

Risk factors of perioperative complications and management with enhanced recovery after primary surgery in women with epithelial ovarian carcinoma in a single center

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Abstract. The present study aimed to evaluate the postoperative complications and the impact of an enhanced recovery programme in patients who underwent primary surgery

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Abbreviations: IPC, initial postoperative chemotherapy; EOC, epithelial ovarian carcinoma; ICU, intensive care unit; FIGO, Federation International of Gynecology and Obstetrics; MDT, multidisciplinary team; ERAS, enhanced recovery after surgery; EUAS, extensive upper abdominal surgery; PDS, primary debulking surgery; IDS, interval debulking surgery; PFS, progression-free survival; OS, overall survival; BMI, body mass index; ASA, American Society of Anesthesiologists; CT, computed tomography; SCS, surgical complexity score; EnBRP, en bloc resection of the pelvis; POPF, postoperative pancreatic fistula; ROC, receiver operating characteristic; OR, odds ratio; CI, confidence interval; MDR, multidrug resistant; GI, gastrointestinal; ALB, albumin; LOS, length of hospital stay; TTC, time-to-chemotherapy

Key words: complications, primary surgery, epithelial ovarian carcinoma, recovery, perioperative

(including extensive upper abdominal surgery) for epithelial ovarian carcinoma (EOC). All patients with stage I-IV ovarian carcinoma who underwent primary surgery were identified, and postoperative complications were evaluated and graded according to the Clavien-Dindo classification. Of 161 patients, 46 (28.57%) underwent surgical staging, 27 (16.77%) standard cytoreduction, 12 (7.45%) en bloc debulking and 76 (47.20%) extraradical debulking. A total of 157 patients (97.52%) achieved optimal tumor reduction (<1 cm). The mean postoperative hospitalization time was 17.33±11.29 days after completion of the initial postoperative chemotherapy (IPC), and the IPC interval was 16.22±10.09 days. A total of 13 patients (8.07%) had grade 3 complications (9 with wound dehiscence, 3 with digestive tract leakage and 1 with a bladder fistula). A total of 2 patients (1.24%) had grade 4-5 complications [1 patient with severe pneumonia returned to the intensive care unit (ICU) for tracheotomy and respiration rehabilitation; the other patient died of septicemia on day 19]. The multivariate analysis of the preoperative factors revealed that a human epididymis protein 4 (HE4) level of ≥717 pM (P=0.015) and Federation International of Gynecology and Obstetrics (FIGO) stage IV (P=0.004; compared with stage IIIC) were associated with grade 3-5 complications. The bootstrap analysis revealed that a cancer antigen 125 (CA125) level of ≥1,012 U/ml (P=0.034), a HE4 level of ≥717 pM (P=0.007) and FIGO stage IV (P=0.002; compared with stage IIIC) were significantly associated with grade 3-5 complications. Meanwhile, the multivariate analysis of the postoperative factors did not reveal any risk factors associated with grade 3-5 complications; the bootstrap analysis revealed that only transfer to the ICU after surgery (P=0.026) was significantly associated with grade 3-5 complications. In conclusion, the study found that application of enhanced recovery after surgery protocols is feasible in patients with EOC, especially in those undergoing advanced extensive upper abdominal surgery, and CA125, HE4 and FIGO stage IV were related with the occurrence of adverse perioperative outcomes.

Introduction

Epithelial ovarian carcinoma (EOC) has the highest worldwide mortality rate among malignant tumors of the female genital tract (1). Owing to the increase in life expectancy, the incidence and mortality rates of ovarian carcinoma are increasing (2). Approximately 70% of cases are diagnosed at advanced stages, half of which demonstrate tumor progression above the pelvic brim (3). Cytoreductive surgery followed by platinum-based combination chemotherapy is a critical element of the standard initial therapy (4), and optimal cytoreduction/debulking surgery involving the pelvis, lower abdominal cavity and upper abdominal cavity can achieve a considerable survival advantage (5,6). A meta-analysis showed that a 10% increase in the optimal cytoreduction rate prolonged the median survival time by 5.5% (7). However, complete cytoreduction depends on three factors: i) physician/surgeon-related factors, including surgical training and multidisciplinary team (MDT) collaboration offered at the center, experience and risk tolerance; ii) patient-related factors, such as performance status and comorbidity; and iii) disease-related factors, such as tumor biological aggressive behaviour and extension of disease. In different centers, the proportion of patients who undergo optimal cytoreduction for advanced disease varies between 15 and 85% (7). Thus, gynecological oncologists could make substantial progress with the help of teamwork and surgical training. Teamwork is also involved in the use of enhanced recovery after surgery (ERAS) protocols, including procedures such as preoperative counseling, tailored anesthesia and analgesia, and early postoperative feeding and mobilization, to improve perioperative management.

The evaluation of the radicality of surgery is mainly based on the surgeon's visual estimation and experience. Extensive upper abdominal surgery (EUAS), including diaphragmatic peritonectomy, splenectomy, partial liver resection and distal pancreatectomy can decrease the residual disease rate in patients with advanced EOC; however, it can increase the incidence of postoperative complications (8,9). Therefore, the final decision of the surgeon on complete tumor resection in primary debulking surgery (PDS) and interval debulking surgery (IDS) remains controversial. Hynninen *et al* (10) found that IDS had significantly worse sensitivity and accuracy than PDS, leading to incomplete tumor resection in potentially resectable areas. The debates still remain regarding the technique for the best progression-free survival (PFS) and overall survival (OS), the incidence rates of postsurgical death and major infective complications, and economic cost of the two types of surgical strategies, considering the competing perspectives of the biology of ovarian carcinoma in relation to the value of aggressive debulking resection (11-14).

Most gynecological oncologists face the dilemma of how to complete complex EUAS procedures, as >50% of cases with optimal cytoreduction require EUAS to attain complete cytoreduction (15,16). Recently, the Department of Obstetrics and Gynecology (The First Affiliated Hospital of University of Science and Technology of China, Hefei, China) has made great progress in ovarian carcinoma surgical procedures with the help of MDT members and ERAS protocols. To date, very few studies have focused on the complications of extraradical debulking surgery in patients with EOC (9,17-20). The present

study assessed and analyzed the risk factors of the complications of primary surgery (including 76 cases of extraradical cytoreduction) and their management in patients with EOC at the Department of Obstetrics and Gynecology.

Materials and methods

Patients. After obtaining approval from the Institutional Review Board of the First Affiliated Hospital of University of Science and Technology of China (approval no. 2021-KY120), the institutional database was retrospectively used to identify all patients with stage I-IV EOC and fallopian tube carcinoma who underwent primary cytoreduction at The First Affiliated Hospital of USTC between December 2017 and 2019. Patients who underwent primary surgery, regardless of whether optimal cytoreduction was attained, were eligible for inclusion into the present study. Individual records of all patients were reviewed, and demographic, clinical, surgical, pathological and follow-up data were extracted. Patients with non-epithelial carcinomas or borderline tumors, or those who received neoadjuvant chemotherapy, were excluded. All tumors were staged according to the Federation International of Gynecology and Obstetrics (FIGO) staging system (21). The body mass index (BMI) of the participants was measured to assess whether they were overweight or obese. BMI (kg/m^2) was calculated by dividing the body weight (kg) by the square of the height (m^2). A BMI of $<18.5 \text{ kg/m}^2$ was classified as underweight, $18.5\text{-}23.9 \text{ kg/m}^2$ as normal weight, $24.0\text{-}27.9 \text{ kg/m}^2$ as overweight and $\geq 28 \text{ kg/m}^2$ as obese (22). The patients' demographic and clinicopathological characteristics are presented in Table I.

EUAS included diaphragmatic peritoneal stripping and/or diaphragmatic resection, splenectomy, distal pancreatectomy, partial liver resection, cardiophrenic angle lymph node resection, portal lymph node resection, partial renal resection and cholecystectomy.

The patients were treated with neoadjuvant chemotherapy based on the adjusted inoperability criteria for primary debulking according to the European Society of Gynecological Oncology ovarian carcinoma surgery guidelines (23) as follows: i) ≥ 80 years of age; ii) stage IV carcinoma based on the findings of biopsy or cytological pathology of neck lymph nodes and pleural fluid; iii) American Society of Anesthesiologists (ASA) score of >4 ; and iv) diffuse deep infiltration of the root of the small bowel mesentery, diffuse carcinomatosis of the small bowel involving large parts such that resection would lead to short bowel syndrome (remaining bowel, $<1.5 \text{ m}$), or diffuse involvement/deep infiltration of the stomach or duodenum and head or middle part of the pancreas observed during laparotomy or laparoscopy. The evaluation was performed under the supervision of two gynecological oncologists and one surgical oncologist.

The ERAS protocol presented in Table II was used in the Department of Obstetrics and Gynecology (The First Affiliated Hospital of University of Science and Technology of China) according to the ERAS® Society recommendations for gynecological oncology surgery (24,25). The exclusion criteria were as follows: i) Metastatic disease; ii) simultaneous or metachronous multiple carcinomas with disease-free survival ≤ 5 years; iii) simultaneous surgery for other diseases; iv) emergency operation; v) neoadjuvant chemoradiotherapy;

Table I. Clinical characteristics of patients (n=161).

Variable	Value
Mean age \pm SD (range), years	54.23 \pm 9.70 (24-77)
Age, n (%)	
<50 years	47 (29.19)
50-59 years	69 (42.86)
60-69 years	33 (20.50)
70-79 years	12 (7.45)
Mean body mass index \pm SD (range), kg/m ²	22.90 \pm 2.85 (16.41-34.55)
Body mass index, n (%)	
<18.5	8 (4.97)
18.5-23.9	102 (63.35)
24-27.9	44 (27.33)
\geq 28	7 (4.35)
Comorbid illnesses, n (%)	52 (32.30)
Multiple comorbid illnesses, n (%)	18 (11.18)
Diabetes	4 (2.48)
Hypertension	18 (11.18)
Breast cancer	4 (2.48)
Other cancer	5 (3.11)
Other diseases	32 (19.88)
American Society of Anesthesiologists score, n (%)	
I	6 (3.73)
II	72 (44.72)
III	78 (48.45)
IV	5 (3.11)
Primary site of disease, n (%)	
Ovary	149 (92.55)
Fallopian tube	10 (6.21)
Ovary + fallopian tube	2 (1.24)
FIGO stage, n (%)	
I	24 (14.91)
II	14 (8.70)
III	91 (56.52)
IV	32 (19.88)
Histology, n (%)	
Serous	128 (79.50)
Low grade	4 (2.48)
Middle grade	0 (0.00)
High grade	121 (75.16)
NA	3 (1.86)
Mucinous	4 (2.48)
Endometrial	4 (2.48)
Low grade	0 (0.00)
Middle grade	1 (0.62)
High-middle grade	1 (0.62)
High grade	1 (0.62)
NA	1 (0.62)
Clear cell	12 (7.45)
Mixed	8 (4.97)
Other ^a	5 (3.11)
Mean preoperative serum CA125 \pm SD (range), units/ml	1,525.04 \pm 2,479.24 (9.50-18,848.00)

Table I. Continued.

Variable	Value
Preoperative serum CA125, n (%)	
<500 U/ml	76 (47.20)
500-1,000 U/ml	17 (10.56)
1,000-2,000 U/ml	30 (18.63)
≥2,000 U/ml	37 (22.98)
NA	1 (0.62)
Mean preoperative serum CA199 ± SD, U/ml	958.99±8,199.25 (0.60-96,649.00)
Preoperative serum CA199, n (%)	
Normal (<37 U/ml)	118 (73.29)
37-500 U/ml	38 (23.60)
≥500 U/ml	7 (4.35)
NA	8 (4.97)
Mean preoperative serum HE4 ± SD (range), pM	478.84±453.70 (4.00-2,148.00)
Preoperative serum HE4, n (%)	
<500 pM	102 (63.35)
500-1,000 pM	37 (22.98)
1,000-1,500 pM	12 (7.45)
≥1,500 pM	8 (4.97)
NA	2 (1.24)
Mean preoperative albumin ± SD (range), g/l	41.04±5.03 (24.90-51.20)
Preoperative albumin, n (%)	
<30 g/l	6 (3.73)
30-35 g/l	12 (7.45)
35-40 g/l	43 (26.71)
≥40 g/l	100 (62.11)
Mean postoperative albumin ± SD (range), g/l	29.58±5.85 (10.00-41.40)
Postoperative albumin, n (%)	
<25 g/l	29 (18.01)
25-30 g/l	42 (26.09)
30-35 g/l	67 (41.61)
≥35 g/l	23 (14.29)
Mean ascites ± SD (range), ml	1,521.38±1,825.15 (0.00-10,000.00)
Ascites, n (%)	
<500 ml	64 (39.75)
500-2,000 ml	40 (24.84)
2,000-5,000 ml	45 (27.95)
≥5,000 ml	12 (7.45)
Mean estimated blood loss ± SD (range), ml	1,224.10±1,286.39 (0-10,000)
Estimated blood loss, n (%)	
<500 ml	39 (24.22)
500-2,000 ml	91 (56.52)
2,000-5,000 ml	27 (16.77)
≥5,000 ml	4 (2.48)
Transfusion within 72 h of surgery, n (%)	111 (68.94)
Mean operative time ± SD (range), min	297.28±118.66 (48.00-680.00)
Operation type, n (%)	
Staging surgery	46 (28.57)
Standard cytoreduction	27 (16.77)
En bloc debulking	12 (7.45)
Extra-radical debulking	76 (47.20)

Table I. Continued.

Variable	Value
Residual disease, n (%)	
No gross residual	148 (91.93)
0.1-1.0 cm	9 (5.59)
>1 cm	4 (2.48)
Surgical complexity score, n (%)	
1-6	99 (61.49)
7-9	27 (16.77)
≥10	35 (21.74)
Mean intensive Care Unit stay after surgery ± SD (range), h	66.73±33.51 (24-144)
Intensive Care Unit use after surgery, n (%)	
Staging surgery	2 (1.24)
Standard cytoreduction	3 (1.86)
Radical cytoreduction	4 (2.48)
Extra-radical cytoreduction	17 (10.56)
Mean postoperative hospital stay ± SD (range), days	17.33±11.29 (6-89)
Postoperative hospital stays, n (%)	
0-14 days	85 (52.80)
15-28 days	58 (36.02)
≥29 days	17 (10.56)
Died before discharge	1 (0.62)
Mean interval of initial postoperative chemotherapy ± SD (range), days	16.22±10.09 (6-63)
Interval of initial postoperative chemotherapy, n (%)	
0-14 days	91 (56.52)
15-28 days	46 (28.57)
≥29 days	17 (10.56)
NA	7 (4.35)
Discharge status, n (%)	
Home	160 (99.38)
Died	1 (0.62)

*Carcinosarcoma (n=1), sarcomatoid carcinoma (n=1), small cell carcinoma (n=2) and high-middle grade adenocarcinoma (n=1). SD, standard deviation; NA, not available as chemotherapy was performed at a local hospital and the patient was lost to follow-up; CA125, cancer antigen 125; HE4, human epididymis protein 4; CA199, cancer antigen 199; FIGO, Federation International of Gynecology and Obstetrics.

vi) age ≥80 years; and vii) ASA score of 5. Preoperative counseling was recommended to the patients, as well as an opioid-sparing multimodal approach for pain management, goal-directed fluid management, and early mobilization and feeding. This required a multidisciplinary team effort and the patient complying with the whole process with the help of their family, nurses and doctors.

Surgical procedure. All patients were evaluated by the MDT using computed tomography (CT) before surgery, with staging surgery, standard cytoreduction (total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy), en bloc debulking and extraradical debulking, as previously described (20,26,27). En bloc debulking and extraradical debulking were performed by a gynecological oncologist, surgical oncologist or hepatopancreatobiliary/liver transplantation surgeon. Preoperatively, the

MDT discussed each case based on the CT scan and history, and prepared the surgical equipment and surgeons. Optimal cytoreduction was defined as the absence of a residual tumor nodule measuring >1 cm in maximal dimension at the end of the surgical procedure. The adjusted Aletti surgical complexity score (SCS) (20,28) was revised, and the USTC-SCS was used to evaluate the complexity of the surgical procedures (Table SI). Complications were graded on a 1-5-point scale according to the Clavien-Dindo classification of surgical complications (Table SII) (29). Grade 3-5 complications lead to invasive radiological intervention, reoperation, unplanned intensive care unit (ICU) admission, chronic disability or death. Perioperative complications were defined as complications occurring within 60 days after surgery. As the present analysis focused on the rate of complications after primary cytoreduction, a test was performed on potential variables that could be associated with preoperative and postoperative complications.

Table II. Overview of the enhanced recovery after surgery pathway utilized in this study.

Operative stage	Intervention	Comment
Preoperative	Nutrition evaluation with NRS 2002 and PG-SGA	NRS 2002 >5 and PG-SGA \geq 9 nutrition intervention for 1-2 weeks before operation
	Bowel prep	Select circumstances with oral antibiotics and mechanical prep
	Venous ultrasound to examine VTE for D-Dimer >3.5 μ g/ml	VTE, subcutaneous heparin; pulmonary embolus
	Respiratory training with a 'Triflow' breathing apparatus	Alternative devices with blowing a balloon every day 20 times
Intraoperative	Goal-directed fluid therapy, temperature control and VTE prophylaxis management	Injected into the fascial and subdermal layers at the end of the case (transversus abdominis plane blocks)
Postoperative	Early feeding without bowel surgical procedure	General diet immediately
	Early ambulation	Physical and occupational therapy services automatically consulted
	Early discontinuation of intravenous fluids	When patient tolerating >400 ml of postoperative fluid per shift
	Multimodal pain medication	Scheduled acetaminophen and NSAIDs
	Chinese traditional medicine wormwood patch or wormwood incense	No recommendation for patients who had a bowel anastomosis. Continued until first bowel movement or time of hospital discharge
	Minimum urine output tolerated 0.3-0.5 ml/kg/h	
	Respiratory training with a 'Triflow' breathing apparatus	Alternative devices with blowing a balloon every day 20 times

VTE, venous thromboembolism; NRS 2002, Nutrition Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment; PE, pulmonary embolism; NSAIDs, non-steroidal anti-inflammatory drugs.

The pelvic and abdominal peritonea with carcinoma were completely debulked when complete cytoreduction was deemed suitable. The procedure was revised following report by Soleymani *et al* (30). En bloc resection of the pelvis (EnBRP) was performed using the 10-step standardised technique described by Tozzi *et al* (27). A zero polydioxanone running suture was used to reconstruct the pleura and a patch (knitted type) was applied only when the diaphragmatic ends were under tension during suturing. To decrease the risk of pneumothorax, the anesthetist manually ventilated the patients, and a 10-Ch Foley catheter was placed in the pleura. The Valsalva manoeuvre, together with suction and catheter removal, was performed at the last stitch. Closed chest drainage was placed in the patients who underwent mesh repair. All patients underwent chest radiography to verify the absence of a pneumothorax after surgery with diaphragmatic resection. Drains were placed in all patients at the locations of diaphragmatic stripping or resection, splenectomy, pancreatic resection and bowel anastomosis.

Although there is no universally accepted grading system for bowel leakage, the definition proposed by Rahbari *et al* (31) is frequently used for rectal carcinoma and comprises a three-grade scale. Grade A requires no therapeutic intervention, grade B requires active intervention without laparotomy and grade C requires laparotomy (31,32).

The presence of a postoperative pancreatic fistula (POPF) was evaluated according to the International Study Group for

Pancreatic Surgery definition: A drain output of any measurable volume of fluid with an amylase level greater than three times the upper institutional normal serum amylase level associated with a clinically relevant development/condition directly related to the POPF. POPF was graded as follows: grade A, biochemical leak; grade B, postoperative pancreatic fistula requires a change in the postoperative management; drains are either left in place >3 weeks or repositioned through endoscopic or percutaneous procedures; grade C, postoperative pancreatic fistula refers to those postoperative pancreatic fistula that require reoperation or lead to single or multiple organ failure and/or mortality attributable to the pancreatic fistula. (33).

All patients received the ERAS protocol before surgery, according to the recommended guidelines (24,25,34,35). The main strategies were analgesia, early oral feeding, early ambulation, anesthesia management and goal-directed fluid therapy (Table II).

Statistical analysis. Statistical analysis was performed using SPSS v.20.0 (IBM Corp.). The mean \pm standard deviation, median (interquartile range), range and count (percentages) values were computed to describe the continuous and categorical variables, respectively. For the categorical variables, differences among the patients with complications were assessed using the χ^2 test or Fisher's exact test, as appropriate. For the continuous variables, differences were evaluated

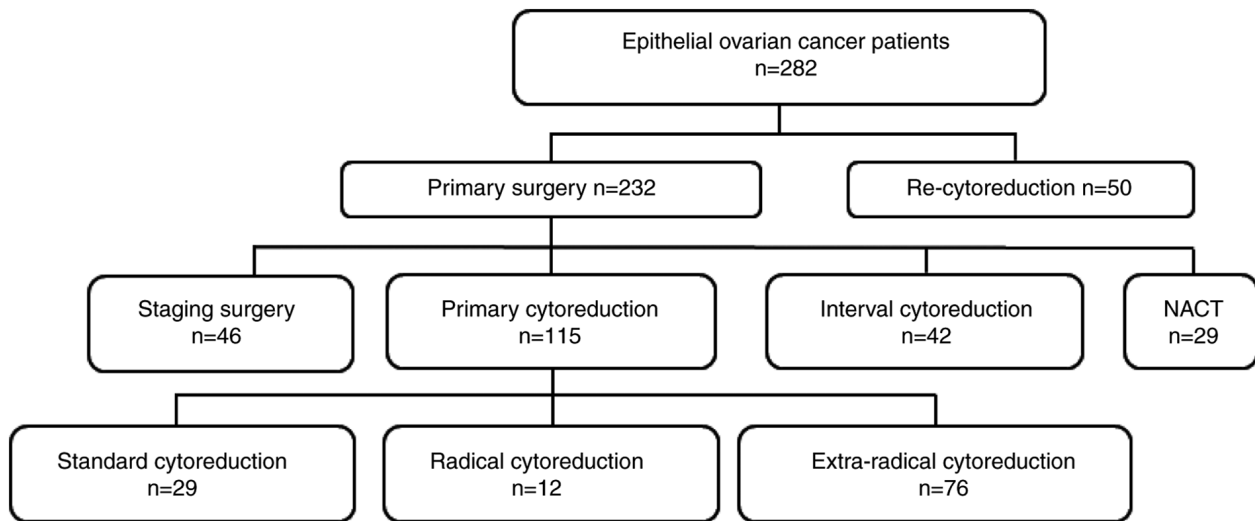


Figure 1. Therapeutic strategy of the patients with epithelial ovarian carcinoma hospitalized between December 2017 and December 2019. NACT, neoadjuvant chemotherapy.

using unpaired Student's t-test or the Mann-Whitney test, as appropriate. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the risk factors associated with the complications. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conventional univariate analysis or multivariate logistic regression analysis to determine the association between the different risk factors and occurrence of grade 3-5 complications. We also conducted a multivariate logistic regression analysis with bootstrapping using SPSS. Statistical significance was set at P-values of <0.05 and all P-values were two-sided. Bootstrapping with 5,000 permuted samples, including 161 patients, was performed.

Results

Characteristics of the patients with EOC according to primary surgery. Between December 2017 and 2019, 282 patients were hospitalised, including 50 patients who underwent recytoreduction owing to a relapse of EOC, 29 who underwent neoadjuvant chemotherapy after evaluation according to the inoperability criteria for primary debulking, 42 who underwent interval cytotoreduction, 46 who underwent primary staging surgery and 115 who underwent primary cytotoreduction (Fig. 1). The demographic and clinicopathological characteristics of 161 patients who underwent primary surgery are presented in Table I. A disseminated pelvic abscess was detected in 1 patient with ovarian carcinoma where the involved ureter was retained without resection in case of anastomosis failure. The other 3 patients in whom optimal debulking was not performed owing to enlarged mesenteric and celiac lymph nodes were technically unsuitable for removal surgery.

Postoperative complications of the patients with EOC according to the primary surgery. As shown in Table III, 33 patients (20.50%) had grade 1-2 complications, such as anemia and venous thrombosis, while 15 patients (9.32%) had grade 3-5 complications. A total of 39 patients had

postoperative complications, of which 24 patients had only grade 1-2 complications, 6 patients had only grade 3-5 complications and 9 patients had both grade 1-2 and grade 3-5 complications Table SIII. The distribution of numbers of complications for each patient is shown in Table SIV. A dehiscence non-infected wound was the most common grade 3-5 complication. A rectal fistula developed in 1 patient, most likely caused by the burning of tumors on the surface of the rectum and a stoma was created 1 week after cytotoreduction. Notably, this patient had a history of cervical squamous carcinoma that was successfully treated by radiotherapy 3 years previously with no recurrence.

Tables IV and SI show the extensive radical procedures that have been partly performed in the patients. Extensive radical cytotoreductions were performed in 76 patients. In total, 2 patients who underwent diaphragm surgical procedures developed pulmonary infection and were admitted to the ICU again, 1 patient died from septic shock due to multidrug resistant (MDR) *Klebsiella pneumoniae* infections, and 1 patient underwent a tracheotomy and recovered after respiratory rehabilitation every day for 18 days as instructed by respiratory therapists. Overall, 2 patients underwent complete diaphragmatic resection and repair, together with splenectomy, hysterectomy, oophorectomy, omentectomy, appendectomy and lymphadenectomy. The other most common surgical procedure was large bowel resection, which was performed in 45 patients (27.95%). Another 8 patients underwent a total colon resection; 2 patients who underwent total colon resection developed an anastomosis fistula identified on radiography and recovered after drainage and rinsing without laparotomy. A single patient who underwent partial rectal resection and colectomy developed a rectal fistula and was treated with stoma creation 1 week after cytotoreduction. Another patient developed a bladder fistula after partial bladder metastatic tumor resection and repair during surgery; bladder repair was performed after six cycles of chemotherapy and the patient then fully recovered. A further patient developed pancreatic leakage and gastric fistula, and fully recovered

Table III. Postoperative complications (n=39, 24.22%).

Complications	n (%)
Grade 1-2	33 (20.50)
Renal Insufficiency	1 (0.62)
Postoperative cognitive dysfunction	1 (0.62)
Atelectasis	2 (1.24)
Wound infection	1 (0.62)
Pulmonary infection	5 (3.11)
Abdominal/pelvic infection	7 (4.35)
Urinary system infection	1 (0.62)
Venous thrombosis	6 (3.73)
Pulmonary embolism	1 (0.62)
Primary intestinal obstruction	3 (1.86)
Anemia	15 (9.32)
Urinary incontinence	1 (0.62)
Arrhythmia	2 (1.24)
Septicemia	1 (0.62)
Biochemical pancreatic fistula	5 (3.11)
Bowel fistula	2 (1.24)
Grade 3-5	15 (9.32)
Closure of dehiscence non-infected wound under anesthesia	9 (5.59)
Pancreatic leakage requiring drainage	2 (1.24)
Gastric fistula requiring drainage	1 (0.62)
Rectum fistula requiring surgery	1 (0.62)
Bladder fistula	1 (0.62)
Respiratory failure	2 (1.24)
Cardiopulmonary failure	1 (0.62)
Septic shock	1 (0.62)
Death	1 (0.62)

following drainage treatment, rinsing and feeding through a gastrointestinal (GI) tube without laparotomy. The detailed data of the 15 patients with grade 3-5 complications are shown in Tables V and SIII.

Risk factor analysis for grade 3-5 complications. The potential risk factors significantly associated with the preoperative risk factors for grade 3-5 complications were first analysed. The variables analyzed are listed in Table V. The univariate analysis demonstrated that a CA125 level of $\geq 1,012$ U/ml ($P=0.001$), an HE4 level of ≥ 717 pM ($P<0.001$) and FIGO stage IV ($P<0.001$; compared with stage IIIC) were associated with grade 3-5 complications. The multivariate analysis revealed that an HE4 level of ≥ 717 pM ($P=0.015$) and FIGO stage IV ($P=0.004$; compared with stage IIIC) were associated with grade 3-5 complications. The bootstrap analysis revealed that a CA125 level of $\geq 1,012$ U/ml ($P=0.034$), an HE4 level of ≥ 717 pM ($P=0.007$) and FIGO stage IV ($P=0.002$, compared with stage IIIC) were significantly associated with grade 3-5 complications. There were no significant associations between age, BMI, ASA score, ascites ($\geq 2,000$ ml), comorbidities, multiple

Table IV. Extensive radical surgical procedures.

Procedure	n (%)
Diaphragm peritonectomy	32 (19.88)
Splenectomy	25 (15.53)
Full-thickness diaphragm resection	16 (9.94)
Partial hepatectomy	6 (3.73)
Distal pancreatectomy	3 (1.86)
Cholecystectomy	3 (1.86)
Cardiophrenic angle lymph nodes resection	2 (1.24)
Portal lymph node	5 (3.11)
Small bowel resection	2 (1.24)
Partial renal resection	1 (0.62)
Ureter resection and anastomosis	1 (0.62)
Total colon resection and anastomosis	8 (4.97)
Partial large bowel resection anastomosis ^a	34 (21.12)
Partial large bowel resection and stoma	11 (6.83)
Inguinal lymph node dissection	2 (1.24)
Part of bladder resection and repair	1 (0.62)

^aPartial large bowel resection included partial rectal resection and colectomy, with the exception of total colon resection.

comorbidities, preoperative hypoalbuminemia (<3.5 g/l) and grade 3-5 complications. The cut off values and ROC curves of the CA125 and HE4 levels related to grade 3-5 complications are presented in Fig. 2.

The potential factors that were significantly associated with the operative risk factors associated with grade 3-5 complications were then assessed. The variables analyzed are presented in Table VI. The univariate analysis demonstrated that an SCS score of ≥ 10 ($P=0.020$), postoperative hypoalbuminemia (<25 g/l) ($P=0.005$), operative blood loss of $\geq 1,100$ ml ($P=0.001$) and postoperative transfer to ICU ($P=0.003$) were associated with grade 3-5 complications. The multivariate analysis did not reveal any risk factors associated with grade 3-5 complications, while the bootstrap analysis revealed that transfer to the ICU after surgery ($P=0.026$) might be associated with such complications.

Length of hospital stay (LOS) and postoperative chemotherapy and prognosis. The mean LOS was 17.33 ± 11.29 days after completion of the initial postoperative chemotherapy, and the mean initial postoperative chemotherapy interval was 16.22 ± 10.09 days (range, 6-63 days).

The mean LOS was 11.29 ± 3.66 and 19.71 ± 12.35 days among the patients who underwent staging surgery and cytoreductive surgery after completion of the initial postoperative chemotherapy, respectively.

A single patient died on postoperative day 19 and did not undertake adjuvant chemotherapy, while another 154 patients (95.65%) underwent adjuvant chemotherapy with carboplatin or carboplatin and paclitaxel after surgery. A further 6 patients were discharged and went to a local hospital for adjuvant chemotherapy and were lost to follow-up. A total of 137 patients (85.09%) completed the initial chemotherapy

Table V. Univariate and multivariate analyses of preoperative risk factors associated with grade 3-5 postoperative complications.

Factor	Univariate analysis		Multivariate analysis		
	OR (95% CI)	P-value	OR (95% CI)	P-value	P-value (bootstrap)
Age, years					
<50	1	-	-	-	-
50-59	1.260 (0.394-4.028)	0.696	-	-	-
60-69	NA	0.071	-	-	-
70-79	0.700 (0.074-6.581)	1.000	-	-	-
BMI, kg/m ²					
<18.5	1	-	-	-	-
18.5-23.9	0.051 (0.055-4.762)	1.000	-	-	-
24-27.9	1.105 (0.115-10.648)	1.000	-	-	-
≥28	1.167 (0.059-22.937)	1.000	-	-	-
ASA (III + IV vs. I + II)	1.082 (0.373-3.135)	0.884	-	-	-
CA125 (≥1,012 U/ml)	6.691 (1.808-24.761)	0.001	3.866 (0.901-16.583)	0.069	0.034
HE4 (≥717 pM)	9.680 (3.045-30.775)	<0.001	4.923 (1.368-17.715)	0.015	0.007
FIGO stage (IV vs. IIIC)	9.446 (2.747-32.478)	<0.001	7.070 (1.888-26.477)	0.004	0.002
Ascites (≥2,000 ml)	2.240 (0.768-6.531)	0.132	-	-	-
Comorbidities	1.042 (0.337-3.216)	1.000	-	-	-
Multiple comorbidities	0.550 (0.068-4.453)	0.892	-	-	-
Preoperative ALB (<35 vs. ≥35 g/l)	1.926 (0.493-7.523)	0.586	-	-	-

Cut-off value of age (≥54.5 years old), CA125 (≥1,012 U/ml), HE4 (≥717 pM) and blood loss (≥1,100 ml) were calculated by ROC curves based on 5,000 bootstrap samples. NA, not available as chemotherapy was performed at a local hospital and the patient was lost to follow-up; CA125, cancer antigen 125; HE4, human epididymis protein 4; ASA, American Society of Anesthesiologists; ROC, receiver operating characteristic; OR, odds ratio; CI, confidence interval; ALB, albumin; FIGO, Federation International of Gynecology and Obstetrics; BMI, body mass index.

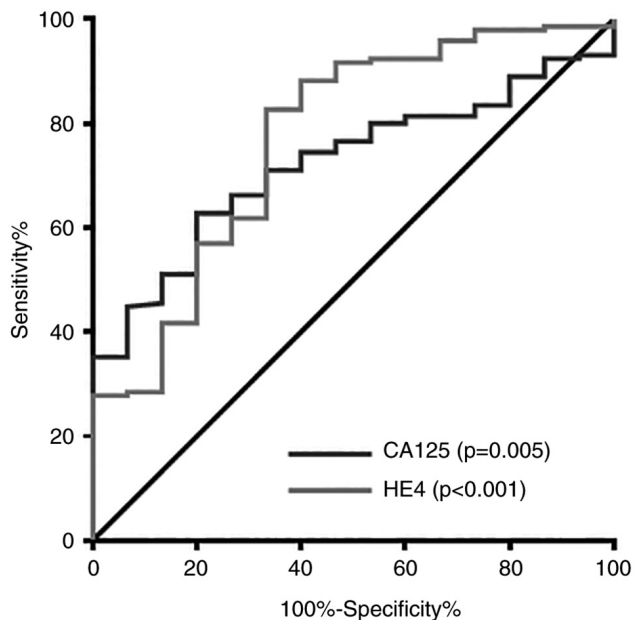


Figure 2. Receiver operating characteristic curves of CA125 and HE4 associated with grade 3-5 complications. CA125, cancer antigen 125; HE4, human epididymis protein 4.

within 4 weeks of surgery, 91 (56.52%) of whom completed the initial chemotherapy within 2 weeks of surgery. Overall,

15 patients did not complete the initial chemotherapy within 4 weeks of surgery for reasons such as closure of the dehiscient non-infected wound, intestinal obstruction, infection and pancreatic or bowel anastomotic leakage. A further 2 patients refused to receive adjuvant chemotherapy immediately after surgery but returned to the hospital to receive chemotherapy >4 weeks after surgery.

Discussion

The benefit of aggressive surgery increasing overall survival must be balanced against the substantial risk of perioperative severe complications. Nowadays, gynecological oncologists emphasize the risk factors associated with perioperative complications such as malnutrition, hypoalbuminemia, low transferrin levels, obesity, insulin resistance, high levels of C-reactive protein, interleukin-6 and increased platelet count (36-38). Moreover, a peritoneal cancer index ≥21 and preoperative albumin concentration ≤33 g/l were also independent predictors of high-grade complications (37,39). Although the ERAS protocol can enhance the rehabilitation of a patient, a recent study showed that 5.8% of 7,029 patients (76.5% from Caucasian ethnicity) in the national surgical quality improvement program database had experienced Clavien-Dindo IV complications, and that 0.9% of patients died within 30 days. This study also confirmed that increased age, emergency surgery, ascites, bleeding disorder, low albumin, higher ASA

Table VI. Univariate and multivariate analyses of the operative factors associated with grade 3-5 postoperative complications.

Factor	Univariate analysis		Multivariate analysis		
	OR (95% CI)	P-value	OR (95% CI)	P-value	P-value (bootstrap)
SCS scores					
1-6	1	-	1	-	-
7-9	2.350 (0.524-10.531)	0.484	-	-	-
≥10	4.700 (1.384-15.964)	0.020	2.526 (0.441-14.480)	0.298	0.352
Postoperative ALB, g/l					
≥30	1	-	1	-	-
25-30	2.263 (0.538-9.529)	0.455	-	-	-
<25	6.841 (1.837-25.473)	0.005	1.686 (0.287-9.907)	0.563	0.446
Estimated blood loss, ml					
<1,100	1	-	1	-	-
≥1,100	6.587 (1.987-21.836)	0.001	1.877 (0.308-11.434)	0.494	0.542
Operative time, min					
≤120	1	-	1	-	-
121-360	0.180 (0.017-1.923)	0.228	-	-	-
>360	1.200 (0.119-12.143)	1.000	-	-	-
ICU					
No	1	-	1	-	-
Yes	5.849 (1.902-17.981)	0.003	4.931 (0.805-30.205)	0.084	0.026

Cut-off value of age (≥54.5 years old), CA125 (≥1,012 U/ml), HE4 (≥717 pM) and blood loss (≥1,100 ml) were calculated by ROC curves based on 5,000 bootstrap samples. ROC, receiver operating characteristic; OR, odds ratio; CI, confidence interval; ALB, albumin; ICU, intensive care unit; SCS, surgical complexity score.

score and a higher extended procedure score are associated with serious perioperative morbidity or mortality (40). The diverse demographics and ethnicities in different countries also create a challenge for clinicians caring for the patients in the perioperative period.

In the present study, cases were not selected from patients with emergency surgery or those >80 years of age (referring to ERAS exclusion criteria), and only preoperative tumor loads, such as CA125 and HE4 levels, and FIGO stage IV were associated with grade 3-5 perioperative complications. The National Institute for Health and Care Excellence has reported that SCS can define a higher risk operation (20), while preoperative higher tumor loading can contribute to much more complex operations and elevated SCS scores. In the present postoperative complication results, it was found that SCS scores, postoperative ALB, blood loss and ICU transfer were associated with grade 3-5 perioperative complications in univariate analysis, but only ICU transfer was associated with complications in multivariate bootstrapping analysis.

A decreased serum ALB level of ≥10 g/l on postoperative day 1 has been reported to be associated with a three-fold increased risk of complications after abdominal surgery (36). In the present analysis, there was no significant relationship between grade 3-5 complications and the albumin level (Table I). Some centers have reported that a decreased preoperative serum albumin (≤35 g/l) level is associated with postoperative complications and OS in patients with EOC (41-44). Cham *et al* (40) also reported the use of preoperative serum

albumin levels in the validation of a risk calculator for adverse perioperative outcomes in women with ovarian carcinoma. In the present study, the patients with a preoperative albumin level of ≥35 g/l accounted for 88.82% of all patients, and there was no association between the preoperative serum albumin level (≤35 g/l) and grade 3-5 complications. Although a postoperative albumin level of ≤25 g/l was associated with grade 3-5 complications in the univariate analysis, there was no significant difference found in the multivariate and bootstrap analyses. Notably, the patients with ovarian carcinoma at the advanced stage were transfused with albumin 20-40 g during surgery and then 10-20 g every day after surgery until a serum albumin level of >30 g/l was achieved. Thus, although the albumin level may be related to the development of postoperative complications, it was assumed that this was prevented by albumin supplementation.

Cham *et al* (40) also used preoperative ascites for the validation of the risk calculator for adverse perioperative outcomes in women with ovarian carcinoma, and the calculator only used negative or positive ascites for scoring, without the exact quantity of ascites. A cohort study in the United States demonstrated that >2,000 ml of ascites was associated with worse PFS and OS, which might be associated with increased immunosuppression (45,46). Günakan *et al* (47) reported that >500 ml of ascites was associated with operative complications upon univariate analysis and that there was no significant difference found upon multivariate analysis. In the present study, 19.25% of the patients had >2,000 ml of ascites;

however, there was no association observed between ascites and complications.

In the present study, a total of 13 cases of grade 3 complications, 1 case of grade 4 complications and 1 case of grade 5 complications were found after primary surgery. The independent preoperative risk factors associated with grade 3-5 complications included the HE4 level and FIGO stage. It is worth noting that there was no comparison for the patients with ovarian cancer of stage I and stage III/IV in this study. Firstly, the patients at early stages achieved staging surgery, while the patients at advanced stages received complete cytoreduction. The different surgery strategies might not be suitable for making comparisons. Secondly, the patients at early stages exhibited a better performance status and nutrition status than those at advanced stages. Therefore, for the complication risk factors, the advanced stages between stage IIIc and stage IV were analyzed.

The CA125 level can also be considered a risk factor according to the bootstrap analysis. Although no independent risk factors associated with the postoperative complications were observed, transfer to the ICU after surgery could be regarded as a risk factor according to the bootstrap analysis. In the univariate analysis, an SCS score of ≥ 10 , a postoperative ALB level of < 25 g/l and an estimated blood loss amount of $\geq 1,100$ ml were also associated with grade 3-5 complications.

Patients with advanced ovarian carcinoma usually have metastases to multiple organs, such as the omentum, paracolic sulcus, diaphragm, liver surface and spleen. A discussion among MDTs should be conducted preoperatively to improve outcomes. The final decision regarding resectability and the goal of achieving < 0.5 mm of residual tumor tissue are based on exploration to offer the opportunity to investigate hidden spaces (e.g. posterior aspect of the spleen, lesser sac and posterior margin of the liver and diaphragm) (48-51). Postoperative management requires a large amount of clinical experience to ensure that patients safely overcome postoperative complications and begin adjuvant chemotherapy within 4 weeks of surgery (52-54). In the Department of Obstetrics and Gynecology (The First Affiliated Hospital of University of Science and Technology of China), 85.09% of the patients were treated with adjuvant chemotherapy within 4 weeks of surgery.

ERAS protocols have been used in gynecological oncology (24,25,55-57), GI surgery, hepatopancreatic surgery and transplantation, and have improved surgical outcomes and reduced hospitalisation times (35,58,59). Evaluation of postoperative complications and identification of risk factors could further improve the outcomes of patients with advanced ovarian carcinoma. In the Department of Obstetrics and Gynecology, ERAS protocols have been used for ~ 2 years. In China, patients do not have a family physician and the majority of the patients in the present study were from the countryside; thus, they were not discharged until they had completed chemotherapy following surgery.

Tozzi *et al* (27) reported that the mean LOS among patients who underwent EnBRP was 10.3 days (range, 6-91 days), while in the present study, the mean LOS was 17.33 ± 11.29 days (range, 6-89 days). The LOS was longer than that in other national centers despite the use of the ERAS protocol. The government is attempting to use daytime wards to resolve such

problems and discharge patients without bowel procedures or other complications on day 4 after surgery. With the help of GI, hepatopancreatic and transplantation surgeries, EUAS was performed and the adjusted SCS scores were revised (20) by naming them USTC-SCS scores, as shown in Table SI. Preoperative and postoperative respiratory training with a 'Triflow' breathing apparatus was recommended for patients with metastases involving the diaphragm as demonstrated on CT scans. This ERAS strategy was particularly used for EUAS to prevent pulmonary infections.

Using ERAS protocols in gynecological surgery has the following advantages: Reduced opioid use, enhanced patient satisfaction, reduced LOS and complications, improved cost effectiveness and decreased readmission rates. However, patients with EOC are distinctly different from those with gynecological carcinoma and other surgical patients. At the time of diagnosis, patients often have an advanced stage with a high symptom burden, including abdominal distension, dyspnea, nausea, GI dysfunction, anemia, cachexia and malnutrition. Further, surgical procedures often include multivisceral resection with a high postoperative morbidity rate (60-64). Thus, ERAS protocols can be used in patients with EOC to help prevent complications, hasten recover, initiate adjuvant chemotherapy on schedule and achieve better patient satisfaction scores. However, the ERAS protocol standard cannot be evaluated using the LOS as a single criterion in patients with EOC.

The problems with ERAS protocols that have not been resolved in China and have resulted in a longer LOS compared with that in other countries are as follows: i) The ideas among medical staff and patients are profoundly traditional; ii) medical administrations do not consider the application of ERAS protocols as the *status quo* in the hospital, including every involved department; iii) the medical treatment costs are very low in China; iv) patients from the countryside would prefer not to travel home after surgery and then return for chemotherapy a few days later; v) the ward beds are cheaper than stays in a hotel and safer for the observation of their conditions until the completion of the initial chemotherapy; vi) patients do not have family physicians in China and if they go home, local hospitals would deny their admission in the presence of any complications; and vii) insurance companies only pay for hospitalisation but not for the costs related to regular visits in clinic.

Although no guidelines on the optimal interval between debulking surgery and the initiation of adjuvant chemotherapy are available, it is recommended that adjuvant chemotherapy be initiated as soon as possible, as this treatment may avoid early tumor growth within the interval. Recent reports showed that delayed initiation of adjuvant chemotherapy was an independent prognostic factor for worse OS after surgery and concluded that a time-to-chemotherapy (TTC) delayed beyond 4 weeks should be avoided (53,65). With the ERAS programme for surgery, the patients in the present study recovered rapidly; 137 patients (85.09%) completed the initial chemotherapy within 4 weeks of surgery, with a mean TTC of 16.22 ± 10.09 days (range, 6-63 days).

Recent studies have shown that 40% of patients diagnosed with ovarian carcinoma have diaphragmatic metastases, with the right diaphragm as the most common metastatic

site (63.3-80%) and with fewer cases involving both sides (5-36%) or the left side only (0.7-15%) (66,67). Intraoperative diaphragmatic evaluation has been suggested for all patients undergoing cytoreductive surgery for advanced ovarian carcinoma (30,66). In the present study, 40.99% (66/161) of the patients were diagnosed with diaphragmatic metastases, including 2 cases of metastases (1.24%) on the left side, 32 cases (19.88%) on the right side and 32 cases (19.88%) on both sides. Among the affected patients, 16 underwent full-thickness diaphragmatic resection and repair, and 5 underwent complete diaphragmatic resection and reconstruction of the diaphragm via patch application (Table SV). The decision to perform full-thickness resection of the diaphragm was based on tumor infiltration of the muscle. For patients undergoing diaphragmatic repair, who would be more likely to develop pleural effusion within 3 days of surgery, closed chest drainage tubes should be placed with continuous low suction (18,67). It is recommended that closed thoracic drainage should be performed routinely after surgery and that chest radiography or CT should be performed 3 days after surgery to assess the condition of the peritoneal effusion and pulmonary atelectasis, and particularly to check for infections. Once infection symptoms appear with closed thoracic drainage, pleural fluid culture and drug sensitivity testing should be performed in a timely manner, as well as bronchioalveolar lavage as part of the ERAS protocol. When tumors from the right diaphragm and spleen have to be removed, attention should be paid to drainage and infection prevention in both abdominal cavities. If both sides of the diaphragmatic abscess develop and patients cannot breathe normally, they should be sent to the ICU. Notably, 4% of patients admitted to the ICU are found to be colonised or infected with strains of *K. pneumoniae* with multi-resistance to ceftazidime, ciprofloxacin and tobramycin (68). Infections with MDR strains are common in patients with chronic diseases, advanced tumor stages, exposure to chemotherapy or immunosuppression. Early identification of *K. pneumoniae* with multi-resistance in pulmonary infections is critical for patients after diaphragmatic resection, which is the main cause of postoperative death.

In the present study, 8 patients (4.97%) underwent a total colectomy. One of the side effects of a total colectomy is the lack of adequate stool concentration and frequent postoperative stool passage (69). To improve the passage frequency, loperamide hydrochloride capsules with a maximum daily dose of 12 mg as permanent medication were administered in the present study. Patients could take this drug after defecation, with an initial dose of 2 mg/day to relieve the symptoms of watery diarrhoea; iron and multivitamins should also be taken to alleviate anemia due to absorption dysfunction (70). The C-reactive protein level after anastomosis should also be routinely assessed to monitor early fistula formation or pelvic infection, in which case the level will increase when an intestinal fistula occurs (71). Type A and B bowel fistulas can resolve through continuous rinsing through a drainage tube and anti-infective treatment (32). Few centers have performed total colon resection, particularly deep anterior resection with ileorectostomies. Son *et al* (72) reported that the risk of anastomotic leakage was highest in patients who underwent a subtotal colectomy.

Although adjuvant chemotherapy can cause dehiscence wounds (73), only 9/161 patients (5.59%) developed dehiscence wounds and underwent retention suturing under general anesthesia in the present study. The literature recommends the use of a retention suture for patients with a high risk of intra-abdominal hypertension to ensure the initiation of adjuvant chemotherapy within 4 weeks of surgery, which may increase bladder pressure and postoperative pain. Delayed wound healing is typical in patients with advanced oncological diseases or immunosuppression or in those receiving chemotherapy (74). Thus, careful wound monitoring and cummerbund use for 3 months postoperatively are recommended.

Patients with ovarian carcinoma are distinctly different from other gynecological surgical patients. Although ERAS has been used for colorectal malignancies and other surgical tumors, only a few relevant published studies are available on the ERAS protocols due to the heterogeneity of ovarian cancer (75-80). At the time of diagnosis, the patients often have an advanced stage disease with complex symptoms, including abdominal distension, dyspnea, impairment of gastrointestinal function and malnutrition, which require aggressive cytoreductive procedures such as multivisceral resections; patients also are prone to a high risk of postoperative morbidity. Thus, the ERAS protocols achieved from other surgical disciplines may be inappropriate to directly apply to patients with ovarian malignancies (81,82). The main dilemmas encountered in the present study were the strong beliefs in traditional surgical paradigms held by the gynecological surgeons and how to manage the extensive surgical procedures with the ERAS protocol. Pain management and goal-directed fluid management were the most important ERAS protocols. Firstly, pain management is an important part of ERAS, especially for the long incisions for the ovarian cytoreduction; freedom from pain can facilitate the early mobility of the patient and an early return of bowel function. Secondly, goal-directed fluid management also plays an important role in the anesthetization process during perioperative fluid management (81,83). Appropriate volume status assessment can decrease postoperative morbidities such as pulmonary and intestinal edema. Table II shows other ERAS protocols used in the present study. It may be difficult to perform randomized controlled trials to make comparisons between the patients with and without ERAS in individuals with ovarian cancer. Firstly, the patients have heterogeneity in tumor burden and nutrition status. Secondly, it may not be ethically feasible to try randomized trials of ERAS protocols given the positive evidence for ERAS elements reported to date. Thirdly, the unproportionate medical insurance and government management may challenge the multicenter and international approach to perform a clinical trial. Efforts should be undertaken to facilitate the work of those institutions willing to revise their perioperative protocols, and cooperative trial groups could be an appropriate platform to establish precise evaluations with regard to the implantation of ERAS protocols in the treatment of patients with ovarian cancer.

In summary, the present study demonstrated that extracardiac debulking is feasible, with a low mortality rate (1/76, 1.3%) during hospitalisation, even among patients with an advanced ASA score (≤ 4). ERAS protocols are useful and support the early initiation of chemotherapy. Wound healing

requires careful supervision and management until adjuvant chemotherapy is completed. Extraradical debulking in combination with ERAS protocols and the early initiation of chemotherapy is feasible and should be performed in select patient populations.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Authors' contributions

ML, TZ, JZ, YL, WC, YX, WZ, RC, WW, GW, JQ, WZ, DW, BN, ZS, YZ were responsible for the conception and design of the study, and critical revisions of the manuscript. YZ and BN drafted the manuscript. ML, TZ, JZ, YL, YX, WZ, RC, WW, GW, JQ, ZS and YZ acquired, analysed and interpreted the data. ML, TZ, JZ, YX, WZ, JQ, RC, WW, GW, WZ, DW, BN, ZS and YZ performed the statistical analysis. BN and YZ confirm the authenticity of all the raw data. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The First Affiliated Hospital of University of Science and Technology of China (approval no. 2021-KY120).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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