ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 34 (2016) 417.e1–417.e8

UROLOGIC ONCOLOGY

Original article

Lymphovascular invasion is associated with oncologic outcomes following radical cystectomy for squamous cell carcinoma of the urinary bladder

Kyle Spradling, B.A[a], Yair Lotan, M.D.[b], Ahmed Shokeir, M.D., Ph.D.[c], Hassan Abol-Enein, M.D., Ph.D.[c], Ahmed Mosbah, M.D.[c], Jacob B. Morgan, M.D.[a], Mohamed Ghoneim, M.D.[c], Ramy F. Youssef, M.D.[a,*]

[a] *Department of Urology, University of California—Irvine, Orange, CA*
[b] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX*
[c] *Department of Urology, Urology and Nephrology Center, Mansoura University, Mansoura, Egypt*

Received 24 January 2016; received in revised form 2 March 2016; accepted 30 March 2016

Abstract

Objective: To evaluate the association of lymphovascular invasion (LVI) with oncologic outcomes of squamous cell carcinoma (SCC) of the urinary bladder following radical cystectomy (RC).

Patients and methods: We performed a retrospective analysis of 1,280 patients who underwent RC for invasive bladder cancer between 1997 and 2003 in Mansoura, Egypt. Only patients with pure urothelial carcinoma of the bladder (UCB) or SCC pathology were included. Using multivariate Cox regression analyses and Kaplan-Meier analyses, prognostic significance of LVI in disease-free survival and cancer-specific survival was evaluated for patients with UCB and SCC.

Results: Our cohort included 519 (59%) patients with UCB and 360 (41%) with SCC. Median patient age and follow-up were 55 years (20–87) and 64 months (0–128), respectively. Median number of lymph nodes (LN) retrieved was 19 (4–70). LVI was present in 288 (32.8%) patients (241 [46.4%] UCB vs. 47 [13.1%] SCC; $P < 0.001$). LVI was an independent predictor of oncologic outcomes in both UCB and SCC groups; however, LVI had more prognostic significance in SCC. LN negative, LVI positive (LVI+/LN−) patients with SCC had higher risk of recurrence and cancer-specific mortality compared to LN positive, LVI negative (LVI−/LN+) patients with SCC (hazard ratio = 2.8 vs. 1.9 and hazard ratio = 3.6 vs. 2.2, respectively).

Conclusion: The presence of LVI is an independent predictor of poor oncologic outcomes after RC and had greater prognostic significance in patients with SCC compared to UCB.

Keywords: Bladder cancer; Urothelial carcinoma; Squamous cell carcinoma; Lymphovascular invasion

1. Introduction

Bladder cancer is the fourth most prevalent malignancy among men in the United States, and it is the most common cancer among Egyptian males [1,2]. Although the incidence of squamous cell carcinoma (SCC) of the bladder is relatively rare in the United States, its incidence is much higher in Egypt [3]. Chronic inflammation caused by schistosomiasis is the main SCC risk factor in the Egyptian population [4].

Despite modern advancements in surgical techniques, such as radical cystectomy (RC), oncological outcomes are still unsatisfactory [5]. Pathologic stage, tumor grade, and lymph node (LN) status are useful prognostic factors for SCC after RC [3]. However, the identification of additional prognostic tools may improve risk stratification for patients with SCC and help identify candidates for multimodal treatment approaches.

In urothelial carcinoma of the bladder (UCB), the presence of lymphovascular invasion (LVI) has been shown to be an independent predictor of oncologic outcomes after RC [6–8]. However, the prognostic significance of LVI in

* Corresponding author. Tel.: +1-714-506-8257; fax: +1-714-456-5062.
E-mail addresses: ryaacoub@uci.edu, merof1@hotmail.com (R.F. Youssef).

http://dx.doi.org/10.1016/j.urolonc.2016.03.023
1078-1439/

SCC has not been previously studied, largely because of the relative rarity of the disease in Western Europe and the United States. Herein, we evaluate the association between LVI and oncologic outcomes of bladder cancer after RC in a large cohort of Egyptian patients, and we compare the prognostic significance of LVI between UCB and SCC.

2. Patients and methods

2.1. Patient population

We retrospectively evaluated 1280 patients who underwent RC and pelvic lymph node dissection (LND) for invasive bladder cancer between 1997 and 2003 at a single institution in Mansoura, Egypt. Only patients with pure UCB or SCC pathology were included. Patients who received adjuvant or neoadjuvant therapy were excluded. A total of 401 patients were excluded because they had adenocarcinoma or other rare histology, mixed histology bladder cancer, inadequate follow-up, insufficient pathological specimens, or a history of adjuvant or neoadjuvant therapy. After obtaining institutional review board approval, a database was constructed of patient clinicopathological characteristics and oncologic outcomes.

2.2. Pathological evaluation

All RC and LND surgical specimens were processed in accordance with standard pathologic procedure, and the number of LNs retrieved were recorded for each patient. The 2 experienced genitourinary pathologists performed reviews of all pathological specimens and recorded histology, pathological stage, tumor grade, presence or absence of concomitant carcinoma *in situ*, evidence of bilharziasis, LN status, and presence or absence of LVI. The presence of tumor cells within an endothelium-lined space lacking underlying muscular walls was defined as LVI. The 1973 World Health Organization tumor grading system was used in assigning tumor grade (1 = well-differentiated to 3 = poorly differentiated). The 2010 American Joint Committee on Cancer TNM staging system was used in assigning pathologic stage.

2.3. Patient follow-up

The follow-up schedule for all patients was every 2 months for the first 6 months, then every 6 months thereafter. Follow-up visits included medical history taking, physical examination, and routine laboratory and imaging studies. Laboratory tests included serum creatinine measurements, liver function tests, alkaline phosphatase levels, complete blood count, urine analysis, and urine cytology. Routine imaging studies included abdominal ultrasonography and chest x-ray. Other imaging studies, including computed tomography, magnetic resonance imaging, and bone scans, were performed if disease progression was suspected based on other clinical findings. Disease progression was defined as the detection of new tumor locally or at distant metastatic sites.

2.4. Oncological outcomes and statistical analysis

Oncologic outcomes were recorded as time from surgery to disease recurrence or cancer-related death. Disease recurrence was defined as the recurrence of tumor locally in the cystectomy bed, positive regional LNs, or the presence of a positive metastasis in a distant organ after RC. Disease-free survival (DFS) was defined as the period of time between the initial date of RC and the detection of disease recurrence. Cancer-specific survival (CSS) was defined as the period of time between the initial date of RC and the date of patient death due to cancer. Chart review was used to determine the cause of death. Kaplan-Meier analyses were performed to estimate univariate probabilities of disease recurrence and cancer survival. The log-rank test was used to determine significant differences. Additionally, multivariate Cox regression analyses were performed to evaluate DFS and CSS after RC. Statistical tests were performed using SPSS version 21.0 (IBM Corporation, NY). Statistical significance was set at 0.05, and all P values were reported as 2-sided.

3. Results

3.1. Patient demographics and clinicopathologic characteristics

Our cohort included 879 patients; 519 (59%) with UCB and 360 (41%) with SCC. Table 1 describes patient and clinicopathological characteristics. Of the patients included, 693 (78.8%) were men and 186 (21.1%) were women. Median patient age at time of diagnosis was 55 years (20–87). Overall, pathologic stage was >T2 in 46% (n = 406) of cases. High tumor grade was detected in 98.3% of UCB cases, whereas 60.0% of SCC cases were low grade ($P < 0.001$). The median number of LNs dissected was 19 (4–70). Overall, LVI was present in 288 (33%) cases, and LN metastases were found in 219 (25%) cases. Both LVI and LN metastases were significantly more common in UCB compared to SCC. Compared to UCB, patients with SCC had a significantly lower incidence of LVI regardless of LN status (Table 1).

3.2. Association of LVI with oncologic outcomes

Median length of follow-up after RC was 64 months (0–128). Overall, 5-year DFS rates and CSS rates were 68.2% and 88.12%, respectively, in patients with UCB vs. 71.2% and 85.32%, respectively, in patients with SCC. There was no significant prognostic effect of bilharzias on