Urodynamic assessment of bladder storage function after radical hysterectomy for cervical cancer

Ting-Ting Cao[1,2,3], Hong-Wu Wen[4], Yu-Nong Gao[5], Qiu-Bo Lyu[6], Hui-Xin Liu[7], Sha Wang[1,2,3], Shi-Yan Wang[1,2,3], Hua-Xin Sun[1,2,3], Na Yu[8], Hai-Bo Wang[9], Yi Li[8], Zhi-Qi Wang[1,2,3], Olivia H. Chang[10], Xiu-Li Sun[1,2,3], Jian-Liu Wang[1,2,3]

[1]Department of Obstetrics and Gynecology, Peking University People's Hospital, Beijing 100044, China;
[2]The Key Laboratory of Female Pelvic Floor Disorders Disease, Beijing 100044, China;
[3]The Research Center of Female Pelvic Floor Disorders Disease of Peking University, Beijing 100044, China;
[4]Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing 100034, China;
[5]Department of Gynecology, Peking University Cancer Hospital & Institute, Beijing 100142, China;
[6]Department of Gynecology, Beijing Hospital, Beijing 100005, China;
[7]Department of Clinical Epidemiology and Biostatistics, Peking University People's Hospital, Beijing 100044, China;
[8]Department of Peking University Medical Information Center, Peking University, Beijing 100191, China;
[9]Department of Peking University Clinical Research Institute, Peking University, Beijing 100191, China;
[10]Center for Urogynecology and Pelvic Reconstructive Surgery, Cleveland Clinic, Cleveland, OH 44195, USA.

Abstract

Background: After radical hysterectomy for cervical cancer, the most common complication is lower urinary tract symptoms. Post-operatively, bladder capacity can alter bladder function for a prolonged period. This study aimed to identify factors affecting bladder storage function.

Methods: A multicenter, retrospective cohort study was conducted. Information of patients with stages IA2 to IIB cervical cancer with urodynamic study results were retrospectively collected from nine hospitals between June 2013 and June 2018 according to the inclusion criteria. Demographic, surgical, and oncological data were collected. The univariate and multivariate logistic regression was used to identify clinical factors associated with bladder storage function.

Results: Two hundred and three patients with cervical cancer had urodynamic testing post-operatively. Ninety-five (46.8%) patients were diagnosed with stress urinary incontinence (SUI). The incidence of low bladder compliance (LBC) was 23.2%. Twenty-seven (13.3%) patients showed detrusor overactivity (DO). Fifty-seven patients (28.1%) presented with a decreased maximum cystometric capacity (DMCC). The probability of composite bladder storage dysfunction was 68.0%. Multivariate analysis confirmed that laparoscopy represents a protective factor for SUI with an odds ratio of 0.498 ($P = 0.034$). Patients who underwent a nerve-sparing procedure were less odds to experience SUI ($P = 0.014$). A significant positive correlation between LBC and DO was observed ($P < 0.001$). A greater length of the resected vagina and chemoradiotherapy were common risk factors for LBC and DO, while radiotherapy exerted a stronger effect than chemotherapy. Additionally, patients who received chemoradiotherapy frequently developed a DMCC. The follow-up time was not correlated with bladder storage function.

Conclusion: A nerve-sparing procedure without longer resected vagina is recommended for protecting the bladder storage function.

Keywords: Radical hysterectomy; Cervical cancer; Urodynamic; Bladder storage function

Introduction

Cervical cancer remains a common gynecological malignancy, despite the implementation of screening guidelines. Patients with cervical cancer presenting with International Federation of Gynecology and Obstetrics (FIGO, 2009) stage IA2, IB, and smaller stage IIB tumors are treated with Piver type III radical hysterectomy (RH) and pelvic lymphadenectomy, with or without adjuvant (chemo-) radiotherapy. This treatment regimen produces a favorable outcome, with a 5-year overall survival rate of up to 80%.[1] However, patients suffer from post-operative urinary and bowel dysfunction. This can be due to surgical trauma and adjuvant therapy, affecting the sympathetic and parasympathetic branches of the autonomous nervous system and blood supply to the pelvic organs.[2] Lower

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001014

Correspondence to: Dr. Xiu-Li Sun, Department of Obstetrics and Gynecology, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, China
E-Mail: sunxiuli918@126.com

Chinese Medical Journal 2020;133(19)

Received: 14-01-2020 **Edited by:** Xiu-Yuan Hao and Xin Chen

urinary tract symptoms (LUTS) are the most common complications of RH, with an incidence ranging from 8% to 86% due to the use of different definitions and diagnostic tools.[3-5] The most commonly reported symptoms after RH include urinary incontinence, urinary retention, and voiding by abdominal straining.[6,7] In addition to voiding dysfunction, bladder storage function also deteriorates significantly.[8]

Many studies have assessed bladder function after RH by recording patients' subjective symptoms or measuring the residual urine volume with ultrasound.[2,9] As shown in the study by Benedetti-Panici *et al*,[6] 15% of patients have incomplete voiding defined as post-void residual volume >30% of bladder capacity after surgery; however, 76% of patients develop LUTS during the 12 months after surgery. Therefore, measurement of post-void residual volume might not be sufficient to evaluate bladder function. An urodynamic study (UDS) provides scientific laboratory reference values for the clinical diagnosis of urinary dysfunction.

Nested in a large multicenter trial to observe the quality of life and pelvic floor function in cervical cancer patients who were treated with RH, the objective of this study is to identify risk factors associated with bladder storage function after RH.

Methods

Ethical approval

This study was approved by the Ethics Committees of all nine hospitals (No.2015PHB050-01), and informed written consent was obtained from all patients before their enrollment in this study. Researchers from all centers received standard training and passed the appraisal.

Study design

This study employs a multicenter, retrospective cohort study design. Information of cervical cancer patients with stage of IA2 to IIB in nine hospitals of Beijing city (Peking University People's Hospital; Peking University First Hospital; Peking University Third Hospital; Cancer Institute and Hospital, Chinese Academy of Medical Sciences; Peking University Cancer Hospital & Institute; The General Hospital of the People's Liberation Army; Beijing Obstetrics and Gynecology Hospital, Capital Medical University; Beijing Chaoyang Hospital, Capital Medical University; and Beijing Hospital) were collected between June 2013 and June 2018.

The following inclusion criteria of cervical cancer patients were used: (1) age ≥18 years, (2) diagnosis of cervical cancer, (3) underwent Piver type III RH, (4) 3 to 24 months after the operation, (5) willing to participate in the study and provide informed consent, and (6) no pre-operative LUTS and pelvic organ prolapse. The use of adjuvant therapy did not prohibit enrollment. The pelvic splanchnic or hypogastric nerves could be preserved during operation. The nerve-sparing procedure was performed according to the operative guidelines described by elsewhere.[10] We considered the following exclusion criteria: previous anti-incontinence procedure or reconstructive pelvic surgery, the presence of severe psychiatric or medical diseases, and intra-operative bladder injury.

Data collection

All demographic, surgical, and oncological data were collected. Multichannel UDS were carried out using Urolabspectrum instrument (Life-Tech, Inc., Stafford, TX, USA) with standard procedures.[11] The bladder was filled with room temperature saline at a rate of 30 mL/min through urethral catheter. The main urodynamic parameters of storage were bladder compliance, detrusor stability, stress urinary incontinence (SUI), and maximum cystometric capacity (MCC), while voiding parameters included flow rates and residual urine volume. Compliance was calculated by dividing the change in the volume (ΔV) by the change in detrusor pressure ($\Delta Pdet$) during the change in bladder volume ($C = \Delta V/\Delta Pdet$). This value was reported in mL/cm H_2O. SUI was assessed by asking patients to cough at a filling volume of 200 mL. Low bladder compliance (LBC) was defined as bladder capacity of less than 20 mL/cm H_2O according to the International Continence Society standard.[12] Detrusor overactivity (DO) was characterized by involuntary detrusor contraction >5 cm H_2O during the filling phase, which may be spontaneous or provoked. The UDS was terminated if patient reported a severe need to urinate, in case of significant leakage development, and the bladder capacity at that time was recorded as MCC. The standard MCC ranged from 350 to 650 mL, while MCC less than 350 mL was defined as decreased MCC (DMCC). Composite bladder storage dysfunction meets the criteria for SUI, LBC, DO, or DMCC.

Statistical analysis

All statistical analyses were performed using SPSS 20.0 (SPSS statistics for Windows, IBM, Armonk, NY, USA). Descriptive statistics were used to summarize the demographic and clinical characteristics. All continuous variables were tested for normality with a Shapiro-Wilk test and described as mean ± standard deviation or median (P25, P75) as appropriate. Categorical variables were described by number and percentage. A logistic regression analysis was used to identify risk factors for bladder storage dysfunction. A two-sided significance level of 5% was used for all analyses. In addition, we examined the correlations among SUI, LBC, DO, and DMCC by calculating Kendall tau-*b* coefficient.

Results

Two hundred and three patients with cervical cancer met the inclusion criteria and underwent UDS assessment. Demographic and oncological characteristics, as well as concomitant conditions, are shown in Table 1. The patients' median age was 47.0 (42.3, 53.5) years. All patients had the history of vaginal delivery and the majority was multipara. In the cohort of 203 patients, 13 (6.4%) had FIGO stage IA2 and 143 (70.4%) had stages IB1 and IIA1. A minority of patients were diagnosed with

Table 1: Demographic and clinical characteristics of 203 patients with cervical cancer.

Characteristics	Values
Age (years), median (P25, P75)	47.0 (42.3, 53.5)
Body mass index (kg/m^2), median (P25, P75)	23.9 (22.1, 25.6)
Parity, *n* (%)	
<2	99 (48.8)
≥2	104 (51.2)
Mode of delivery, *n* (%)	
Natural labor	169 (83.3)
Caesarean	34 (16.7)
Chronic pulmonary disease, *n* (%)	61 (30.0)
FIGO clinical stage, *n* (%)	
IA2	13 (6.4)
IB1 and IIA1	143 (70.4)
IB2 and IIA2	36 (17.7)
IIB	11 (5.4)
Surgical approach, *n* (%)	
Laparoscopic	142 (70.0)
Abdominal	61 (30.0)
Operation time (min), median (P25, P75)	240.0 (180.0, 275.0)
Blood loss (mL), median (P25, P75)	200.0 (100.0, 400.0)
Length of the resected cardinal ligament, *n* (%)	
3 cm	183 (90.1)
>3 cm	20 (9.9)
Length of the resected uterosacral ligament, *n* (%)	
3 cm	194 (95.6)
>3 cm	9 (4.4)
Length of the resected vagina, *n* (%)	
3 cm	175 (86.2)
>3 cm	28 (13.8)
Oophorectomy, *n* (%)	
Yes	68 (33.5)
No	135 (66.5)
Nerve-sparing procedure, *n* (%)	
Yes	44 (21.7)
No	159 (78.3)
Histology, *n* (%)	
Squamous	164 (80.8)
Others	39 (19.2)
Grading, *n* (%)	
G3	47 (23.2)
G1 and G2	156 (76.8)
Chemotherapy, *n* (%)	59 (29.1)
Radiotherapy, *n* (%)	15 (7.4)
Chemoradiotherapy, *n* (%)	50 (24.6)
Follow-up time (months), median (P25, P75)	12.1 (6.4, 17.7)
MCC (mL), median (P25, P75)	421.0 (185.0, 670.0)
Bladder storage dysfunction, *n* (%)	
SUI	95 (46.8)
LBC	47 (23.2)
DO	27 (13.3)
DMCC	57 (28.1)
Composite bladder storage dysfunction	138 (68.0)

FIGO: International Federation of Gynecology and Obstetrics; MCC: Maximum cystometric capacity; SUI: Stress urinary incontinence; LBC: Low bladder compliance; DO: Detrusor overactivity; DMCC: Decreased maximum cystometric capacity.

stages IB2, IIA2, and IIB. Sixty-one patients (30.0%) had chronic pulmonary disease with persistent coughing.

RH was most commonly performed laparoscopically (70.0%), and none of the procedures were converted to abdominal surgery. The median operation time and intraoperative blood loss were 240.0 min and 200.0 mL. The length of resected parametrium and vagina were generally 3 cm, and were measured during the operation. Intraoperative nerve injury to the pelvic splanchnic and bladder branch nerve occurred in 159 (78.3%) patients.

Post-operative histopathological results revealed G1 or G2 grade squamous carcinoma in the majority of patients. Seventy-nine (38.9%) patients did not receive adjuvant therapy, while the others underwent chemotherapy or radiotherapy pre- or post-operatively according to the tumor size and histology.

On UDS, ninety-five (46.8%) patients were diagnosed with SUI. The incidence rate of LBC was 23.2%. Twenty-seven (13.3%) patients suffered from DO. Median MCC was 421.0 (185.0, 670.0) mL and 57 (28.1%) patients had DMCC. The probability of composite bladder storage dysfunction was 68.0%. The date of UDS examination from surgery was defined as the follow-up time and the median was 12.1 months.

Univariate and multivariate regression analyses were used to determine predictors for bladder storage dysfunction after RH. Variables with a $P < 0.100$ in the univariate analysis, a nerve-sparing procedure, and the follow-up time were selected to construct the multivariate analysis model. The results are presented in Tables 2 and 3.

On univariate analysis, laparoscopic surgery and nerve-sparing procedure were protective factors for SUI (odds ratio [OR]: 0.367 and 0.343, respectively). An extended duration of the operation protected against SUI ($P = 0.001$). In the multivariate analysis, protective factors included laparoscopy (OR: 0.498, 95% confidence interval [CI] 0.261–0.947, $P = 0.034$). Patients who underwent the nerve-sparing procedure were less likely to suffer from SUI (OR: 0.361, 95% CI: 0.164–0.794, $P = 0.014$). The operation time was also confirmed as a protective factor in the multivariate analysis.

The univariate analysis of LBC showed that an extended operation time was a protective factor (OR: 0.996, 95% CI: 0.993–1.000, $P = 0.038$), while the multivariate analysis did not confirm this finding (OR: 1.001, 95% CI: 0.997–1.006, $P = 0.594$). Regarding the length of the resected vagina, 3 cm was a protective factor in the univariate analysis (OR: 0.194, 95% CI: 0.084–0.440, $P < 0.001$). Additionally, chemoradiotherapy was a favorable factor for LBC (OR: 0.295, 95% CI: 0.130–0.671, $P = 0.004$). However, the multivariate analysis did not confirm this result, showing that chemoradiotherapy was a risk factor (OR: 4.087, 95% CI: 1.612–10.363; $P = 0.003$). The results of the multivariate analysis also showed an effect of the length of the resected vagina. Neither univariate nor multivariate analysis revealed associations between the follow-up time and a nerve-sparing procedure with LBC.

According to the results of the univariate analysis, the length of the resected vagina = 3 cm was a protective factor for DO (OR: 0.304, 95% CI: 0.118–0.786, $P = 0.014$), while chemoradiotherapy was a risk factor (OR: 2.190, 95% CI: 0.733–6.539, $P = 0.044$). Patients with younger ages tended to suffer from DO (OR: 0.945, 95% CI: 0.905–0.987, $P = 0.011$). However, in the multivariate analysis, an older age was the strongest risk factor for DO (OR: 1.084, 95% CI: 1.030–1.141, $P = 0.002$). Laparoscopic surgery and increased operative blood loss were risk factors for DO (OR: 5.761, 95% CI: 1.156–28.709, $P = 0.033$; OR: 1.001, 95% CI: 1.000–1.002, $P = 0.034$, respectively). The adjustment of OR for the length of the

Table 2: Univariate analysis of bladder storage dysfunction after radical hysterectomy.

	SUI		LBC		DO		DMCC	
Variables	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age (years)	1.023 (0.993–1.054)	0.140	0.975 (0.942–1.010)	0.157	0.945 (0.905–0.987)	0.011	1.037 (0.009–0.497)	0.066
Body mass index (kg/m^2)	0.980 (0.895–1.072)	0.654	1.049 (0.941–1.170)	0.390	0.890 (0.787–1.007)	0.065	1.097 (0.963–1.248)	0.163
Parity								
<2	0.974 (0.561–1.691)	0.926	1.127 (0.587–2.164)	0.720	0.575 (0.249–1.325)	0.194	0.900 (0.318–2.544)	0.842
≥ 2	1	–	1	–	1	–	1	–
Mode of delivery								
Natural labor	0.645 (0.307–1.355)	0.247	1.550 (0.738–3.254)	0.247	0.360 (0.081–1.598)	0.179	0.747 (0.276–2.024)	0.566
Caesarean	1	–	1	–	1	–	1	–
Concomitant disease								
Chronic pulmonary disease	0.794 (0.435–1.448)	0.452	1.442 (0.724–2.875)	0.298	0.791 (0.316–1.981)	0.616	1.691 (0.769–3.717)	0.191
Other disease	1	–	1	–	1	–	1	
FIGO clinical stage								
IA2	0.250 (0.043–1.443)	0.121	4.000 (0.693–23.089)	0.121	–	–	–	–
IB1 and IIA1	0.714 (0.208–2.447)	0.592	1.400 (0.409–4.797)	0.592	0.853 (0.102–7.138)	0.884	0.338 (0.064–1.783)	0.201
IB2 and IIA2	1.042 (0.268–4.045)	0.953	0.960 (0.247–3.728)	0.953	0.227 (0.026–2.000)	0.182	0.769 (0.127–4.654)	0.775
IIB	1	–	1	–	1	–	1	–
Surgical approach								
Laparoscopic	0.367 (0.197–0.684)	0.002	2.111 (0.949–4.695)	0.067	2.754 (0.910–8.338)	0.073	0.741 (0.287–1.909)	0.534
Abdominal	1	–	1	–	1	–	1	–
Operation time (min)	0.994 (0.990–0.998)	0.001	0.996 (0.993–1.000)	0.038	0.996 (0.992–1.001)	0.102	1.002 (0.997–1.007)	0.427
Blood loss (mL)	1.000 (0.999–1.000)	0.404	1.000 (0.999–1.000)	0.281	0.999 (0.999–1.000)	0.095	1.000 (0.999–1.001)	0.761
Length of the resected cardinal ligament								
3 cm	1.359 (0.531–3.482)	0.522	0.406 (0.155–1.063)	0.066	0.410 (0.136–1.239)	0.114	3.840 (0.584–25.241)	0.161
>3 cm	1	–	1	–	1	–	1	–
Length of the resected uterosacral ligament								
3 cm	3.223 (0.653–15.907)	0.151	1.057 (0.212–5.269)	0.946	0.282 (0.066–1.204)	0.087	0.410 (0.047–3.564)	0.419
>3 cm	1	–	1	–	1	–	1	–
Length of the resected vagina								
3 cm	0.862 (0.388–1.914)	0.715	0.194 (0.084–0.440)	<0.001	0.304 (0.118–0.786)	0.014	0.574 (0.189–1.744)	0.328
>3 cm	1	–	1	–	1	–	1	–
Oophorectomy (yes *vs.* no)	1.326 (0.739–2.378)	0.344	1.445 (0.673–3.104)	0.346	0.992 (0.420–2.341)	0.985	1.129 (0.527–2.420)	0.755
Nerve-sparing procedure (yes *vs.* no)	0.343 (1.400–6.060)	0.004	0.819 (0.361–1.865)	0.632	1.637 (0.663–4.042)	0.285	0.529 (0.209–1.340)	0.179
Histology								
Squamous	1.524 (0.746–3.112)	0.248	1.475 (0.604–3.599)	0.393	2.057 (0.587–7.215)	0.260	0.598 (0.253–1.416)	0.242
Others	1	–	1	–	1	–	1	–
Grading								
G3	0.567 (0.289–1.110)	0.098	1.581 (0.759–3.294)	0.221	1.190 (0.469–3.016)	0.714	0.880 (0.378–2.049)	0.767
G1 and G2	1	–	1	–	1	–	1	–
Adjuvant therapy								
No	1	–	1	–	1	–	1	–
Chemotherapy	0.605 (0.307–1.195)	0.148	0.965 (0.391–2.382)	0.939	2.190 (0.733–6.539)	0.160	2.551 (0.938–6.938)	0.067
Radiotherapy	1.076 (0.349–3.317)	0.898	0.542 (0.149–1.967)	0.351	1.872 (0.340–10.304)	0.471	2.173 (0.547–8.627)	0.270
Chemoradiotherapy	0.777 (0.381–1.585)	0.488	0.295 (0.130–0.671)	0.004	2.190 (0.733–6.539)	0.044	3.026 (1.118–8.196)	0.029
Follow-up time (months)	0.990 (0.950–1.032)	0.644	1.004 (0.955–1.055)	0.879	1.005 (0.945–1.069)	0.878	1.031 (0.976–1.091)	0.275

SUI: Stress urinary incontinence; LBC: Low bladder compliance; DO: Detrusor overactivity; DMCC: Decreased maximum cystometric capacity; OR: Odds ratio; CI: Confidence interval; –: No data.

resected vagina = 3 cm and chemoradiotherapy did not alter their associations with DO. Additionally, radiotherapy exerted a greater effect than chemotherapy ($P = 0.048$ *vs.* $P = 0.763$). Moreover, no effects of the follow-up time and nerve-sparing procedure on DO were observed.

The univariate analysis revealed that chemoradiotherapy was an independent risk factor for DMCC (OR: 3.026, 95% CI: 1.118–8.196, $P = 0.029$). The other factors were not associated with DMCC. This result was also confirmed in the multivariate analysis.

The supplemental table presents the correlations of UDS parameters, http://links.lww.com/CM9/A279. A significant positive correlation between LBC and DO was observed (Kendall tau-$b = 0.542$, $P < 0.001$).

Discussion

In patients with cervical cancer treated with RH, 72% of patients reported bladder dysfunction post-operatively, particularly LBC and SUI, which significantly influenced quality of life.[13] In this study, UDS is used to evaluate bladder storage function, focusing on the risk factors for post-operative SUI, LBC, DO, and DMCC. The surgical approach, nerve injury, length of the resected vagina, and adjuvant therapy are associated with bladder storage dysfunction. Patients with LBC are susceptible to DO.

Previous studies confirmed a significantly higher SUI rate in cervical cancer patients after surgery, reaching approximately 40%,[14,15] which was similar to the results from our study. As shown in the study by Chen *et al*,[3] storage dysfunction was represented by abnormal compliance, and the long-term bladder function was marked by a significant reduction in BC. Urinary incontinence might disappear within 6 to 12 months after RH. In our study, 23.2% and 13.3% of patients suffer from LBC and DO, respectively. The 28.1% of patients are diagnosed with DMCC.

Nowadays, laparoscopy is more frequently chosen for RH due to its minimal invasiveness, but the potential hazards include a longer operation time and potential for thermal injury. However, the comparison of post-operative bladder function between patients who underwent laparoscopic and abdominal surgery remains controversial.

Table 3: Multivariate analysis of bladder storage function after radical hysterectomy.

	SUI		LBC		DO		DMCC	
Variables	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Age (years)	–	–	–	–	1.084 (1.030–1.141)	0.002	1.040 (0.996–1.086)	0.078
Body mass index (kg/m^2)	–	–	–	–	1.147 (0.984–1.326)	0.079	–	–
Surgical approach								
Laparoscopic	0.498 (0.261–0.947)	0.034	2.331 (0.851–6.384)	0.100	5.761 (1.156–28.709)	0.033	–	–
Abdominal	1	–	1	–	1	–	–	–
Operation time (min)	0.995 (0.992–0.999)	0.006	1.001 (0.997–1.006)	0.594	–	–	–	–
Blood loss (mL)	–	–	–	–	1.001 (1.000–1.002)	0.034	–	–
Length of the resected cardinal ligament								
3 cm	–	–	1.504 (0.331–6.822)	0.597	–	–	–	–
>3 cm	–	–	1	–	–	–	–	–
Length of the resected uterosacral ligament								
3 cm	–	–	–	–	0.956 (0.085–10.814)	0.971	–	–
>3 cm	–	–	–	–	1	–	–	–
Length of the resected vagina								
3 cm	–	–	0.224 (0.076–0.662)	0.007	0.321 (0.104–0.992)	0.048	–	–
>3 cm	–	–	1	–	1	–	–	–
Nerve-sparing procedure (yes *vs.* no)	0.361 (0.164–0.794)	0.014	0.807 (0.317–2.056)	0.654	2.271 (0.734–7.022)	0.154	2.158 (0.754–6.174)	0.151
Grading								
G3	0.541 (0.263–1.116)	0.096	–	–	–	–	–	–
G1 and G2	1	–	–	–	–	–	–	–
Adjuvant therapy					–	–		
No	–	–	1	–	1	–	1	–
Chemotherapy	–	–	1.425 (0.513–3.955)	0.497	1.332 (0.207–8.574)	0.763	2.762 (0.972–7.854)	0.057
Radiotherapy	–	–	1.920 (0.468–7.875)	0.365	3.552 (1.013–12.457)	0.048	2.856 (0.684–11.919)	0.150
Chemoradiotherapy	–	–	4.087 (1.612–10.363)	0.003	3.716 (1.069–12.915)	0.039	3.241 (1.165–9.017)	0.024
Follow-up time (months)	1.013 (0.969–1.059)	0.569	0.991 (0.938–1.046)	0.735	0.321 (0.104–0.992)	0.428	1.025 (0.963–1.091)	0.433

SUI: Stress urinary incontinence; LBC: Low bladder compliance; DO: Detrusor overactivity; DMCC: Decreased maximum cystometric capacity; OR: Odds ratio; CI: Confidence interval; –: No data.

According to Colombo *et al*,[16] urinary incontinence was reduced in the laparoscopic group. A randomized controlled trial showed a significant difference in bladder function between the groups at two weeks after surgery, but a statistically significant difference was not observed at six weeks or four months.[17] In our multivariate analysis, the laparoscopic approach reduces the occurrence of SUI. We speculate that this difference is potentially explained by the possibility of sparing the nerves during laparoscopy. The urethral sphincter plays an important role in the pathophysiology of SUI after RH. This impaired urethral pressure after surgery, which leads to SUI, may be related to the damage of the pelvic plexus and pudendal nerves with a loss of periurethral tone. The extension of the inferior hypogastric plexus in the posterior part of the uterosacral ligaments is easier to preserve with the laparoscopy.[7] The hypogastric nerves form the upper limit of the pelvic plexus and the vesical branches. A nerve-sparing procedure is a strong protective factor for SUI, consistent with several studies.[18,19] Moreover, the extension of the operation time also protects against SUI, as a sufficient operation time is helpful for patients undergoing a nerve-sparing procedure.

Currently, there is conflicting data on whether chemoradiotherapy affects bladder capacity and compliance. Lin *et al*[20] did not observe a significant difference in the results of LBC between the RH-only group and a combination group that underwent surgery with radiation. Katepratoom *et al*[21] observed a lower MCC and BC in patients receiving concurrent chemoradiotherapy, consistent with other studies.[22,23] Chemoradiotherapy is a stronger independent risk factor than other factors for LBC and DMCC in our study. One explanation is that patients with cervical cancer are frequently treated with the chemotherapeutic drug ifosfamide, which produces microscopic alterations in bladder mucosa, such as edema, exocytosis, and hemorrhage.[24] These changes may result in lower bladder capacity. Radiation-induced bladder injury may result from direct cell killing through DNA double-strand breaks and the activation of cytokines and growth factors causing fibrosis and reduced elasticity.[25] Chemotherapy causes radiosensitization in S phase following the effect of radiation on M phase. This sensitization may increase the damaging effects of radiation when used concurrently.[26] Accordingly, patients who are treated with chemoradiotherapy may be prone to experiencing bladder dysfunction.

Notably, LBC positively correlates with DO. Persistent LBC might influence the vesical pressure, leading to detrusor dysfunction. A complex of storage symptoms are associated with LBC and DO, consisting of urgency with or without urinary incontinence and usually with increased frequency and nocturia. In our study, common risk factors for LBC and DO were identified, such as the length of resected vagina and chemoradiotherapy. A potential explanation is that the resection of the upper one-third of the vagina can damage the pelvic nerves. A meta-analysis compared the clinical efficacy of adjuvant chemotherapy with that of chemotherapy plus pelvic irradiation and did not observe a significant difference in the recurrence rate between the two groups.[27] As radiotherapy is a stronger risk factor than chemotherapy for bladder storage function, and older patients with cervical cancer are more frequently diagnosed with DO, adjuvant radiotherapy should be avoided if an alternative post-operative strategy can be used, particularly in elderly patients.[28] Laparoscopy and increased operative blood loss were identified as risk factors for DO, whereas laparoscopy was protective against SUI. This effect may be attributed to the heat generated by laparoscopic instruments, such as monopolar and bipolar. Conventional

monopolar tissue resection is a phenomenon that occurs at temperatures >100°C, primarily through a process of cellular water vaporization. The temperature at which bipolar coagulation produces is >60°C. A review reports that exposure to heat greater than 45°C for significantly reduces bladder function.[29]

The major strength of our study is the measurement of UDS parameters in cervical cancer patients who underwent RH. This number of patients is comparatively larger than previous studies, and this study is one of the few reports focusing on bladder storage function and revealing the risk and protective factors for dysfunction. Additionally, the current sample size of this study represents enough power to detect the association of clinical factors such as nerve-sparing and surgical approach with SUI (power = 0.891 and power = 0.919, respectively). The limitations of this study are its retrospective nature, lack of pre-operative UDS, and survival data. Another limitation is that we do not have the information of cervical cancer patients who met the inclusion criteria but had no UDS results, which represents a potential selection bias.

In conclusion, this study finds that the incidence of bladder storage dysfunction after RH was 68%, with SUI being the most common finding on UDS. Protective factors against bladder storage dysfunction include a nerve-sparing procedure and preservation of the vagina. As our study demonstrates that patients who have received radiotherapy have higher odds of bladder storage dysfunction, we recommend bladder training. However, further prospective randomized controlled studies with a large number of patients should be performed to investigate bladder function, quality of life, and long-term follow-up.

Funding

This study was supported by grants from the National Key R&D Program of China (2018YFC2002200 and 2018YFC2002204) and the Beijing Municipal Science & Technology Commission (No. D151100001915003).

Conflicts of interest

None.

References

1. Li H, Ruan WJ, Liu LQ, Wan HF, Yang XH, Zhu WF, *et al*. Impact of Taurine on the proliferation and apoptosis of human cervical carcinoma cells and its mechanism. Chin Med J 2019;132:948–956. doi: 10.1097/CM9.0000000000000162.
2. Derks M, van der Velden J, Frijstein MM, Vermeer WM, Stiggelbout AM, Roovers JP, *et al*. Long-term pelvic floor function and quality of life after radical surgery for cervical cancer: a multicenter comparison between different techniques for radical hysterectomy with pelvic lymphadenectomy. Int J Gynecol Cancer 2016;26:1538–1543. doi: 10.1097/IGC.0000000000000776.
3. Chen GD, Lin LY, Wang PH, Lee HS. Urinary tract dysfunction after radical hysterectomy for cervical cancer. Gynecol Oncol 2002;85:292–297. doi: 10.1006/gyno.2002.6614.
4. Wallin E, Falconer H, Radestad AF. Sexual, bladder, bowel and ovarian function 1 year after robot-assisted radical hysterectomy for early-stage cervical cancer. Acta Obstet Gynecol Scand 2019; 98:1404–1412. doi: 10.1111/aogs.13680.
5. Pieterse QD, Maas CP, ter Kuile MM, Lowik M, van Eijkeren MA, Trimbos JB, *et al*. An observational longitudinal study to evaluate miction, defecation, and sexual function after radical hysterectomy with pelvic lymphadenectomy for early-stage cervical cancer. Int J Gynecol Cancer 2006;16:1119–1129. doi: 10.1111/j.1525-1438.2006.00461.x.
6. Benedetti-Panici P, Zullo MA, Plotti F, Manci N, Muzii L, Angioli R. Long-term bladder function in patients with locally advanced cervical carcinoma treated with neoadjuvant chemotherapy and type 3-4 radical hysterectomy. Cancer 2004;100:2110–2117. doi: 10.1002/cncr.20235.
7. Zullo MA, Manci N, Angioli R, Muzii L, Panici PB. Vesical dysfunctions after radical hysterectomy for cervical cancer: a critical review. Crit Rev Oncol Hematol 2003;48:287–293. doi: 10.1016/s1040-8428(03)00125-2.
8. Oda Y, Todo Y, Hanley S, Hosaka M, Takeda M, Watari H, *et al*. Risk factors for persistent low bladder compliance after radical hysterectomy. Int J Gynecol Cancer 2011;21:167–172. doi: 10.1097/IGC.0b013e318204c3df.
9. Plotti F, Zullo MA, Montera R, Angioli R, Pierluigi BP. Bladder function after laparoscopic nerve-sparing radical hysterectomy. Gynecol Oncol 2011;120:315. doi: 10.1016/j.ygyno.2010.10.027.
10. Wang W, Li B, Zuo J, Zhang G, Yang Y, Zeng H, *et al*. Evaluation of pelvic visceral functions after modified nerve-sparing radical hysterectomy. Chin Med J 2014;127:696–701. doi: 10.3760/cma.j.issn.0366-6999.20132485.
11. Rosier P, Schaefer W, Lose G, Goldman HB, Guralnick M, Eustice S, *et al*. International Continence Society Good Urodynamic Practices and Terms 2016: urodynamics, uroflowmetry, cystometry, and pressure-flow study. Neurourol Urodyn 2017;36:1243–1260. doi: 10.1002/nau.23124.
12. Drake MJ, Doumouchtsis SK, Hashim H, Gammie A. Fundamentals of urodynamic practice, based on International Continence Society good urodynamic practices recommendations. Neurourol Urodyn 2018;37:S50–S60. doi: 10.1002/nau.23773.
13. Laterza RM, Sievert K-D, De Ridder D, Vierhout ME, Haab F, Cardozo L, *et al*. Bladder function after radical hysterectomy for cervical cancer. Neurourol Urodyn 2015;34:309–315. doi: 10.1002/nau.22570.
14. Laterza RM, Salvatore S, Ghezzi F, Serati M, Umek W, Koelbl H. Urinary and anal dysfunction after laparoscopic versus laparotomic radical hysterectomy. Eur J Obstet Gynecol Reprod Biol 2015;194:11–16. doi: 10.1016/j.ejogrb.2015.08.005.
15. Plotti F, Angioli R, Zullo MA, Sansone M, Altavilla T, Antonelli E, *et al*. Update on urodynamic bladder dysfunctions after radical hysterectomy for cervical cancer. Crit Rev Oncol Hematol 2011;80:323–329. doi: 10.1016/j.critrevonc.2010.12.004.
16. Colombo PE, Bertrand MM, Gutowski M, Mourregot A, Fabbro M, Saint-Aubert B, *et al*. Total laparoscopic radical hysterectomy for locally advanced cervical carcinoma (stages IIB, IIA and bulky stages IB) after concurrent chemoradiation therapy: surgical morbidity and oncological results. Gynecol Oncol 2009;114:404–409. doi: 10.1016/j.ygyno.2009.05.043.
17. Kucukmetin A, Biliatis I, Naik R, Bryant A. Laparoscopically assisted radical vaginal hysterectomy versus radical abdominal hysterectomy for the treatment of early cervical cancer. Cochrane Database Syst Rev 2013;CD006651. doi: 10.1002/14651858.CD006651.pub3.
18. Kanao H, Fujiwara K, Ebisawa K, Hada T, Ota Y, Andou M. Various types of total laparoscopic nerve-sparing radical hysterectomies and their effects on bladder function. J Gynecol Oncol 2014;25:198–205. doi: 10.3802/jgo.2014.25.3.198.
19. Chen L, Zhang WN, Zhang SM, Yang ZH, Zhang P. Effect of laparoscopic nerve-sparing radical hysterectomy on bladder function, intestinal function recovery and quality of sexual life in patients with cervical carcinoma. Asian Pac J Cancer Prev 2014;15:10971–10975. doi: 10.7314/apjcp.2014.15.24.10971.
20. Lin HH, Sheu BC, Lo MC, Huang SC. Abnormal urodynamic findings after radical hysterectomy or pelvic irradiation for cervical cancer. Int J Gynaecol Obstet 1998;63:169–174. doi: 10.1016/s0020-7292(98)00158-1.
21. Katepratoom C, Manchana T, Amornwichet N. Lower urinary tract dysfunction and quality of life in cervical cancer survivors after concurrent chemoradiation versus radical hysterectomy. Int Urogynecol J 2014;25:91–96. doi: 10.1007/s00192-013-2151-6.
22. Chuang FC, Kuo HC. Management of lower urinary tract dysfunction after radical hysterectomy with or without radiotherapy

for uterine cervical cancer. J Formos Med Assoc 2009;108:619–626. doi: 10.1016/s0929-6646(09)60382-x.
23. Oh JK, Choo MS, Lee J, Park NH, Oh SJ. Short-term effect of radical hysterectomy with or without adjuvant radiation therapy on urodynamic parameters in patients with uterine cervical cancer. Int Neurourol J 2012;16:91–95. doi: 10.5213/inj.2012.16.2.91.
24. Dornelas-Filho AF, Pereira VBM, Wong DVT, Nobre LMS, Melo AT, Silva CMS, *et al*. Neutrophils contribute to the pathogenesis of hemorrhagic cystitis induced by ifosfamide. Int Immunopharmacol 2018;62:96–108. doi: 10.1016/j.intimp.2018.06.031.
25. Lind H, Waldenstrom AC, Dunberger G, al-Abany M, Alevronta E, Johansson KA, *et al*. Late symptoms in long-term gynaecological cancer survivors after radiation therapy: a population-based cohort study. Br J Cancer 2011;105:737–745. doi: 10.1038/bjc.2011.315.
26. Song S, Song C, Kim HJ, Wu HG, Kim JH, Park NH, *et al*. 20 year experience of postoperative radiotherapy in IB-IIA cervical cancer patients with intermediate risk factors: impact of treatment period and concurrent chemotherapy. Gynecol Oncol 2012;124:63–67. doi: 10.1016/j.ygyno.2011.09.033.
27. Lee KB, Shim SH, Lee JM. Comparison between adjuvant chemotherapy and adjuvant radiotherapy/chemoradiotherapy after radical surgery in patients with cervical cancer: a meta-analysis. J Gynecol Oncol 2018;29:e62. doi: 10.3802/jgo.2018.29.e62.
28. Gammie A, Kaper M, Steup A, Yoshida S, Dorrepaal C, Kos T, *et al*. What are the additional signs and symptoms in patients with detrusor underactivity and coexisting detrusor overactivity? Neurourol Urodyn 2018;37:2220–2225. doi: 10.1002/nau.23565.
29. Yarmolenko PS, Moon EJ, Landon C, Manzoor A, Hochman DW, Viglianti BL, *et al*. Thresholds for thermal damage to normal tissues: an update. Int J Hyperthermia 2011;27:320–343. doi: 10.3109/02656736.2010.534527.

How to cite this article: Cao TT, Wen HW, Gao YN, Lyu QB, Liu HX, Wang S, Wang SY, Sun HX, Yu N, Wang HB, Li Y, Wang ZQ, Chang OH, Sun XL, Wang JL. Urodynamic assessment of bladder storage function after radical hysterectomy for cervical cancer. Chin Med J 2020;133:2274–2280. doi: 10.1097/CM9.0000000000001014