



Original Research

Predictors of female genital organ involvement in radical cystectomy for urothelial carcinoma of the bladder: A single-center retrospective analysis of 112 female patients



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HIGHLIGHTS

- Female patients with muscle invasive bladder cancer are traditionally treated with anterior exenteration.
- There was no guideline for female genital organ-sparing surgery in cases to need radical cystectomy.
- Tumor location at TUR-B, maximum tumor size or hydronephrosis at CT were predictors for female genital organ involvement.

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ABSTRACT

Objectives: To evaluate predictors of organ involvement and oncological outcomes after radical cystectomy with anterior exenteration in female patients.

Methods: Among 1198 patients who underwent radical cystectomy for the bladder tumor between 1990 and 2015, 178 (14.9%) patients were female. They were divided into two groups according to pelvic involvement in pathology. Their medical records and pathology and image findings were reviewed retrospectively. Non-urothelial cell carcinoma and no genital organ pathology were excluded. Multivariate logistic regression was performed to predict factors associated with female organ involvement.

Results: Out of 112 eligible female patients with urothelial cell carcinoma, 11 (9.8%) had female genital organ involvement. Female genital organ involvement occurred primarily in the uterus (63.6%) mostly. The 5-year overall survival rates were 67.3% in the non-involvement group and 18.9% in the involvement group. On multivariate analysis Tumor location of trigone or bladder neck at transurethral resection of bladder tumor (TUR-B) (odds ratio [OR] 19.84, 95% confidence interval [CI] 2.89–230.68, $p = 0.0056$), maximum tumor size at computed tomography (CT) (OR 2.17, 95% CI 1.29–4.34, $p = 0.0095$), and hydronephrosis at CT (OR 17.61, 95% CI 2.28–296.26, $p = 0.0158$) were associated with female organ involvement.

Conclusions: Tumor location of trigone or bladder neck at TUR-B, maximum tumor size at CT or hydronephrosis at CT were significant factors to predict female genital organ involvement. Preoperative recognition of female genital organ involvement could increase the decision to perform genital organ-sparing surgeries.

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1. Introduction

Bladder cancer is the fifth most common kind of cancer, with an estimated 16,390 deaths, and the incidence in women was one-

third of that for men according to the 2016 data from the United States [1]. The 5-year estimated overall survival rate of female patients was 73.1% and 79.5% for male patients [2]. Although controversial, the gender gap in survival may be due to delayed diagnoses as a result of misunderstanding symptoms, anatomical differences, and differential exposure to carcinogens. Thus, more intense treatment options may be warranted for women with bladder cancer [3]. Notably, about 30% cases of bladder cancer are

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muscle invasive, and patients are treated with radical cystectomy and pelvic lymph node dissection [4]. Female patients with muscle invasive bladder cancer are traditionally treated with anterior exenteration that not only includes the bladder but also the urethra, uterus, fallopian tubes, ovaries, and the upper third of the anterior vagina without any evidence of invasion to these regions [5]. Although anterior exenteration can be helpful to remove locally advanced tumors or non-diagnosed cancer of genital organs, elimination of genital organs immensely affects reproductive and sexual functions [6]. Sparing genital organs is not a difficult feat to achieve during radical cystectomy. Particularly, female organ-sparing surgeries have been shown to have significant prognostic results, however, standard surgical guidelines are lacking [7]. The aim of the present study was to confirm the incidence of female genital organ involvement at the time of radical cystectomy to treat urothelial cell carcinoma of the bladder and to identify clinico-pathological factors associated with such female genital organ involvement.

2. Materials and methods

A total of 1198 patients underwent radical cystectomy for bladder cancer at our Medical Center via the open technique between 1990 and 2015. Among them, 178 (14.9%) patients were female, and 32 patients with (18.0%) non-urothelial cell carcinoma and 47 patients (26.4%) with no genital organ pathology were excluded. These patient groups were excluded because we wanted to confirm the association between urothelial cell carcinoma and female genital organ involvement. In our study cohort, 112 women who underwent anterior exenteration were included and retrospectively assessed. The study was approved by the relevant Institutional Review Board.

The bladder, lymph nodes, uterus, cervix, fallopian tubes, ovaries, and the vagina of each patient were examined by expert pathologists. Tumor staging was performed according to the American Joint Commission on Cancer TNM classification, 7th edition, and grade was recorded as per 1973 World Health Organization recommendations. Additionally, subtype of variant histology, in situ carcinoma, lymphovascular invasion, and surgical margin involvement were also inspected. Retrospectively collected clinicopathological data included age at the time of surgery, weight, height, past medical history, American Society of Anesthesiologists classification, prior medical records of transurethral resection of bladder tumor (TUR-B), chemotherapy, type of urinary diversion, and postoperative follow-ups. Radiological computed tomography (CT) images were recorded, including clinical TNM stage, longest diameter of detected tumors, and hydronephrosis. If CT was performed several times before or after TUR-B, we checked all CTs and selected the maximum diameter of tumor. The diameters were measured by two readers separately, and inter-reader agreements correlated well (Spearman correlation coefficient = 0.921, $p < 0.001$).

Clinicopathological and radiological data were compared between two groups that were divided by female genital organ involvement of urothelial cell carcinoma of the bladder. A Kolmogorov–Smirnov test was used to confirm the normality of the data. Pearson's Chi-square test was used for categorical variables, and the Student's *t*-test or Mann–Whitney *U* test was used for continuous variables. Receiver operating characteristic curve analysis was used to determine cutoff values of the tumor diameter. Kaplan–Meier curve analysis was used for overall survival. The significant factors of multiple logistic analysis were combined and calculated to determine sensitivity, specificity, accuracy, positive predictive value, and negative predictive value. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using

SPSS 12.0 (SPSS Inc., Chicago, IL, USA) and R (version 3.1.3; R Project for Statistical Computing: <http://www.r-project.org/>). Our methods were guided by Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria [8].

3. Results

Out of 112 female patients with urothelial cell carcinoma, 11 (9.8%) had female genital organ involvement (Table 1). The median follow-up period was 27.3 months. The median age was 67.0 years (interquartile range 60.75–73.0). Between the non-involvement and involvement groups, there was no significant difference regarding age, body mass index, hypertension and diabetes history, American Society of Anesthesiologists classification, type of urinary diversion, and chemotherapy. However, the involvement group (81.8%) had more tumors on trigone or neck at TUR-B ($p < 0.001$) than the non-involvement group (16.0%). Concerning maximum tumor size at CT, the involvement group was significantly larger than the non-involvement group (5.6 ± 1.6 cm vs. 2.8 ± 1.8 cm, $p < 0.001$). Additionally, hydronephrosis at CT ($p = 0.001$) was observed more in the involvement group (81.8%) than in the non-involvement group (26.5%). In the involvement group, clinical T4a stage was diagnosed in 3 (27.3%) patients, but 8 (72.7%) patients were underestimated to T3 or less at preoperative CT. For the non-involvement group, 9 (9.6%) patients were overestimated to T4. Seven cases in the non-involvement group did not have CT data before radical cystectomy. All cases in the involvement group were determined to be T4a, grade 3, and have invasive urothelial cell carcinoma. The non-involvement group had 8 (7.9%) T0 patients, 4 (4.0%) Ta patients, 9 (8.9%) Tis patients, 12 (11.9%) T1 patients, 26 (25.7%) T2 patients, and 42 (41.6%) T3 patients. Positive lymph nodes at pathology was found in 26 (25.7%) patients of the non-involvement group and 5 (38.5%) patients of the involvement

Table 1
Basic characteristics of patients who underwent radical cystectomy with anterior exenteration ($n = 112$).

Female organ involvement	No ($n = 101$)	Yes ($n = 11$)	<i>p</i>
Age	67.0 [61.0; 73.0]	64.0 [61.0; 71.5]	0.567
Body mass index	23.6 [21.6; 25.6]	24.1 [21.1; 26.2]	0.826
Hypertension	53 (52.5%)	4 (36.4%)	0.485
Diabetes mellitus	17 (16.8%)	2 (18.2%)	1.000
ASA			0.581
-1	7 (7.0%)	0 (0.0%)	
-2	88 (88.0%)	10 (90.9%)	
-3	5 (5.0%)	1 (9.1%)	
Tumor location at TUR-B (trigone or bladder neck)	16 (16.0%)	9 (81.8%)	<0.001
Multiple tumors at TUR-B	52 (72.2%)	9 (81.8%)	0.412
Subtype of variant histology at TUR-B	14 (12.7%)	3 (27.3%)	0.630
Duration from TUR-B to cystectomy (days)	29.0 [19.0; 57.0]	35.0 [27.5; 68.5]	0.331
Clinical T stage			0.213
-≤3	85 (90.4%)	8 (72.7%)	
-4	9 (9.6%)	3 (27.3%)	
Clinical lymph node	3 (3.2%)	1 (9.1%)	0.887
Maximum tumor size at CT	2.9 [1.5; 4.1]	5.6 [5.0; 7.3]	<0.001
Hydronephrosis at CT	26 (26.5%)	9 (81.8%)	0.001
Type of urinary diversion			0.841
-Non-orthotopic	66 (65.3%)	8 (72.7%)	
-Orthotopic	35 (34.7%)	3 (27.3%)	
Neoadjuvant chemotherapy	14 (13.9%)	2 (18.2%)	1.000
Adjuvant chemotherapy	13 (12.9%)	2 (18.2%)	0.980

ASA: American Society of Anesthesiologists classification, TUR-B: transurethral resection of bladder tumor, CT: computed tomography.

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