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ORIGINAL RESEARCH

Enhanced recovery after surgery (ERAS) protocols in patients with advanced ovarian cancer undergoing ultra-radical cytoreductive surgery with intestinal resection and anastomosis: a retrospective study

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Abstract

To evaluate the feasibility and effectiveness of enhanced recovery after surgery (ERAS) in the perioperative management of patients with advanced ovarian cancer. We collected and retrospectively analyzed the data of patients with advanced ovarian cancer who underwent tumor debulking surgery with intraoperative intestinal resection and anastomosis at our center from May 2020 to May 2022. All patients achieved R0 tumor debulking and were divided into an ERAS and a control group based on their perioperative interventions. The feasibility and effectiveness of ERAS were evaluated by comparing intensive care unit (ICU) admission rates, ICU stay time, hospital stay, time from surgery to postoperative chemotherapy, and incidence of postoperative complications. A total of 40 patients with advanced ovarian cancer, 18 in the ERAS group and 22 in the control group, were eligible for this study. We observed no significant differences in baseline data and surgical conditions. Regarding postoperative recovery, there was no significant difference in the ICU admission rate, length of ICU stay, and the incidence of postoperative complications. While the ERAS group had a shorter time interval from surgery to postoperative chemotherapy, 16 (9–18) days *vs.* 20 (10–24) days ($p = 0.042$), and a shorter hospital stay, 20 (18–21) days *vs.* 24 (19–28) days ($p = 0.025$). The ERAS strategy might improve postoperative recovery and shorten the time interval from surgery to postoperative chemotherapy and hospital stay in patients with advanced ovarian cancer who underwent ultra-radical cytoreductive surgery, without increasing the incidence of complications.

Keywords

Enhanced recovery after surgery; Cytoreductive surgery; Intestinal resection; Ovarian cancer

1. Introduction

Ovarian cancer is one of the three major malignant tumors in gynecology. In 2016, there were an estimated 57,200 newly-developed cases and 27,200 deaths associated with ovarian cancer in China [1], currently causing huge socio-economical issues. Ovarian cancer is usually asymptomatic in its early stages, a large proportion of the patients are diagnosed when the disease has reached an advanced stage, resulting in poor treatment outcomes and prognosis, with a 5-year survival rate of <40% [2]. In terms of treatments in this group of patients, maintenance therapy using poly (ADP-ribose) polymerase (PARP) inhibitors was shown to decrease ovarian cancer-related mortality [3]. The routine treatment for advanced ovarian cancer is primary debulking surgery (PDS) followed by postoperative platinum-based chemotherapy. Platinum-based neoadjuvant chemotherapy (NACT), usually 2–4 courses, followed by sequential interval debulking surgery (IDS) and postoperative platinum-based chemotherapy might be considered when the patient's general condition is poor, has multiple comorbidities, or when the risk to benefit ratio of tumor debulking might be unsatisfactory [4].

The outcomes of ovarian cancer tumor debulking surgery are mainly defined as (1) R0: no residual tumor, (2) R1: residual tumor diameter $\leq$ 1 cm, and (3) R2: residual tumor diameter >1 cm [5]. Studies have shown that, regardless of PDS or IDS, intraoperative tumor debulking (the degree of tumor surgical resection) improves patient outcomes, and it was even shown that the survival benefit of advanced ovarian cancer patients could be significantly improved if R0 tumor debulking might be achieved [6–8]. Comparatively, residual lesions negatively influence patients' prognoses [9]. Clinically, considering that extensive metastases in the pelvic and abdominal cavities may have already occurred by the time of diagnosis in most advanced ovarian cancer cases, it was proposed that in addition to routine resection of the entire uterus, bilateral ovaries, fallopian tubes, and omentum, the surgical scope might be extended to also include tumor-invaded regions such as the peritoneum, diaphragm, part(s) of the liver, spleen, gallbladder and bowel, also known as ovarian cancer ultra-radical surgery [10, 11]. It was previously reported that a large scope and a prolonged duration of ovarian cancer cytoreduction could lead to poorer postoperative recovery [12]. Meanwhile, ovarian cancer is associated with a high risk of intestinal metastasis, resulting in a high rate of intestinal resection and anastomosis in ovarian cancer debulking surgery, which has contributed to higher risks of multiple serious postoperative complications such as anastomotic leakage and infection, which might be life-threatening and delay sequential chemotherapy [13, 14].

Platinum-based chemotherapy is an important adjuvant therapy for ovarian cancer. Studies have shown that a shorter time from cytoreductive surgery to chemotherapy could lead to better prognosis. Therefore, several strategies have been proposed to maximize the shortening time to chemotherapy [9, 15]. In this regard, enhanced recovery after surgery (ERAS) refers to the comprehensive application of a series of evidence-based optimization measures in the perioperative period to reduce psychological and physical damage and improve postoperative recovery. ERAS protocols envelopes the whole perioperative period and require multiple-disciplinary collaboration, such as professionals in surgery, anesthesia, nursing, nutrition and physiotherapy [16]. ERAS has been implemented in our center for decades and has gradually progressed from being adopted mainly in the perioperative management of patients with benign tumors to play a significant role in the management of malignant tumors. This study retrospectively investigated the efficacy of ERAS in the postoperative recovery of ovarian cancer patients undergoing cytoreduction together with intestinal resection and anastomosis.

2. Patients and Methods

2.1 Patients

The data of advanced ovarian cancer patients admitted to our center from May 2020 to May 2022 were retrospectively screened. Inclusion criteria were: (1) age less than 70 years; (2) patients with advanced epithelial ovarian cancer having the International Federation of Gynecology and Obstetrics (FIGO) stage III–IV disease; (3) satisfactory tumor debulking during surgery, achieved R0 debulking; and (4) intestinal resection and anastomosis during the tumor debulking surgery. Exclusion criteria were: (1) severe comorbidities; (2) mental illnesses leading to inability to cooperate; (3) concurrent other malignant tumors. Cases that met all criteria were divided into an ERAS group or a control group based on their perioperative interventions.

The perioperative interventions are shown in Table 1. In both groups, the following indicators were recorded: preoperative routine bowel preparation, normothermia maintenance, goal-directed fluid therapy, multimodal analgesia, thromboprophylaxis and early ambulation. Differences between the 2 groups were mainly based on the following 5 interventions for the ERAS group: (1) Patients in the EARS group received oral metronidazole on the basis of routine preoperative bowel preparation; (2) Patients in the EARS group drank carbohydrate drink 4–6 hours prior to surgery instead of intravenous glucose and electrolytes to improve metabolism. This drink was available and the main ingredients were: water, maltodextrin, crystalline fructose, glucose, vitamins, *etc.* The amount taken orally before the operation was about 355 mL. (3) Intercostal nerve block anesthesia before anesthesia resuscitation to relieve postoperative pain; (4) Patients in the EARS group received early feeding with small amounts of enteral nutrition preparations several times on the 3rd day after operation, the control group patients received feedings on the 5th day; (5) Patients in the EARS group had their urinary catheters removed in 48–72 hours after surgery, while the control group patients generally had their urinary catheters removed more than 72 hours after surgery.

2.2 Study indicators

Baseline and surgical information were collected, and ICU admission rate, ICU stay time, hospital stay, time interval from postoperative to chemotherapy and the incidence and severity of postoperative complications were analyzed to evaluate the feasibility and effectiveness of ERAS. The baseline data included age, body mass index (BMI), American society of anesthesiologists (ASA) score, preoperative hemoglobin and albumin levels, tumor histology, FIGO stage, comorbidities, and debulking method (PDS/IDS). Surgical information included operative time, intraoperative bleeding, scope of operation, placement of drainage tubes, intestinal resection and anastomosis status.

2.3 Statistical analysis

All statistical analyses were conducted using the SPSS v25.0 statistical software (IBM Corporation, Chicago, Illinois, United States). Continuous variables with normal distribution are presented as mean $\pm$ standard deviation(SD); non-normal variables are reported as median (interquartile range), and the two-group t-test or Mann-Whitney U test was used for intergroup data comparison, respectively. The composition ratio of qualitative information was described as n (percentage), and qualitative data were compared using the (χ^2 test or Fisher's exact test. A p value < 0.05 was considered statistically significant.

3. Results

3.1 Patient characteristics

A total of 40 eligible patients were included in this study, including 18 patients in the ERAS group and 22 patients in the control group. There were no significant baseline differences in age, BMI, ASA score, preoperative hemoglobin and albumin levels, tumor histological type and FIGO stage, comorbidities and PDS and IDS ratio between the two groups ($p > 0.05$ for all characteristics) (Table 2).

TABLE 1. Perioperative interventions for the ERAS group and the control group.

Setting	ERAS group	Control group
Pre-admission		
	Patient education on ERAS protocol	Same
	Blood glucose and blood pressure monitor and control	Same
	Reverse anemia to hemoglobin over 80 g/L	Same
	Reverse hypoproteinemia to albumin over 30 g/L	Same
	Surgery 10 days after neoadjuvant chemotherapy	Same
Preoperative		
	Routine bowel preparation	Same
	Oral antibiotics	-
	Carbohydrate drink 4–6 hours prior to surgery	IV fluid infusion routinely
Intra-operative		
	Normothermia maintenance	Same
	Goal-directed fluid therapy	Same
	Intercostal nerve block anesthesia before anesthesia resuscitation	-
Postoperative		
	Early feeding	-
	Early urinary catheter removal	-
	Multimodal analgesia	Same
	Thromboprophylaxis	Same
	Early ambulation	Same

ERAS: Enhanced recovery after surgery; IV: intravenous.

TABLE 2. Baseline information of the ERAS group and control group.

Characteristics	ERAS group (n = 18)	Control group (n = 22)	*p* value
Mean age, years (±SD)	54.8 ± 8.8	54.6 ± 10.2	0.926
Mean BMI, kg/m² (±SD)	23.0 ± 2.9	21.9 ± 2.8	0.251
ASA risk, n (%)			
2	6 (33.3%)	10 (45.5%)	0.436
3	12 (66.7%)	12 (54.5%)	
Preoperative hemoglobin, n (%)			
≥110 g/dL	8 (44.4%)	10 (55.6%)	0.949
<110 g/dL	10 (45.5%)	12 (54.5%)	
Preoperative albumin, n (%)			
≥40 g/L	7 (38.9%)	10 (45.5%)	0.676
<40 g/L	11 (61.1%)	12 (54.5%)	
Histology, n (%)			
Serous carcinoma	17 (94.4%)	19 (86.4%)	0.613
Serous & clear cell carcinoma	1 (5.6%)	3 (13.6%)	
FIGO stage, n (%)			
III	10 (55.6%)	13 (59.1%)	0.822
IV	8 (44.4%)	9 (40.9%)	
Comorbidities, n (%)			
Hypertension	2 (11.1%)	4 (18.2)	0.673
Diabetes	1 (5.6%)	1 (4.5%)	1.000
PDS, n (%)	7 (38.9%)	6 (27.3%)	0.435
IDS, n (%)	11 (61.1%)	16 (72.7%)	

ERAS: Enhanced recovery after surgery; PDS: primary debulking surgery; IDS: interval debulking surgery; BMI: body mass index; SD: standard deviation; FIGO: the International Federation of Gynecology and Obstetrics; ASA: American society of anesthesiologists.

TABLE 3. Surgical information for the ERAS group and control group.

Variables	ERAS group (n = 18)	Control group (n = 22)	*p* value
Median operative time, minutes (range)	370 (290–519)	444 (359–501)	0.399
Median intraoperative bleeding, mL (range)	650 (300–1200)	500 (300–1000)	0.899
Number of draining tubes placed, n (%)			
1	11 (61.1%)	12 (54.5%)	0.676
2	7 (38.9%)	10 (45.5%)	
Scope of operation, n (%)			
Pelvic peritonectomy	11 (61.1%)	15 (68.2%)	0.641
Diaphragmatic resection	9 (50.0%)	10 (45.5%)	0.755
Lymphadenectomy	8 (50.0%)	8 (36.4%)	0.401
Partial hepatectomy	5 (27.8%)	6 (27.3%)	0.972
Appendicectomy	3 (16.7%)	3 (13.6%)	1.000
Splenectomy	1 (5.6%)	2 (9.1%)	1.000
Cholecystectomy	1 (5.6%)	1 (4.5%)	1.000
Intestinal segments removed, n (%)			
1	16 (88.9%)	19 (86.4%)	0.810
2	2 (11.1%)	3 (13.6%)	

ERAS: Enhanced recovery after surgery.

TABLE 4. Postoperative outcomes of the ERAS group and control group.

Variables	ERAS group (n = 18)	Control group (n = 22)	*p* value
ICU admission, n (%)	9 (50.0%)	13 (59.1%)	0.750
Median length of ICU stay, day (range)	0.5 (0–2.25)	1 (0–2)	0.863
Median hospital stay, day (range)	20 (18–21)	24 (19–28)	0.025
Median time interval from surgery to postoperative chemotherapy, day (range)	16 (9–18)	20 (10–24)	0.042
Clavien-Dindo complication , n (%)			
Level I–II	7 (38.9%)	9 (40.9%)	0.897
Level III	1 (5.6%)	1 (4.5%)	1.000

ERAS: Enhanced recovery after surgery; ICU: intensive care unit.

3.2 Surgical information

All patients in both groups achieved R0 tumor debulking. The operation time, intraoperative bleeding, number of drainage tubes placed after the operation and the scope of surgery (operation of pelvic peritoneum, diaphragm, lymph nodes, parts of liver, appendix, spleen and gallbladder) were not statistically different between both groups. The median operative time was 370 minutes (range 290–519) in the ERAS group and 444 minutes (range 359–501) in the control group, ($p = 0.399$). The median intraoperative bleeding in the ERAS group compared to the control group was 650 mL (range 300–1200) *vs.* 500 mL (range 300–1000), ($p = 0.899$). The rate of patients with 1 drainage tubes placed was 61.1% and 54.5%, and the rate of patients with 2 drainage tubes placed was 38.9% and 45.5%, respectively, ($p = 0.676$). All patients in both groups underwent intestinal resection and anastomosis, the rate of patients with 1 intestinal segment removed was 88.9% and 86.4%, and the rate of patients with 2 intestinal segments removed was 11.1% and 13.6%, respectively, and there was no significant difference in the number of intestinal sections removed between the two groups ($p = 0.810$) (Table 3).

3.3 Postoperative outcomes

The details of postoperative recovery situation are shown in Table 4. There we found was no significant difference in the ICU admission rate and length of ICU stay between the ERAS group and the control group. However, compared with the control group, the patients from the ERAS group had a shorter median time interval from surgery to postoperative chemotherapy, 16 (9–18) days *vs.* 20 (10–24) days ($p = 0.042$), and so as the hospital stay, 20 (18–21) days *vs.* 24 (19–28) days ($p = 0.025$). The rate of Clavien-Dindo level I–II complications was 38.9% and 40.9%, respectively, ($p = 0.897$), and the main types of Clavien-Dindo level I–II complications were anemia, hypoalbuminemia, fever and pain, which were corrected after active medical management. There was 1 case of Clavien-Dindo level III complications in each of the two groups, both of which were anastomotic leakage, and both patients underwent enterostomy.

4. Discussion

This study demonstrated that for patients with FIGO stage III–IV ovarian cancer who underwent enterectomy-enterostomy with R0 debulking surgery, the implementation of ERAS protocols could shorten the time interval from surgery to postoperative chemotherapy and hospital stay without increasing the risks of postoperative complications. For advanced ovarian cancer patients who underwent ultra-radical cytoreductive surgery, the feasibility and effectiveness of the ERAS scheme have been demonstrated, providing a theoretical basis for its clinical promotion.

We focused on a specific patient population with advanced ovarian cancer who underwent intestinal resection and intestinal anastomosis during cytoreductive surgery and had multiple negative factors affecting prognosis. Ovarian cancer is diagnosed at an advanced stage due to its special biological behavior, with extensive metastases in the pelvic and abdominal cavities. The degree of cytoreduction in ovarian cancer surgery affects the prognosis of patients, indicating that a more complete cytoreduction would lead to better treatment outcomes. Advanced ovarian cancer has a high probability of intestinal metastasis, so intestinal resection is often required during tumor debulking surgery to achieve better cytoreduction, thus, better prognosis, which was mainly observed in low rectosigmoid resection [17, 18]. A previous study showed that in patients with stage IIIC– IV advanced ovarian cancer, the rate of bowel resection was as high as 53.2% in intermediate cytoreductive surgery [19]. Our study also revealed that in patients with advanced ovarian cancer, ultra-radical resection would increase the operation time, cause more blood loss and complicated intra- and postoperative status.

The risk of complications after intestinal resection is higher than in patients without intestinal resection, and the incidence of complications after multiple intestinal resection was found to be higher than that of single intestinal resection, mainly comprising the following complications: infection, sepsis, pelvic abscess, respiratory distress, pulmonary embolism, anastomotic rupture, intestinal fistula [12, 20–22]. Our study showed consistent results where complications happened in nearly half of the patients in both groups, which were at a higher level. The most serious complication was anastomotic leakage, which required reoperation.

Ultra-radical resection of ovarian cancer can improve the prognosis of patients despite the increased surgical scope leading to an increased risk in complications [23, 24]. A retrospective study of 483 patients with intermediate debulking surgery for ovarian cancer reported a median overall survival time of 64 months after surgery in patients without residual tumors and 35 months for those with residual tumor(s) [25]. This survival benefit indicates the possible necessity of ultra-radical resection in these patients. Developments in the ERAS strategy have helped minimize collateral damage and maximize the survival benefit of surgeries for ovarian cancer patients [26].

ERAS is currently widely used in gynecological oncology. It has been proven to effectively shorten the length of hospital stay [27], reduce complications, and decrease hospitalization costs [28, 29]. However, due to the complexity of ovarian cancer surgery and the high risks of complications, there are relatively few ERAS interventions performed on ovarian cancer tumor debulking surgery. Previous studies confirmed that patients who underwent ERAS had significantly shorter hospitalization time and quicker postoperative time to chemotherapy [30], all without increasing the risks of complications [31]. In addition, patient compliance with ERAS was reported to be positively correlated with ERAS in shortening the length of hospital stay and reducing medical costs [32, 33].

In this study, the ERAS strategy comprised of interventions that were validated in early studies [34] and our experiences to promote early recovery, while the ERAS strategies for colon cancer were also considered as sigmoid colon and rectum were the most commonly involved parts in ovarian cancer patients [18]. A study of 20,740 patients found that patients with colorectal cancer who received mechanical bowel preparation and preoperative oral antibiotics before surgery had lower postoperative infections, hospital stays and medical costs than those who received mechanical bowel preparation alone [35]. Preoperative carbohydrates drink and early postoperative feeding in patients with colorectal cancer surgery were shown to improve patient satisfaction with treatment, reduce postoperative complications and shorten hospitalization costs [36, 37]. Intercostal nerve block anesthesia is most commonly used for analgesia in thoracic surgery. Considering it is often necessary to remove the upper abdominal tissues, including the diaphragm, during ultra-radical surgery for ovarian cancer, therefore, the surgical incision may extend to the upper abdominal wall, which is in the lower inferior intercostal neurological level, so intercostal nerve block anesthesia is used for postoperative analgesia after ultra-radical surgery for ovarian cancer [38]. The ability of early postoperative urinary catheter removal to promote rehabilitation may be related to the promotion of earlier patient ambulation. We found similar results indicating that ERAS could significantly shorten both hospital stay and the time interval from surgery to postoperative chemotherapy by 16.7% and 20.0%, respectively. This result is important because earlier postoperative chemotherapy has been associated with better outcomes, while delaying the time to chemotherapy was shown to negatively affect the OS and PFS of these patients [9, 14]. Further, our results also showed that the implementation of ERAS protocols did not cause an increase in the incidence of complications compared with the non-ERAS group. The methods used in ERAS should be made on evidence-based medicine involving the management of the entire perioperative period and multidisciplinary cooperation and requiring the active participation and cooperation of patients and their relatives, which could otherwise decrease the potential beneficial effects of ERAS.

This study had several limitations. First, this is a retrospective study with a relatively small amount of specific patients, leading to a relatively low evidence level. Second, no survival analyses, such as FPS and OS, were performed, thus indicating a lack of direct evidence to show the effects of ERAS on patients' outcomes. Lastly, the ERAS interventions implemented in this study were relatively limited, indicating the need for more multiple disciplinary interventions.

5. Conclusions

This retrospective study demonstrated that the ERAS strategy could speed up postoperative recovery and shorten the time to postoperative chemotherapy and hospital stay in ovarian cancer patients who underwent intestinal resection and anastomosis during cytoreductive surgery, without increasing the incidence of complications, which is worthy of further clinical investigations for potential wide clinical application. In addition, we will continue to optimize the ERAS strategy in clinical practice and intend to perform prospective controlled trials to provide more reliable evidence for the promotion of ERAS.

AUTHOR CONTRIBUTIONS

Qin Zhang and Cuirong Lei worked together on study design, data collection and analysis, and manuscript writing. Both authors contributed equally to the study. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This single-center retrospective study was approved by the Institutional Ethics Committee of the Chongqing University Cancer Hospital (Approval number: CZLS2022169-A).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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