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ORIGINAL ARTICLE

Local and systemic recurrence patterns of urothelial cancer after radical cystectomy



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Received 8 May 2013; accepted 4 July 2013

Available online 21 April 2014

KEYWORDS

Distant metastasis;
Local recurrence;
Radical cystectomy;
Survival;
Urothelial carcinoma

Abstract The aim of this study was to evaluate the local recurrence and distant metastasis rates for urothelial carcinoma of the bladder after radical cystectomy and to identify the predictive factors for local recurrence and distant metastasis. The study population was 347 consecutive patients treated with radical cystectomy for urothelial carcinoma of the bladder at our institution. Local recurrence, distant metastasis, and both local and distant recurrence rates were 49 (14.1%) months, 96 (27.7%) months, and 17 (4.9%) months, respectively. The mean follow-up times to recurrence were 14.37 ± 13.25 months (range, 2–60 months) and 14.43 ± 15.72 months (range, 2–109 months) for local recurrence and distant metastasis, respectively ($p = 0.808$). The mean post-recurrence disease-specific survival (PRDSS) times for local, distant, and both local and distant recurrences were 17.82 ± 3.18 months, 4.16 ± 0.39 months, and 11.41 ± 2.73 months, respectively ($p < 0.001$). The predictive factors for local recurrence and distant metastasis were stage and nodal involvement ($p < 0.001$). Sex, grade, lymphovascular invasion (LVI), carcinoma *in situ* (CIS), and lymph node density (LND; 10% cut-off value) were not predictors for recurrence in the results of the multivariate analysis. The current study demonstrated that stage and pathological nodal involvement were independent predictors of local recurrence and distant metastasis. The results of this study suggest that the early diagnosis and intervention of invasive bladder cancer cases may decrease the number of high stage and lymph node positive cases that have a high risk of local and distant recurrences. The adjuvant treatment options in the presence of risk factors for recurrence may improve survival outcomes.

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Conflicts of interest: All authors declare no conflicts of interest.

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<http://dx.doi.org/10.1016/j.kjms.2014.03.011>

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Introduction

Bladder cancer is the second most common tumor in the urogenital system and one of the most important causes of mortality and morbidity [1]. Most patients diagnosed with urothelial carcinoma of the bladder have superficial tumors; yet 20–40% of the patients have muscle and perivesical tissue invasion, even at the beginning. Half of the patients with invasive tumors already have metastasis, or metastasis can emerge later on.

Radical cystectomy is the gold standard in the treatment of muscle-invasive bladder cancer and patients with noninvasive tumors in whom intravesical therapy failed. Although radical cystectomy is the gold standard, about one-third of patients relapse and die from the disease [2]. The main reason for cancer specific mortality in patients treated with radical cystectomy is related to distant metastasis. In addition, long-term survival is very rare after local recurrence. For that reason, it is thought that local recurrences are as significant as distant metastasis for disease-specific survival [3].

Recurrences following cystectomy are usually seen in the 2nd year or 3rd year and their frequencies are 4–29% for local recurrences and 22–38% for distant metastasis. The upper urinary system relapse rate is 3–8% and urethral recurrence rate is 6–10%, which generally develops 2–3 years after cystectomy. Although cisplatin-based chemotherapy following recurrences shows relatively positive response rates, it still has a weak effect on subsequent survival [3].

The current study evaluated local and systemic recurrence patterns in patients treated with radical cystectomy for urothelial bladder cancer and attempted to define the predictive factors influencing local and systemic recurrences.

Methods

Data of 475 patients who underwent radical cystectomy for invasive bladder cancer in our clinic between 1991 and 2011 were retrospectively analyzed. Criteria for inclusion in the study were as follows: (1) urothelial carcinoma diagnosis in the pathological evaluation of the cystectomy specimen; and (2) the availability of follow-up data in cases after recurrences. Exclusion criteria were: (1) local or systemic metastasis at diagnosis; (2) cases of newly developed urothelial carcinomas in the upper urinary system or urethra; and (3) patients in which primary definitive treatments failed and who underwent salvage cystectomy. A total of 347 patients met the above criteria and were included in the study. In the current study, 49 (14.1%) patients had local recurrences, 96 (27.7%) patients had systemic recurrences, and 17 (4.9%) cases had both local and systemic recurrences.

All pathological data were evaluated using a standard protocol. The American Joint Committee on Cancer 2009 staging system and World Health Organization 1973 grading system were used [4,5]. Pathological staging is defined as organ-confined (T0/Ta/TIS/T1/T2, N0), extravesical (T3/T4, N0), and lymph-node involvement (node-positive) (Any T, N1–3). Lymph node density (LND) is defined as the

number of positive lymph nodes divided into the total number of removed lymph nodes [6]. Primary tumor properties such as lymphovascular invasion (LVI) and the presence of concomitant carcinoma *in situ* (CIS) were recorded.

All patients received a standard surgical procedure including radical cystectomy, pelvic lymphadenectomy, and various urinary diversions [1]. All patients who underwent cystectomy for invasive bladder cancer were followed at 3 month periods for the first 2 years, 6 month periods for 3 years, and annually for the following years. Physical examination, chest radiography, and blood biochemistry were routinely performed during follow-up. Intravenous pyelography, ultrasonography, and computed tomography were used in the 3rd month, 6th month, and 12th month after surgery and annually later on or on the occasion that a relapse was suspected. Local recurrences were defined as those occurring within the soft tissue field of exenteration, which is inside the bony pelvis. Distant recurrences were those occurring outside the pelvis [1,3]. Time to recurrence (TTR) was defined as the period from the date of cystectomy to the date when the first recurrence was diagnosed; post-recurrence follow-up was the time after the recurrence (TAR). Post-recurrence disease-specific survival (PRDSS) graphics are based on TAR.

Independent samples *t* test was used to determine relationships between continuous variables. Pearson's Chi-square test was used to evaluate categorical variables. The logrank test and the Kaplan–Meier method were applied for the univariate analysis [7,8]. Multivariate Cox proportional hazards model was used to calculate predictive values of independent relationships between categorical variables that were prognostic in the univariate analysis [7]. Analyses were calculated using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). All *p* values were two-sided and $p \leq 0.05$ was considered statistically significant.

Results

A total of 347 patients were included in the study. The mean patient age at surgery was 61.50 ± 8.87 years. There were 321 male and 26 female patients. Patient demographic and clinicopathological characteristics are summarized in Table 1. In the current study, 49 (14.1%) patients had local recurrence, 96 (27.7%) patients had systemic recurrence, and 17 (4.9%) cases had both local and systemic recurrences. The characteristics of patients with local and systemic recurrences are shown in Table 2.

Local recurrence rates were 8.2% in organ-confined disease, 17.6% in extravesical disease, and 23.2% in lymph node positive disease in this study. Systemic metastasis frequency was 13.5% in organ-confined disease, 39.6% in extravesical disease, and 45.1% in cases with lymph node involvement.

Patients were grouped according to recurrence sites (local, systemic, and local and systemic). Actuarial estimated DSS at 5 years was 28.3% for the local recurrence group, 0.43% for the systemic metastasis group, and 11.8% for the both local and systemic recurrence group. Mean DSS times were 41.07 ± 6.79 months for the local recurrence group, 18.30 ± 2.03 months for the systemic metastasis

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