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Initial experience with extraperitoneal laparoscopic radical cystectomy with pelvic organ-preserving and orthotopic neobladder techniques for bladder cancer in female patients

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**Competing interests**
The authors declare that they have no competing interests.

**Authors’ contributions**
Han Yang, Zongliang Zhang and Ke Wang created the study design and contributed equally to this work. Han Yang, Kai Zhao, Yulian Zhang and Xinbao Yin drafted the manuscript. GuanQun Zhu, Zongliang Zhang, NianZeng Xing, Ke Wang, ZhenLin Wang critically reviewed the manuscript. YuanMing Sui, XueYu Li, Chen Li, QingLei Wang quality control of data and algorithms, and manuscript editing. All the authors read and approved the final manuscript.
Data Availability Statement
All data generated or analysed during this study are included in this article.

Abbreviations

ELRC: extraperitoneal laparoscopic radical cystectomy; ERAS: enhanced recovery after surgery;
LRC: laparoscopic radical cystectomy; ONB: orthotopic neobladder; RC: Radical cystectomy

Abstract

Objective: To present the extraperitoneal laparoscopic radical cystectomy (ELRC) technique, and initial outcomes of organ-preserving and orthotopic neobladder (ONB) techniques for bladder cancer in selected females.

Patients and methods: Data including patient characteristics, operative time, blood loss, transfusion rate, length of hospital stay, and pathologic outcomes, as well as 30- and 90-day complications were collected between April 2018 and May 2021 from females who underwent ONB after ELRC. Regular follow-up focused on patients' oncological and functional outcomes, and postoperative sexual function status was assessed using the Female Sexual Function Index (FSFI).

Results: Eleven females with a mean age of 53 years who underwent ELRC with pelvic organ-preservation and ONB were analyzed retrospectively. All procedures were completed successfully. The mean operative time was 264.82 ± 33.81 min, and the average intraoperative blood loss was 128 ± 18.19 mL. All patients had negative pathological margins and no lymph node metastases. The average hospital stay was
10.72 days. The single J ureteral stent and catheter were usually removed 3 - 4 weeks after the procedure. The FIFS assessment of postoperative sexual function showed that the patients were relatively satisfied.

Conclusions: ELRC with pelvic organ preservation and ONB technology was a safe and feasible surgical strategy for the selected female patients. Preserving organs and vascular nerve bundles seemed to be safe in oncological and produced encouraging functional results. Further rigorous prospective studies with more patients and long-term follow-up data are needed to assess the oncologic and functional results.
Introduction

Urologists are aware of the potentially harmful effects of prostatectomy on the health of males and pay great attention to sexual issues before and after surgery. However, urologists were poorly aware of sexual function and vaginal prolapse in women undergoing radical cystectomy (RC) surgery and exhibited a low level of attention to postoperative quality-of-life conditions. (1) The routine removal of the anterior vaginal wall can significantly affect the postoperative vaginal length and vaginal support, which may lead to pelvic organ prolapse. Risk factors such as vaginal shortening, vaginal stump prolapse, and urinary diversion may lead to a high incidence of postoperative sexual dysfunction (2, 3).

The development of laparoscopic and robot-assisted technologies, as well as the increased experience of urologists and an improved understanding of the female pelvic anatomy, have contributed to the RC and orthotopic neobladder (ONB) techniques that are being used in female patients (4). However, concerns about continence, positive urethral margins, and oncology outcomes remain. In recent years, attempts to preserve organs and sexual function for female patients were done with transabdominal or open procedures. In this study, we performed the extraperitoneal laparoscopic radical cystectomy (ELRC) approach, to protect the patient's potency, improve their quality of life and oncological and functional results, and simultaneously reduce abdominal stimulation and accelerate recovery.

2. Materials and methods

We retrospectively collected the medical records including patient characteristics, operative
time, blood loss, transfusion rate, length of stay, and pathologic outcomes, as well as the 30-
and 90-day complications of female patients who underwent RC at The Affiliated Hospital of
Qingdao University (Qingdao, China) between April 2018 and May 2021. The patients were
followed for a minimum of six months after surgery, and were asked about their quality of life
and continence status. There was full communication with the patients prior to surgery about
which procedure would produce the best oncologic and functional outcomes, as well as the
advantages and disadvantages, and the relationship between the patient and their significant
others was understood. Their postoperative libido, lubrication, orgasm, satisfaction, and painful
sexual dysfunction were assessed using the Female Sexual Function Index (FSFI)(5). Patients
were asked questions about sexual function and their current function was compared to their
preoperative status. The patients' recurrence-free survival (RFS) and overall survival (OS) were
also evaluated during follow-up. OS was defined as the time from diagnosis to death from any
cause. RFS was the time from diagnosis until the first recurrence (local or distant metastasis)
due to any cause. The study was approved by the Ethics Committee of the Affiliated Hospital of
Qingdao University (Qingdao, China), and all patients signed informed consent. All procedures
were performed by an experienced team. The enhanced recovery after surgery (ERAS) protocol
was managed in the perioperative period.

2.1 Inclusion criteria

Preoperative, evaluation including a detailed history and physical examination,
ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) of the
abdomen and pelvis, bone scan and cystoscopy were performed. Biopsies were taken of tumors,
as well as the bladder triangle and the internal urethral opening. The inclusion criteria were: tumors and away from the bladder base, bladder neck and free internal genital organs; sexually active preoperatively, and good compliance. The exclusion criteria were: 1) tumor in the bladder neck, trigone or urethral, 2) metastatic disease, 3) a history of prior pelvic radiotherapy, 4) stress incontinence or incompetent urethra, 5) prolapse of the pelvic organs of II° and greater and 6) severe organ dysfunction. Factors such as patient age and manual dexterity were taken into account.

2.2 Operation techniques

A 5 cm longitudinal incision was created under the navel. The subsequent extraperitoneal space that was created and the placement of five trocars were performed as presented, as we previously described(6) (Fig 1A). The bilaterally round ligament of the uterus was isolated and severed (Fig 1B), the ureters were identified (Fig 1C), and carefully isolated to the ureterovesicule junction and transected. The correct plane between the posterior wall of the bladder and the uterus was identified using the uterine round ligament as a proximal tracer marker. The umbilical artery and the superior vesical arteries were identified and transected (Fig 1D). Using a combination of blunt and sharp methods, the posterior bladder wall was mobilized along the peritoneum (Fig 1E). Because of the peritoneal spacing, there was absolutely no fear of damaging the uterine trace, fallopian tubes, or ovaries. The lateral pedicle was ligated close to the bladder for separation with the help of Hem-o-lok clips. Mobilization between the posterior bladder wall and the anterior vaginal wall plane was performed close to the bladder wall, and the same procedure was used for the lateral pedicles of the bladder. These meticulous
manipulations were done to maintain the integrity of the vagina to avoid damaging the neurovascular bundle and interrupting the integrity of the pelvic floor during dissection.

Next, using scissors, the proximal urethra was carefully sectioned anteriorly at the bladder neck (Fig 1F). The bladder neck was closed using a Hem-o-lok clip prior to detaching the urethra to avoid tumor implantation (Fig 1G). At this point, the posterior wall of the bladder was separated from the anterior wall of the vagina using a retrograde approach. Further intraoperative frozen sections excluded proximal urethral involvement. A transurethral 3-channel 20 Fr Foley catheter was inserted before anastomosis to provide a marker for urethral-ileal anastomosis (Fig 1H). Bilateral pelvic lymphadenectomy was performed, including the external iliac vessels and the obturator fossa region.

The peritoneum was opened in the right iliac fossa, and the target ileum was marked 15-20 cm from the upper ileocecal region (Fig 1I). The ONB procedure was the same as we previously described(7). The patients were instructed to perform clean intermittent catheterization when necessary. Detailed clinical and outpatient records were collected retrospectively.

2.3 Statistical analysis

SPSS 25.0 software was used for the statistical analyses. The Wilcoxon rank-sum test was use for paired samples to compare postoperative and postoperative outcomes, and P< 0.05 was considered to indicate significant differences.

3. Results

A total of 11 females with bladder cancer underwent ELRC with pelvic organ preservation
and ONB at our institution between April 2018 and May 2021. The general patient information is presented in Table 1.

All procedures were completed successfully. Table 2 shows the perioperative parameters and pathological and follow-up results. One patient received a blood transfusion. All patients had negative pathological margins and no lymph node metastases were observed. Patients received energy drinks on the first postoperative day and were given liquid food after the resumption of bowel movements. Solid food was gradually increased according to the patient's tolerance. Extraperitoneal drainage tubes were removed an average of 5 - 6 days after surgery. The average hospital stay was 10.72 days. The single J ureteral stent and catheter were usually removed 3 - 4 weeks after the procedure. None of the patients experienced serious complications. The most common early complications included urinary tract infections and lymphatic cysts. Four patients presented with urinary tract infections, one of whom presented with pyelonephritis. Two patients presented with lymphatic cysts, one of whom recovered after one week of ultrasound-guided puncture drainage. The early 30-day complications that occurred included a urinary tract infection and leakage in one patient, which resolved after conservative treatment. Late 90-day complications included one patient with a uretero-intestinal anastomotic stricture who improved after surgical treatment.

The median follow-up time was 16.00 ± 7.28 mo. Three patients experienced daytime continence immediately upon catheter removal, and night-time continence was reported by two patients. At the six-month follow-up, daytime and night-time continence were reported in five and four patients, respectively. In the six patients who completed the 12-month follow-ups, 100% and 83.3% daytime and night-time continence rates were achieved, respectively (Supplementary
Table 1). Two patients developed symptoms of increased residual urine output during the follow-up period, which was treated by clean intermittent self-catheterization.

We advocated for patients to resume sexual intercourse six weeks after surgery. At six months of follow-up, the patients agreed to and completed the FSFI questionnaire. Table 3 shows that the average postoperative median FSFI scores of the patients were 17.3. All patients felt good about themselves and were satisfied with the operation performed.

4. Discussion

Sexual dysfunction appears to be a common problem after standard RC, especially in younger patients. The development of pelvic organ-sparing techniques has been driven by increased attention to patients’ quality of life (8). Preoperatively, females may not have the same urgent desire for preserving sexual function as males. Nevertheless, postoperatively, they often experience vaginal dryness, loss of interest and pleasure, and even pain and dyspareunia, which can seriously affect a woman’s quality of life, relationships, and psychological state. Indeed, most sexually active females have a strong desire to maintain a good sex life and quality of life, even in the face of major pelvic surgery (9). This requires more meticulous and refined manipulations to protect the normal female anatomy and function.

Zippe et al. (10) reported that more than 50% of 27 women who underwent RC surgery experienced sexual dysfunction. They also mentioned that postoperative FSFI scores in female patients were not significantly associated with different types of urinary diversion. However, Ali-El-Dein et al. (11) reported a significant difference in postoperative FSFI scores in patients with or without nerve-sparing. A clearer preoperative diagnosis and a better understanding of
pelvic structure and function, as well as improved surgical techniques have led to relatively conservative surgical techniques for treating female bladder cancer patients who require cystectomy. These relatively conservative techniques are known as pelvic organ preservation techniques, which include preservation of the neurovascular bundle, vagina, and uterus. Such sexual function preservation techniques may lead to better sexual and urinary functional outcomes after RC surgery (12). Previous studies reported that women who received ONB after RC without nerve preservation had higher FSFI scores than those who underwent stoma or ileal diversion. The reason for this may be the change in physical appearance, which has negative physiological effects on the patient and her partner (13, 14). Supplementary Table 2 lists the postoperative characteristics and treatment of patients in previous studies. Complaints of sexual dysfunction in female patients after RC surgery can be seen, including difficulty with intercourse, pain, shortening or narrowing of the vagina, vaginal dryness, and a decrease in desire. In the present study, a decrease in postoperative FSFI scores compared to the preoperative period was also seen. But there were no such complaints such as the loss of libido and difficulty in penetration. This may be due to the careful and delicate technique to protect the anatomical structures and nerves. The ultimate objective of the ONB reconstruction is to provide a low-pressure urine storage space to maintain to satisfactory daytime and night-time continence states (15). Taking into account the almost normal urination pattern after the operation, ONB has become the optimal patients choice (16).

Extraperitoneal laparoscopic bladder-freeing is a delicate procedure that carefully protects the integrity of the peritoneum. The separation of the bladder from the anterior vaginal wall needs to be performed close to the bladder wall, thereby preserving the integrity of the anterior
vaginal wall. If the dissection is limited to around the tip and lateral margins of the vagina as described by Koie et al (17), the operation is unlikely to damage the pelvic support. That is, the gynecological organs and pubourethral ligament are functionally preserved and thus less likely to cause pelvic organ descent or prolapse. Moreover, the intact anterior vaginal wall can significantly reduce the incidence of neobladder-vaginal fistulas (18). Again, no such complications were observed in our study.

No statistical differences were observed in the local recurrence rate of vaginal preservation compared to conventional RC (17, 19). Positive marginal pathology was associated with postoperative urethral recurrence, as reported by Gakis et al (20). To our knowledge, the urethra is rarely involved in patients whose tumors do not invade the neck of the bladder. In addition, some studies reported that the incidence of bladder cancer invading gynecological organs was only 2.6 - 5%. It has also been shown that RC with pelvic organ-preservation is oncologically safe (17, 21). These results are consistent with our follow-up results. In addition, it is necessary to follow standardized surgical procedures for carefully selected female patients to avoid any adverse oncological results. To ensure oncological safety, we carefully excluded patients with metastatic disease, salvage cystectomy, and a history of prior pelvic radiotherapy. It is worth mentioning that the operative procedures carried out in the present study, the average time of cystectomy was approximately 60 minutes due to the surgical skills of the operators and the close cooperation of the team.

Previous studies showed that impaired sexual function was considered the main reason for poor postoperative self-assessment (9). Furthermore, incontinence, especially night-time incontinence, has a serious negative impact on the quality of life of ONB patients (22).
Meticulous dissection and preservation of the neurovascular bundle on the lateral and anterior walls of the vagina have been reported to preserve sexual function in females(9). Several studies reported that the rate of postoperative continence in female patients undergoing sexuality preserving RC was greater than 90%. One study reported that vaginal lubrication was sufficient and no local recurrence was found after organ-preserving operations(23), consistent with the results obtained in our study.

The ELRC technique reduces inflammatory responses caused by damage to the pelvic wall and small intestine, thus theoretically, reducing the risk of postoperative ileus(24). It is also confined to the extraperitoneal cavity in case of undesirable outcomes such as infections, urinary leakage or intestinal leakage. In the early follow-up, a patient developed urine leakage, which was resolved using conservative methods such as antibiotics and the appropriate extension of the drainage time. Moreover, with management using the ERAS protocol, all patients recovered quickly and did not complain about pain. One patient developed osphyalgia, and hydronephrosis was observed during an examination. The patient was finally diagnosed with a left ureter-oenteric anastomotic stricture. After laparoscopic ureter-ileum re-anastomosis, she made a full recovery.

The oncologic follow-up results of many patients who received ELRC and urinary diversion were not significantly different from those of traditional transabdominal surgery. Due to different factors, multitudes of female patients lost the chance to accept ONB surgery and underwent only urinary diversion treatments Thus we collected 11 cases with definite diagnoses. Although neither the surgical technique of the extraperitoneal route nor the concept of functional preservation is unique to us, the combination of the two may allow for more protection for women with bladder cancer and the results are very promising to date.
The limitation of our report that it was a single-center retrospective study lacking a control group. Firstly, we did not evaluate perioperative health-related quality of life and urodynamic studies. Moreover, some functional results were provided as feedback through outpatient consultations, instead of through effective questionnaires. Third, although a small effect of pelvic preservation on female sexual function was found in this study, it is difficult to draw clear conclusions because of the small sample size, the short-term follow-up period, and the imperfect assessment. The current results should be further confirmed by the addition of control cases of conventional RC surgery without the preservation of nerves and organs. Larger prospective cohort studies and detailed, long-term follow-up results are also needed.

5. Conclusion

ELRC with pelvic organ preservation and ONB technology is a safe and feasible surgical strategy for the treatment of bladder cancer in female patients. Through short-term follow-up, preserving the organs and vascular nerve tracts for selected females seemed to be oncologically safe and showed encouraging functional outcomes. However, further rigorous prospective studies with more patients and long-term follow-up data are needed to assess oncologic and functional results.

Reference


17. Koie, T., S. Hatakeyama, T. Yoneyama, Y. Hashimoto, N. Kamimura, and C. Ohyama,


Figure legend:

Figure 1 (A) The intraperitoneal cavity was created and enlarged. (B) The round ligament of the uterus was identified. (C) The ureter was identified and mobilized. (D) The umbilical, uterine and supravesicular arteries were carefully identified. (E) The assistant helped to maintain proper tension to free the posterior bladder wall from the peritoneum. (F) The proximal urethra was carefully sectioned anteriorly at the bladder neck using scissors. (G) The bladder neck was closed using a Hem-o-lok clip prior to detaching the urethra. (H) Cystectomy completed. (I) The target ileum was marked using a 4-0 absorbable suture.
Table 1 – Demographic characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>11</td>
</tr>
<tr>
<td>Age (year)</td>
<td>53±10.92</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>24.42±3.06</td>
</tr>
<tr>
<td>History of prior pelvic or abdominal surgery (n)</td>
<td>3</td>
</tr>
<tr>
<td>Comprehensive treatment (n)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>TUR-BT</td>
<td>7</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>3</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>1</td>
</tr>
<tr>
<td>Clinical stage (n)</td>
<td></td>
</tr>
<tr>
<td>cTis</td>
<td>1</td>
</tr>
<tr>
<td>cT1</td>
<td>4</td>
</tr>
<tr>
<td>≥cT2</td>
<td>6</td>
</tr>
</tbody>
</table>

BMI: Body mass index; TUR-BT: Transurethral resection of bladder tumour
Table 2 – Perioperative patient characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of cystectomy (min)</td>
<td>61.36±8.686</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>264.82±33.81</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>128±18.19</td>
</tr>
<tr>
<td>Blood transfusion (n)</td>
<td>1</td>
</tr>
<tr>
<td>Lymph node positive (n)</td>
<td>0</td>
</tr>
<tr>
<td>Surgical margins positive (n)</td>
<td>0</td>
</tr>
<tr>
<td>Drainage time (d)</td>
<td>5.45±1.03</td>
</tr>
<tr>
<td>Length of stay (d)</td>
<td>10.72±1.68</td>
</tr>
<tr>
<td>Time to ureter stent and transurethral catheter removal (d)</td>
<td>22.18±3.74</td>
</tr>
<tr>
<td>Pathological stage (n)</td>
<td></td>
</tr>
<tr>
<td>pTis carcinoma in situ</td>
<td>1</td>
</tr>
<tr>
<td>pT1</td>
<td>2</td>
</tr>
<tr>
<td>≥pT2</td>
<td>8</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>16.00±7.28</td>
</tr>
<tr>
<td>OS n (%)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>RFS n (%)</td>
<td>11 (100%)</td>
</tr>
</tbody>
</table>

OS: Overall survival; RFS: Recurrence-free survival
Table 3. Comparison of preoperative and postoperative FSFI.

<table>
<thead>
<tr>
<th>FSFI</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desire, median (25%-75%)</td>
<td>3.0 (2.4-3.6)</td>
<td>2.4 (1.8-3.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Arousal, median (25%-75%)</td>
<td>3.6 (3.0-4.2)</td>
<td>2.7 (2.1-4.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Lubrication, median (25%-75%)</td>
<td>3.3 (3.0-3.9)</td>
<td>3.3 (1.8-3.9)</td>
<td>0.085</td>
</tr>
<tr>
<td>Orgasm, median (25%-75%)</td>
<td>3.6 (3.2-4.0)</td>
<td>2.8 (2.0-4.0)</td>
<td>0.016</td>
</tr>
<tr>
<td>Satisfaction, median (25%-75%)</td>
<td>3.6 (2.8-4.0)</td>
<td>2.8 (2.0-3.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pain, median (25%-75%)</td>
<td>3.6 (3.2-4.8)</td>
<td>3.2 (2.8-3.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Total, median (25%-75%)</td>
<td>20.9 (18.5-21.9)</td>
<td>17.3 (15.4-19.6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

FSFI: Female Sexual Function Index