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Oncologic, Perioperative Outcomes of Female Radical Cystectomy: Results from a Multicenter Study in Korea

Ji Sung Shim, MD, PhD[1]
Ho Kyung Seo, MD, PhD[2]
Ja Hyeon Ku, MD, PhD[3]
Byong Chang Jeong, MD, PhD[4]
Bumsik Hong, MD, PhD[5]
Seok Ho Kang, MD, PhD[1]
UCART (Urothelial Cancer-Advanced Research and Treatment Group in Korea) Group

[1]*Department of Urology, Korea University School of Medicine, Seoul, [2]Department of Urology, National Cancer Center, Goyang, [3]Department of Urology, Seoul National University School of Medicine, Seoul, [4]Department of Urology, Sungkyunkwan University School of Medicine, Seoul, [5]Department of Urology, Asan Medical Center, University of Ulsan, College of Medicine, Seoul, Korea*

Purpose
The lower incidence of bladder cancer among women has led to a lack of information on female radical cystectomy (RC). This study aimed to analyze the characteristics related with female RC in a cohort from multiple academic institutions.

Materials and Methods
This was a retrospective review of 384 female patients who underwent RC for bladder cancer. Epidemiologic, perioperative variables including urologic referral period with consequent pathologic stage distributions were assessed. The changes in surgical techniques over time were illustrated. Also, we evaluated recurrence-free survival (RFS) at 2 and 5 years and overall survival (OS) at 5 years with stage-specific analyses using the Kaplan-Meier method.

Results
The mean follow-up time was 35 months (interquartile rage [IQR], 9 to 55). The average time to urologic referral with initial symptoms was 5.5 (IQR, 1 to 6) months and over 20% of patients visited clinics after 6 months. In subsequent stage distributions according to referral period, T2 or higher stage distributions were abruptly increased after 1 year. Overall 2-year/5-year RFS rates were 0.72/0.57 and 5-year OS was 0.61. Notable surgical descriptions were as follows: 91% of patients underwent open RC; 80% of patients underwent an ileal conduit; and 83% of patients received anterior exenteration. However, the proportions of robotic surgery, orthotopic neobladder and organ sparing cystectomy have increased recently.

Conclusion
We identified the general characteristics and changes in pattern of female RC. Our results also suggest that women are susceptible to delays in referral to an urologist and are at greater risk for worse prognosis.

Correspondence: Seok Ho Kang, MD, PhD
Department of Urology, Korea University
College of Medicine, 73 Inchon-ro,
Seongbuk-gu, Seoul 02841, Korea
Tel: 82-2-920-5530
Fax: 82-2-928-7864
E-mail: mdksh@korea.ac.kr

Co-correspondence: Bumsik Hong, MD, PhD
Department of Urology, Asan Medical Center,
88 Olympic-ro 43-gil, Songpa-gu,
Seoul 05505, Korea
Tel: 82-2-720-1684
Fax: 82-2-720-3728
E-mail: bshong@amc.seoul.kr

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Introduction

Women are two to four times less likely to develop bladder cancer than men [1]. Although anatomy or surgical technique differs between sexes in performing radical cystectomy (RC), the lower prevalence of female bladder cancer has inevitably led to a lack of information. The absolute number of women undergoing RC is increasing worldwide recently [2], making the overall information on the surgery more necessary.

There were some issues related to the female RC. The first is about the specific surgical technique with changes in procedure. For example, ileal conduits have been widely used for urinary diversion, because women were initially excluded from orthotopic neobladder (ONB) reconstruction due to concerns about urethral recurrence (oncologic aspect) and postoperative urinary incontinence or hypercontinence (functional aspect). However, established indications for ONB and improvements in the understanding of the rhabdosphincter anatomy have led to the increased use of ONB. In addition, the proportion of laparoscopic or robotic surgery has increased with the development of minimally invasive surgery, and the rate of organ sparing surgery has changed which makes the pattern of female cystectomy different from that performed in the past. In this regard, it will be useful to investigate the various surgical methods for performing female RC and changes over time.

Second, even if clinicians recognize the importance of demographic heterogeneity in the management of patients with bladder cancer, the effects of gender on incidence, staging, prognosis, complications, and survival are controversial [3,4]. Previous studies demonstrated impaired outcomes in women and that they are more likely to undergo RC at the advanced tumor stage [3,5]. For this reason, risk factor exposure due to anatomical features, and hormonal differences by sex have been suggested for these differences [6]. Also, delayed urological care of women who present with hematuria was continuously proposed [7].

In our study, we investigated the characteristics related with female RC, to search for perioperative, oncologic outcomes as well as epidemiologic factors, and aspects of surgical technique transition.

Materials and Methods

1. Patient deposition and follow-up

A total of five tertiary referral centers provided data. This study comprised 384 female patients with muscle invasive disease or recurrent Ta, T1, or carcinoma *in situ* refractory to transurethral resection of bladder tumor who underwent RC and bilateral pelvic lymph node dissection with urinary diversion between 2007 and 2016. All patients had pathologic documentation of bladder cancer and with no evidence of distant metastasis at the time of RC. Patients were followed up postoperatively every 3 to 4 months for the first year, semiannually for the second year and annually thereafter. At regular follow up, disease recurrence was checked which defined as pathologic or radiographic evidence of cancer after cystectomy.

2. Epidemiologic factors and perioperative variables

Risk factors exposure history (smoking, chemical exposure to occupation–dye, paint, metal, and petroleum) and other various basic information were recorded. Also, the perioperative outcomes including operation time, estimated blood loss and mean hospital stay were evaluated. The durations from the onset of symptoms (hematuria, lower urinary tract symptoms, flank pain, etc.) to the urologic referral were recorded. Thereafter, pathologic T category distribution ($\leq$ T1, T2, T3, and T4) of patients were assessed by referral period (within 1, 3, 6, and 12 months and over 1 year).

3. Evaluation of oncologic outcome

We evaluated recurrence-free survival (RFS) at 2 and 5 years with overall survival (OS) at 5 years with stage-specific analyses. Patients who did not experience recurrence were censored at the time of last follow-up for RFS analysis. Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis and cause of death was determined by the treating physician, by chart review corroborated by death certificates. Also, final T and N category, margin status and histologic distributions were described.

4. Changes in surgical technique in female RC during 10 years

The relative specific changes in surgical proportions and changes over ten years were analyzed as follows: (1) open/laparoscopic/robotic surgery, (2) type of urinary diversion (ileal conduit/ONB/continent cutaneous urinary diversion), and (3) anterior exenteration/organ sparing RC.

5. Surgical technique description: anterior exenteration

For RC without uterine preservation, identification of the whitish vaginal outer wall is important. A landmark can be made by inserting ringed forceps into the vagina, and a peri-

toneal incision would be placed in the Douglas pouch just below the vaginal fundus. After ligation of the dorsomedial pedicle, excision of the vaginal wall covering the trigone can be performed without significant blood loss. Considering the location of the tumor, raising the caudal resection of anterior vaginal wall to the cephalad direction than the urethral resection plane may reduce the risk of vesicovaginal fistula [8] which is further reduced when electrocautery is avoided to the tissue borders required for approximation.

6. Surgical technique description: organ-sparing RC

Basically, organ-sparing RC could be performed in the absence of invasive cancer in the trigone, dorsal or lateral side wall (unifocal, ≤ cT2b). The surgical techniques are slightly different for each surgeon, but based on the following method which has been described for both open [9] and robotic approaches [10]. The infundibulo-pelvic, broad, and round ligaments are preserved and related vessels (including distal vessels, which go to the paravaginal tissue and pelvic plexus) should be identified as they cross close to the ureters. It is important to identify the plane on the outer surface of the vaginal wall after incision of the uterovesical junction. The dorsomedial bladder pedicle would be extensively resected or the plane of anteroventral vagina could be resec-

ted for nerve sparing. In addition, for continence preservation for the ONB, dissection in the retropubic space should be aimed at preserving the endopelvic fascia, pubo-urethrovesical attachments, with minimal trauma to the levator muscles and periurethral tissue.

7. Analysis

RFS and OS probabilities were estimated using the Kaplan-Meier method and differences between groups were assessed using the log-rank test. All analyses were performed and illustrated using SPSS ver. 20.0 (IBM Corp., Armonk, NY) and Sigmaplot ver. 13.0 (Systat Software Inc., San Jose, CA). p-values of < 0.05 were considered statistically significant.

8. Ethical statement

This study was approved by the ethics committees and the Institutional Review Boards of each hospital (IRB No. ED-10120) that participated in the study, and the requirement for the patients to provide consent was waived.

Table 1. Baseline patient characteristics

	Value (n=384)
Age (yr)	66±10
BMI (kg/m²)	23.8±3.7
Time to urological referral (mo)	2 (1-6)
Within 1 mo (%)	45.4
Within 3 mo (%)	18.9
Within 6 mo (%)	15.2
Within 12 mo (%)	13.8
Over 1 year	6.7
Risk factors exposure	
None	357 (93.0)
Smoking	20 (5.2)
Radiation exposure	7 (1.8)
Other chemical exposure (metal, paint, petroleum, etc.)	0
Preoperative chemotherapy	65 (17)
Follow-up period (mo)	24 (9-51)
Perioperative outcomes	
Operation time (min)	410 (350-477)
EBL (mL)	800 (450-1,300)
Hospital stays (day)	19 (14-25)

Values are presented as mean±standard deviation, median (interquartile range), or number (%). BMI, body mass index; EBL, estimated blood loss.

Results

1. Baseline characteristics and descriptive data on operation

The mean patient age was 66 years (interquartile range [IQR], 59 to 73) and the median follow-up period was 24 months (IQR, 9 to 51). Neoadjuvant chemotherapy was administered to 65 women (17%). In the analysis of perioperative outcomes, the median operation time was 410 minutes (IQR, 350 to 477) and the median length of hospital stay was 19 (IQR, 14 to 25) (Table 1).

Among the initial symptoms, gross hematuria alone or in combination with any other symptoms accounted for 66% of all cases. This was followed by, 6.5% for dysuria, 2.3% for microscopic hematuria, and 16.7% for other symptoms such as urgency or flank pain (Fig. 1).

2. Time to urologic referral and differences in pathologic T category according to the period

The median time to urologic referral was 2 months (IQR, 1 to 6) and 45.4% of all patients visited clinics within one month while over 20% of the patients visited the hospital after 6 months from the onset of symptoms (Table 1).

We analyzed the differences in pathologic T category according to the period for the urologic referral from symptom onset. T2 or lower stage occurred in 67% of patients who visited clinics within 1 month. Not much difference in T2 or lower stage distribution ($\leq$ T1, 56%; T2, 59%; and T3, 60%) in patients who visited within 1 year, T2 or higher proportion increased significantly and was present in 87% of patients who visited clinics after 1 year (Fig. 2).

3. Oncologic outcomes

The overall 2-year/5-year RFS rates were 0.72/0.57 and 5-year OS was 0.61 for all patients. The results of stage specific analyses are depicted in Table 2 (pT2, pT3, pT4, pTany, and/or lymph node disease) (Table 2) [11-13].

In the analysis of recurrence distribution, local and distant recurrence occurred in 31 (8%) and 84 (22%) patients in our study. There were no significant differences in the most common location and rate of recurrence from other large-scale studies [14,15]. There was only one patient with peritoneal carcinomatosis and 14 patients experienced recurrence of secondary urothelial carcinoma in the upper urinary tract (12 patients) and urethra (2 patients). The distribution of recurrence locations is shown in Table 3.

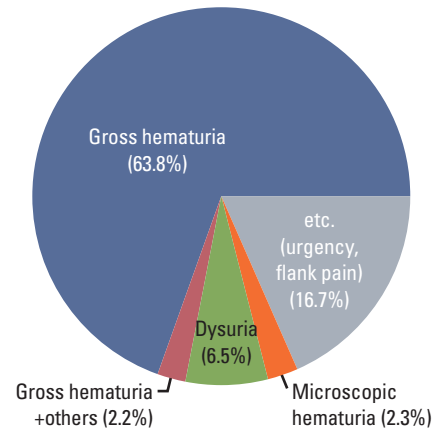The margin positivity rate was 8% in our study which constituted 3% for Ta/T1/T2 and 5% for T3/T4, respectively.

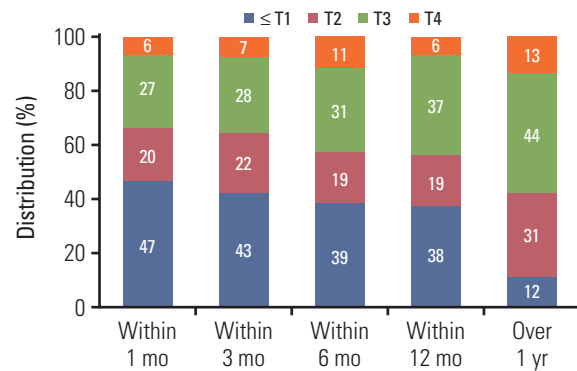
Fig. 1. Descriptions of the initial symptoms.

Fig. 2. Differences in pathologic T category according to the period for the urologic referral from symptom onset (T2 category and over proportion is dramatically increased after 1 year as 88%).

Among the patients, 98 subjects (26%) were found to have lymph node–positive disease. The histology of the tumors in the current series was predominantly urothelial carcinoma (85%) followed by adenocarcinoma and squamous cell carcinoma.

4. Present status of surgical methods of female RC

Most of the operations were performed by the open method (91.4%) and the proportion of laparoscopic or robotic surgeries was about 8.6%. In trend, the composition of the number of surgeries did not vary much, with the number of open surgeries being slightly increased with the growth of robotic surgery, recently (Fig. 3A). In the analysis of the urinary diversion type, ileal conduits were performed in 80% of

Table 2. Outcomes of female radical cystectomy by stage

	2-Year RFS (%)	5-Year RFS (%)	5-Year OS (%)
Reference/Cystectomy series			
Stein et al. (2001) [11]	-	68	66
Madersbacher et al. (2003) [12]	-	62	59
Hautmann et al. (2006) [13]	-	66	58
Current study			
Overall	72	57	61
pT2N0	70	52	60
pT3 or higher			
pT3N0	62	49	56
pT4N0	49	42	45
pTanyN1-2	48	35	38
p-value[a)]		0.113	0.033

RFS, recurrence-free survival; OS, overall survival. [a)]Log-rank test.

Table 3. Distribution of recurrence locations and incidences among female patients underwent radical cystectomy

Variable, frequency of recurrence by site	No. (%) (n=384)
Local recurrence	31 (8.0)
Cystectomy bed	13 (3.3)
PLND template	18 (4.7)
Distant recurrence	84 (21.9)
Lung	24 (6.3)
Liver	14 (3.6)
Bone	25 (6.5)
Extrapelvic lymph node	12 (3.1)
Peritoneal carcinomatosis	1 (0.3)
Others (brain, adrenal, pancreas, bowel)	8 (2.1)
Secondary urothelial carcinoma	14 (3.6)
Upper urinary tract	12 (3.1)
Urethra	2 (0.5)

PLND, pelvic lymph node dissection.

patients; ONB diversions were performed in 16% of patients, and continent cutaneous diversions were performed in 3% of patients. In the recent 5 years, the increasing tendency of ONB reconstruction was shown (Fig. 3B). On surgical range, 51 patients (13%) underwent organ sparing RC while 318 (83%) patients received anterior pelvic exenteration. However, the number of patients who underwent organ-sparing RC had increased recently in the trend analysis (Fig. 3C).

5. Complication rate

The total complication rate was 47% and 70% of complications occurred within 30 days (127 patients) of surgery. The incidence of major and minor complications were 16% (62 patients) and 31% (119 patients), respectively. The most common complication categories were infectious (13%; most common [m/c] urinary tract infection) wound (9%; m/c dehiscence), gastrointestinal (8%; m/c ileus), as shown in Table 4. When only high-grade complications were considered, wound problems and genitourinary complications (8%, m/c ureteral leakage/stricture) were the most prominent in all categories.

Discussion

It is known that women present with more advanced disease and a greater proportion die of the bladder cancer [16]. Kluth et al. [5] found a link between female gender and an increased risk of mortality following RC. In large cohort of reference cystectomy series (Table 2), overall 5 year RFS and OS were reported at about 62%-68% and 58%-66%, respectively. Compared with these studies, our study showed worse 5 year RFS at 57% while the 5 year OS of 61% did not show a significant difference. In other studies on female RC (Table 5) [2,17-20], OS and RFS were generally lower than those of reference studies, which were consistent with our study.

It is insufficient to explain the worse oncologic outcomes in females by epidemiologic factors. In our study, only 5% of females were smokers (5.2%-7.9% of women vs. 39.4%-66.3%
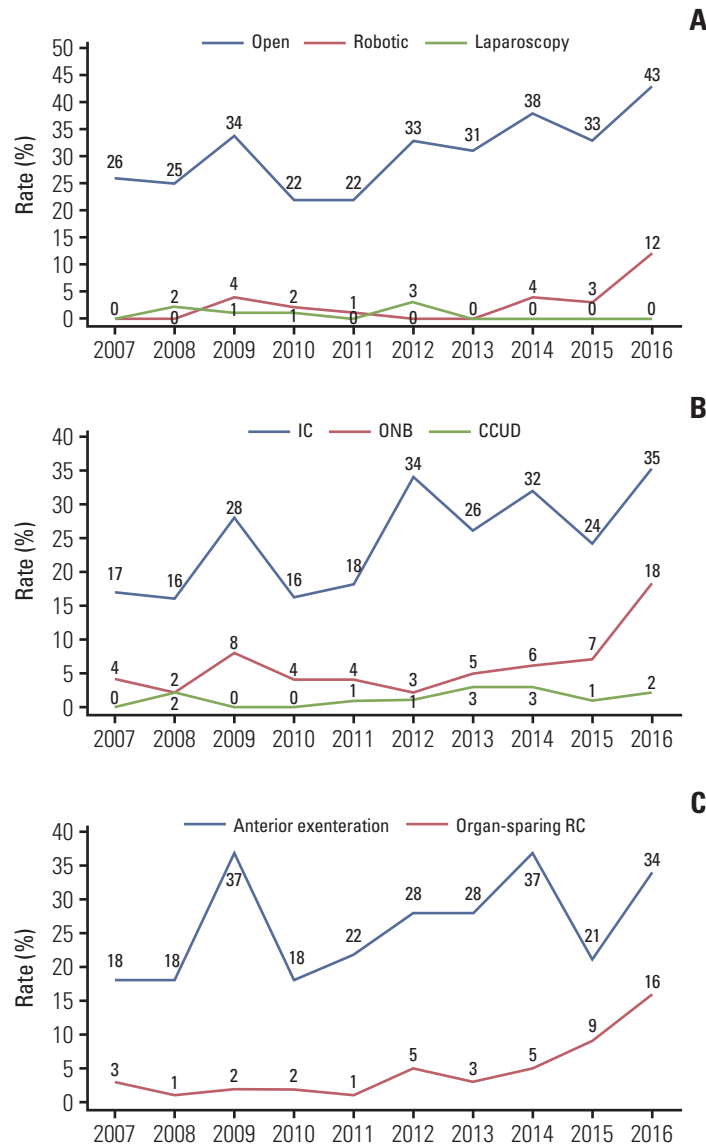
Fig. 3. Changes in the rates of each surgical technique of female radical cystectomy during 10 years. (A) Open/laparoscopy/robotic. (B) Ileal conduit (IC)/orthotopic neobladder (ONB)/continent cutaneous urinary diversion (CCUD). (C) Anterior exenteration/organ sparing radical cystectomy (RC).

of men for the last 20 years, data from Statistics Korea [21]) and even after combination with 2% of radiated patients, 93% of the cohorts had no exposure to any risk factors. In addition, despite the argument that perioperative factors could also play a role (women have longer operative times, more blood loss, and greater risk of complications than men) [22], the evidence is insufficient as well as inconsistent with the results of our study.

While some studies reported that men and women might metabolize carcinogens differently [23,24], it is quite possible

that tumor biology, anatomic factors as well as delays in diagnosis may eventually answer this puzzling trend. One notable finding of our results is about urological referral pattern. In previous study, when a woman was referred, the time to referral was universally longer [25]. The most common symptom of bladder cancer is known to be either microscopic or macroscopic hematuria, which occurred in 66% of our cohort. Johnson et al. [7] reported that the adjusted hazard ratio of male referral to the urologist was 1.65 (95% confidence interval, 1.31 to 2.08) compared with female referral

Table 4. Summary of the common complications experienced

	No. (%) (n=384)
Total complication rate	181 (47.1)
Within 30 days	127 (33.0)
Within 90 days	39 (10.1)
Over 90 days	15 (4.0)
Major complication rate (Clavien grade 3-5)	62 (16.1)
Minor complication rate (Clavien grade 1-2)	119 (31.0)
Complication[a]	181
Infectious (UTI and FUO)	51 (13.2)
Wound (dehiscence and infection)	36 (9.3)
GI (ileus and diarrhea)	31 (8.0)
GU (ureteral leakage/stricture and parastomal hernia	29 (7.6)
Bleeding (transfusion and NA)	21 (5.5)
Cardiac (arrhythmia and NA)	2 (0.6)
Etc. (DVT, lymphocele, pneumonia, hematoma)	11 (2.9)

UTI, urinary tract infection; FUO; fever of unknown origin; GI, gastrointestinal; GU, genitourinary; NA, not available; DVT, deep vein thrombosis; m/c, most common.
[a]m/c and 2nd m/c.

[7]. Because bladder cancer is less common in women, medical doctors may be less prone to consider this diagnosis at the woman's first visit. In addition, the higher frequency of urinary tract infections (UTI) among women or postmenopausal bleeding may lead to less extensive investigation thus delaying primary treatment. Although UTI is most common among women < 40 years old, older women with gross hematuria might still undergo a limited evaluation due to the presumptive diagnoses of UTI. In our study, more than 36% of patients had a urologic referral after 3 months of symptom onset and 20% even after 6 months. Previously,

several studies documented poorer survival when the interval between cancer diagnosis and definitive treatment prolonged [26,27]. While there is not much difference in T2 or lower stage distribution (generally 60%) in patients who visited within 1 year, T2 or higher portion increased significantly after 1 year which may have affected low RFS of our cohorts.

The anatomical differences between men and women are also important considerations. Male bladders have a thicker detrusor probably because of the need to void at higher intravesical pressures to overcome outflow resistance caused by the hyperplastic prostate gland. The thicker muscle may delay extravesical extension, and perhaps retard the development of metastases. Another anatomic difference that may affect disease progression is that the replacement of periurethral tissue in men by the prostate gland and its capsule may block the angiolymphatic extension of the tumor that is seen in women [28]. Also, differences in hormones have been discussed as possible causes of bladder cancer biology. The cell line of urothelial carcinoma is known to express both androgens and estrogens. The normal female urothelium expresses a higher density of estrogen receptors in the bladder trigone and posterior bladder neck than in men. In addition, this site and the roof of the vagina share an embryonic origin which is the most common site for invasion [29].

The present study details the contemporary trends regarding the distribution of urinary diversion among female patients undergoing RC for bladder cancer. Although a minority of patients received a continent diversion overall (16% with ONB), a key finding in this study suggests that its use is indeed gradually increasing. For patients who are considering RC, the choice of urinary diversion should be largely based on the feasibility of performing the operation safely and the ability to provide long-term care according to each patient's overall health and preference. After the 1980s, ONB has been performed for selected patients with improved knowledge of female pelvic anatomy. Also urethral recur-

Table 5. Survival analysis in a several series of female radical cystectomy

Study	Study design	Series size	Urinary diversion	Mean follow-up period (mo)	Organ sparing (%)	5-Year OS (%)	5-Year RFS (%)
Granberg et al. (2008) [17]	Retrospective	53	ONB	29.2	17	83	85
Ali-El-Dein (2009) [18]	Retrospective	180	ONB	57	-	-	66
Stein et al. (2009) [19]	Retrospective	120	ONB	102	-	58	62
Large et al. (2010) [20]	Retrospective	92	ONB (47), IC (45)	34/24	-	65/58	-
Messer et al. (2014) [2]	Observational study	890	ONB, IC, CCUD	31	-	52	69
Current study	Retrospective	384	ONB, IC, CCUD	35	13	61	57

OS, overall survival; RFS, recurrence-free survival; ONB, orthotopic neobladder; IC, ileal conduit; CCUD, continuous continent urinary diversion.

rence is reported to have a low rate (≤ 2%) in women [30].

Another trend identified in our study is the low rate of organ sparing cystectomy at about 13% and significant growth in the recent 5 years. This is thought to be a result of increased understanding of the anatomy, development of the surgical technique, and increased interest in the functional outcome. In fact, uterine preservation in some selected ONB patients helps prevent chronic retention (hypercontinence resulting from kinking of the ONB-urethral junction) by providing adequate back support. There is also a psychologic advantage to be gained by preserving the genital organs especially in the relatively young age groups. Therefore, organ preserving trials would be weighed for the preserva-

tion of the uninvolved internal genital organs in selected women during RC.

While it is informative to assess the general characteristics of female RC it is essential to acknowledge the limitations of our study; first, the retrospective methodology and possible selection bias, and that our study was conducted on women and did not compare with male patients; therefore, comparison with a reference large cystectomy series is necessary.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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