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RESEARCH ARTICLE

The effect of enhanced recovery program for patients undergoing partial laparoscopic hepatectomy of liver cancer

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Abstract
Objective To analyze the results after the introduction of enhanced recovery after surgery (ERAS) protocols, a randomized study was performed to compare the outcomes of laparoscopic hepatectomy under ERAS or traditional care.
Methods Patients undergoing laparoscopic hepatectomy from April 2014 to October 2014 were included and randomly divided into Control group (CG) and ERAS. Primary outcome was quality of life (QoL) and length of hospital stay (LOS). Secondary endpoints were percentage readmission, mortality, duration to first flatus, complications, hospital costs, conversions and blood loss.
Results Thirteen patients withdrew after randomization. Eighty-six patients completed the study, 48 ERAS and 38 CG. Postoperative LOS was significantly reduced in ERAS [6 (4–8) versus 10 (7–15) days, $P = 0.04$]. First flatus occurred earlier in ERAS than CG [2(1–4) versus 3(2–5) days, $P = 0.02$]. The average perioperative charges were 9470 ± 1540 in CG and only 7742 ± 1200 in ERAS ($P = 0.03$), with no differences in readmission rate, blood loss, conversions to open surgery, mortality or surgical complications. The median AUC (area under a curve) of QoL was considerably improved in ERAS ($P = 0.04$).
Conclusions This study suggests that ERAS is feasible and safe for laparoscopic hepatectomy.

Keywords Enhanced recovery after surgery (ERAS) · Laparoscopy · Hepatectomy · Quality of life

Introduction

The concept of enhanced recovery after surgery (ERAS) has been widely used in surgical perioperative period in recent years. ERAS was first introduced by the Kehlet [1] and then developed rapidly in European and American countries. ERAS refers to the application of various effective methods as to reduce surgical stress and complication during preoperative, intraoperative and postoperative periods [2, 3]. It generally includes preoperative education, improved anesthesia and analgesia methods, and postoperative rehabilitation (early oral intake and deambulation). ERAS can alleviate the physiological and psychological trauma of patients, thus reducing stress response and complications during perioperative period. Meanwhile, ERAS can promote intestine functional recovery, shorten the length of hospital stay (LOS), reduce hospital cost and protein loss, maintain water balance, and improve satisfaction during perioperative period [4]. Accumulating studies have demonstrated that ERAS is beneficial in colorectal, urologic and gastric surgeries [5–7]. But so far there is limited report regarding the application of ERAS in hepatectomy, either open or laparoscopic.

Laparoscopic liver resection was first introduced in 1990s [8]. Over the past decade, minimally invasive surgery

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technology has developed rapidly and has replaced the traditional operation in multi-domain [9]. Accompanied with the innovation and application of artificial cavity, stereo laparoscope, incision hemostasis devices, intraoperative ultrasound instrument and other new auxiliary equipment, the range of laparoscopic operation has expanded from laparoscopic fenestration for liver cysts, laparoscopic biopsies to wedge resections [10, 11]. Moreover, the miniaturization of cavity mirrors and robotechnology greatly contributed to the rehabilitation of the patients.

Ever since Reich first performed laparoscopic hepatectomy for benign liver cancer in 1991, laparoscopic hepatectomy is still a difficult surgery with high risks nowadays, due to the uncontrolled bleeding, air embolism and the potential for malignant planting. Recently, there are retrospective case reviews indicating that laparoscopic hepatectomy is safe for both malignant and benign liver lesions [12, 13]. The safety and feasibility of laparoscopy for minor liver resections has been previously demonstrated. Several cohort studies have suggested that laparoscopic left lateral sectionectomy should be accepted as standard of care. Hepatic major resections whether open or laparoscopic can be technically challenging and potentially morbid. Bleeding remains the greatest concern, and is the most common reason for conversion. The more common source of bleeding is parenchymal transection. To date, major anatomic liver resections are increasingly reported by several centers worldwide [14].

However, data on the implementation of ERAS in liver surgery are sparse [15–17]. The added value of an ERAS program in laparoscopic liver surgery has not been explored. Here, the outcomes of laparoscopic liver resection after the implantation of an ERAS program in a randomized study were reported.

Methods

Participants and recruitment

Patients undergoing laparoscopic liver resections between April 2014 and October 2014 were enrolled and divided into two groups: Control group (CG) with standard perioperative cares and ERAS with enhanced recovery after surgery at the Sun Yat-sen University Cancer Center. Randomization was done by a nurse who was not involved in this study. The randomization sequence of group allocation was generated by an independent statistician from Sun Yat-sen University. The patients were assigned either to the ERAS group or to the CG group. The medical team (doctors, nurses) and patients and their families are not implemented blinding, but data collection and collation were implemented blinding.

The ERAS program was introduced by a multidisciplinary team to all the patients. All lesions <10 cm and benign and malignant liver lesions suitable for laparoscopy were included. Exclusion criteria: infection, long-term blood dissemination, surface lymph node metastasis, serious cardio-cerebrovascular disease or other important organ function disorder. The surgery was performed by the same liver surgeons in both groups. The study was approved by the research ethics committee of the Sun Yat-sen University Cancer Center and consent was obtained from the patients. The research conforms to the provisions of the Declaration of Helsinki in 1995.

Laparoscopic surgery

Patients received antibiotics and antithrombotic prophylaxis before surgery. All patients had the same standardized anesthesia. Patients were maintained at French position, 30° slope according to different pathological site. The CO_2 pneumoperitoneum pressure was 13 mmHg. Trocar inserting location depended on the size and the location of the lesions, similar with the laparoscopic cholecystectomy method. If the lesions were located in the left side of the liver, the main hole under xiphoid should be moved to the frame edge of left midclavicular. Trocar was inserted into the laparoscope to observe the size and location of space-occupying lesion. Afterwards, ultrasound knife was used to isolate ligaments around liver. Titanium clip was usually used to shut and block the blood flow. For partial hepatectomy, titanium clips were removed after hemostasis, and the left hepatic blood flow was restored. For the right partial hepatectomy, the liver was pretreated with microwave coagulation or electric coagulation rods, and then subjected to ultrasonic knife [18].

Malignant liver tumor resection was carried out 1.5–2 cm away from the tumor margin. Hemostatic gauze can be pasted on the surface of the wound. Peritoneal cavity drainage tube was indwelled. The resected specimen was placed into the collection bag, which was taken out by expanding the umbilical incision.

Clinical pathway

Patients in control group underwent routine nursing, such as fasting for 12 h, and 4 h drinking forbidden before surgery. Nurses should be familiar with the medical records of patient, and should carry on the routine preoperative education and conventional psychological education to patients. Laxatives (polyethylene glycol electrolyte powder) were orally taken 1 day before the surgery. Nurses should observe wound within 1–2 days post operation to find whether the pipeline is blocked. Nurses should pay attention to the drainage liquid, the analgesic effect and

complications and assist patients to turn over, expectoration and observe gastrointestinal function recovery. If gastrointestinal tract restores peristalsis, anus exhaust and defecation without abdominal pain or abdominal distension, patients can be advanced to feed liquid food, then gradually to ordinary food.

Patients in ERAS group underwent conventional perioperative care combined with enhanced rehabilitation nursing. The ERAS clinical pathway was implemented for the patients at the time a decision was made for surgery, including pre-surgery education (details about rehabilitation time of each stage, suggestions to promote rehabilitation, suggestions about early oral feeding and out-of-bed), preoperative preparation (reducing the fasting time from conventional 12–2 h, preoperative oral glucose administration, antibiotic prophylaxis, nausea and vomiting prophylaxis, and prevention of hypothermia) and postoperative rehabilitation programs (early oral intake and deambulation without using laxatives, control of infusion volume, enteroplegia) to promote the recovery of intestinal function. Gastric tube or drainage tube will not be routinely indwelled in surgeries. Whether the peritoneal cavity drainage tube should be indwelled or not depends on the hemorrhage and hemostasis status. Urine catheter will be indwelled in both groups. Urine catheter was removed at the first day postoperation in ERAS group, while urine catheter was removed at 2 or 3 days postoperation in the control group. Fluid infusion should be restricted to <2500 mL/day. Water intake began at 4 h after surgery and liquid diet restored 12 h after surgery. Patients were encouraged to do ambulation and stretch gradually (1 day postoperation), so as to avoid deep venous thrombosis. Patients can discharge from hospital when they reach certain criteria, as assessed by a nurse who was blinded to the group allocation. The standards were: normal body temperature, tolerance of food, no incision infection, independent mobility, pain relieved by oral analgesia, and willingness to be discharged [19].

Outcome measures

Primary outcome was quality of life (QoL) and length of hospital stay (LOS). LOS was defined from day of surgery to day of discharge. A satisfaction questionnaire was filled out by patients after discharge. Secondary endpoints were percentage readmission, mortality, functional recovery, complications, hospital costs, conversions and blood loss. To monitor QOL in patients, the Chinese version of the EuroQol five-dimension (EQ-5D) test will be applied, indexed by visual analog scale (VAS). QOL assessment will be carried out at 2, 4, 6, 8, 10, 20, 30, 40 days after surgery [20].

Statistical analysis

The outcomes were evaluated, and patients who received ERAS and those who received common care were compared. The values are expressed as the mean ± SD or median (interquartile range). Comparison of categorical variables was performed using the Chi-square test or the Fisher exact test, as appropriate. The median and ranges of continuous parameters were compared using the Mann–Whitney *U* test. Repeated measures of ANOVA were applied to test within-subjects effects and between-subject effects of QoL. Analysis was performed using SPSS 16.0. *P* values less than 0.05 were considered statistically significant.

Results

Thirteen patients withdrew after randomization due to changes of their original cancer staging. Eighty-six patients completed the study, 48 ERAS and 38 CG (Fig. 1). Compared with two groups of clinical data, there is no statistical significance in sex, age and ASA score (Table 1). In the ERAS group, early oral intake and mobilization were introduced the same evening of surgery (6–8 h). Postoperative hospitalization days range from 2 to 10 days, with a median of 6 days. In ERAS group, postoperative LOS was significantly reduced than CG [6 (4–8) versus 10 (7–15) days, $P = 0.04$]. As described in Table 2, significant changes were observed in QoL scores for ERAS group over time. There was a main effect of time ($F = 123.46$, $P = 0.03$) and a significant group-by-time interaction ($F = 8.13$, $P = 0.02$). In both groups, the QoL measures after surgery showed an initial decrement from baseline (Fig. 2). QoL over the first month after surgery was considerably improved in the ERAS group. The median AUC (area under a curve) was higher in the ERAS group than CG (36.9 versus 35.2, $P = 0.04$).

Anal exhaust is earlier than CG [2 (1–4) versus 3 (2–5) days, $P = 0.02$]. There was only one case of readmission in both groups (1 versus 1, $P = 1.0$), due to a urinary tract infection in the CG and postoperative bile leakage in the ERAS. There was no statistical significance between blood loss, conversions, mortality and surgical complications, as shown in Table 3. The average perioperative hospital costs were 9470 ± 1540 in the control group and only 7742 ± 1200 in the ERAS group ($P = 0.03$). In the ERAS group, neither epidural pumps nor opioids during postoperative time were indicated. Conversion to open surgery was similar in both groups (4.2 versus 7.9 %, $P = 0.79$), caused principally by difficulty in hemorrhage control of portal pedicles.

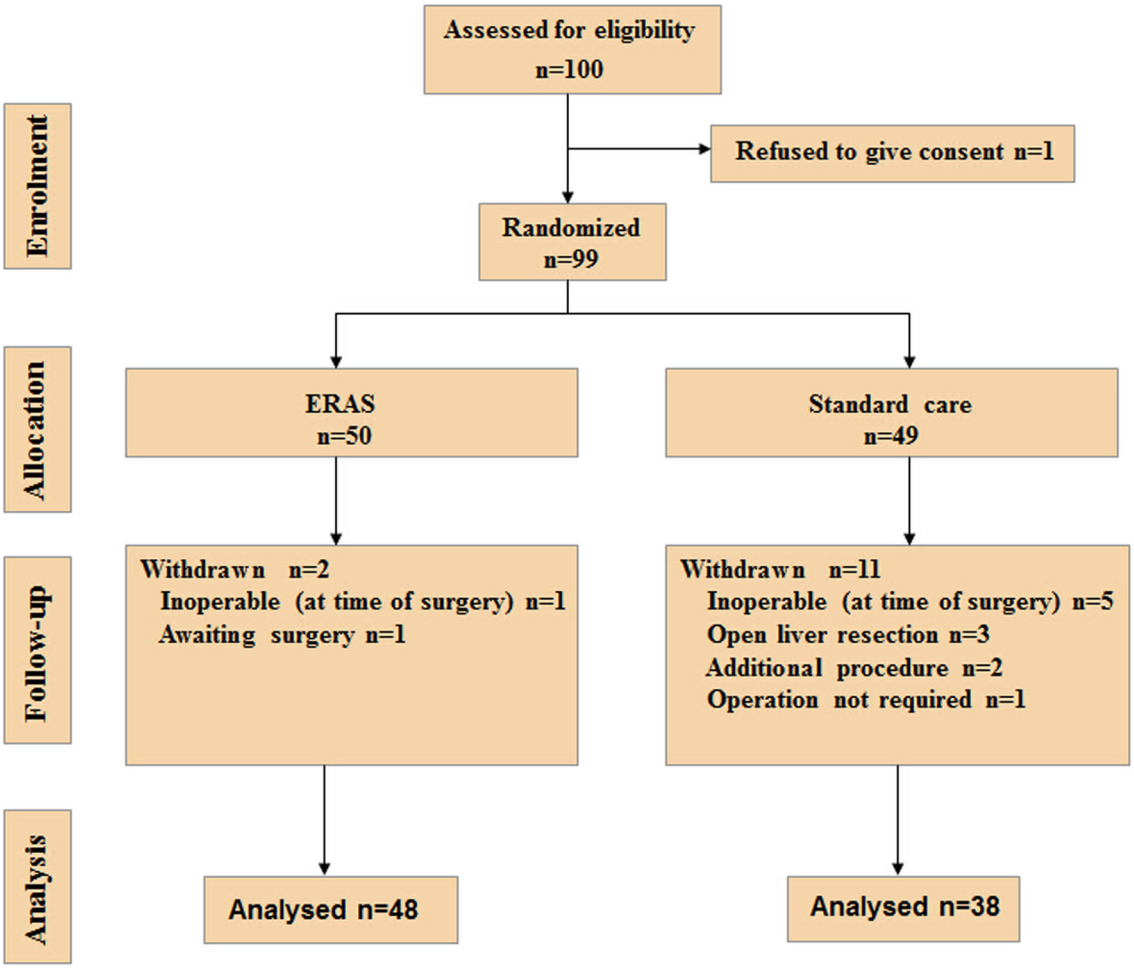

Fig. 1 CONSORT diagram for the trial

Table 1 Clinicopathological characteristics of the patients

Parameter	ERAS program ($N = 48$)	Traditional care ($N = 38$)	P value
Male:female ratio	22:26	18:20	NS
Age (years)[a]	56.3 ± 16.3	60.4 ± 20.7	NS
ASA score I/II/III	10/26/2	12/24/2	NS
Diagnosis			NS
Colorectal Mets	20	16	
HCC	11	8	
Benign	17	14	
Laparoscopic resection			
Bisegmentectomy or left lateral sectionectomy	43	36	NS
Segmentectomy or wedge resection	5	2	NS
Tumor size (cm)[a]	4.4 ± 3.9	5.9 ± 4.5	NS

NS not significant

[a] Mean ± SD

In ERAS group, no anastomotic leakage, bleeding, lung infection occurred. Four patients have mild abdominal distension and nausea after eating, and the symptoms were relieved after taking gastrointestinal medicine. One case had postoperative bile leakage and was cured by adequate drainage for 2 weeks. The abscess was cured by puncture

drainage. One patient had constipation and remained in hospital longer. In the traditional care group, one patient had a urinary tract infection, which was treated by antibiotics, and another with diabetes mellitus appeared to have liver infection 1 month after discharge from hospital. Two patients with cirrhosis appeared to have postoperative ascites, which was cured by diuresis. One patient was treated for a hypokalemia and another for atrial fibrillation. All cases underwent intraoperative and postoperative pathological diagnosis. At the writing of this article (December 2014), there were 1 case of planting metastasis on the right side of Trocar puncture hole 5 months after laparoscopic resection of liver cancer and three cases of intrahepatic metastasis. There were 17 enhanced recovery elements used in this program. For each of these elements, there was a high compliance rate (Table 4).

Nutritional status and preoperative electrolyte level were monitored in the two groups. In ERAS group, 8 cases are low in potassium or sodium levels after surgery, while in control group, 17 cases are low in sodium or potassium levels ($P = 0.004$). There was no statistically significant difference between body mass and serum transferrin levels ($P = 0.85$).

Table 2 Repeated measures data of ANOVA: QOL assessment at 2, 4, 6, 8, 10, 20, 30, 40 days after surgery

Outcome	Effect					
	Group		Time		Group × time	
	F	*P*	*F*	*P*	*F*	*P*
QOL	79.39	0.04	123.46	0.03	8.13	0.02

QOL quality of life

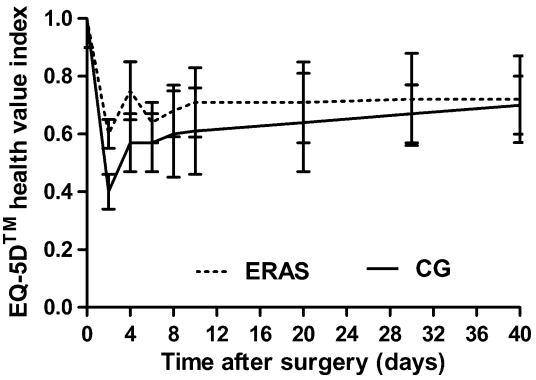

Fig. 2 Comparison of median health value index scores between patients in ERAS group or in control group. *Error bars* 95 % confidence intervals

Discussion

Recently, fast-track surgery has been widely used in postoperative period after surgical treatment. It is characteristic of reducing physiological and psychological trauma as well as patient's stress response and complications during

Table 3 Surgical results

	ERAS program ($N = 48$)	Traditional care ($N = 38$)	*P* value
Operating time (min)[b]	181 (130)	178 (134)	0.87
Conversion	2 (4.2 %)	3 (7.9 %)	0.79
Blood loss (mL)[a]	350 ± 170	338 ± 190	0.34
Hospital costs[a]	7742 ± 1200	9470 ± 1540	0.03
Patients transfused	9 (18.8 %)	11 (29.0 %)	0.27
Duration to first flatus (days)[b]	2 (1–4)	3 (2–5)	0.02
Postoperative LOS (days)[b]	6 (4–8)	10 (7–15)	0.04
Complications	7 (14.6 %)	6 (15.8 %)	0.88
Grade I	4	2	
Grade II	1	2	
Grade III[a]	1	1	
Grade III [b]	1	1	
Grade IV[a]	0	0	
Grade IV[b]	0	0	
Grade V	0	0	
Readmissions	1 (2.1 %)	1 (2.6 %)	1.0
Electrolyte imbalance	8 (16.7 %)	17 (44.7 %)	0.004
Mortality	0	0	N/A

[a] Mean ± SD

[b] Median (interquartile range)

Table 4 Compliance with ERAS core elements

	No. who followed element
Preoperative	
Preoperative education + counseling	48
Minimal preoperative fasting	48
Avoid laxatives	48
Perioperative	
Prevention of hypothermia	48
No routine drainage of the peritoneal cavity	48
No standard nasogastric drainage	48
Start intake of water/free fluids	48
Early mobilization	48
Antibiotic prophylaxis	48
Nausea and vomiting prophylaxis	48
Urinary catheter: 1 days only	38
Postoperative days 1–3	
Daily review of discharge criteria	48
Intravenous fluids discontinued POD 2	44
Analgesia—thoracic epidural	46
Nutritional care (supplements)	48
Glucose control	48
Mobilization (twice daily)	48

POD postoperative day

postoperative period. Meanwhile, it can shorten the recovery time. Anxiety, fear, hunger, anesthesia, and pain can all stimulate stress response, thus aggravating the risk of complications and the economic burden on the family [21]. Therefore, it is necessary to reduce the stress reaction during the perioperative period, especially for patients with liver cancer, whose physiological functions have endured damage to different degrees.

In the Louisville consensus meeting on laparoscopic liver surgery, it was stated that laparoscopy should be standard practice in experienced hands [22]. Currently, laparoscopy in colorectal cancer has been widely used. It has many advantages, such as slightly interfering with the body immune systems, small surgical trauma, short hospital stay and fewer complications [23]. It is consistent with the aim of ERAS. Herein, laparoscopic hepatectomy was combined with ERAS to verify whether this program could obtain a better curative effect or not.

According to a series of evidence-based medical evidences, accelerated rehabilitation protocols could reduce patients' physical and psychological trauma [24, 25]. In this study, ERAS program consistently obtained similar effect for patients undergoing laparoscopic hepatectomy. Before starting the ERAS program, patients and their relatives were informed of background knowledge involved. Specifically, it should be emphasized that LOS can be shortened and the recovery can be accelerated, to alleviate the tension and anxiety of patients.

Research shows that 2-h fasting before surgery is essential to avoid aspiration pneumonia, which can be caused by inhaling gastric contents during anesthesia [26–28]. If preoperative fasting time is too long, the feeling for polydipsia, anxiety and dehydration can be amplified, as well as preoperative stress reaction, thus directly affecting the safety of anesthesia. Administration of glucose at 2 h before operation can significantly reduce the sense of hunger and thirsty and insulin resistance so as to improve the comfort, the safety and the tolerance during the perioperative period [29, 30]. Moreover, the early postoperative recovery of gastrointestinal function could also alleviate the damage in intestinal mucosal induced by fasting [31]. No gastric tube indwelling, no enema, no powerful laxatives, and early removal of urethral catheter (1 day postoperation) contributed to the satisfaction of ERAS program.

Postoperative long-term bedding will decrease muscle strength, damage lung function and antioxidative capacity, aggravate venous stasis and thrombosis. Based on the minimally invasive characteristics of laparoscopic surgery, early ambulation can be achieved. However, early enteral nutrition has not been widespread, especially in primary hospitals. Early feeding could promote intestinal peristalsis, maintain the function of intestinal mucosa, stimulate the portal circulation and the vagus nerve excitement, and avoid the alteration of intestinal flora. A meta-analysis showed that the early recovery of oral diet could reduce infection after abdominal operation, shorten the time of hospitalization and reduce the incidence of anastomotic leakage. In ERAS group, there were 8 cases low in potassium or sodium levels after surgery, while there were 17 cases low in electrolyte in the control group. The electrolyte imbalance in the control group was mainly caused by oral bowel catharsis plus enema for intestinal preparation. Transferrin is a sensitive index for nutrition, and postoperative serum transferrin level was higher in the ERAS group than the control group, although the difference was not statistic significant. Malnutrition in the control group is attributed to the long postoperative fasting time.

Research shows that the reduction in liquid infusion is beneficial to reduce complications and shorten LOS. Some scholars proposed that perioperative restricted fluid administration could maintain effective circulating blood volume, ensure the oxygen transport and maintain electrolyte balance [28]. Restricted fluid administration could also reduce lung compliance, avoid interstitial edema, and avoid increasing cardiac load, thereby reducing the postoperative complications [32, 33]. Intestinal edema, delayed gastric emptying, wound and cardiopulmonary

complications are all recognized manifestations of volume overload [34]. A multicenter clinical study found that oral rehydration therapy until 2 h before surgery was safe and feasible in the low-risk Japanese surgical population. Physicians are encouraged to use this practice to maintain the amount of water in the body and electrolytes and to improve the patient's comfort [35]. Continuous epidural analgesia is effective for the treatment of postoperative intestinal paralysis. On the other hand, intestinal paralysis after laparoscopic surgery has close relationship with pneumoperitoneum [36]. The pneumoperitoneum pressure plays a critical role in the process. In recent years, suspension technology overcomes this problem effectively.

For liver cancer patients with long-term constipation, paraffin oil can be applied orally to prevent hepatic encephalopathy. Moreover, intraoperative hypothermia can reduce the activity of thrombin, thereby increasing the amount of bleeding and the risk of arrhythmia. Therefore, the temperature of patients should maintain between 36 and 37 °C during the operation. Some surgeons suggested that regular drainage tube placement can be omitted in liver resection. But in this research, for the patients with unsatisfied bleeding and wound surface, postoperative drainage was indispensable. The timing of tube removal depended on the color, quantity, and element of drainage liquid in 24 h postoperation.

Laparoscopic liver resection is associated with better QOL [37]. This study demonstrated that QoL over the first month after surgery was considerably improved in the ERAS group. A recent systematic review found that, although there was no evidence that ERAS negatively affected QoL or patient satisfaction, there was no solid evidence for an improvement either [38]. Many of them used only single-dimensional tools to measure QoL (such as pain and fatigue scores only). Only ten studies were included in this review and the studies may have been too small to detect any differences. Jones and his colleagues reported that patients treated in the enhanced recovery programs recovered faster, and had improved QoL in open liver resection [19].

When randomizing patients with a strong treatment inclination, there is a potential bias exists. When patients cannot be blinded to their treatment allocation they may be resentful if they do not receive their wished treatment, and therefore they may have poor compliance [13]. On the opposite, patients having their wished treatment may have pleasant compliance. As evidenced by the cochrane meta-analysis, simply employing ERAS does not guarantee improved results. What is more important is that there is stringent overseeing of protocol adherence by all members of the team together [39]. In a recent randomized clinical trial, compliance was 73 % in the ERAS group compared with 40 % in CG. Outcomes have been improved with higher rates of compliance [27].

Conclusions

For liver cancer patients undergoing laparoscopic resection, accelerated rehabilitation surgical program with a high level of compliance is safe and feasible, which can effectively promote gastrointestinal and liver function restoration. ERAS can also improve the quality of life and reduce the length of hospital stay as well as hospitalization expenses.

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Conflict of interest There are no conflicts of interest.

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