# Enhanced recovery after surgery protocol for prostate cancer patients undergoing laparoscopic radical prostatectomy

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## Abstract

**Objective:** To determine the value of an enhanced recovery after surgery (ERAS) protocol for prostate cancer patients undergoing laparoscopic radical prostatectomy (LRP).

**Methods:** We conducted a retrospective cohort study using clinical data for 288 patients who underwent LRP in our hospital from June 2010 to December 2016. A total of 124 patients underwent ERAS (ERAS group) and the remaining 164 patients were allocated to the control group. ERAS comprised prehabilitation exercise, carbohydrate fluid loading, targeted intraoperative fluid resuscitation and keeping the body warm, avoiding drain use, early mobilization, and early postoperative drinking and eating.

**Results:** The times from LRP to first water intake, first ambulation, first anal exhaust, first defecation, pelvic drainage-tube removal, and length of hospital stay (LOS) were all significantly shorter, and hospitalization costs and the incidence of postoperative complications were significantly lower in the ERAS group compared with the control group. No deaths or reoperations occurred in either group, and there were no readmissions in the ERAS group, within 90 days after surgery.

**Conclusion:** ERAS protocols may effectively accelerate patient rehabilitation and reduce LOS and hospitalization costs in patients undergoing LRP.

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## Introduction

The enhanced recovery after surgery (ERAS) protocol, first reported by Kehlet,[1] involves a series of evidence-based procedures for optimizing perioperative treatment with the aim of reducing the physical and psychological stresses of surgical trauma and thus accelerating patient rehabilitation. ERAS aims to not only reduce the length of hospital stay (LOS), but also reduce the patient's systemic stress response using modified postoperative care protocols. ERAS is currently widely used in patients undergoing gastrointestinal surgery[2] and has reduced postoperative morbidity rates and LOS following colorectal surgery.[3] However, many ERAS components are specific to abdominal surgery and its application in urological surgery, especially laparoscopic radical prostatectomy (LRP), is relatively rare.[4] This study aimed to explore the possible application of ERAS in patients with prostate cancer undergoing LRP and to evaluate its safety and efficacy. Herein we report our experience of the ERAS protocol in 288 LRP patients in our institution.

## Methods

### Patients

This was a retrospective cohort study of 288 patients undergoing LRP at the Department of Urological Surgery, Affiliated Yantai Yuhuangding Hospital of Qingdao University, from June 2010 to December 2016. Patients were aged 20 to 79 years, in good physical condition, with prostate cancer confirmed by preoperative prostate tissue biopsy. All patients had T1–T2 tumor treated with LRP, T3a tumor treated with LRP and adjuvant hormone therapy or radiation therapy, depending on the surgery outcome, or T3b–T4 tumor that did not infiltrate the urethral sphincter or attach to the pelvic wall, treated with LRP and auxiliary comprehensive therapy. The exclusion criteria were: emergency surgery; severe cardiovascular disease, pulmonary dysfunction, severe hemorrhagic tendency, or blood clotting disorders that significantly increased surgical risk; obesity (body mass index (BMI) $>30$ kg/m$^2$) or malnutrition (BMI $<15$ kg/m$^2$); bone metastasis or other distal metastasis; and life expectancy $<10$ years. Of the 288 patients, 124 admitted from October 2014 to December 2016 who underwent perioperative ERAS were selected as the ERAS group. The remaining 164 patients, who were admitted from June 2010 to September 2016 and received traditional perioperative treatment, were designated as the control group.

This study was approved by the Ethics Committee of Affiliated Yantai Yuhuangding Hospital of Qingdao University. Written informed consent was obtained from all patients and their close relatives for all procedures and for the use of their clinical data in publications.

### Perioperative treatment

Patients in the ERAS group received treatment according to modifications of the protocols described by Pisarska et al.,[5] Lassen et al.,[6] Braga et al.,[7] and Guyatt et al.[8]

Patients in the control group received conventional perioperative care (Table 1).

The main elements of ERAS included preoperative explanation of the ERAS concept and its potential advantages to patients, a reduced fasting period before surgery, no bowel preparation, and prophylactic antithrombotic, antiepileptic, and antibiotic medications. During surgery, patients received multiple local anesthesia combinations instead of general anesthesia, body-warming procedures to prevent hypothermia, a reduced number of pelvic drainage tubes (one instead of two), and limitation of Ringer's lactate solution for venous transfusion to 1000 mL. After surgery, patients were allowed to take clear liquid and liquid food shortly after the operation, compared with 2 to 3 days of clear-liquid restriction in patients receiving the conventional care protocol. Ambulation was encouraged from 4 hours after surgery compared with from 3 days in the conventional protocol. Prophylactic medication included antithrombotic, anti-stress, antibiotic, and mucosa-protectant drugs, with oral pain killers instead of use of an anesthesia and analgesia pump. Drainage tubes were removed earlier and venous transfusion was limited to <500 mL.

### Observation parameters

The postoperative observation parameters were: time from LRP to first water intake, first ambulation, first anal exhaust, first defecation, ureteral catheter removal, and pelvic drainage-tube removal; LOS; LOS for patients without complications; and hospitalization costs. The total cost for each patient, including costs of blood tests, imaging examinations, surgery, drugs, and nursing, etc., were calculated in US dollars (USD). Operative parameters included operation time, blood loss, and postoperative complications (vomiting, urinary fistula, intestinal obstruction, pneumonia, urinary tract infection, and deep venous thrombosis). Postoperative mortality, reoperation, and 90-day readmission rates were also determined.

### Follow-up

Patients underwent follow-up via telephone calls and/or hospital revisits. Follow-up included assessment/examination of urination, erectile function, and postoperative complications.

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corporation, Armonk, NY, USA). Quantitative data conforming to a Gaussian distribution were presented as mean ± standard deviation and analyzed using group $t$-tests. Numerical data were compared using $\chi^2$ or Fisher's exact tests. $P$ values <0.05 were considered statistically significant.

## Results

A total of 288 patients successfully underwent LRP. Their characteristics are presented in Table 2. The ERAS protocol was implemented in 124 (43.1%) patients. There was no significant difference in terms of age, PSA level, BMI, Gleason score, or TMN stage between the groups who received ERAS and those who received conventional postoperative care (Table 2).

The times from LRP to first water intake, first ambulation, first anal exhaust, first defecation, and pelvic drainage-tube removal in the ERAS group were all significantly shorter than those in the control group (all $P<0.001$) (Table 3). Among all patients, ERAS reduced LOS from an average of 9.2 to 3.8 days, and from an average of 8.0 to 3.3 days among patients without complications. Hospitalization costs were also reduced from an average of USD

**Table 1.** Perioperative treatment procedures in the ERAS and control groups

| Procedure | ERAS (n=124) | Control (n=164) |
|---|---|---|
| *Preoperative* | | |
| Education | ERAS concept education | Conventional therapy education |
| Fasting | No food intake for 6 hours before surgery; no liquid intake for 2 hours before surgery (oral administration of 1000 mL of 10% glucose 1 day before and 500 mL 2 hours before surgery) | No food or liquid intake for 12 hours before surgery |
| Bowel preparation | No | Cleansing enema 1 night before and on the morning of surgery |
| Prophylactic medication | Subcutaneous injection of 5000 U of low-molecular-weight heparin 12 hours before surgery; oral use of 4 mg ondansetron 2 hours before surgery; use of antibiotics 30 minutes before surgery; wearing of stretch socks before surgery | Use of antibiotics 3 days before surgery |
| *Intraoperative* | | |
| Anesthesia | Total intravenous anesthesia + epidural anesthesia + incision local infiltration anesthesia | General anesthesia with endotracheal intubation |
| Body warming | Reduce patient's body exposure time; raise operating-room temperature; preheat intravenous transfusion fluids | No |
| Use of drainage tubes | One pelvic drainage tube; one ureteral catheter | Two pelvic drainage tubes; one ureteral catheter |
| Venous transfusion | 1000 mL of Ringer's lactate solution | No limitation on volume of venous transfusion |
| *Postoperative* | | |
| Food and water intake | Clear liquid 2 hours after surgery; liquid food 4 hours after surgery | Clear liquid 2–3 days after surgery |
| Ambulation | Encourage 2 hours of bedside activity 4 hours after surgery; >6 hours of off-bed activity day after surgery | Encourage bedside activity beginning 3 days after surgery |
| Prophylactic medication | Subcutaneous injection of 5000 U of heparin daily from day after surgery to hospital discharge to prevent thrombus; oral intake of 300 mg of ibuprofen every 12 hours; oral intake of 10 mg of prednisone day after surgery to prevent stress response; oral intake of antibiotics and omeprazole to prevent infection and protect gastric mucosa | Routine use of anesthesia and analgesia pump; intravenous injection of a gastric mucosa-protectant drug and antibiotics |
| Drainage-tube removal | 2–3 days after surgery | When drainage volume is <10 mL for 3 consecutive days |
| Venous transfusion | ≤500 mL | No limitation on volume of venous transfusion |

7200 to USD 6100. The time from LRP to ureteral catheter removal did not differ significantly between the two groups (Table 3), and operation time and surgical blood loss were also similar in both groups. Patients were followed up for 14 to 86 months (median, 36.5 months), during which time 11 patients (8.9%) in the ERAS group developed postoperative complications, including six cases of vomiting, two of pneumonia, two urinary tract infections, and one of case of atrial fibrillation, while 22 patients (13.4%) in the control group developed postoperative complications, including seven cases of vomiting, two of urine leakage, three intestinal obstructions, four cases of pneumonia, three urinary tract infections, one deep venous thrombosis, and two atrial fibrillations. The incidence of postoperative complications was significantly lower in the ERAS group ($P=0.036$) (Table 3). Two patients in the control group were readmitted for dysuria caused by urethral stricture, which was successfully treated by urethral dilation. None of the study patients died or underwent reoperation.

**Table 2.** Characteristics of patients in the ERAS and control groups

| Characteristic | ERAS (n=124) | Control (n=164) | P |
|---|---|---|---|
| Age (years) | 70.9 ± 3.6 | 70.0 ± 4.3 | 0.329 |
| PSA level (ng/mL) | 44.5 ± 22.3 | 36.8 ± 23.2 | 0.126 |
| BMI (kg/m$^2$) | 20.3 ± 1.5 | 20.4 ± 1.4 | 0.853 |
| Gleason score, n (%) | | | 0.397 |
| ≤6 | 52 (42) | 75 (46) | |
| 7 | 36 (29) | 43 (26) | |
| ≥8 | 36 (29) | 46 (28) | |
| Clinical stage, n (%) | | | 0.794 |
| T1–T2c | 40 (32) | 52 (32) | |
| T3a | 44 (35) | 48 (29) | |
| T3b–T4 | 40 (32) | 64 (39) | |

PSA, prostate-specific antigen; BMI, body mass index. Age, PSA level, and BMI shown as mean ± standard deviation.

**Table 3.** Surgical recovery parameters in patients in the ERAS and control groups

| Parameter | ERAS | Control | P |
|---|---|---|---|
| First intake of clear liquid, hours | 2.5 ± 0.6 | 30.1 ± 12.9 | <0.001 |
| First ambulation, hours | 8.7 ± 2.2 | 73.1 ± 4.7 | <0.001 |
| First anal exhaust, hours | 8.8 ± 7.1 | 30.6 ± 23.3 | <0.001 |
| First defecation, hours | 17.0 ± 5.0 | 81.1 ± 36.2 | <0.001 |
| Ureteral catheter removal, days | 6.5 ± 0.5 | 6.6 ± 0.7 | 0.246 |
| Drainage-tube removal, days | 2.5 ± 0.5 | 7.8 ± 1.1 | <0.001 |
| LOS, days | 3.8 ± 1.7 | 9.2 ± 2.7 | <0.001 |
| LOS in patients without complications, days | 3.3 ± 0.4 | 8.0 ± 0.8 | <0.001 |
| Hospitalization cost, thousand USD | 6.1 ± 0.4 | 7.2 ± 0.4 | <0.001 |
| Operation time, minutes | 102.0± 24.0 | 106.0±32.1 | 0.154 |
| Blood loss, mL | 151.1±32.5 | 164.3±41.5 | 0.143 |
| Postoperative complications, n (%) | 11 (8.9) | 22 (13.4) | 0.036 |
| Vomiting | 6 (4.8) | 7 (4.3) | |
| Urine leakage | 0 | 2 (1.2) | |
| Intestinal obstruction | 0 | 3 (1.8) | |
| Pneumonia | 2 (1.6) | 4 (2.4) | |
| Urinary tract infection | 2 (1.6) | 3 (1.8) | |
| Deep venous thrombosis | 0 | 1 (0.6) | |
| Other* | 1 (0.8) | 2 (1.2) | |

LOS, length of stay; USD, US dollars. All time data and hospitalization costs shown as mean ± standard deviation.
*One case of atrial fibrillation in the ERAS group and one case of urinary incontinence and one stress ulcer in the control group.

## Discussion

In this study, we compared multiple postoperative recovery parameters between 288 patients with prostate cancer undergoing LRP with either traditional postoperative care or ERAS. The result suggested that the use of ERAS protocols may effectively accelerate patient rehabilitation and reduce LOS, without increasing postoperative complications or readmission rates.

Prostate cancer is the most common malignant tumor among men in the USA. After a century of development, radical prostatectomy has become the gold standard for treating localized prostate cancer.[9] Radical prostatectomy is accompanied by extensive operative trauma, a high risk of intraoperative hemorrhage, and a high rate of operative mortality, as well as high risks of pneumonia, deep vein thrombosis, and anastomotic leakage as a result of prolonged postoperative bed rest; however, the development of laparoscopic technology has greatly reduced the incidence of postoperative complications.[10] Prostate cancer mostly occurs in elderly men (the average age in the present study was 70.3 years), whose physical state is therefore generally weaker than that of recipients of other surgeries. Patients' low operative tolerance has thus limited the clinical application of radical prostatectomy, and accelerating the rehabilitation of elderly patients remains a problem in urological surgery.

Kehlet first proposed the concept of ERAS in 1997.[1] ERAS consists of optimizing a series of procedures during perioperative treatment.[11] In many countries, physicians have applied the ERAS protocol to multiple disciplines, including anorectal surgery, orthopedics, urological surgery, and gynecology.[12–15] However, although Li introduced and promoted ERAS in China in 2007, its integration into urological surgery has been relatively slow, and there have been few reports of ERAS use by Chinese researchers. ERAS is a novel evidence-based optimization of the perioperative treatment model aimed at reducing the stress of surgical trauma and accelerating patient rehabilitation.[16] Patients receiving ERAS are normally discharged 2 to 4 days after their operation, and the patient's general condition, nutritional state, and organ functions are rapidly restored during the postoperative hospitalization period and subsequent follow-up.[17] The implementation of ERAS represents not only the development of a single discipline, but importantly also a collaboration among surgical departments, anesthesiologists, and nurses. Encouraging the patients' active participation in ERAS and promoting cooperation between patients and doctors provide the foundation for the application of ERAS, leading to increased patient compliance with ERAS and improving clinical outcomes after surgery.

ERAS promotes the use of rapid- and short-acting anesthetics to reduce intraoperative stress, accelerate recovery, promote early ambulation, restore gastrointestinal peristalsis, promote wound healing, shorten LOS, and reduce hospitalization costs. A previous study of intraoperative hemodynamic management in non-cardiac surgery showed that sufficient liquid and energy intakes before surgery ensured effective perioperative tissue perfusion, which, combined with controlling the volume of intraoperative fluid transfusion, helped to prevent edema caused by fluid overload.[18] During surgery, reducing the patient's body exposure time, raising the operating-room temperature, and preheating the intravenous transfusion fluids may help to prevent hypothermia, thus reducing the risks of intraoperative and postoperative complications such as incision wound infection and hemorrhage.[19] Furthermore, prolonged bed rest after surgery is likely to cause deep vein thrombosis, and the ERAS protocol thus encourages patients to undertake

ambulation after LRP sooner than conventionally suggested, both to avoid the formation of deep vein thrombosis and stimulate bowel movement.[20] Combined with prophylactic medications, ERAS can help to prevent nausea and vomiting, thus enabling the early resumption of an oral diet after surgery, which also aids patient recovery.[21] The ERAS protocol can not only accelerate patient recovery and shorten LOS, but can also reduce the incidence of long-term complications compared with conventional postoperative care protocols. No ERAS patients in the present study were readmitted within 90 days after LRP during 1 to 6 months of postoperative follow-up. In the UK and most other developed countries, health care costs are largely covered by insurance; however, the cost of surgery and hospitalization represent huge burdens for most families in China, and accelerated recovery from LRP is thus especially important for patients. Minimally invasive surgery including ERAS has been proved to be a safe and a cost-effective alternative to open surgery in a low medical care-expenditure country,[22] and we believe that it may also be suitable for LRP patients in most developing countries worldwide.

Although ERAS is widely implemented in Europe and the United States, surgeons' acceptance of some important ERAS protocol elements remains low in many areas[23] and its application in China is still in the preliminary stages. Although the ERAS protocol has become an accepted guideline for colorectal surgery worldwide,[24] conventional pretreatment models for complex urological surgeries such as radical prostatectomy remain difficult to change, and some perioperative treatment concepts are still controversial and poorly complied with. Implementation of the ERAS protocol thus represents a major improvement in terms of optimizing urological surgery procedures.

This study had some obvious limitations. First, it was a retrospective cohort study and could thus have been influenced by many elements, such as the proficiency of the surgeons, the learning curves of the staff, and differences among patients (e.g., BMI and comorbidity). Second, the data were derived from a single team, which might have influenced the comparative results. More studies with larger numbers of patients are therefore needed to confirm these results.

## Conclusion

We confirmed that application of the ERAS protocol may effectively accelerate patient rehabilitation and reduce LOS and hospitalization costs in patients undergoing LRP for prostate cancer. Furthermore, ERAS may be implemented safely and effectively, without increasing postoperative complication or readmission rates.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

### Funding

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