RC face recurrence during follow up. Early and distant recurrences are associated with shortest survival expectancies.

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Keywords: Bladder cancer; Radical cystectomy; Recurrence; Metastases

Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the treatment of choice for muscle

invasive and high risk non-muscle invasive bladder cancer (BCa) patients.¹ However, the overall estimated 5-year recurrence and cancer specific mortality (CSM) rates range from 30 to 52% and from 28 to 35%,^{2–6} respectively.

At the time there is a paucity of data about clinical patterns of recurrence after RC. Specifically, previous reports focused on specific aspects of recurrences, such as: single site of recurrence,^{7–12} timing,^{13,14} presence of symptoms^{15–17} or

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survival after recurrence^{18–21} while a paper describing natural recurrence patterns and survival expectations after recurrence is missing in a monocentric population with long follow up. Assessing locations and timing of recurrence could be of a paramount importance in order to select patients to propose for adjuvant or salvage strategies and to optimize follow up schedules. In fact, although previous reports investigated the ability of several characteristics to predict recurrence and survival^{22–24} at the time this event is considered a non-eradicated unfortunate event.

For these reasons, there is a need to improve knowledge among recurrence patterns and survival expectations after this occurrence. Following these considerations, in the present study, we presented the natural recurrence history of a large mono-institutional series of BCa patients reporting survival expectations among different recurrence sites.

Materials and methods

Study population

In this institutional review board approved study, a prospectively maintained institutional RC registry concerning the period of time between 1992 and 2012 was queried for clinically localized urothelial BCa at the time of surgery. A retrospective chart review was conducted on the final cohort to collect data concerning postoperative recurrences. Patients found with non-transitional carcinoma of the bladder were removed from our analyses ($n = 143$, 11.4%) resulting in a population of 1110 patients. Patients were staged preoperatively with pelvic/abdominal computerized tomography, bone scan and chest X-ray. All patients included in the study underwent open RC with standard pelvic lymph node dissection (PLND). The minimal limits of the node dissection consisted of the genitofemoral nerve (laterally), bladder (medially), bifurcation of common iliac vessels (cephalad), femoral canal (caudally), hypogastric vessels (poster medially) and of the obturator fossa (poster laterally). Some patients had a more extended PLND, according to the preference of the operating surgeon. Lymph node is submitted as separate specimen, rather than as en bloc that has been shown to optimize pathological evaluation of nodes count.²⁵ Neoadjuvant chemotherapy or adjuvant chemotherapy was prescribed when indicated and accordingly to patients and physicians preferences. Pathological data included tumor grade (according to 1998 WHO/ISUP consensus classification), tumor and nodal stage (according to VI edition TNM classification),²⁶ the presence of lymphovascular invasion, carcinoma in situ and surgical margin status. Patients were generally evaluated every 3–4 months postoperatively for the first year, semiannually for the second year, and annually thereafter. Examinations included radiological imaging with computer tomography scan or magnetic resonance imaging in all patients. Intravenous pyelography, cystoscopy, urine cytology, urethral washings and bone scan were carried out if indicated.

Primary and secondary end points

The primary end point was to describe clinical recurrences after RC in BCa patients. Clinical recurrence was defined as any radiological evidence of tumor relapse regardless the presence of symptoms. In case of uncertain diagnosis of recurrence, abdomen and pelvis ultrasounds, bone scan, intravenous pyelography, urinary cytology, urethral washings and cystoscopy for orthotopic bladder substitutions were additionally case to case completed. Percutaneous, laparoscopic or open biopsy confirmation of recurrence was only pursued in those patients for whom the diagnostic uncertainty could not be dissolved by imaging. Clinical recurrences were categorized as local (cystectomy bed or PLND template), distant recurrences (including lung, liver, bone, extra pelvic lymph node,

Table 1

Descriptive characteristics for the cohort of 1110 patients with non-metastatic bladder cancer that underwent radical cystectomy.

Variables	Entire cohort (n = 1110)
Age at surgery, years	
Mean	66.8
Median (IQR)	68 (60–74)
Year of surgery	
1992–2000	242 (21.8%)
2001–2007	427 (38.5%)
2008–2012	441 (39.7%)
Gender	
Male	934 (84.1%)
Female	176 (15.9%)
Preoperative hydronephrosis	241 (21.7%)
Charlson comorbidity index	
0–1	875 (78.8%)
≥ 2	235 (21.2%)
Body mass index, kg/m²	
Mean	25.9
Median (IQR)	25.3 (23.5–27.9)
Removed lymph nodes	
Mean	18.4
Median (IQR)	17 (11–25)
Positive lymph nodes	
Mean	2.49
Median (IQR)	0 (0–1)
Pathological stage	
pT0–T2	507 (45.7%)
pT3	391 (35.2%)
pT4	212 (19.1%)
N stage	
0	726 (65.4%)
1	110 (9.9%)
2	233 (21.0%)
3	41 (3.7%)
Grading	
G1	7 (0.6%)
G2	148 (13.3%)
G3	956 (86.1%)
Carcinoma in situ	266 (24.0%)
Lymphovascular invasion	93 (8.4%)
Positive surgical margin	97 (8.7%)
Neoadjuvant chemotherapy	31 (2.8%)
Adjuvant chemotherapy	148 (13.3%)

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